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Therapeutic Area	Alias	Indication	Trial ID	Trial Title	Trial Phase	
Neuroscience	B4Z-US-HFBC	Attention-Deficit/ Hyperactivity Disorder (ADHD)	634	Safety and Pharmacokinetic Study of Tomoxetine Hydrochloride in Pediatric Patients with ADHD	1	
Neuroscience	B4Z-MC-HFBD	Attention-Deficit/ Hyperactivity Disorder (ADHD)	1585	A Randomized, Double-Blind Study of Tomoxetine Hydrochloride, Methylphenidate Hydrochloride, and Placebo in Pediatric Outpatients with Attention Deficit/Hyperactivity Disorder	2	
Neuroscience	B4Z-MC-HFBK	Attention-Deficit/ Hyperactivity Disorder (ADHD)	1586	A Randomized, Double-Blind Study of Tomoxetine Hydrochloride, Methylphenidate Hydrochloride, and Placebo in Pediatric Outpatients with Attention-Deficit/Hyperactivity Disorder	2	
Neuroscience	B4Z-MC-HFBE	Attention-Deficit/ Hyperactivity Disorder (ADHD)	1855	Randomized, Double-Blind, Placebo-Controlled, Variable Discontinuation Study of Tomoxetine Hydrochloride in Children with Attention-Deficit/Hyperactivity Disorder	2	
Neuroscience	B4Z-MC-HFBF	Attention-Deficit/ Hyperactivity Disorder (ADHD)	2097	Long-Term, Open-Label, Safety Study of Tomoxetine Hydrochloride in Patients, 6 Years and Older	2	
Neuroscience	B4Z-MC-LYAFa	Attention-Deficit/ Hyperactivity Disorder (ADHD)	2552a	Relapse Prevention After 10-Week and 52-Week Treatment with Tomoxetine Hydrochloride in Children with Attention-Deficit/Hyperactivity Disorder	2/3	
Neuroscience	B4Z-MC-LYAFb	Attention-Deficit/ Hyperactivity Disorder (ADHD)	2552b	Relapse Prevention After 10-Week and 52-Week Treatment with Tomoxetine Hydrochloride in Children with Attention-Deficit/Hyperactivity Disorder	2/3	
Neuroscience	B4Z-MC-LYAD	Attention-Deficit/ Hyperactivity Disorder (ADHD)	2553	A Randomized, Double-Blind, Placebo- and Comparator-Controlled Study of Tomoxetine Hydrochloride in Recreational Drug Users	3	
Neuroscience	B4Z-MC-LYAA	Attention-Deficit/ Hyperactivity Disorder (ADHD)	2556	A Phase III Randomized, Double-Blind Comparison of Placebo and Tomoxetine Hydrochloride in Adult Outpatients with DSM-IV Attention-Deficit/Hyperactivity Disorder.	3	
Neuroscience	B4Z-MC-LYAB	Attention-Deficit/ Hyperactivity Disorder (ADHD)	2561	A Phase III Open-Label Safety and Efficacy Study of Tomoxetine Hydrochloride in Outpatients with ADHD, Ages 6 to 18 Years	3	
Neuroscience	B4Z-MC-LYAT	Attention-Deficit/ Hyperactivity Disorder (ADHD)	2746	Efficacy, Tolerability, and Safety of Once-Daily Atomoxetine Hydrochloride versus Placebo in Children with Attention-Deficit/Hyperactivity Disorder	3	

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Neuroscience	B4Z-MC-LYAC	Attention-Deficit/ Hyperactivity Disorder (ADHD)	3468	A Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Comparison of Fixed-Dose Ranges (mg/kg/day) of Tomoxetine with Placebo in Child and Adolescent Outpatients with ADHD, Aged 8 to 18 Years	3	
Neuroscience	B4Z-MC-LYAO	Attention-Deficit/ Hyperactivity Disorder (ADHD)	4642	A Phase III Randomized, Double-Blind Comparison of Placebo and Tomoxetine Hydrochloride in Adult Outpatients with DSM-IV Attention-Deficit/Hyperactivity Disorder.	3	
Neuroscience	B4Z-MC-LYAQ	Attention-Deficit/ Hyperactivity Disorder (ADHD)	4668	Safety and Efficacy of Atomoxetine or Atomoxetine Plus Fluoxetine in the Treatment of Mixed Attentional and Affective Disorders	3	
Neuroscience	B4Z-MC-LYAR	Attention-Deficit/ Hyperactivity Disorder (ADHD)	4671	Long-Term, Open-Label Safety Study of Atomoxetine Hydrochloride in Adult Outpatients with DSM-IV Attention-Deficit/Hyperactivity Disorder	3	
Neuroscience	B4Z-MC-LYAS	Attention-Deficit/ Hyperactivity Disorder (ADHD)	4908	A Randomized, Double-Blind Study of Tomoxetine Hydrochloride and Placebo in Pediatric Outpatients with Attention Deficit/Hyperactivity Disorder and Comorbid Tic Disorders	3	
Neuroscience	B4Z-MC-LYAU	Attention-Deficit/ Hyperactivity Disorder (ADHD)	5001	A Double-Blind Crossover Study of Tomoxetine Hydrochloride and Methylphenidate Effects on Neural Activity in Attention-Deficit/Hyperactivity Disorder	3	
Neuroscience	B4Z-US-LYAV	Attention-Deficit/ Hyperactivity Disorder (ADHD)	5002	Sleep and Cognitive/Neuropsychological Function in Children with Attention-Deficit/Hyperactivity Disorder Before and During Treatment with Tomoxetine Hydrochloride and Stimulants	4	
Neuroscience	B4Z-MC-LYAWa	Attention-Deficit/ Hyperactivity Disorder (ADHD)	5003a	A Double-Blind, Placebo-Controlled Trial of Atomoxetine Hydrochloride to Evaluate Efficacy in the School Setting in Children Ages 8 to 12 Years with Attention- Deficit/Hyperactivity Disorder– Acute Treatment Period (Visit 1 through Visit 7)	3	
Neuroscience	B4Z-MC-LYAWb	Attention-Deficit/ Hyperactivity Disorder (ADHD)	5003b	A Double-Blind, Placebo-Controlled Trial of Atomoxetine Hydrochloride to Evaluate Efficacy in the School Setting in Children Ages 8 to 12 Years with Attention- Deficit/Hyperactivity Disorder	4	
Neuroscience	B4Z-MC-LYAX	Attention-Deficit/ Hyperactivity Disorder (ADHD)	5004	A Randomized, Double-Blind, Placebo-Controlled Study of Atomoxetine Hydrochloride in Adolescents with Attention-Deficit/Hyperactivity Disorder and Comorbid Depressive Disorder	3	
Neuroscience	B4Z-MC-LYBB	Attention-Deficit/ Hyperactivity Disorder (ADHD)	5197	A Phase 3 Open-Label Safety and Efficacy Study of Tomoxetine Hydrochloride in Pediatric Outpatients (6 to 18 Years) with ADHD	3	
Neuroscience	B4Z-JE-LYBC	Attention-Deficit/ Hyperactivity Disorder (ADHD)	5285	A Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Comparison of Fixed-Dose Ranges of Atomoxetine Hydrochloride in Child Outpatients with Attention-Deficit/Hyperactivity Disorder	2/3	

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Neuroscience	B4Z-JE-LYBD	Attention-Deficit/ Hyperactivity Disorder (ADHD)	5286	An Open-Label, Dose-Titration Safety Study of Atomoxetine Hydrochloride in Outpatient Japanese Children with Attention Deficit/Hyperactivity Disorder	2	
Neuroscience	B4Z-US-LYBG	Attention-Deficit/ Hyperactivity Disorder (ADHD)	5670	A Randomized, Double-Blind, Placebo-Controlled Trial of Once Daily Atomoxetine Hydrochloride to Evaluate Efficacy in the Treatment of Attention-Deficit/Hyperactivity Disorder in Children Ages 6-12 with an Assessment of Evening Behavior	3	
Neuroscience	B4Z-US-LYBH	Attention-Deficit/ Hyperactivity Disorder (ADHD)	5671	Placebo-Controlled Study of the Effects of Atomoxetine Hydrochloride on Bladder Control in Children with Nocturnal Enuresis	3b	
Neuroscience	B4Z-MC-LYBI	Attention-Deficit/ Hyperactivity Disorder (ADHD)	5831	A Randomized, Double-Blind Comparison of Atomoxetine Hydrochloride, Extended-Release Methylphenidate Hydrochloride (Concerta), and Placebo in Pediatric Outpatients with DSM-IV Attention-Deficit/Hyperactivity Disorder	3	
Neuroscience	B4Z-MC-LYBN	Attention-Deficit/ Hyperactivity Disorder (ADHD)	6066	Noradrenergic Augmentation of SSRI Therapy in Patients with Depression Unresponsive or Incompletely Responsive to SSRI Monotherapy	4	
Neuroscience	B4Z-MC-LYBO	Attention-Deficit/ Hyperactivity Disorder (ADHD)	6425	A Randomized, Double-Blind, Placebo- and Comparator-Controlled Study of Atomoxetine Hydrochloride in a Drug-Abusing Population	1/2	
Neuroscience	B4Z-US-LYBPa	Attention-Deficit/ Hyperactivity Disorder (ADHD)	6477a	A Randomized, Double-Blind, Placebo-Controlled Study of Atomoxetine Hydrochloride in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder and Comorbid Anxiety	3b	
Neuroscience	B4Z-US-LYBPb	Attention-Deficit/ Hyperactivity Disorder (ADHD)	6477b	A Randomized, Double-Blind, Placebo-Controlled Study of Atomoxetine Hydrochloride in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder and Comorbid Anxiety	3b	
Neuroscience	B4Z-UT-S003	Attention-Deficit/ Hyperactivity Disorder (ADHD)	6639	An Open-Label Pilot Study of Atomoxetine for Attention Deficit and Hyperactive/Impulsive Behavior Problems in Children and Adolescents with Autistic Spectrum Disorders	4	
Neuroscience	B4Z-SO-LY15	Attention-Deficit/ Hyperactivity Disorder (ADHD)	6671	A Randomized, Double Blind, Placebo Controlled Study of the Broader Efficacy of Atomoxetine Hydrochloride in the Treatment of Attention-Deficit/Hyperactivity Disorder in Swedish Children and Adolescents	3b	
Neuroscience	B4Z-MC-LYBR	Attention-Deficit/ Hyperactivity Disorder (ADHD)	6934	A Randomized, Double-Blind Comparison, Safety and Efficacy Trial of Atomoxetine Hydrochloride and Methylphenidate Hydrochloride in Pediatric Outpatients with DSM-IV Attention-Deficit/Hyperactivity Disorder	3	

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Neuroscience	B4Z-BP-LYBS	Attention-Deficit/ Hyperactivity Disorder (ADHD)	6962	A Randomized, Controlled, Open-Label Study of the Broader Efficacy of Atomoxetine Hydrochloride in the Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in Children and Adolescents	3b	
Neuroscience	B4Z-MC-LYBU	Attention-Deficit/ Hyperactivity Disorder (ADHD)	7065	A Randomized, Double-Blind Comparison of Atomoxetine Hydrochloride Augmented with Either Extended-Release Methylphenidate Hydrochloride (Concerta®) or Placebo in Children with Attention-Deficit/Hyperactivity Disorder (ADHD) Who Have Not Responded to Stimulant Mono Therapy	3	
Neuroscience	B4Z-MC-LYBV	Attention-Deficit/ Hyperactivity Disorder (ADHD)	7066	A Double-Blind Study of Functional Outcomes with Atomoxetine-Hydrochloride and Placebo in Adult Outpatients with DSM-IV Attention-Deficit/Hyperactivity Disorder	4	
Neuroscience	B4Z-MC-LYBX	Attention-Deficit/ Hyperactivity Disorder (ADHD)	7068	A Randomized, Double-Blind Comparison of Atomoxetine Hydrochloride and Placebo in Child and Adolescent Outpatients with Attention-Deficit/Hyperactivity Disorder and Comorbid Oppositional Defiant Disorder	3	
Neuroscience	B4Z-MC-LYBY	Attention-Deficit/ Hyperactivity Disorder (ADHD)	7069	Atomoxetine Treatment of Adults with ADHD and Comorbid Alcohol Abuse: A Randomized, Placebo-Controlled Trial	4	
Neuroscience	B4Z-SB-LYDE	Attention-Deficit/ Hyperactivity Disorder (ADHD)	7233	An Open-label Study on Effectiveness and Tolerability of Atomoxetine as Perceived by Patients, Parents, and Physicians in Adolescents with Attention-Deficit/Hyperactivity Disorder in Germany	3	
Neuroscience	B4Z-CA-LYCS	Attention-Deficit/ Hyperactivity Disorder (ADHD)	7649	A Phase IIIb Open-label Trial of Atomoxetine Hydrochloride to Evaluate Academic Outcome in Children Ages 8 to 11 Years with Attention-Deficit/Hyperactivity Disorder	3b	
Neuroscience	B4Z-MC-LYCG	Alzheimer's Disease	7951	Atomoxetine Augmentation of Cholinesterase Inhibitor Therapy in Patients with Alzheimer's Disease	2/3	
Neuroscience	B4Z-MC-LYCI	Attention-Deficit/ Hyperactivity Disorder (ADHD)	7953	An Open-Label, Multicenter, Pilot Study of the Safety and Efficacy of Transitioning from a Stimulant Medication to Atomoxetine in Pediatric and Adolescent Outpatients with DSM IV Attention-Deficit/Hyperactivity Disorder (ADHD)	4	
Neuroscience	B4Z-MC-LYCK	Attention-Deficit/ Hyperactivity Disorder (ADHD)	7955	A Double-Blind, Crossover Comparison of Atomoxetine Hydrochloride and Placebo in Child Outpatients with Attention-Deficit/Hyperactivity Disorder, Reading Disorder, or Comorbid Attention-Deficit/Hyperactivity Disorder and Reading Disorder	3	
Neuroscience	B4Z-US-LYCC	Attention-Deficit/ Hyperactivity Disorder (ADHD)	7972	Evaluation of Continuous Symptom Treatment of ADHD: A Placebo-Controlled Double-Blind Assessment of Morning-Dosed or Evening-Dosed Strattera	3	

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Neuroscience	B4Z-US-LYCD	Attention-Deficit/ Hyperactivity Disorder (ADHD)	7974	Maintenance of Benefit after 8-Week and 52-Week Treatment with Atomoxetine Hydrochloride in Adolescents with Attention-Deficit/Hyperactivity Disorder	4	
Neuroscience	B4Z-US-LYCE	Attention-Deficit/ Hyperactivity Disorder (ADHD)	7975	Open-Label Treatment with Atomoxetine Hydrochloride in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder and Comorbid Dyslexia	4	
Neuroscience	B4Z-TW-S010	Attention-Deficit/ Hyperactivity Disorder (ADHD)	8160	Efficacy, Tolerability, and Safety of Once-Daily Atomoxetine Hydrochloride versus Placebo in Taiwanese Children and Adolescents with Attention-Deficit/Hyperactivity Disorder	3b	
Neuroscience	B4Z-MC-LYCL	Attention-Deficit/ Hyperactivity Disorder (ADHD)	8226	Guiding Dose Increases in Patients Incompletely Responsive to Usual Doses of Atomoxetine by Determining Plasma Atomoxetine Concentrations: A Randomized, Double-Blind Study	4	
Neuroscience	B4Z-FW-LYCT	Attention-Deficit/ Hyperactivity Disorder (ADHD)	8619	A Study to Evaluate Single Dose and Multiple Dose Pharmacokinetics of Atomoxetine Hydrochloride in Chinese Healthy Subjects	1	
Neuroscience	B4Z-US-LYCU	Attention-Deficit/ Hyperactivity Disorder (ADHD)	9040	Efficacy and Safety of Once-Daily Atomoxetine Hydrochloride in Adults with ADHD Over An Extended Period of Time (6 Months): With a Brief Evaluation of Executive Cognition	4	
Neuroscience	B4Z-MW-LYCZ	Attention-Deficit/ Hyperactivity Disorder (ADHD)	9081	Efficacy, Tolerability, and Safety of Once-Daily Atomoxetine Hydrochloride versus Placebo in Russian Children and Adolescents with Attention-Deficit/Hyperactivity Disorder	3b	
Neuroscience	B4Z-SB-LYDD	Attention-Deficit/ Hyperactivity Disorder (ADHD)	9496	An Open-label Study on Effectiveness and Tolerability of Atomoxetine as Perceived by Patients, Parents, and Physicians in Children with Attention-Deficit/Hyperactivity Disorder in Germany	3	
Neuroscience	H8V-FW-LTBD	Attention-Deficit/ Hyperactivity Disorder (ADHD)	9586	An Exploratory Study, using Atomoxetine, on Central Nervous System (CNS) Biomarkers	1	
Neuroscience	B4Z-CA-S012	Attention-Deficit/ Hyperactivity Disorder (ADHD)	9684	A 3-Month, Open-Label Study of Atomoxetine in Children with Attention-Deficit/Hyperactivity Disorder; Symptomatic and Functional Outcomes	4	
Neuroscience	B4Z-CA-S013	Attention-Deficit/ Hyperactivity Disorder (ADHD)	9721	An Open-Label Pilot Study of Atomoxetine Hydrochloride to Evaluate Neuropsychological Function in Children Ages 6 to 10 Years with Attention-Deficit/ Hyperactivity Disorder	4	
Neuroscience	B4Z-US-LYDQ	Attention-Deficit/ Hyperactivity Disorder (ADHD)	9855	A Double-Blind Placebo-Controlled Study of Atomoxetine Hydrochloride in the Treatment of Adults with ADHD and Comorbid Social Anxiety Disorder	4	

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Neuroscience	B4Z-FW-LYDP	Attention-Deficit/ Hyperactivity Disorder (ADHD)	9916	The Haemodynamic Effects of Inhaled Salbutamol in the Absence and Presence of Atomoxetine	1
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Summary ID#634

Clinical Study Summary: Study B4Z-US-HFBC

Title of Study: Safety and Pharmacokinetic Study of Tomoxetine Hydrochloride in Pediatric Patients with ADHD	
Investigator: This single-center study included 1 principal investigator.	
Study Center: This study was conducted at 1 study center in the United States.	
Length of Study: 11 months Date first patient enrolled: 14 October 1997 Date last patient completed: 17 September 1998	Phase of Development: 1B
Objectives: The primary objective of study B4Z-MC-HFBC (HFBC) was to evaluate the safety and effectiveness of atomoxetine (formerly called tomoxetine) hydrochloride in pediatric patients, aged 7 through 13 years at the time of entry into the study, who met <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</i> (DSM-IV) criteria for Attention-Deficit/Hyperactivity Disorder (ADHD). The following secondary objectives were identified for this study: • To identify a dose range of atomoxetine hydrochloride that provides maximal therapeutic benefit in the reduction of symptoms of ADHD in outpatient children, aged 7 through 13 years, with the disorder. • To evaluate the single-dose and steady-state pharmacokinetics of atomoxetine hydrochloride in a population of children, aged 7 through 13 years. • To compare the steady-state plasma concentrations achieved and pharmacokinetics attained in this population with that characterized in adult populations from historical data.	
Study Design: This was a Phase 1B, single-site, open-label, dose titration (10- to 90-mg total daily dose) study of up to 17 weeks' duration. Study participants were children, aged 7 through 13 years at the time of entry into the study. This study included two study periods: Study Period I (Screening) and Study Period II (Acute Treatment, Single-Dose Pharmacokinetics, and Steady-State Discontinuation Pharmacokinetics).	
Number of Patients: Planned to Enroll: 36 Enrolled: 30 Completed: 22	
Diagnosis and Main Criteria for Inclusion: Patients were included in the study only if they met all of the following criteria: patients were at least 7 years of age but less than 14 years of age (patients may have had their 14 th birthday during the study) and met DSM-IV diagnostic criteria for ADHD, by clinical assessment; laboratory results, including serum chemistries, hematology, and urinalysis, showed no significant abnormalities (laboratory deviations requiring acute medical intervention) and there was no clinical information that, in the judgment of the physician, should preclude a patient's participation at study entry; electrocardiogram (ECG) results showed no clinically significant abnormalities; educational level and degree of understanding was such that the patients and their parents (or legal representatives) could communicate suitably with the investigator and study coordinator; patients were of normal intelligence as assessed clinically or by formal psychometric testing; and patients and their parents (or legal representatives) had been judged to be reliable to keep appointments for clinic visits and all tests and examinations required by the protocol.	
Test Product, Dose, and Mode of Administration: Atomoxetine hydrochloride (LY139603): 10 to 90 mg/d; twice daily;	
Duration of Treatment: Mean of 68 days (range of 8 to 100 days).	
Reference Therapy, Dose, and Mode of Administration: None.	

Variables:

Efficacy: The primary efficacy criterion was the change from baseline to endpoint in the Attention-Deficit/Hyperactivity Disorder- Rating Scale-IV-Parent Version:Investigator-Administered and Scored (ADHDRS-IV-Parent: Inv) Total score. Changes from baseline to endpoint in secondary efficacy measures were also computed. Endpoint, rather than change scores, for the Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Improvement (CGI-ADHD-I) score and the Clinical Global Impressions-Efficacy Index (CGI-EI) were assessed, as these scales inherently measure change.

Safety: The following safety measures were collected: adverse events (every visit); vital signs, height and weight, and concomitant medications (every visit); drug screening (as appropriate); urinalysis (Visit 1 and Visit 13); 12-lead ECGs (Visit 1, Visit 4, Visit 6, Visit 8, Visit 10, and Visit 13, or at discontinuation); and hematological and serum chemistry studies (Visit 1, Visit 4, Visit 7, Visit 10, and Visit 13).

Pharmacokinetic: Blood samples were drawn after single (Visit 2) or multiple (Visit 13) oral dose administration of atomoxetine for measurement of atomoxetine, 4-hydroxyatomoxetine, and *N* desmethyatomoxetine plasma concentrations for pharmacokinetic assessment.

Evaluation Methods:

Statistical: Efficacy analyses were performed on all enrolled patients with a baseline and at least one postbaseline measurement. Safety analyses were performed on all enrolled patients. Summary statistics computed included the mean, median, standard deviation, range, and 2-sided 95% confidence intervals on the mean change from baseline score. Wilcoxon signed-rank test was used to assess whether mean changes were significantly different from zero. The correlation between efficacy measures was assessed using Spearman's correlation coefficients.

Pharmacokinetic: Noncompartmental pharmacokinetic analysis was performed after single and multiple oral dose administration of atomoxetine.

Summary:

Patient Disposition: Thirty patients participated in the treatment phase; 21 of these also participated in one or both pharmacokinetic studies. Because 2 patients participated in both pharmacokinetic studies, the results are based on 23 observations in 21 patients. Seven patients participated in the 24-hour Single Dose Pharmacokinetic Study prior to the treatment phase; 16 patients participated in the 24-hour Steady-State Discontinuation Pharmacokinetic Study following the treatment phase.

Patient Demographics: Table HFBC.1 shows a summary of patient characteristics for patients (both entered and enrolled), including age, gender, origin, DSM-IV ADHD subtype, grade in school, and height and weight at Visit 1. Entered and enrolled populations were similar. The patient population was predominantly male (83.3% of enrolled patients) and Caucasian (76.7% of enrolled patients), with a mean age of 10.1 years in the enrolled patients (range 7.0 years to 14.0 years). The majority of ADHD patients had mixed DSM-IV subtype (72.7% of enrolled patients with a subtype diagnosis). Two-thirds of the enrolled patients were in the 4th, 5th, or 6th grade. Cytochrome P450 2D6 (CYP2D6) genotype characterization revealed that all 30 enrolled patients were extensive metabolizer (EM) patients.

Efficacy: The primary efficacy outcome instrument was the ADHDRS-IV-Parent: Inv. Analysis of baseline to endpoint change (last-observation-carried-forward [LOCF]) with this measure revealed a statistically significant decrease in the ADHDRS-IV-Parent: Inv Total score beginning with Visit 3 (1 week after beginning treatment with atomoxetine) and continuing through the final visit. As Table HFBC.2 shows, the mean reduction at endpoint was 15.2 (95% confidence interval [-20.3, -10.2]), which represented a mean percentage decrease of 37% from baseline. More than 50% of the reduction occurred during the first 3 weeks of treatment. Statistically significant decreases were also seen in both the Inattention and Hyperactivity-Impulsivity subscales of the ADHDRS-IV-Parent: Inv (Table HFBC.2).

Table HFBC.3 presents a summary of changes from baseline for all other secondary efficacy measures. Significant reductions ($p < .001$) were seen for the Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder –Severity (CGI-ADHD-S) and for the Cognitive Problems/Inattention, Hyperactivity, and ADHD Index subscales of the Conners' Parent Rating Scale-Revised: Short Form

(CPRS-R:S). The reduction seen in the CPRS-R:S Oppositional subscale did not reach statistical significance ($p=.085$). Endpoint, rather than change scores, for the CGI-ADHD-I and the CGI-EI were assessed, because these scales inherently measure change. Sixteen patients (59.2%) met CGI-ADHD-I criteria (a score of 2 or less at endpoint) as treatment responders using an intent-to-treat analysis. In addition, 16 patients (59.2%) had endpoint scores on the CGI-EI indicating moderate or marked improvement with minimal or no adverse events. Too few teacher ratings were available for analyses of teacher rated instruments.

All patients began open-label treatment with 10 mg/d (0.1 to 0.4 mg/kg/d) atomoxetine hydrochloride at Visit 2, and their dosage was adjusted at the investigator's discretion by up to 10 mg/d at each visit. Because of the dose-titration design, the mean maximum and mean final prescribed daily doses were higher in the group of patients who were in the study longer (completing at least Visit 8). The mean maximum prescribed daily dose for the 24 patients completing at least Visit 8 (80.0 mg/d; range 40 to 90 mg/d) was 88.9% of the maximum prescribed daily dose allowed in the study (90.0 mg/d). The mean maximum weight-adjusted prescribed dose was 2.0 mg/kg/d (range 1.1 to 3.5 mg/kg/d). The mean final prescribed daily dose was 64.8 mg/d (1.6 mg/kg/d) in all 30 enrolled patients and 76.5 mg/d (1.9 mg/kg/d) in the 24 patients completing at least Visit 8. For the 24 patients completing at least Visit 8, doses steadily increased from Visit 2 (10.0 mg/d; 0.25 mg/kg/d) to Visit 10 (75.0 mg/d; 1.86 mg/kg/d). The mean prescribed daily dose levels for Visits 10 through 12 remained fairly constant (75.0 to 76.1 mg/d; 1.86 to 1.92 mg/kg/d). Because dose and time in the study are confounded, no definitive conclusions about dose response could be drawn.

Table HFBC.4 shows mean values for selected single-dose and steady-state pharmacokinetic parameters. There was only a slight increase in the mean steady-state maximum plasma concentration ($C_{ss,max}$) compared to the mean single-dose maximum plasma concentration (C_{max}), after normalizing to a 1 mg/kg dose, suggesting minimal accumulation of atomoxetine at steady-state for this dosage regimen. This degree of accumulation was predictable based on the prescribed dosing interval and the elimination rate constant in the single-dose pharmacokinetics. The mean half-life, apparent oral plasma clearance, and apparent volume parameters were similar between the single-dose and steady-state studies in the pediatric patients, suggesting linear pharmacokinetics. An initial comparison between children and adults using historical adult data from previous Phase I studies showed the pharmacokinetics in pediatric patients and adult subjects were similar, after adjustment for body weight.

Safety: Of the 30 patients enrolled in this study, 29 were prescribed doses of atomoxetine ranging from 10 to 90 mg/d. Duration of treatment ranged from 8 to 100 days.

Table HFBC.5 provides a summary of treatment-emergent adverse events occurring in at least 5% (2 patients) of the 30 enrolled patients. Of the enrolled patients, 83.3% reported at least one treatment-emergent adverse event. No adverse events reported met Food and Drug Administration (FDA) criteria for serious adverse events. The most commonly reported treatment-emergent adverse events (occurring in $\geq 5\%$ of the patients) were rhinitis (33.3%), headache (20.0%), anorexia (typically captured as "decreased appetite;" 16.7%), dizziness (16.7%), nervousness (13.3%), somnolence (13.3%), abdominal pain (10.0%), amnesia (10.0%), asthenia (10.0%), flu syndrome (6.7%), infection (6.7%), and pain (6.7%). One case of pneumonia was reported. Two patients discontinued the study due to adverse events, both due to headache (mild in severity) at Visit 3.

As Table HFBC.6 shows, statistically significant mean changes from baseline were noted for the following laboratory measures: leukocyte counts, neutrophils, lymphocytes, platelet counts, inorganic phosphorus, mean cell volume, albumin, alkaline phosphatase, urea nitrogen, creatine phosphokinase, and total protein. None of the changes required dosage adjustment or any other intervention.

Table HFBC.7 summarizes the baseline, endpoint, and change to endpoint for vital signs (sitting systolic blood pressure, sitting diastolic blood pressure, heart rate, temperature, weight, and height). Diastolic blood pressure and height were statistically significantly ($p < .05$) increased from baseline to endpoint. In addition, statistically significant elevations in heart rate were observed from Visits 5 through 12 (Figure

HFBC.1). However, a mean decrease of approximately 9 bpm at the final visit resulted in an overall lack of statistical significance from baseline to endpoint. The return to normal heart rate was most likely the result of the conduct of the Steady-State Discontinuation Pharmacokinetic assessment performed at Visit 13. Because the majority of patients were preparing to begin the 24-hour pharmacokinetic measurement period, they were instructed not to take study medication on the morning of Visit 13, and vital signs were taken while patients may have been off medication. Therefore, the Visit 12 assessment may more accurately reflect changes in vital signs attributable to atomoxetine.

Table HFBC.8 lists baseline, endpoint, and change to endpoint for ECG parameters, including QTc interval, QT interval, RR interval, PR interval, QRS interval, and ECG heart rate. Statistically significant decreases were seen at the $p < .01$ level in QT interval. However, the mean change in the corrected QT interval was not statistically significantly different from zero. A statistically significant increase in ECG heart rate was seen at the $p < .01$ level, consistent with the pharmacodynamic effects of atomoxetine, a nonstimulant norepinephrine enhancer.

Atomoxetine hydrochloride
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Table HFBC.1. Characteristics of ADHD Patients in Study B4Z-MC-HFBC

Variable	Entered (n=35)				Enrolled (n=30)			
	N	Mean	SD	Min, max	N	Mean	SD	min, max
Age (yr)	35	10.0	1.8	7.0, 14.0	30	10.1	1.8	7.0, 14.0
Height (in)	32	55.0	4.6	47.0, 66.5	30	55.2	4.6	47.0, 66.5
Weight (kg)	32	41.4	13.8	25.0, 77.2	30	42.4	13.7	25.0, 77.2
	N	n	Percentage		N	n	Percentage	
Gender	35				30			
Male		27	77.1			25	83.3	
Female		8	22.9			5	16.7	
DSM-IV ADHD Subtype	24				22			
Hyperactivity/Impulsivity		0	0.0			0	0.0	
Inattention		7	29.2			6	27.3	
Mixed		17	70.8			16	72.7	
School Grade	34				30			
1 st		4	11.8			3	10.0	
2 nd		2	5.9			2	6.7	
3 rd		3	8.8			3	10.0	
4 th		9	26.5			8	26.7	
5 th		8	23.5			6	20.0	
6 th		6	17.6			6	20.0	
7 th		1	2.9			1	3.3	
8 th		1	2.9			1	3.3	

(continued)

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Table HFBC.1. Characteristics of ADHD Patients Enrolled in Study B4Z-MC-HFBC (concluded)

Variable	Entered (n=35)			Enrolled (n=30)		
	N	n	Percentage	N	n	Percentage
Origin	35			30		
AF		4	11.4		3	10.0
CA		27	77.1		23	76.7
HP		4	11.4		4	13.3
Previous Stimulant Use	35	16	45.7	30	15	50.0

Note that all enrolled patients were determined to be extensive metabolizers.

Abbreviations: AF = African-American; CA = Caucasian; HP = Hispanic; min = minimum; max = maximum; see Section 4, List of Abbreviations, for others.

Source Data: RMP.B4ZSHFBC.SASPGM(FDEMOG), ACDO(CRIS) program RMP.B4ZP.SASPGM(DE1AIFBC).

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Table HFBC.2. ADHDRS-IV-Parent: Inv—Mean Baseline, Endpoint, and Change from Baseline to Endpoint Values, Study B4Z-MC-HFBC

Variable	n	Baseline		Endpoint		Change		Change p-Value ^a
		Mean	SD	Mean	SD	Mean	SD	
Total Score	27	41.1	8.4	25.9	12.9	-15.2	12.5	< .001
Hyperactivity/Impulsivity Subscale	27	19.6	5.1	12.1	7.7	-7.5	7.5	< .001
Inattention Subscale	27	21.4	4.3	13.7	6.1	-7.7	5.9	<.001

^a p-Values are from Wilcoxon signed-rank test on change from baseline to endpoint (LOCF) scores. All enrolled patients with at least one postbaseline measurement.

The 95% confidence interval on the LOCF mean change from baseline to endpoint for the total score is (-20.2, -10.3).

Source Data: RMP.B4ZSHFBC.SASPGM(FEFFLOCF).

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Table HFBC.3. Secondary Efficacy Measures – Summary of Changes from Baseline, Study B4Z-MC-HFBC

Variable	n	Baseline		Endpoint		Change		p-Values within Group*
		Mean	SD	Mean	SD	Mean	SD	
ADHDRS-IV-Teacher								
Total	4	31.0	16.0	27.8	8.5	-3.3	10.9	--
Hyperactivity/Impulsivity	5	16.8	10.2	15.6	7.0	-1.2	4.6	--
Inattention	4	16.5	6.9	14.3	4.6	-2.3	5.9	--
CGI-ADHD-S	27	5.1	0.8	3.8	0.9	-1.4	1.1	<.001
CGI-ADHD-I	27			2.2	1.0			
CGI-EI	26			6.1	4.0			
CPRS-R:S								
Oppositional subscale	27	9.2	5.2	7.9	4.9	-1.4	4.4	.085
Cognitive problems subscale	27	14.1	3.7	10.5	4.2	-3.6	4.1	<.001
Hyperactivity subscale	27	11.8	4.4	8.9	5.2	-3.0	3.5	<.001
ADHD index	27	27.9	6.1	21.1	8.2	-6.8	6.4	<.001
ODD total	25	13.4	7.4	11.4	6.4	-2.0	7.0	.136
CCPT (overall index)	20	7.8	6.5	9.9	6.7	2.1	5.9	.114

Note: N = 27 (total number of patients in the treatment group having a baseline and at least one postbaseline measurement). The overall patient count (n) may be less than N due to some patients not having the variable in both the baseline and postbaseline visits.

Abbreviations: SD = standard deviation.

* The significance of a location shift from zero of the change from baseline within the treatment group is tested by the Wilcoxon signed-rank test procedure.

Dash = too small a sample.

Source Data: RMP.B4ZSHFBC.SASPGM (FEFFLOCF), ACDO(CRIS) program RMP.B4ZP.SASPGM (FBCLS03D).

Table HFBC.4. Mean Single-Dose and Steady-State Pharmacokinetic Parameters Calculated for EM Pediatric Patients After Atomoxetine Administration.

Pharmacokinetic Parameter ^a	Pediatric Single-dose (n=7)	Pediatric Steady-state (n=16)
Dose (mg)	10 mg	20 to 45 mg twice daily
Body weight (kg)	39 ± 11	44 ± 16
C _{max} or C _{ss,max} , (ng/mL)/(mg/kg)	533 ± 173	584 ± 268
T _{max} , (hr)	2.15 ± 1.36	1.54 ± 0.50
t _{1/2} (hr)	3.12 ± 0.60	3.28 ± 0.44
CL/F or CL _{ss} /F (L/hr)	17.3 ± 6.2	20.3 ± 8.0
(L/hr/kg)	0.455 ± 0.159	0.477 ± 0.195
V _z /F (L)	74.4 ± 18.5	95.9 ± 41.2
(L/kg)	1.96 ± 0.47	2.25 ± 1.00

^a Parameters are listed as mean ± standard deviation

Abbreviations: EM = extensive metabolizer.

Table HFBC.5. Summary of Treatment-Emergent Adverse Events in 30 Enrolled Patients – All Events Occurring in at Least 5% of the Patients, Study B4Z-MC-HFBC

Adverse Event	n	Percentage
Any TESS	25	83.3
Rhinitis	10	33.3
Headache	6	20.0
Anorexia	5	16.7
Dizziness	5	16.7
Nervousness	4	13.3
Somnolence	4	13.3
Abdominal pain	3	10.0
Amnesia	3	10.0
Asthenia	3	10.0
Flu syndrome	2	6.7
Infection	2	6.7
Pain	2	6.7

n = number of patients reporting the specific treatment-emergent adverse event.

Source Data: RMP.B4ZP.SASPGM(AS2AIFBC).

Table HFBC.6. Summary of Laboratory Changes from Baseline for Enrolled Patients, Study B4Z-MC-HFBC

Laboratory Test (Unit)	n	Baseline		Endpoint		Change		p-Values within Group*
		Mean	SD	Mean	SD	Mean	SD	
Complete Blood Count								
Hematocrit (actual count)	25	0.40	0.03	0.39	0.03	-0.01	0.03	.155
Hemoglobin (mmol/L[Fe])	25	8.01	0.64	8.01	0.65	-0.01	0.42	.868
Erythrocyte count (Tl/L)	25	4.64	0.35	4.66	0.34	0.02	0.27	.600
Leukocyte count (GI/L)	25	7.30	1.48	6.15	2.22	-1.16	2.08	<.001
Bands (GI/L)	25	0.00	0.00	0.01	0.03	0.01	0.03	1.00
Neutrophils, segmented (GI/L)	25	3.77	1.21	3.17	1.99	-0.60	1.82	.001
Lymphocytes (GI/L)	25	2.91	0.62	2.36	0.67	-0.55	0.70	<.001
Monocytes (GI/L)	25	0.46	0.14	0.41	0.26	-0.04	0.25	.070
Eosinophils (GI/L)	25	0.13	0.09	0.15	0.16	0.02	0.14	.825
Basophils RMP.B (GI/L)	25	0.05	0.02	0.04	0.03	-0.01	0.03	.236
Mean cell volume [MCV] (fL)	25	85.2	3.5	83.3	3.0	-1.9	3.1	.005
Platelet count (GI/L)	25	306.0	58.2	278.2	57.7	-27.8	37.7	<.001
Blood Chemistry								
AST/SGOT (U/L)	25	26.76	8.03	28.92	11.95	2.16	902	.419
ALT/SGPT (U/L)	25	22.60	16.66	22.28	23.50	-0.32	12.17	.355
Creatine phosphokinase (U/L)	25	176.3	103.0	152.5	76.6	-23.8	72.2	.035
Alkaline phosphatase (U/L)	25	231.3	66.5	213.2	55.8	-18.1	36.5	.008
GGT [GGPT/SGGT/YGGT] (U/L)	25	13.32	3.67	13.16	4.10	-0.16	3.57	.315
Urea nitrogen (mmol/L)	25	5.16	0.88	4.58	1.08	-0.57	0.99	.009
Calcium (mmol/L)	25	2.37	0.09	2.36	0.06	-0.01	0.09	.791
Inorganic phosphorus (mmol/L)	25	1.68	0.15	1.54	0.18	-0.15	0.20	<.001
Total protein (g/L)	25	70.9	3.7	69.8	3.4	-1.1	3.0	.049
Albumin (g/L)	25	43.6	2.6	42.4	2.3	-1.1	1.9	.007

(continued)

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Table HFBC.6. Summary of Laboratory Changes from Baseline for Enrolled Patients, Study B4Z-MC-HFBC (concluded)

Laboratory Test (Unit)	n	Baseline		Endpoint		Change		p-Values within Group*
		Mean	SD	Mean	SD	Mean	SD	
Blood Chemistry (continued)								
Glucose, non-fasting (mmol/L)	25	5.25	0.74	5.11	0.57	-0.14	0.95	.523
Uric acid (μmol/L)	25	209.6	44.2	209.6	53.6	0.0	35.4	.989
Cholesterol (mmol/L)	25	4.27	0.60	4.14	0.49	-0.13	0.55	.280
Creatinine (mmol/L)	25	46.0	10.5	46.0	8.8	0.0	8.5	1.00
Bilirubin, total (μmol/L)	25	8.6	4.2	8.8	4.0	0.2	3.9	.840
Electrolytes								
Sodium (mmol/L)	25	140.2	2.5	139.7	1.7	-0.5	2.9	.236
Potassium (mmol/L)	25	4.05	0.32	4.01	0.25	-0.04	0.33	.661
Chloride (mmol/L)	25	103.7	2.6	103.1	3.0	-0.6	4.0	.422
Bicarbonate, HCO ₃ (mmol/L)	25	25.61	1.97	24.95	2.02	-0.66	2.66	.267
Urinalysis-specific gravity (no units)	22	1.03	0.01	1.02	0.01	-0.00	0.01	.147

* The significance of a location shift from zero of the change from baseline within a treatment group was tested by the Wilcoxon signed-rank test procedure.
 n = total number of patients in each treatment group having the variable in both baseline and postbaseline visits.
 Source Data: ACDO (CRIS) program RMP.B4ZP.SASPGM (FBCLS03A)

Table HFBC.7. Vital Sign Summary – Mean Baseline, Endpoint, and Change from Baseline to Endpoint Values, Study B4Z-MC-HFBC

Vital Sign	n	Baseline		Endpoint		Change		p-Value ^a
		Mean	SD	Mean	SD	Mean	SD	
Systolic blood pressure (mm Hg)	27	109.1	12.4	110.5	11.6	1.4	12.6	.912
Diastolic blood pressure (mm Hg)	27	59.1	7.0	67.3	11.8	8.3	15.2	.013
Heart rate (bpm)	26	87.7	12.7	88.6	13.4	0.9	17.4	.708
Temperature (°C)	27	36.8	0.4	36.8	0.4	-0.0	0.6	.511
Weight (kg)	27	43.4	14.1	43.2	15.2	-0.2	2.6	.411
Height (cm)	27	141.8	11.7	142.6	11.4	0.7	1.4	.010

n = number of enrolled patients with a baseline and at least one postbaseline measurement; SD = standard deviation.

^a p-Values are from Wilcoxon signed-rank test on change from baseline to endpoint (LOCF) scores.

All vital signs were taken in the sitting position.

Source Data: ACDO (CRIS) program RMP.B4ZP.SASPGM(FBCLS06C) and
RMP.B4ZP.SASPGM(FBCLS03B)

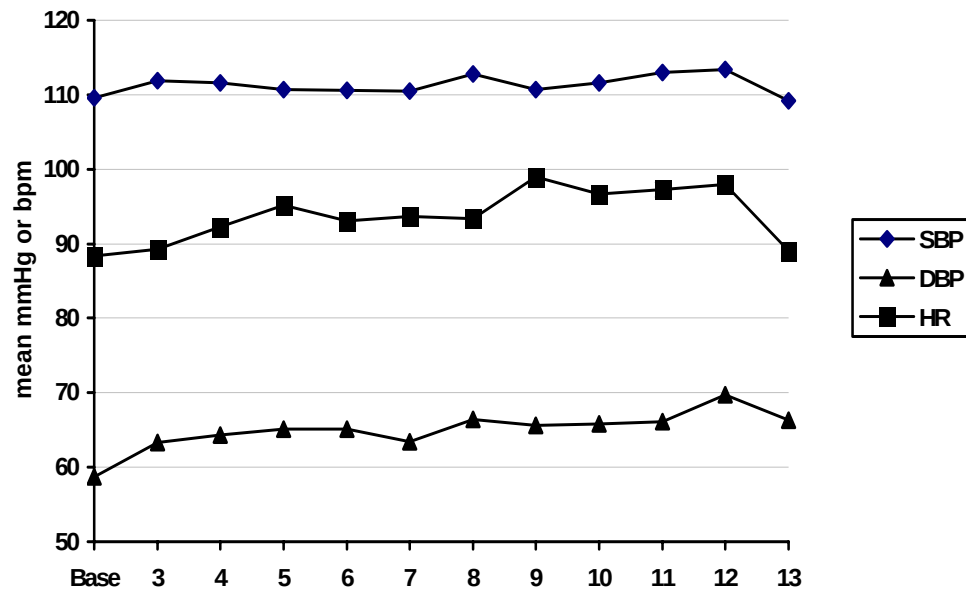


Figure HFBC.1. Vital sign summary, repeated least squares means, Study B4Z-MC-HFBC.

Source Data: RMP.B4ZSHFBC.SASPGM(FVITALS)

Table HFBC.8. ECG Intervals Analyses – Mean Baseline, Endpoint, and Change from Baseline to Endpoint Values, Study B4Z-MC-HFBC

ECG Parameter	n	Baseline		Endpoint		Change		p-Value ^a
		Mean	SD	Mean	SD	Mean	SD	
QTc interval	27	420.2	20.6	417.8	23.0	-2.3	26.0	.467
QT interval	27	360.0	19.0	345.2	29.4	-14.8	26.4	.006
RR interval	27	0.74	0.08	0.69	0.12	-0.05	0.12	.058
PR interval	27	0.139	0.024	0.139	0.027	0.000	0.014	.748
QRS interval	27	0.084	0.011	0.081	0.010	-0.003	0.013	.300
ECG heart rate	27	84.0	10.2	91.3	14.0	7.3	12.7	.007

n = number of enrolled patients with a baseline and at least one postbaseline measurement; SD = standard deviation.

^a p-Values are from Wilcoxon signed-rank test on change from baseline to endpoint (LOCF) scores.

Source Data: RMP.B4ZP.SASPGM(ES3AIFBC) and
RMP.B4ZSHFBC.SASPGM(FECG).

Summary ID#1585

Clinical Study Summary: Study B4Z-MC-HFBD

Title of Study: A Randomized, Double-Blind Study of Tomoxetine Hydrochloride, Methylphenidate Hydrochloride, and Placebo in Pediatric Outpatients with Attention-Deficit/Hyperactivity Disorder	
Investigators: This multicenter study included 8 principal investigators (PIs).	
Study Centers: This study was conducted at 7 study centers in the United States. (One site had two PIs; hence the seeming discrepancy of 8 PIs at 7 study centers.)	
Length of Study: 15 months Date first patient enrolled: 19 November 1998 Date last patient completed: 17 February 2000	Phase of Development: 2
Objectives: The primary objective of this study was to evaluate the efficacy of atomoxetine (formerly called tomoxetine) compared with placebo in the combined strata of pediatric patients who met <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</i> (DSM-IV) criteria for Attention-Deficit/Hyperactivity Disorder (ADHD). Efficacy was determined by a comparison of mean change from baseline to endpoint using an intent-to-treat analysis of the primary outcome measure, the investigator administered and scored Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version (ADHDRS-IV-Parent:Inv) Total score, for atomoxetine- and placebo-treated patients. Four secondary objectives were identified for this study: - To compare the safety of atomoxetine with placebo in a population of pediatric patients who met DSM-IV criteria for ADHD. - To compare the efficacy of atomoxetine with placebo in children who had not had prior treatment with psychostimulants (stimulant-naïve patient stratum) using an intent-to-treat analysis of the ADHDRS-IV-Parent: Inv. - To compare percentages of responders among atomoxetine-treated and placebo-treated patients who had completed a minimum of 3 weeks (Visit 6 data) of active treatment during Study Period II. Determination of clinical response was based on the ADHDRS-IV-Parent:Inv and the Clinical Global Impressions-ADHD-Improvement (CGI-ADHD-I) scores. - To validate the study design in the event atomoxetine failed to separate from placebo with an analysis comparing the efficacy of methylphenidate hydrochloride with placebo in the stimulant-naïve stratum using an intent-to-treat analysis of the ADHDRS-IV-Parent:Inv. This analysis was chosen to allow for an informed internal decision regarding further development of atomoxetine for ADHD.	
Study Design: Study HFBD was a Phase 2 stratified, randomized, double-blind, parallel, outpatient study of 147 pediatric outpatients, aged 7 through 12 years, who met diagnostic criteria for DSM-IV ADHD. Prior to randomization at Visit 3, patients were stratified into two groups that were determined by their prior exposure to psychostimulants. The first stratum included patients who had no prior history of treatment with psychostimulants (stimulant-naïve stratum). Patients in stimulant-naïve stratum were randomized in a 3:3:2 ratio to double-blind treatment with atomoxetine, placebo, or methylphenidate hydrochloride (hereafter referred to as methylphenidate). The second stratum included children who had been treated at any time with a psychostimulant (stimulant - prior-exposure stratum). Children in this second stratum were randomized to double-blind treatment with atomoxetine or placebo (randomization ratio 1:1). There was no methylphenidate treatment group in the stimulant - prior-exposure stratum.	
Number of Patients: <u>Stimulant-Naïve Stratum:</u> Planned: At least 64 patients in the stimulant-naïve stratum Randomized: 30 atomoxetine, 20 methylphenidate hydrochloride, 27 placebo	

Completed: 22 atomoxetine, 11 methylphenidate hydrochloride, 24 placebo <u>Stimulant-Prior-Exposure Stratum:</u> Planned: At least 128 patients in both strata combined Randomized: 35 atomoxetine, 35 placebo Completed: 27 atomoxetine, 23 placebo
Diagnosis and Main Criteria for Inclusion: Patients were children at least 7 years of age but less than 13 years of age at Visit 1 who met DSM-IV diagnostic criteria for ADHD. Each patient's score from the ADHDRS-IV-Parent:Inv was at least 1.5 standard deviations above the age/gender norm for their diagnostic subtype.
Test Product, Dose, and Mode of Administration: <u>Stimulant-Naïve Stratum:</u> Atomoxetine: 5-mg, 10-mg, and 20-mg capsules; 5 to 90 mg/day, given twice daily, before and after school (except for the 5-mg capsule, which could be given as a single dose); placebo was given at midday dose. <u>Stimulant-Prior-Exposure Stratum:</u> Atomoxetine: 5-mg, 10-mg, 20-mg capsules; 5 to 90 mg/day, given twice daily, before and after school (except for the 5-mg capsule, which could be given as a single dose).
Duration of Treatment: 9 weeks.
Reference Therapy, Dose, and Mode of Administration: <u>Stimulant-Naïve Stratum:</u> Methylphenidate hydrochloride: 5-mg, 10-mg capsules; 5 to 60 mg/day, given twice daily, before school and midday (except for the 5-mg capsule, which could be given as a single dose); placebo was given after school. <u>Stimulant-Prior-Exposure Stratum:</u> None
Variables: <u>Efficacy:</u> Efficacy analyses for the primary efficacy measure, the ADHDRS-IV-Parent:Inv Total score, included all randomized patients who had a baseline and at least one postbaseline ADHDRS-IV-Parent:Inv Total score. Of the 147 randomized patients, 145 met criteria for inclusion in the ADHDRS-IV-Parent:Inv efficacy analyses. Two patients were enrolled, but did not have postbaseline efficacy measurements. These patients were excluded from ADHDRS-IV-Parent:Inv efficacy analyses according to the protocol analysis plans. All patients in the primary efficacy analysis took at least one dose of study drug. <u>Safety:</u> Analysis of adverse events included the 147 enrolled patients who took at least one dose of study drug. The analysis for clinical laboratory studies, vital signs, and electrocardiogram (ECG) data included patients who received at least one dose of study drug and had a baseline and a postbaseline measurement. <u>Pharmacokinetic:</u> All patients provided blood samples for assessment of plasma concentrations and pharmacokinetics of atomoxetine, 4-hydroxyatomoxetine, and N-desmethylatomoxetine.
Evaluation Methods: <u>Statistical:</u> The primary efficacy analysis was an F-test for a treatment difference between atomoxetine and placebo from an analysis of variance (ANOVA) model on change from baseline to endpoint ADHDRS-IV-Parent:Inv Total scores. Change scores were computed using a last-observation-carried-forward (LOCF) approach. The primary ANOVA model contained terms for treatment, investigative site, and stimulant-prior-exposure stratum. For secondary efficacy and safety measures, treatment differences in mean change scores from continuous measures were assessed using ANOVA, while Fisher's exact test was used to assess treatment differences in binary data.
Summary: <u>Patient Disposition:</u> One hundred ninety-nine (199) patients entered Study B4Z-MC-HFBD (HFBD). Of those, 52 were not randomized (that is, were discontinued prior to randomization at Visit 3). Patients were not randomized for the following reasons: lost to follow-up (N = 5); personal conflict (N = 15); entry criteria not met (N = 28); and physician's decision (N = 4). Of the 199 patients entered, 147 were screened in Study Period I (Medication Washout, Screening, and Assessment), and were subsequently randomized to Study Period II (Stratified, Randomized, Double-Blind,

Acute Treatment) at Visit 3. At Visit 3, 65 were randomized to atomoxetine, 62 to placebo, and 20 to methylphenidate. Of the 147 patients who were randomized, 107 (72.8%) completed Study Period II and proceeded to Study Period III (Single-Blind Discontinuation from Study Drug).

Patient Demographics: Table HFBD.1 shows demographic characteristics for all enrolled patients. Of the 147 enrolled patients, 81.0% were male; 83.0% were Caucasian; 52.4% had no prior stimulant exposure; and 91.8% were in the 2nd to 6th elementary school grades (United States). The mean age was 9.7 years (range of 7.0 to 12.9), and the mean intelligence quotient (IQ) was 106.0 (range 71 to 144).

No statistically significant differences were seen in patient characteristics at baseline between atomoxetine and placebo in the combined strata.

In the stimulant-naïve stratum, patient characteristics at baseline for the methylphenidate hydrochloride (hereafter referred to as methylphenidate) group were similar to the atomoxetine and placebo treatment groups. The only statistically significant differences were found for the percentage of male patients (atomoxetine 66.7%, placebo 85.2%, and methylphenidate 95.0%; $p = .035$).

Efficacy: The protocol-specified primary analysis was a treatment comparison of mean change from baseline to endpoint ADHDRS-IV-Parent:Inv Total scores between atomoxetine and placebo in the combined strata using an ANOVA model. As shown in Table HFBD.2, this analysis demonstrated statistically significantly greater reduction in severity of ADHD symptoms for atomoxetine-treated patients as compared with placebo-treated patients (mean changes: atomoxetine -15.6, placebo -5.5; $p < .001$). This mean reduction in ADHD symptoms on atomoxetine represented a 38% reduction in symptoms from baseline. Examination of the T-scores indicated the mean reduction for patients treated with atomoxetine was from 3.3 standard deviations above the norm to 1.6 standard deviations above the norm.

Secondary analyses utilizing the ADHDRS-IV-Parent:Inv scale also supported the conclusions from the primary efficacy analysis. In the combined strata, statistical significance favoring atomoxetine over placebo was observed beginning with Visit 4 (Week 1) and continuing for the remainder of the acute treatment study period. In addition, atomoxetine was statistically superior to placebo at reducing both inattentive (mean changes: atomoxetine -7.5, placebo -3.0; $p < .001$) and hyperactive/impulsive symptoms (mean changes: atomoxetine -8.0, placebo -2.5; $p < .001$). The percentages of patients meeting response criteria (defined as having at least a 25% improvement in ADHDRS-IV-Parent:Inv total score) were statistically greater on atomoxetine (64%) as compared to placebo (25%). Treatment differences were consistent across subgroups, including groups based on stimulant-prior-exposure stratum, ADHD subtype, and comorbid ODD. Atomoxetine was statistically significantly superior to placebo at reducing the severity of ADHD symptoms within the group of patients meeting criteria for the combined ADHD subtype and within the group of patients meeting criteria for primarily inattentive ADHD.

Secondary variables also supported the efficacy of atomoxetine for the acute treatment of ADHD in pediatric patients (see Table HFBD.3 through Table HFBD.5). Atomoxetine was statistically significantly superior to placebo at reducing symptoms measured by the Clinical Global Impressions – ADHD – Severity (CGI-ADHD-S) and improvement scale (both overall and evening components), as well as the hyperactivity subscale of the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S). No statistically significant differences between atomoxetine and placebo were observed for the Restricted Academic Situation test (RAS) total percentage. A high percentage of patients completed the study (75.4% atomoxetine, 75.8% placebo) with few discontinuations due to lack of efficacy (9.2% atomoxetine, 11.3% placebo).

Following discontinuation of atomoxetine treatment (Study Period III), scores for the former atomoxetine-treated patients increased to near the levels of the placebo treated group.

In the stimulant-naïve stratum, methylphenidate demonstrated efficacy statistically superior to placebo on multiple measures. For mean change from baseline to endpoint on the primary efficacy measure (the ADHDRS-IV-Parent:Inv Total score), the methylphenidate treatment group showed a mean reduction of 17.3 versus a mean reduction of 4.2 for the placebo treatment group ($p = .0003$). Methylphenidate also demonstrated efficacy statistically superior to placebo on many of the secondary efficacy measures,

including the ADHDRS-IV-Parent:Inv Inattentive subscale score (mean changes: methylphenidate -9.0, placebo -1.9; $p=.0009$), the ADHDRS-IV-Parent:Inv Hyperactive/Impulsive subscale score (mean changes: methylphenidate -8.4, placebo -2.3; $p=.0010$), the CGI-ADHD-S (mean changes: methylphenidate -1.5, placebo -0.3; $p=.0006$), the CGI-ADHD-I (mean changes: methylphenidate 2.4, placebo 3.6; $p=.0006$), the ADHD Index of the CPRS-R:S (mean changes: methylphenidate -11.6, placebo -0.9; $p=.0005$), the hyperactivity subscale of the CPRS-R:S (mean changes: methylphenidate -5.3, placebo -1.1; $p=.0011$), the cognitive subscale of the CPRS-R:S (mean changes: methylphenidate -6.1, placebo -0.1; $p=.0006$), and the RAS total percentage score (mean changes: methylphenidate -5.1, placebo +5.0; $p=.0346$). Methylphenidate, as was true for atomoxetine, did not differ significantly from placebo on the oppositionality subscale of the CPRS-R:S ($p=.7482$). Methylphenidate was numerically superior to atomoxetine on several efficacy measures; however, the differences were not statistically significant.

In summary, in a population of patients aged 7 to 13 years with a DSM-IV diagnosis of ADHD, atomoxetine was statistically superior to placebo at reducing symptoms of ADHD. Efficacy was observed on both primary and secondary measures, including both inattentive and hyperactive/impulsive symptoms. The efficacy of atomoxetine was consistent across stimulant - prior-exposure stratum and other patient subgroups. The onset of efficacy of atomoxetine occurred after the first week of treatment and persisted through the remainder of the active treatment phase. The observed statistical superiority of methylphenidate as compared to placebo in the stimulant-naïve stratum provided further validity to the results of this study.

Safety: No serious adverse events occurred in the atomoxetine treatment group, while 2 serious adverse events occurred in the placebo group (gastroenteritis and suicidal ideation). In the atomoxetine group, 4 of 65 patients (6.2%) discontinued due to nonserious adverse events (nervousness, vomiting, hostility, chest pain). Three of 62 (4.8%) of those taking placebo discontinued due to nonserious ($n=2$) or serious ($n=1$) adverse events (somnolence, hyperkinesia, depression). In the methylphenidate group, 2 of 20 (10%) discontinued due to nonserious adverse events (headache, somnolence). Table HFBD.6 summarizes the treatment-emergent adverse events by incidence, for events that occurred in at least 5% of the patients in either the tomoxetine or placebo group. A statistically significantly higher percentage of patients in the atomoxetine treatment group as compared with the placebo treatment group reported treatment-emergent anorexia (typically captured as “decreased appetite;” 22% versus 7%; $p=.021$). No other statistically significant differences between atomoxetine and placebo were observed for any specific event. Anorexia (typically captured as “decreased appetite”) was reported by 35% of patients in the methylphenidate group.

Summaries of the mean change from Study Period II baseline to endpoint in vital sign measures (diastolic and systolic blood pressure, heart rate, weight, height, and temperature) for atomoxetine-treated and placebo-treated patients in the combined strata are provided in Table HFBD.7. Mean changes for stimulant-naïve patients in the methylphenidate treatment group are also provided in this table as a reference. In the combined strata, the atomoxetine group had a statistically significantly greater increase than the placebo group in heart rate, with mean increases of 11.2 and 2.3 beats per minute (bpm), respectively ($p<.001$). In this study, change in mean diastolic blood pressure was not significantly different in the atomoxetine group (+1.1 mm Hg) as compared to the placebo group (+0.6 mm Hg; $p=.787$). Atomoxetine-treated patients had a statistically significant decrease in weight. The mean change in weight was -0.5 kg for the atomoxetine group and +1.4 kg for the placebo group ($p<.001$).

Table HFBD.1. Summary of Demographics and Other Patient Characteristics Including WISC-III IQ and WRAT3-Tan Test Scores, All Randomized Patients B4Z-MC-HFBD

Variable	Tomox. (N=65)	Methyl (N=20)	Placebo (N=62)	Total (N=147)
Sex: No. (%)				
No. Patients	65	20	62	147
Female	18 (27.7)	1 (5.0)	9 (14.5)	28 (19.0)
Male	47 (72.3)	19 (95.0)	53 (85.5)	119 (81.0)
Origin: No. (%)				
No. Patients	65	20	62	147
African Descent	7 (10.8)	1 (5.0)	4 (6.5)	12 (8.2)
Western Asian	0	0	1 (1.6)	1 (0.7)
Caucasian	54 (83.1)	18 (90.0)	50 (80.6)	122 (83.0)
Hispanic	2 (3.1)	1 (5.0)	4 (6.5)	7 (4.8)
Other	2 (3.1)	0	3 (4.8)	5 (3.4)
Age: yrs.				
No. Patients	65	20	62	147
Mean	9.58	9.13	10.03	9.71
Median	9.32	8.61	10.27	9.82
Standard Dev.	1.60	1.58	1.55	1.60
Minimum	7.06	7.03	7.18	7.03
Maximum	12.92	12.45	12.81	12.92
Height: cm				
No. Patients	63	20	61	144
Mean	138.93	137.15	139.52	138.93
Median	137.50	137.00	138.50	138.00
Standard Dev.	10.27	9.86	9.57	9.89
Minimum	122.50	122.50	124.50	122.50
Maximum	167.00	163.00	161.00	167.00
Unspecified	2	0	1	3
Weight: kg				
No. Patients	63	20	61	144
Mean	38.21	35.61	38.14	37.82
Median	34.10	32.40	35.90	35.00
Standard Dev.	13.58	11.10	10.48	11.97
Minimum	25.00	25.00	24.40	24.40
Maximum	98.60	68.50	75.70	98.60
Unspecified	2	0	1	3
Family History of ADHD-Mother				
No. Patients	65	20	62	147
N	44 (67.7)	16 (80.0)	47 (75.8)	107 (72.8)
U	9 (13.8)	2 (10.0)	11 (17.7)	22 (15.0)
Y	12 (18.5)	2 (10.0)	4 (6.5)	18 (12.2)
Family History of ADHD-Father				
No. Patients	65	20	62	147
N	37 (56.9)	14 (70.0)	31 (50.0)	82 (55.8)
U	15 (23.1)	2 (10.0)	14 (22.6)	31 (21.1)
Y	13 (20.0)	4 (20.0)	17 (27.4)	34 (23.1)
Family History of ADHD-Grandparents				
No. Patients	65	20	62	147
N	43 (66.2)	17 (85.0)	44 (71.0)	104 (70.7)
U	13 (20.0)	2 (10.0)	11 (17.7)	26 (17.7)
Y	9 (13.8)	1 (5.0)	7 (11.3)	17 (11.6)

(continued)

Table HFBD.1. Summary of Demographics and Other Patient Characteristics Including WISC-III IQ and WRAT3-Tan Test Scores, All Randomized Patients B4Z-MC-HFBD (Continued)

Variable	Tomox. (N=65)	Methyl (N=20)	Placebo (N=62)	Total (N=147)
Family History of ADHD-Siblings				
No. Patients	65	20	62	147
N	35 (53.8)	12 (60.0)	41 (66.1)	88 (59.9)
N/A	7 (10.8)	1 (5.0)	4 (6.5)	12 (8.2)
U	9 (13.8)	2 (10.0)	6 (9.7)	17 (11.6)
Y	14 (21.5)	5 (25.0)	11 (17.7)	30 (20.4)
Prior Stimulant Exposure				
No. Patients	65	20	62	147
N	30 (46.2)	20 (100)	27 (43.5)	77 (52.4)
Y	35 (53.8)	0	35 (56.5)	70 (47.6)
DRD4 Allele				
No. Patients	65	20	62	147
2-2	0	0	1 (1.6)	1 (0.7)
2-4	9 (14.1)	4 (20.0)	4 (6.6)	17 (11.7)
2-7	1 (1.6)	0	1 (1.6)	2 (1.4)
3-3	1 (1.6)	0	0	1 (0.7)
3-4	5 (7.8)	1 (5.0)	3 (4.9)	9 (6.2)
3-7	1 (1.6)	0	0	1 (0.7)
4-4	28 (43.8)	8 (40.0)	25 (41.0)	61 (42.1)
4-6	0	0	1 (1.6)	1 (0.7)
4-7	16 (25.0)	7 (35.0)	20 (32.8)	43 (29.7)
4-8	1 (1.6)	0	0	1 (0.7)
5-7	0	0	1 (1.6)	1 (0.7)
7-7	2 (3.1)	0	5 (8.2)	7 (4.8)
Unspecified	1	0	1	2
Grade in School				
No. Patients	65	20	62	147
1	3 (4.6)	0	2 (3.2)	5 (3.4)
2	14 (21.5)	7 (35.0)	9 (14.5)	30 (20.4)
3	14 (21.5)	5 (25.0)	11 (17.7)	30 (20.4)
4	10 (15.4)	4 (20.0)	11 (17.7)	25 (17.0)
5	12 (18.5)	3 (15.0)	16 (25.8)	31 (21.1)
6	8 (12.3)	1 (5.0)	10 (16.1)	19 (12.9)
7	4 (6.2)	0	2 (3.2)	6 (4.1)
8	0	0	1 (1.6)	1 (0.7)
WISC full scale IQ				
No. Patients	64	20	62	146
Mean	104.55	109.65	106.24	105.97
Median	105.00	111.00	105.00	105.00
Standard Dev.	13.63	14.75	15.12	14.43
Minimum	76.00	85.00	71.00	71.00
Maximum	142.00	144.00	134.00	144.00
Unspecified	1	0	0	1

(continued)

Table HFBD.1. Summary of Demographics and Other Patient Characteristics Including WISC-III IQ and WRAT3-Tan Test Scores, All Randomized Patients B4Z-MC-HFBD (Continued)

Variable	Tomox. (N=65)	Methyl (N=20)	Placebo (N=62)	Total (N=147)
WRAT Reading Raw Score				
No. Patients	65	20	62	147
Mean	31.86	31.55	32.37	32.03
Median	32.00	30.00	33.00	32.00
Standard Dev.	7.23	4.94	5.92	6.39
Minimum	16.00	25.00	21.00	16.00
Maximum	48.00	40.00	45.00	48.00
WRAT Reading Standard Score				
No. Patients	65	20	62	147
Mean	99.26	102.00	97.81	99.02
Median	102.00	101.00	99.00	100.00
Standard Dev.	14.79	11.21	13.37	13.74
Minimum	63.00	82.00	71.00	63.00
Maximum	125.00	120.00	126.00	126.00
WRAT Reading Absolute Score				
No. Patients	65	20	62	147
Mean	493.64	493.85	494.67	494.10
Median	494.00	492.00	495.00	494.00
Standard Dev.	16.77	10.81	13.39	14.62
Minimum	452.00	479.00	469.00	452.00
Maximum	526.00	513.00	521.00	526.00
WRAT Spelling Raw Score				
No. Patients	65	20	62	147
Mean	27.28	26.00	27.05	27.01
Median	27.00	24.50	26.50	26.00
Standard Dev.	5.77	5.50	5.16	5.46
Minimum	17.00	20.00	17.00	17.00
Maximum	42.00	41.00	40.00	42.00
WRAT Spelling Standard Score				
No. Patients	65	20	62	147
Mean	98.49	97.65	95.03	96.92
Median	98.00	97.00	93.00	96.00
Standard Dev.	14.60	12.80	14.12	14.17
Minimum	69.00	77.00	69.00	69.00
Maximum	134.00	127.00	136.00	136.00
WRAT Spelling Absolute Score				
No. Patients	65	20	62	147
Mean	492.26	488.98	491.88	491.65
Median	492.00	486.50	491.50	491.00
Standard Dev.	13.95	13.24	12.57	13.24
Minimum	462.00	473.00	462.00	462.00
Maximum	523.00	520.70	519.00	523.00

(continued)

Table HFBD.1. Summary of Demographics and Other Patient Characteristics Including WISC-III IQ and WRAT3-Tan Test Scores, All Randomized Patients B4Z-MC-HFBD (Concluded)

Variable	Tomox. (N=65)	Methyl (N=20)	Placebo (N=62)	Total (N=147)
WRAT Arithmetic Raw Score				
No. Patients	65	20	62	147
Mean	26.63	25.55	26.97	26.63
Median	27.00	25.00	28.00	27.00
Standard Dev.	5.37	6.45	5.87	5.71
Minimum	17.00	12.00	15.00	12.00
Maximum	40.00	39.00	38.00	40.00
WRAT Arithmetic Standard Score				
No. Patients	65	20	62	147
Mean	96.37	97.15	93.31	95.18
Median	95.00	97.50	94.50	95.00
Standard Dev.	12.59	18.02	15.42	14.62
Minimum	67.00	50.00	46.00	46.00
Maximum	119.00	140.00	124.00	140.00
WRAT Arithmetic Absolute Score				
No. Patients	65	20	62	147
Mean	491.50	488.45	492.01	491.30
Median	491.00	489.00	496.00	491.00
Standard Dev.	12.69	15.98	14.33	13.82
Minimum	465.00	453.00	461.00	453.00
Maximum	519.00	517.00	516.00	519.00

Population: Tomoxetine, Methylphenidate, and Placebo Patients from both Strata who took at least 1 dose of study drug.
Initial Visit ONLY
Input data from RMP.SAS.B4ZM.MCHFBD SW
Output stored as RMP.B4Z0.HFBDCTRM(DE1C2007)
XDES0001

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**Table HFBD.2. ADHDRS-IV-Parent:Inv Total Score Change from Baseline to Endpoint – Study Period II
 B4Z-MC-HFBD**

		n	Baseline		Endpoint		Change		p-Value ^a
			Mean	SD	Mean	SD	Mean	SD	
Combined									
	Tomoxetine	64	41.2	8.9	25.6	14.6	-15.6	13.7	0.0001
	Placebo	61	41.4	7.9	35.9	13.3	-5.5	11.6	---
Stimulant-Naïve Stratum									
	Tomoxetine	30	39.4	9.0	24.3	13.9	-15.1	11.8	0.0015
	Placebo	27	39.6	8.3	35.4	12.6	-4.2	10.8	---
	Methylphenidate ^b	20	38.6	6.5	21.3	13.5	-17.3	14.2	0.0003
Prior-Exposure Stratum									
	Tomoxetine	34	42.8	8.7	26.9	15.3	-16.0	15.3	0.0091
	Placebo	34	42.9	7.4	36.3	14.1	-6.6	12.3	---

^a Between treatment group p-Values are from pairwise tests of treatment differences in mean change from baseline to endpoint (last visit carried forward) scores versus placebo using least squares means from an ANOVA model with terms for investigator and treatment (in each strata) or terms for investigator, treatment and strata (combined group).

^b P-Value for Tomoxetine versus Methylphenidate comparison in the Stimulant-Naïve stratum is 0.4219.

Source Data: program: locf.sas

Table HFBD.3. CGI-ADHD-Severity and CGI-ADHD-Severity:Evening
Summary of Endpoint and Change Values –
Study Period II – Combined Strata
B4Z-MC-HFBD

Measure	Endpoint Scores - All Enrolled							Endpoint Mean (SD)	Change Mean (SD)	p-Value ^a
	Patients									
	1	2	3	4	5	6	7			
CGI-ADHD-Severity										
Tomoxetine	4	8	19	12	16	2	3	3.7 (1.5)	-1.2 (1.4)	.0032
Placebo	0	5	7	19	23	5	2	4.4 (1.2)	-0.5 (1.0)	
CGI-ADHD-Severity:Evening										
Tomoxetine	3	9	17	15	14	3	3	3.8 (1.4)	-1.2 (1.4)	0.0028
Placebo	0	5	7	20	20	7	2	4.4 (1.2)	-0.5 (1.1)	

^a The p-values are from least square mean comparisons of change scores using an ANOVA model with terms for therapy, pooled investigator, and strata.

CGI-Severity Scores are Defined as:

- 1 = Normal, Not Ill
- 2 = Minimally Ill
- 3 = Mildly Ill
- 4 = Moderately Ill
- 5 = Markedly Ill
- 6 = Severely Ill
- 7 = Very Severely Ill

Source Data: eagle:\programs_g\rmp\b4zs\HFBD\final analysis\locf_cgi.sas

Table HFBD.4. CGI-ADHD-Improvement and CGI-ADHD-Improvement:Evening, Summary of Endpoint Values – Study Period II – Combined Strata, B4Z-MC-HFBD

		Endpoint Scores - All Enrolled Patients							Mean (SD)	p-Value ^a
		1	2	3	4	5	6	7		
CGI-ADHD-Improvement										
	Tomoxetine	7	23	11	19	3	1	0	2.9 (1.2)	.0005
	Placebo	2	7	12	34	6	0	0	3.6 (0.9)	
CGI-ADHD-Improvement: Evening										
	Tomoxetine	6	22	13	18	2	2	1	3.0 (1.3)	0.0027
	Placebo	2	7	11	33	8	0	0	3.6 (1.0)	

^a The p-values are from pairwise treatment differences in mean endpoint value (last observation carried forward) versus placebo using least squares means from an ANOVA model with terms for pooled investigator, treatment and strata.

CGI-Improvement Scores are Defined as:

- 1 = Very Much Improved
- 2 = Much Improved
- 3 = Minimally Improved
- 4 = No Change
- 5 = Minimally Worse
- 6 = Much Worse
- 7 = Very Much Worse

Source Data: eagle:\programs._g\rmp\b4zs\HFBD\final analysis\locf_end.sas

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Table HFBD.5. Conners' Parent Rating Scale-Revised:Short Form– ADHD Index, Hyperactivity, Cognitive, and Oppositional Subscales - Change from Baseline to Endpoint – Study Period II – Combined Strata B4Z-MC-HFBD

Measure	n	Baseline		Endpoint		Change		p-Value ^a
		Mean	SD	Mean	SD	Mean	SD	
ADHD Index Subscale								
Tomoxetine	59	27.4	6.2	21.8	9.8	-5.7	10.4	0.1094
Placebo	54	28.7	5.8	26.1	8.0	-2.6	8.4	
Hyperactivity Subscale								
Tomoxetine	59	11.2	4.9	7.2	5.9	-4.0	5.2	0.0089
Placebo	54	11.8	4.5	10.3	5.2	-1.5	4.1	
Cognitive Subscale								
Tomoxetine	58	13.9	3.8	11.0	5.5	-2.9	5.6	0.1512
Placebo	54	14.8	3.3	13.5	4.4	-1.3	5.1	
Oppositional Subscale								
Tomoxetine	59	8.9	5.0	8.4	5.5	-0.5	4.3	0.3746
Placebo	54	9.0	5.1	7.9	4.9	-1.2	4.4	

^a Between treatment group p-values are from pairwise tests of treatment differences in mean change from baseline to endpoint (last-visit-carried-forward) scores versus placebo using least squares means from an ANOVA model with terms for pooled investigator, treatment and strata (combined group).

Source Data: eagle:\programs_g\rm\p\b4zs\HFBD\final analysis\locf_cprs.sas

**Table HFBD.6. Summary of Treatment-Emergent Adverse Events
with $\geq 5\%$ Incidence
Study Period II, Combined Strata plus Methylphenidate
B4Z-MC-HFBD**

Event	Tomoxetine (N=65)		Placebo (N=62)		p-value* (T vs P)	Methylphenidate (N=20)	
	n	%	n	%		n	%
Headache	26	40	21	34	0.582	11	55
Rhinitis	24	37	25	40	0.719	4	20
Abdominal Pain	24	37	15	24	0.129	9	45
Anorexia	14	22	4	7	0.021	7	35
Pharyngitis	13	20	14	23	0.829	2	10
Cough Increased	13	20	10	16	0.648	3	15
Vomiting	8	12	7	11	1.000	1	5
Nervousness	8	12	4	7	0.365	2	10
Nausea	6	9	10	16	0.291	5	25
Insomnia	6	9	5	8	1.000	7	35
Emotional Lability	6	9	2	3	0.274	1	5
Fever	5	8	7	11	0.554	2	10
Asthenia	5	8	4	7	1.000	0	0
Somnolence	5	8	4	7	1.000	3	15
Diarrhea	4	6	4	7	1.000	3	15
Dizziness	4	6	2	3	0.680	4	20
Gastrointestinal Disorder	4	6	2	3	0.680	0	0
Accidental Injury	3	5	4	7	0.713	1	5
Allergic Reaction	2	3	5	8	0.266	0	0
Flu Syndrome	2	3	4	7	0.433	2	10
Contact Dermatitis	0	0	4	7	0.054	1	5

* P-value between tomoxetine and placebo (T versus P) are based on Fisher's exact test.

Baseline: Visits 1 - 3; Endpoint: Visits 4 - 12

Source Data: RMP.B4ZO.HFBDCTRM (AE2A101A), RMP.B4ZO.HFBDCTRM (AE2A1004),
RMP.B4ZO.HFBDCTRM (AE2C101A), & RMP.B4ZO.HFBDCTRM (AE2A1005)

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Table HFBD.7. Summary of Vital Signs Data
Mean Change from Baseline to Endpoint
Study Period II, Combined Strata plus Methylphenidate
B4Z-MC-HFBD

Variable	Tomoxetine				Placebo				Chg T v P pval	Methylphenidate			
	N	Baseline mean (sd)	Change mean (sd)	w/i p- val	N	Baseline mean (sd)	Change mean (sd)	w/i p-val		N	Baseline mean (sd)	Change mean (sd)	w/i p-val
Diastolic BP Average (mm Hg)	64	63.2 (10.0)	+1.1 (10.7)	0.335	61	60.7 (7.8)	+0.6 (8.7)	0.654	0.787	20	63.2 (7.0)	+0.4 (6.7)	0.840
Systolic BP Average (mm Hg)	64	104 (14)	+2.9 (12.1)	0.068	61	103 (11)	+0.5 (8.6)	0.536	0.198	20	103 (11)	+2.5 (8.9)	0.216
Heart Rate Average	64	84.1 (11.3)	+11.2 (13.1)	<0.001	61	83.0 (9.6)	+2.3 (12.6)	0.122	<.001	20	82.2 (8.8)	+8.2 (10.5)	0.003
Weight (KG)	64	38.1 (13.7)	-0.5 (1.5)	0.005	61	38.6 (10.6)	+1.4 (1.3)	<.001	<.001	20	35.9 (11.5)	-0.4 (1.5)	0.214
Height (cm)	56	138 (10)	+0.7 (1.9)	0.003	54	140 (10)	+1.2 (1.7)	<.001	0.125	18	138 (9)	+1.3 (2.3)	0.009
Temp (Cent.)	64	36.8 (0.4)	+0.1 (0.5)	0.085	61	36.8 (0.4)	-0.0 (0.5)	0.910	0.241	20	37.0 (0.5)	-0.0 (0.7)	0.694

Abbreviations: sd = standard deviation; w/i-p val = within group p-values, based on Wilcoxon's signed rank test; Chg T v P pval = p-value for a treatment effect (tomoxetine versus placebo) on change scores from an ANOVA model with a term for treatment.

Baseline: Visits 1 – 3; Endpoint: Visits 4 – 12

Source Data: RMP.B4ZO.HFBDCTRM(VI3D1004) & RMP.B4ZO.HFBDCTRM(VI3D2005)

Summary ID#1586

Clinical Study Summary: Study B4Z-MC-HFBK

Title of Study: A Randomized, Double-Blind Study of Tomoxetine Hydrochloride, Methylphenidate Hydrochloride, and Placebo in Pediatric Outpatients with Attention-Deficit/Hyperactivity Disorder	
Investigators: This multicenter study included 13 principal investigators (PIs) with randomized patients.	
Study Centers: This study was conducted at 10 study centers in the United States. (One site did not randomize any patients and four sites had two PIs each; hence the seeming discrepancy of 13 PIs with randomized patients at 10 study centers.)	
Length of Study: 8 months Date first patient enrolled: 17 February 1999 Date last patient completed: 21 October 1999	Phase of Development: 2
Objectives: The primary objective of this study was to evaluate the efficacy of atomoxetine (formerly called tomoxetine) compared with placebo in the combined strata of pediatric patients who met <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</i> (DSM-IV) criteria for Attention-Deficit/Hyperactivity Disorder (ADHD). Efficacy was determined by a comparison of mean change from baseline to endpoint using an intent-to-treat analysis of the primary outcome measure, the investigator administered and scored Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version (ADHDRS-IV-Parent:Inv) Total score, for atomoxetine- and placebo-treated patients. Four secondary objectives were identified for this study: - To compare the safety of atomoxetine with placebo in a population of pediatric patients who met DSM-IV criteria for ADHD. - To compare the efficacy of atomoxetine with placebo in children who had not had prior treatment with psychostimulants (stimulant-naïve patient stratum) using an intent-to-treat analysis of the ADHDRS-IV-Parent: Inv. - To compare percentages of responders among atomoxetine-treated and placebo-treated patients who had completed a minimum of 3 weeks (Visit 6 data) of active treatment during Study Period II. Determination of clinical response was based on the ADHDRS-IV-Parent: Inv and the Clinical Global Impressions-ADHD-Improvement (CGI-ADHD-I) scores. - To validate the study design in the event atomoxetine failed to separate from placebo with an analysis comparing the efficacy of methylphenidate hydrochloride (hereafter referred to as methylphenidate) with placebo in the stimulant-naïve stratum using an intent-to-treat analysis of the ADHDRS-IV-Parent: Inv. This analysis was chosen to allow for an informed internal decision regarding further development of atomoxetine for ADHD.	
Study Design: Study B4Z-MC-HFBK (HFBK) was a Phase 2 stratified, randomized, double-blind, parallel, outpatient study of 144 pediatric outpatients, aged 7 through 12 years, who met diagnostic criteria for DSM-IV ADHD. Prior to randomization at Visit 3, patients were stratified into two groups that were determined by their prior exposure to psychostimulants. The first stratum included patients who had no prior history of treatment with psychostimulants (stimulant-naïve stratum). Patients in stimulant-naïve stratum were randomized to double-blind treatment with atomoxetine, placebo, or methylphenidate (randomization ratio: 3:3:2). The second stratum included children who had been treated at any time with a psychostimulant (stimulant-prior-exposure stratum). Children in this second stratum were randomized to double-blind treatment with atomoxetine or placebo (randomization ratio 1:1). There was no methylphenidate treatment group in the stimulant-prior-exposure stratum.	
Number of Patients: <u>Stimulant-Naïve Stratum:</u>	

Planned: At least 64 patients in the stimulant-naïve stratum Randomized: 26 atomoxetine, 18 methylphenidate hydrochloride, 26 placebo Completed: 21 atomoxetine, 15 methylphenidate hydrochloride, 20 placebo <u>Stimulant-Prior-Exposure Stratum:</u> Planned: At least 128 patients in both strata combined Randomized: 38 atomoxetine, 36 placebo Completed: 32 atomoxetine, 25 placebo
Diagnosis and Main Criteria for Inclusion: Patients were children at least 7 years of age but less than 13 years of age at Visit 1, who met DSM-IV diagnostic criteria for ADHD. Each patient's score from the ADHDRS-IV-Parent:Inv was at least 1.5 standard deviations above the age/gender norm for their diagnostic subtype.
Test Product, Dose, and Mode of Administration: <u>Stimulant-Naïve Stratum:</u> Atomoxetine: 5-mg, 10-mg, and 20-mg capsules; 5 to 90 mg/day, given twice daily, before and after school (except for the 5-mg capsule, which could be given as a single dose); placebo was given at midday dose. <u>Stimulant-Prior-Exposure Stratum:</u> Atomoxetine: 5-mg, 10-mg, 20-mg capsules; 5 to 90 mg/day, given twice daily, before and after school (except for the 5-mg capsule, which could be given as a single dose).
Duration of Treatment: 9 weeks.
Reference Therapy, Dose, and Mode of Administration: <u>Stimulant-Naïve Stratum:</u> Methylphenidate: 5-mg, 10-mg capsules; 5 to 60 mg/day, given twice daily, before school and midday (except for the 5-mg capsule, which could be given as a single dose); placebo was given after school. <u>Stimulant-Prior-Exposure Stratum:</u> None
Variables: <u>Efficacy:</u> Efficacy analyses for the primary efficacy measure, the ADHDRS-IV-Parent:Inv Total score, included all randomized patients who had a baseline and at least 1 postbaseline ADHDRS-IV-Parent:Inv Total score. Of the 144 randomized patients, 140 met criteria for inclusion in the ADHDRS-IV-Parent:Inv efficacy analyses. Four patients were enrolled, but did not have postbaseline efficacy measurements. These patients were excluded from ADHDRS-IV-Parent:Inv efficacy analyses according to the protocol analysis plans. All patients in the primary efficacy analysis took at least one dose of study drug. <u>Safety:</u> Analysis of adverse events included the 143 enrolled patients who took at least one dose of study drug (1 patient [HFBK-18-3720] enrolled in the study, but discontinued at Visit 3 before receiving study drug). The analysis for clinical laboratory studies, vital signs, and electrocardiogram (ECG) data included patients who received at least one dose of study drug and had a baseline and a postbaseline measurement. <u>Pharmacokinetic:</u> All patients provided blood samples for assessment of plasma concentrations and pharmacokinetics of atomoxetine, 4-hydroxyatomoxetine, and N-desmethyatomoxetine.
Evaluation Methods: <u>Statistical:</u> The primary efficacy analysis was an F-test for a treatment difference between atomoxetine and placebo from an analysis of variance (ANOVA) model on change from baseline to endpoint ADHDRS-IV-Parent:Inv Total scores. Change scores were computed using a last-observation-carried-forward (LOCF) approach. The primary ANOVA model contained terms for treatment, investigative site, and stimulant-prior-exposure stratum. For secondary efficacy and safety measures, treatment differences in mean change scores from continuous measures were assessed using ANOVA, while Fisher's exact test was used to assess treatment differences in binary data.
Summary: <u>Patient Disposition:</u> Two hundred ten (210) patients entered Study HFBK. Of those, 66 were not randomized (that is, were discontinued prior to randomization at Visit 3). Patients were not randomized for the following reasons: lost to follow-up (N = 2); personal conflict (N = 13); entry criteria not met (N = 48);

sponsor's decision (N = 1); and physician's decision (N = 2).

Of the 210 patients entered, 144 were screened in Study Period I (Medication Washout, Screening, and Assessment), and were subsequently randomized to Study Period II (Stratified, Randomized, Double-Blind, Acute Treatment) at Visit 3. At Visit 3, 64 were randomized to atomoxetine, 62 to placebo, and 18 to methylphenidate. Of the 210 patients who entered this study, 113 completed Study Period II, and proceeded to Study Period III (Single-Blind Discontinuation from Study Drug).

Patient Demographics: Table HFBK.1 shows demographic characteristics for enrolled patients. Of the 144 enrolled patients, 81.3% were male; 80.6% were Caucasian; 48.6% had no prior stimulant exposure; and 91.0% were in the 2nd to 6th elementary school grades (United States). The mean age was 9.9 years (range of 7.0 to 12.8), and the mean intelligence quotient (IQ) was 104.3 (range 77 to 155).

Patients were required to meet DSM-IV criteria for ADHD following clinical examination and with the ADHD module of the Kiddie Schedule for Affective Disorders and Schizophrenia: Epidemiological Module for Affective Disorders: ADHD (KSADS-E:ADHD). Seventy-seven and eight-tenths percent (77.8%) of these patients met criteria for the combined ADHD subtype, with 20.8% classified as predominately inattentive and 1.4% as hyperactive/impulsive. Comorbid DSM-IV diagnoses were assessed using both the Diagnostic Interview for Children and Adolescents-IV (DICA-IV) and clinical assessment. The most common comorbid diagnoses (confirmed by clinical assessment) were oppositional defiant disorder (ODD) (36.2%), elimination disorders (11.3%), phobias (11.3%), dysthymia (4.3%), generalized anxiety disorder (3.5%), and major depressive disorder (MDD) (2.1%). All other comorbid diagnoses were found in less than 2% of the patients. All patients, except for patient 18-3716 who was randomized but had no postbaseline efficacy data, were identified by genotype as extensive metabolizer (EM) patients of cytochrome P450 2D6 (CYP2D6) substrates. Five patients were identified by genotype as ultra-rapid metabolizer (UM) patients of CYP2D6 substrates, which is a small subset of the EM population.

In the combined strata, the atomoxetine treatment group had statistically significantly lower mean Wechsler Intelligence Scale for Children-3rd Edition-Revised (WISC-III-R) total scores (atomoxetine 101.4, placebo 107.7, $p = .018$) and Wide Range Achievement Test 3 (WRAT3) arithmetic standard scores (atomoxetine 91.0, placebo 97.5, $p = .007$) than the placebo treatment group. No other statistically significant differences were seen in patient characteristics at baseline between atomoxetine and placebo.

In the stimulant-naïve stratum, patient characteristics at baseline for the methylphenidate group were similar to the atomoxetine and placebo treatment groups. The only statistically significant differences were found for the percentage of patients with phobias as determined by the DICA-IV (atomoxetine 37.5%, placebo 28.0%, and methylphenidate 66.7%; $p = .040$). Percentages of patients with phobias confirmed by clinical assessment did not differ between treatment groups.

Efficacy: The protocol-specified primary analysis was a treatment comparison of mean change from baseline to endpoint ADHDRS-IV-Parent:Inv Total scores between atomoxetine and placebo in the combined strata using an ANOVA model. As shown in Table HFBK.2, this analysis demonstrated statistically significantly greater reduction in severity of ADHD symptoms for atomoxetine-treated patients as compared with placebo-treated patients (mean changes: atomoxetine -14.4, placebo -5.9; $p < .001$). This mean reduction in ADHD symptoms on atomoxetine represented a 38% reduction in symptoms from baseline. Examination of the T-scores indicated the mean reduction for patients treated with atomoxetine was from 2.75 standard deviations above the norm to 1.2 standard deviations above the norm (1.5 was the lower limit to qualify for entry into the study).

Secondary analyses utilizing the ADHDRS-IV-Parent:Inv scale also supported the conclusions from the primary efficacy analysis. Statistical efficacy for atomoxetine was observed by the third week. In addition, atomoxetine was statistically superior to placebo at reducing both inattentive (mean changes: atomoxetine -7.6, placebo -3.0; $p < .001$) and hyperactive/impulsive symptoms (mean changes: atomoxetine -6.9, placebo -2.9; $p = .002$). The percentages of patients meeting response criteria (defined as having at least a 25% improvement in ADHDRS-IV-Parent:Inv Total score) were statistically greater on atomoxetine (58.7%) as compared to placebo (40.0%). Treatment differences were consistent across subgroups,

including groups based on stimulant-prior-exposure stratum, ADHD subtype, and comorbid ODD. In particular, atomoxetine was statistically significantly superior to placebo at reducing the severity of ADHD symptoms within the group of patients meeting criteria for the combined ADHD subtype and within the group of patients meeting criteria for primarily inattentive ADHD.

Secondary efficacy variables are reported in Table HFBK.3 through Table HFBK.5. Atomoxetine was statistically significantly superior to placebo at reducing symptoms measured by the Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) and improvement scale (both overall and evening components), as well as the ADHD Index hyperactivity, and cognitive subscales of the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S). No statistically significant differences between atomoxetine and placebo were observed for the oppositionality subscale of the CPRS-R:S and the Restricted Academic Situation test (RAS) total percentage. A high percentage of atomoxetine patients completed the study (82.8% atomoxetine, 72.6% placebo) with few atomoxetine discontinuations due to lack of efficacy (6.3% atomoxetine, 16.1% placebo).

Following discontinuation of atomoxetine treatment (Study Period III), scores for the former atomoxetine-treated patients increased to near the levels of the placebo treated group.

In the stimulant-naïve stratum, methylphenidate demonstrated efficacy statistically superior to placebo on multiple measures. This included the ADHDRS-IV-Parent:Inv Total and subscale scores, CGI-ADHD-S and CGI-ADHD-I, and the ADHD Index and cognitive subscales of the CPRS-R:S. Methylphenidate, as was true for atomoxetine, did not differ significantly from placebo on the oppositionality subscale of the CPRS-R:S or the RAS total percentage. Methylphenidate was numerically superior to atomoxetine on several efficacy measures, however, the differences were not statistically significant.

In summary, in a population of patients aged 7 to 13 years with a DSM-IV diagnosis of ADHD, atomoxetine was statistically superior to placebo at reducing symptoms of ADHD. Efficacy was observed on both primary and secondary measures, including both inattentive and hyperactive/impulsive symptoms. The efficacy of atomoxetine was consistent across prior-stimulant-exposure stratum and other patient subgroups. The onset of efficacy of atomoxetine was noted at 1 week and statistically significant by Week 3. The observed superiority of methylphenidate as compared to placebo in the stimulant-naïve stratum provided further validity to the results of this study.

Safety: The safety of acute treatment with atomoxetine was assessed by solicited and unsolicited adverse events, laboratory values, changes in vital signs, and ECG intervals. Of the 144 enrolled patients, 143 (64 atomoxetine, 62 placebo, and 17 methylphenidate) took at least one dose of study drug and were included in adverse event analyses. All patients (except for 1 patient who was randomized to placebo and then discontinued at Visit 4 when it was discovered he was a poor metabolizer) were genotypically CYP2D6 extensive metabolizer (EM) patients. The mean final dose of atomoxetine was 1.5 mg/kg and the mean number of days of atomoxetine therapy was 68.7 (range 12 to 104 days).

No serious adverse events occurred in the atomoxetine treatment group, while 1 serious adverse event (encephalopathy) occurred in the placebo group. Two of 64 atomoxetine-treated patients (3.1%) were discontinued for nonserious adverse events (tics, initially reported as movement disorder, and nervousness).

Table HFBK.6 summarizes the treatment-emergent adverse events by incidence, for events that occurred in at least 5% of the patients. A statistically significantly higher percentage of patients in the atomoxetine treatment group as compared with the placebo treatment group reported treatment-emergent anorexia (22% versus 8%; $p=.045$). The actual event was usually described as "loss of appetite," which was mapped to "anorexia." No other statistically significant differences between atomoxetine and placebo were observed for any specific event. The percentages of treatment-emergent anorexia (captured as "decreased appetite") was similar between the atomoxetine and methylphenidate treatment groups.

For laboratory measurements, there were statistically significant treatment differences between atomoxetine and placebo in mean changes from Study Period II baseline to endpoint for hemoglobin, hematocrit, monocytes, ALT, alkaline phosphatase, and uric acid. There were no statistically significant differences between atomoxetine and placebo in the percentages of patients with out-of-range treatment-

emergent laboratory values.

Summaries of the mean change from Study Period II baseline to endpoint in vital sign measures (diastolic and systolic blood pressure, heart rate, weight, height, and temperature) for atomoxetine-treated and placebo-treated patients in the combined strata are provided in Table HFBK.7. Mean changes for stimulant-naïve patients in the methylphenidate treatment group are also provided in this table as a reference. In the combined strata, the atomoxetine treatment group had a statistically significantly greater increase than the placebo treatment group in diastolic blood pressure and heart rate. The mean change in diastolic blood pressure average was +3.0 mm Hg for the atomoxetine group compared with -0.2 mm Hg for the placebo group ($p = .031$). In both the atomoxetine-treated and placebo-treated patients, mean systolic blood pressure increased by 0.7 mm Hg. This change was not statistically significant within or between groups. The mean change in heart rate average was +7.2 beats per minute (bpm) for the atomoxetine group and +0.6 bpm for the placebo group ($p = .003$). Atomoxetine-treated patients had a statistically significant decrease in weight. The mean change in weight was -0.5 kg for the atomoxetine group and +1.5 kg for the placebo group ($p < .001$).

Analysis of ECG data revealed a statistically significant increase in mean heart rate ($p = .023$) and decreases in mean PR ($p = .008$) and QRS ($p = .025$) intervals. There was no evidence for an increase in corrected QT interval on atomoxetine treatment; in fact in this study, the mean QTc interval decreased.

Analysis of safety data from the 1-week study-drug discontinuation period (Study Period III) showed that the only discontinuation-emergent adverse event reported by $\geq 5\%$ of patients in any group was pharyngitis in 5.7% of patients in the atomoxetine group and 2.2% of patients in the placebo group. Upon discontinuation from atomoxetine, a statistically significant increase in weight was observed (mean increase of 0.5 kg).

Table HFBK.1. Summary of Demographics and Other Patient Characteristics Including WISC-III IQ and WRAT3-Tan Test Scores
All Randomized Patients
B4Z-MC-HFBK

Variable	Tomox. (N=64)	Methyl (N=18)	Placebo (N=62)	Total (N=144)
Sex: No. (%)				
No. Patients	64	18	62	144
Female	13 (20.3)	2 (11.1)	12 (19.4)	27 (18.8)
Male	51 (79.7)	16 (88.9)	50 (80.6)	117 (81.3)
Origin: No. (%)				
No. Patients	64	18	62	144
African Descent	5 (7.8)	1 (5.6)	7 (11.3)	13 (9.0)
Caucasian	49 (76.6)	13 (72.2)	54 (87.1)	116 (80.6)
East/Southeast A	1 (1.6)	0	0	1 (0.7)
Hispanic	4 (6.3)	3 (16.7)	0	7 (4.9)
Other	5 (7.8)	1 (5.6)	1 (1.6)	7 (4.9)
Age: yrs.				
No. Patients	64	18	62	144
Mean	9.81	9.73	9.95	9.86
Median	9.70	10.05	9.93	9.88
Standard Dev.	1.59	1.66	1.49	1.55
Minimum	7.00	7.36	7.36	7.00
Maximum	12.46	12.27	12.79	12.79
Height: cm				
No. Patients	63	18	60	141
Mean	137.40	137.75	138.93	138.10
Median	136.00	136.50	138.00	137.00
Standard Dev.	9.75	9.86	9.68	9.69
Minimum	118.00	124.00	120.00	118.00
Maximum	167.50	158.50	165.00	167.50
Unspecified	1	0	2	3
Weight: kg				
No. Patients	63	18	61	142
Mean	35.61	35.53	36.68	36.06
Median	31.60	32.40	32.40	32.00
Standard Dev.	10.52	8.58	10.89	10.41
Minimum	23.80	23.90	24.80	23.80
Maximum	74.30	49.50	71.40	74.30
Unspecified	1	0	1	2
Family History of ADHD-Mother				
No. Patients	64	18	62	144
N	55 (85.9)	15 (83.3)	52 (83.9)	122 (84.7)
U	5 (7.8)	2 (11.1)	4 (6.5)	11 (7.6)
Y	4 (6.3)	1 (5.6)	6 (9.7)	11 (7.6)
Family History of ADHD-Father				
No. Patients	64	18	62	144
N	42 (65.6)	12 (66.7)	43 (69.4)	97 (67.4)
U	10 (15.6)	3 (16.7)	7 (11.3)	20 (13.9)
Y	12 (18.8)	3 (16.7)	12 (19.4)	27 (18.8)
Family History of ADHD-Grandparents				
No. Patients	64	18	62	144
N	55 (85.9)	15 (83.3)	52 (83.9)	122 (84.7)
U	7 (10.9)	2 (11.1)	7 (11.3)	16 (11.1)
Y	2 (3.1)	1 (5.6)	3 (4.8)	6 (4.2)

(continued)

Table HFBK.1. Summary of Demographics and Other Patient Characteristics Including WISC-III IQ and WRAT3-Tan Test Scores
All Randomized Patients
B4Z-MC-HFBK (continued)

Variable	Tomox. (N=64)	Methyl (N=18)	Placebo (N=62)	Total (N=144)
Family History of ADHD-Siblings				
No. Patients	64	18	62	144
N	41 (64.1)	14 (77.8)	32 (51.6)	87 (60.4)
N/A	3 (4.7)	0	1 (1.6)	4 (2.8)
U	3 (4.7)	1 (5.6)	5 (8.1)	9 (6.3)
Y	17 (26.6)	3 (16.7)	24 (38.7)	44 (30.6)
Prior Stimulant Exposure				
No. Patients	64	18	62	144
N	26 (40.6)	18 (100)	26 (41.9)	70 (48.6)
Y	38 (59.4)	0	36 (58.1)	74 (51.4)
DRD4 Allele				
No. Patients	64	18	62	144
1-4	0	0	1 (1.6)	1 (0.7)
2-2	1 (1.6)	1 (5.6)	1 (1.6)	3 (2.1)
2-4	12 (18.8)	2 (11.1)	7 (11.3)	21 (14.6)
2-7	4 (6.3)	1 (5.6)	2 (3.2)	7 (4.9)
3-4	3 (4.7)	0	2 (3.2)	5 (3.5)
3-7	1 (1.6)	0	1 (1.6)	2 (1.4)
4-4	19 (29.7)	9 (50.0)	20 (32.3)	48 (33.3)
4-5	1 (1.6)	1 (5.6)	3 (4.8)	5 (3.5)
4-6	1 (1.6)	0	3 (4.8)	4 (2.8)
4-7	19 (29.7)	2 (11.1)	18 (29.0)	39 (27.1)
5-6	0	0	1 (1.6)	1 (0.7)
5-7	0	2 (11.1)	0	2 (1.4)
7-7	3 (4.7)	0	3 (4.8)	6 (4.2)
Grade in School				
No. Patients	64	18	62	144
1	3 (4.7)	0	1 (1.6)	4 (2.8)
2	10 (15.6)	5 (27.8)	11 (17.7)	26 (18.1)
3	18 (28.1)	2 (11.1)	11 (17.7)	31 (21.5)
4	7 (10.9)	4 (22.2)	12 (19.4)	23 (16.0)
5	11 (17.2)	3 (16.7)	12 (19.4)	26 (18.1)
6	11 (17.2)	3 (16.7)	11 (17.7)	25 (17.4)
7	4 (6.3)	1 (5.6)	3 (4.8)	8 (5.6)
8	0	0	1 (1.6)	1 (0.7)
WISC full scale IQ				
No. Patients	64	17	62	143
Mean	101.39	102.76	107.65	104.27
Median	100.00	100.00	105.00	104.00
Standard Dev.	13.64	18.97	15.70	15.43
Minimum	81.00	77.00	81.00	77.00
Maximum	139.00	155.00	148.00	155.00

(continued)

Table HFBK.1. Summary of Demographics and Other Patient Characteristics Including WISC-III IQ and WRAT3-Tan Test Scores
All Randomized Patients
B4Z-MC-HFBK (continued)

Variable	Tomox. (N=64)	Methyl (N=18)	Placebo (N=62)	Total (N=144)
WRAT Reading Raw Score				
No. Patients	63	17	62	142
Mean	31.38	31.24	32.13	31.69
Median	32.00	31.00	33.00	32.00
Standard Dev.	6.93	6.58	5.95	6.44
Minimum	15.00	21.00	22.00	15.00
Maximum	48.00	42.00	43.00	48.00
Unspecified	1	0	0	1
WRAT Reading Standard Score				
No. Patients	63	17	62	142
Mean	96.13	97.12	97.13	96.68
Median	97.00	96.00	96.50	96.50
Standard Dev.	15.96	12.55	13.18	14.33
Minimum	46.00	69.00	62.00	46.00
Maximum	128.00	115.00	139.00	139.00
Unspecified	1	0	0	1
WRAT Reading Absolute Score				
No. Patients	63	17	62	142
Mean	492.48	492.37	494.41	493.31
Median	494.00	493.00	495.00	494.00
Standard Dev.	15.76	15.13	13.44	14.64
Minimum	448.00	469.00	470.00	448.00
Maximum	526.00	517.30	518.00	526.00
Unspecified	1	0	0	1
WRAT Spelling Raw Score				
No. Patients	63	17	62	142
Mean	26.70	27.00	27.23	26.96
Median	26.00	26.00	27.00	26.50
Standard Dev.	5.90	6.14	5.52	5.73
Minimum	13.00	19.00	18.00	13.00
Maximum	39.00	41.00	42.00	42.00
Unspecified	1	0	0	1
WRAT Spelling Standard Score				
No. Patients	63	17	62	142
Mean	94.83	97.00	95.45	95.36
Median	93.00	93.00	95.00	93.00
Standard Dev.	13.87	12.47	13.28	13.38
Minimum	63.00	75.00	69.00	63.00
Maximum	126.00	124.00	130.00	130.00
Unspecified	1	0	0	1
WRAT Spelling Absolute Score				
No. Patients	63	17	62	142
Mean	490.61	491.29	492.08	491.33
Median	491.00	491.00	492.00	491.50
Standard Dev.	14.79	15.04	13.07	14.00
Minimum	454.00	470.00	468.00	454.00
Maximum	517.00	520.70	523.00	523.00
Unspecified	1	0	0	1

(continued)

Table HFBK.1. Summary of Demographics and Other Patient Characteristics Including WISC-III IQ and WRAT3-Tan Test Scores
All Randomized Patients
B4Z-MC-HFBK (concluded)

Variable	Tomox. (N=64)	Methyl (N=18)	Placebo (N=62)	Total (N=144)
WRAT Arithmetic Raw Score				
No. Patients	63	17	62	142
Mean	25.92	26.88	28.16	27.01
Median	26.00	25.00	28.00	27.00
Standard Dev.	5.45	6.03	5.63	5.66
Minimum	13.00	18.00	18.00	13.00
Maximum	38.00	38.00	39.00	39.00
Unspecified	1	0	0	1
WRAT Arithmetic Standard Score				
No. Patients	63	17	62	142
Mean	91.02	96.29	97.47	94.46
Median	90.00	95.00	98.50	94.50
Standard Dev.	14.47	13.31	11.76	13.48
Minimum	48.00	76.00	69.00	48.00
Maximum	116.00	124.00	118.00	124.00
Unspecified	1	0	0	1
WRAT Arithmetic Absolute Score				
No. Patients	63	17	62	142
Mean	489.86	492.22	494.97	492.37
Median	490.00	489.00	496.00	491.00
Standard Dev.	13.08	14.04	12.84	13.22
Minimum	457.00	468.00	468.00	457.00
Maximum	516.00	516.00	517.00	517.00
Unspecified	1	0	0	1

Population: Tomoxetine, Methylphenidate, and Placebo Patients from both Strata who took at least 1 dose of study drug.

Initial Visit ONLY

Input data from RMP.SAS.B4ZM.MCHFBKSW

Output stored as RMP.B4ZO.HFBKCTRM(DE1C2025)

XDES0001

Atomoxetine hydrochloride
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Approved: 11 November 2004

**Table HFBK.2. ADHDRS-IV-Parent:Inv Total Score Change from Baseline to Endpoint – Study Period II
 B4Z-MC-HFBK**

		Baseline		Endpoint		Change		p-Value ^a
	n	Mean	SD	Mean	SD	Mean	SD	
Combined Stratum								
Tomoxetine	63	37.8	7.9	23.3	14.3	-14.4	13.0	0.0003
Placebo	60	37.6	8.0	31.7	14.4	-5.9	13.0	---
Stimulant-Naïve Stratum								
Tomoxetine ^b	25	36.6	7.4	18.6	14.9	-18.0	13.2	0.0936
Placebo	24	35.9	7.0	26.8	14.0	-9.1	11.7	---
Methylphenidate ^b	17	37.9	11.2	14.7	13.7	-23.2	16.4	0.0071
Stimulant-Prior-Exposure Stratum								
Tomoxetine	38	38.6	8.2	26.5	13.1	-12.1	12.4	0.0059
Placebo	36	38.7	8.5	35.0	13.9	-3.7	13.5	---

^a Between treatment group p-values are from pairwise tests of treatment differences in mean change from baseline to endpoint (last-visit-carried-forward) scores versus placebo using least squares means from an ANOVA model with terms for investigator and treatment (in each stratum) or terms for investigator, treatment and strata (combined group).

^b The p-value for tomoxetine vs. methylphenidate comparison in the stimulant-naïve stratum is 0.2085.

Source Data: eagle:\programs._g\rmp\b4zs\hfbk\final analysis\locf.sas

**Table HFBK.3. CGI-ADHD-Severity and CGI-ADHD-Severity:Evening
Summary of Endpoint and Change Values –
Study Period II – Combined Strata
B4Z-MC-HFBK**

Measure		Endpoint Scores - All Enrolled							Endpoint Mean (SD)	Change Mean (SD)	p-Value ^a
		Patients									
		1	2	3	4	5	6	7			
CGI-ADHD-Severity											
Tomoxetine		8	12	8	21	12	2	0	3.4 (1.4)	-1.5 (1.4)	0.0009
Placebo		1	7	7	14	27	5	0	4.2 (1.2)	-0.7 (1.2)	
CGI-ADHD-Severity:Evening											
Tomoxetine		7	14	8	21	10	3	0	3.3 (1.4)	-1.4 (1.3)	0.0033
Placebo		1	8	8	15	23	6	0	4.1 (1.3)	-0.7 (1.3)	---

^a The p-values are from least square mean comparisons of change scores using an ANOVA model with terms for therapy, pooled investigator, and strata.

CGI-Severity Scores are Defined as:

- 1 = Normal, Not Ill
- 2 = Minimally Ill
- 3 = Mildly Ill
- 4 = Moderately Ill
- 5 = Markedly Ill
- 6 = Severely Ill
- 7 = Very Severely Ill

Source Data: eagle:\programs._g\rmp\b4zs\hfbk\final analysis\locf_cgi.sas

Table HFBK.4. **CGI-ADHD-Improvement and CGI-ADHD-Improvement:Evening, Summary of Endpoint Values – Study Period II – Combined Strata, B4Z-MC-HFBK**

Measure	Endpoint Scores - All Enrolled Patients							Mean (SD)	p-Value ^a	
	1	2	3	4	5	6	7			
CGI-ADHD-Improvement										
Tomoxetine	19	9	15	16	4	0	0	2.6 (1.3)	0.0001	
Placebo	3	12	9	28	7	2	0	3.5 (1.2)	---	
CGI-ADHD-Improvement: Evening										
Tomoxetine	19	9	14	17	4	0	0	2.7 (1.3)	0.0004	
Placebo	4	13	6	29	7	2	0	3.5 (1.2)	---	

^a The p-values are from pairwise treatment differences in mean endpoint value (last observation carried forward) versus placebo using least squares means from an ANOVA model with terms for pooled investigator, treatment and strata.

CGI-Improvement Scores are Defined as:

- 1 = Very Much Improved
- 2 = Much Improved
- 3 = Minimally Improved
- 4 = No Change
- 5 = Minimally Worse
- 6 = Much Worse
- 7 = Very Much Worse

Source Data: eagle:\programs._g\rmp\b4zs\hfbk\final analysis\locf_end.sas

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Table HFBK.5. Conners' Parent Rating Scale-Revised:Short Form– ADHD Index, Hyperactivity, Cognitive, and Oppositional Subscales - Change from Baseline to Endpoint – Study Period II – Combined Strata B4Z-MC-HFBK

Measure	n	Baseline		Endpoint		Change		p-Value ^a
		Mean	SD	Mean	SD	Mean	SD	
ADHD Index Subscale								
Tomoxetine	61	26.5	6.6	17.7	10.0	-8.8	9.8	0.0002
Placebo	60	26.3	5.7	24.2	9.1	-2.1	9.6	---
Hyperactivity Subscale								
Tomoxetine	61	10.1	5.1	6.5	5.7	-3.6	5.0	0.0165
Placebo	60	10.0	4.9	8.6	5.8	-1.4	4.9	---
Cognitive Subscale								
Tomoxetine	61	13.2	4.0	9.2	5.8	-4.0	5.7	0.0007
Placebo	60	13.1	3.5	12.7	4.8	-0.4	5.7	---
Oppositional Subscale								
Tomoxetine	61	9.4	5.2	7.7	5.2	-1.7	4.9	0.7200
Placebo	60	8.9	4.7	7.4	5.4	-1.5	4.3	---

^a Between treatment group p-values are from pairwise tests of treatment differences in mean change from baseline to endpoint (last-visit-carried-forward) scores versus placebo using least squares means from an ANOVA model with terms for pooled investigator, treatment and strata (combined group).
 Source Data: eagle:\programs_g\rmp\b4zs\hfbk\final analysis\locf_cprs.sas

Table HFBK.6. Summary of Treatment-Emergent Adverse Events with $\geq 5\%$ Incidence
Study Period II, Combined Strata plus Methylphenidate B4Z-MC-HFBK

Event	Tomoxetine (N=64)		Placebo (N=62)		p-value* (T vs P)	Methylphenidate (N=17)	
	n	%	n	%		n	%
Abdominal Pain	16	25	12	19	0.523	2	12
Anorexia	14	22	5	8	0.045	5	29
Headache	13	20	14	23	0.830	6	35
Vomiting	11	17	8	13	0.620	4	24
Rhinitis	9	14	15	24	0.177	1	6
Nervousness	9	14	4	7	0.242	4	24
Pharyngitis	8	13	5	8	0.560	2	12
Somnolence	7	11	6	10	1.000	1	6
Nausea	7	11	3	5	0.324	1	6
Emotional Lability	6	9	2	3	0.274	2	12
Flu Syndrome	5	8	1	2	0.208	1	6
Cough Increased	4	6	4	7	1.000	3	18
Diarrhea	4	6	4	7	1.000	3	18
Rash	4	6	7	11	0.360	0	0
Personality Disorder	4	6	2	3	0.680	0	0
Unexpected Benefit	4	6	2	3	0.680	0	0
Hostility	4	6	0	0	0.119	0	0
Fever	3	5	5	8	0.488	5	29
Insomnia	3	5	6	10	0.320	3	18
Accidental Injury	3	5	6	10	0.320	1	6
Dyspepsia	3	5	2	3	1.000	2	12
Contact Dermatitis	2	3	2	3	1.000	1	6
Pain	1	2	4	7	0.204	0	0

* P-value between tomoxetine and placebo (T vs P) are based on Fisher's exact test.

Baseline: Visits 1 - 3; Endpoint: Visits 4 - 12

Source data: RMP.B4ZO.HFBKCTRM (AE2A101A), RMP.B4ZO.HFBKCTRM (AE2A1029),
RMP.B4ZO.HFBKCTRM (AE2C101A), & RMP.B4ZO.HFBKCTRM (AE2C1029)

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Table HFBK.7. Summary of Vital Signs Data
Mean Change from Baseline to Endpoint
Study Period II, Combined Strata plus Methylphenidate
B4Z-MC-HFBK

Variable	Tomoxetine				Placebo				Chg T v P pval	Methylphenidate			
	N	Baseline mean (sd)	Change mean (sd)	w/i p-val	N	Baseline mean (sd)	Change mean (sd)	w/i p-val		N	Baseline mean (sd)	Change mean (sd)	w/i p-val
Diastolic BP Average (mm Hg)	63	63.4 (8.0)	+3.0 (8.2)	0.010	60	63.8 (8.2)	-0.2 (8.0)	0.927	0.031	17	62.4 (7.4)	+1.4 (8.8)	0.540
Systolic BP Average (mm Hg)	63	104 (9)	+0.7 (9)	0.572	60	103 (9)	+0.7 (9)	0.402	0.973	17	103 (7)	+3.6 (6)	0.038
Heart Rate Average	63	85.3 (11.1)	+7.2 (12.7)	<.001	60	87.4 (10.1)	+0.6 (11.9)	0.931	0.003	17	84.8 (8.5)	+3.6 (14.2)	0.554
Weight (KG)	63	35.8 (10.1)	-0.5 (1.4)	<.001	61	36.9 (10.9)	+1.5 (1.5)	<.001	<.001	17	36.2 (8.6)	-0.1 (1.4)	0.734
Height (cm)	57	137 (8)	+0.9 (1.5)	<.001	56	139 (9)	+0.9 (1.4)	<.001	0.892	15	139 (10)	+2.8 (2)	<.001
Temp (Cent.)	63	36.7 (0.4)	-0.1 (0.5)	0.375	60	36.7 (0.4)	+0.1 (0.4)	0.040	0.094	17	36.8 (0.3)	-0.4 (0.7)	0.015

Abbreviations: sd = standard deviation; w/i-p = within group p-values, based on Wilcoxon's signed rank test; Chg T v P pval = p-value for a treatment effect (tomoxetine vs. placebo) on change scores from an ANOVA model with a term for treatment.

Baseline: Visits 1 – 3; Endpoint: Visits 4 – 12

Source data: RMP.B4ZO.HFBKCTRM(VI3K101A) & RMP.B4ZO.HFBKCTRM(VI3K2029)

Summary ID#1855

Clinical Study Summary: Study B4Z-MC-HFBE

Title of Study: Randomized, Double-Blind, Placebo-Controlled, Variable Discontinuation Study of Tomoxetine Hydrochloride in Children with Attention-Deficit/Hyperactivity Disorder	
Investigators: This multicenter study included 32 principal investigators (PIs).	
Study Centers: This study was conducted at 23 study centers in the United States. (Nine sites had two PIs each; hence the seeming discrepancy of 32 PIs at 23 study centers.)	
Length of Study: 2 years Date first patient enrolled: 25 August 1998 Date last patient completed: 05 September 2000	Phase of Development: 2
Objectives: The primary objective of this study was to test the hypothesis that atomoxetine (formerly called tomoxetine)-treated Attention-Deficit/Hyperactivity Disorder (ADHD) responders randomized to continued treatment with atomoxetine hydrochloride would demonstrate statistically significantly longer time to relapse than atomoxetine-treated ADHD responders who were randomized to treatment with placebo. The secondary objectives of Study B4Z-MC-HFBE (HFBE) were to assess the following issues in an outpatient population of boys, aged 7 through 15 years, and girls, aged 7 through 9 years (at the time of study entry): • The long-term safety and tolerability of atomoxetine. • The reliability, responsiveness, and relationship among efficacy variables with a compound (methylphenidate hydrochloride) proven efficacious in the treatment of ADHD. • The reliability, responsiveness, and relationship among efficacy variables of a new clinical entity (atomoxetine) for the treatment of ADHD. • The effects of atomoxetine and methylphenidate hydrochloride, independent of one another, on measures of working memory, attention, and executive function.	

Study Design: Study HFBE was a Phase 2, multicenter, double-blind, placebo-controlled outpatient study in boys who were at least 7 years of age but less than 16 years of age at Visit 1 and girls who were at least 7 years of age but less than 9 years of age at Visit 1 who met *Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition* (DSM-IV) criteria ADHD.

Study Period I was an assessment/evaluation and drug washout phase for those children and adolescents taking any medication excluded by the protocol. During this period, eligibility was determined and a cytochrome P450 2D6 (CYP2D6) genotype was obtained for each patient. At Visit 2 eligible patients were randomized to open-label treatment with either atomoxetine (LY139603) or methylphenidate hydrochloride, beginning Study Period II. Study Period II consisted of up to 10 weeks (the recommended visit interval was 7 days) of active treatment in which eligible patients were randomized to open-label treatment with either atomoxetine hydrochloride or methylphenidate hydrochloride (administered as Ritalin.).

Because the pharmacokinetics of atomoxetine are influenced by CYP2D6 polymorphic metabolism, patients were characterized as extensive metabolizer (EM) or poor metabolizer (PM) patients prior to randomization. The majority of the population were EM patients of atomoxetine; however, a small percentage (~7%) had a reduced ability to form the hydroxylated metabolite of atomoxetine (PM patients) resulting in a longer half-life and higher steady-state concentrations of the drug and its N-desmethyl metabolite. Patients randomized to treatment with atomoxetine who were characterized as PM patients were assigned different dosages of atomoxetine than patients randomized and treated with atomoxetine who were characterized as EM patients. This differential dosing was decided upon because at the time this study was undertaken, the tolerability and safety of the full dose-range planned for use in EM patients had not been assessed in PM patients (it has subsequently been explored in PM patients in a series of clinical pharmacology and clinical studies).

Atomoxetine-treated patients who met predefined response criteria during Study Period II entered Study Period III, a randomized, double-blind, placebo-controlled, variable-discontinuation treatment period of up to 48 weeks' duration. During Study Period III, some atomoxetine-treated responders had therapy with atomoxetine discontinued and began treatment with placebo according to a schedule to which the investigator was blinded. Each patient's total daily dose (TDD) was the same as that which resulted in response during Study Period II. Relapse (loss of significant efficacy) was assessed at each visit according to predefined relapse criteria. Patients who relapsed during Study Period III were eligible to participate in Study B4Z-MC-HFBE (HFBE), an open-label treatment study of atomoxetine. Patients who completed Study Period III were entered into Study Period IV, a double-blind, placebo-controlled treatment period in which study drug was variably tapered and discontinued.

Methylphenidate-treated patients who completed Study Period II entered Study Period III, a 1-week study drug discontinuation phase. Methylphenidate responders and methylphenidate-treated patients who did not meet response criteria at Visit 8 or later, or who discontinued due to an adverse event during Study Period II may have been eligible to participate in Study HFBE provided they were compliant with the protocol during Study Period II. Atomoxetine-treated patients who met response criteria during Study Period II, and who elected not to participate in Study Period III were not eligible to participate in Study HFBE.

Number of Patients:

Planned: 160 atomoxetine, 38 methylphenidate

Randomized: 184 atomoxetine, 44 methylphenidate

Completed Study Period II: Open Label: 118 atomoxetine, 25 methylphenidate

Diagnosis and Main Criteria for Inclusion: Patients were children at least 7 years of age but less than 16 years of age at Visit 1 (girls were at least 7 years of age but less than 9 years of age at Visit 1) who met DSM-IV diagnostic criteria for ADHD. Each patient's score from the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) was at least 1.5 standard deviations above the age/gender norm for their diagnostic subtype, and patients met the lifetime criteria for ADHD on the Kiddie Schedule for Affective Disorders and

Schizophrenia: Epidemiological Module for ADHD (K-SADS-E:ADHD) Module.
Test Product, Dose, and Mode of Administration: Atomoxetine; 5-mg, 10-mg, and 20-mg capsules; 5 mg/day to 90 mg/day, given in divided doses twice daily.
Duration of Treatment: Study Period II: Open Label: Up to approximately 10 weeks. Study Period III: Variable Discontinuation or Continued on Atomoxetine: Up to approximately 48 weeks.
Reference Therapy, Dose, and Mode of Administration: Methylphenidate; 5-mg, 10-mg, 20-mg tablets; 5 mg/day to 60 mg/day, given in divided doses 1 to 3 times daily. Also placebo capsules.
Variables: Efficacy: The primary measures of efficacy were the Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Improvement (CGI-ADHD-I) and the ADHDRS-IV-Parent:Inv Total score. Safety: Adverse events were collected by open-ended discussion (unsolicited) and through the Barkley Behavior and Adverse Events Questionnaire-Modified (BBAEQ-M). Other safety measures collected were vital signs, laboratory values, and electrocardiogram (ECG).
Evaluation Methods: Statistical: The distribution of number of days to relapse were estimated for each treatment group using the Kaplan-Meier product limit estimator. Treatment differences in the distributions were assessed using the log-rank test. Other analysis methods include: Fisher's exact test for binary data, Chi-Square Tests for other categorical data, Wilcoxon signed-rank test for changes in vital signs, ECG and lab values, and analysis of variance (ANOVA) for other continuous measures. Missing values were handled using a last-observation-carried-forward (LOCF) method.
Summary: Patient Disposition: Figure HFBE.1 shows the flow of patients and their disposition. Following screening during Study Period I, patients were randomized to open-label treatment in Study Period II. At the start of Study Period II, 184 patients were assigned to atomoxetine and 44 patients were assigned to methylphenidate. Of the 44 patients assigned to methylphenidate, 25 completed Study Period II and 19 were discontinued. Of the 184 patients assigned to atomoxetine, 118 completed Study Period II and 66 were discontinued. Twenty-three (23) patients of the 118 atomoxetine patients who completed Study Period II met the predefined response criteria and entered Study Period III, but relapsed prior to randomization. Seventy-nine (79) of the 118 atomoxetine patients who completed Study Period II met the predefined response criteria, entered Study Period III, and were randomized. Of those 79 patients, 20 were randomized to receive placebo in the first phase of Study Period III and 59 were randomized to continue on atomoxetine. Three (3) of the 20 patients randomized to placebo completed the first phase of Study Period III and 17 were discontinued while 16 of the 59 patients randomized to continue treatment with atomoxetine completed the first phase of Study Period III and 43 were discontinued. All 16 atomoxetine-treated patients who completed the first phase of Study Period III entered the second phase of Study Period III, in which 4 of the patients were randomized to receive placebo and 12 were randomized to continue on atomoxetine. Of the 4 patients assigned to placebo in the second phase of Study Period III, 3 completed Study Period III and 1 was discontinued. Of the 12 patients assigned to atomoxetine in the second phase of Study Period III, 10 completed Study Period III and continued into Study Period IV; the other 2 patients were discontinued. Ten (10) patients entered Study Period IV, 3 of which were randomized to receive no taper and 7 of which were randomized to the taper group. All 3 patients in the no-taper group completed the study period. Six (6) of the 7 patients in the taper group completed the study period and 1 patient in the taper group was discontinued. Patient Demographics: Table HFBE.1 summarizes selected demographic and baseline characteristics of the patients in Study Period II. Of the 228 enrolled patients, 92.5% were male and 76.8% were Caucasian.

The mean age was 10.4 years (range of 7.0 to 15.8) and the mean intelligence quotient (IQ) was 104.4 (range of 73.0 to 147.0). Patients were moderately ill at baseline with an overall mean ADHDRS-IV-Parent:Inv Total score of 39.0 (range of 9.0 to 54.0) and an overall mean Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity (CGI-ADHD-S) score of 4.8 (range of 2.0 to 7.0). With the exception of gender, there were no statistically significant differences in the specified demographic or baseline characteristics between the two treatment groups.

Patients were required to meet the DSM-IV criteria for ADHD following clinical examination and with the ADHD module of the KSADS-E:ADHD. Seventy-five and nine-tenths percent (75.9%) of these patients met criteria for the combined ADHD subtype, with 22.8% classified as predominately inattentive and 1.3% as hyperactive/impulsive. Comorbid DSM-IV diagnoses were assessed using both the Diagnostic Interview for Children and Adolescents-IV (DICA-IV) and clinical assessment. The most common comorbid diagnoses from the DICA-IV were oppositional defiant disorder (52.9%), phobias (21.1%), elimination disorder (16.7%), conduct disorder (10.1%), major depressive disorder (6.6%), dysthymic disorder (6.6%), psychological stressor (6.6%), obsession (6.2%), and compulsion disorder (5.3%). All other comorbid diagnoses from the DICA-IV were found in less than 2% of the patients. The only statistically significant differences were found for the percentage of patients with phobias as determined by the DICA-IV (atomoxetine 18%, and methylphenidate 34.1%; $p=.024$).

Efficacy: Study HFBE comprised two main parts: an initial, unblinded period during which children with ADHD were randomized to either atomoxetine or methylphenidate, and a second phase in which patients randomized to atomoxetine who had achieved a pre-defined reduction in symptoms were further randomized to continued atomoxetine treatment or to discontinuation under double-blind conditions. The data from the open-label phase comparing atomoxetine with methylphenidate are presented in Table HFBE.2, Table HFBE.3, Table HFBE.4, and Table HFBE.5. Figure HFBE.2 and Table HFBE.6 show the data and analysis from the first potential therapy change to the second potential therapy change during the variable-discontinuation phase of the study. The time to relapse analysis presented in Figure HFBE.2 was the primary efficacy analysis for this study.

The initial, acute therapy phase provided an opportunity to assess the comparative efficacy of atomoxetine and methylphenidate. This comparison was not meant to be definitive, as the number of patients in the methylphenidate group was limited and treatment assignment was not blind. With these caveats, the results suggested that acute outcomes were similar for the two treatment groups. Mean reduction in symptoms as assessed by each of the symptom measures including the ADHDRS-IV-Parent scores, mean CGI-ADHD-S scores, as well as the proportions of patients in each group with no or minimal symptoms and marked improvement at endpoint (CGI-ADHD-S scores of 1 or 2, and CGI-ADHD-I scores of 1 or 2, respectively) were not different between groups.

The results of Study HFBE showed that atomoxetine was not statistically significantly different compared to placebo in the prevention of relapse in children with ADHD whose symptoms initially remitted following an acute period of treatment with atomoxetine (Figure HFBE.2). Outcomes with respect to relapse rates, final ADHDRS-IV-Parent scores and CGI-ADHD-S were not statistically significantly different between atomoxetine and placebo following randomization (Table HFBE.6).

Several factors could have accounted for the failure to demonstrate efficacy. However, in the absence of an active comparator, the results of Study HFBE could not be definitively interpreted (that is, there was no way to distinguish between a 'negative' study [a demonstration of inefficacy] and a 'failed' study [a study that failed to demonstrate a drug effect due to methodological problems]).

Following randomization, patients who discontinued could enter an open-label trial of atomoxetine in which they would be assured of getting atomoxetine, creating an 'incentive' for patients to discontinue early from the trial in both the placebo and atomoxetine arms. This appeared to have occurred. Among patients randomized to atomoxetine, a total of 56 relapsed while on double-blind therapy. Of these, 51 patients chose to enter open-label treatment in Study HFBF or Study B4Z-MC-LYAI (LYAI). Efficacy data obtained during these open-label studies were available for 48 of these patients as of November 2000.

Among these patients there was a mean 22.1 point decrease in ADHDRS-IV-Parent Total scores from a baseline of 38.9, so that that most of these children no longer fell into a range of clinically significant symptoms. Of these patients, 31/48 (64.6%) had a T-score ≤ 60 , within 1 standard deviation of their age and sex norm, and 36/48 (75.0%) had a T-score ≤ 65 , within 1.5 standard deviations of their age and sex norm. Because the majority of children who relapsed during double-blind therapy had only limited symptoms during subsequent open-label therapy with atomoxetine, this suggests that either the improvement was non-specific, the relapse was non-specific, or some combination of the two.

In this trial, the point of randomization was blinded to patients and their families. The results showed that 23 patients relapsed after entering Study Period III but prior to randomization actually occurring (that is, while still on atomoxetine). Loss of drug efficacy is one possible explanation for this result, another is that family anxiety about entering the double-blind phase of the study played a role in symptom return, or some combination of the two.

Finally, the study design in this trial was overly complex. There were multiple points of therapy changes and differing lengths of treatment as well as unbalanced randomizations and limited numbers of patients for many comparisons, all of which decreased the statistical power of the study to detect treatment effects.

Safety: Table HFBE.7 shows reporting frequencies of treatment-emergent adverse events that occurred in at least 5% of patients, exposed to atomoxetine. The only statistically significant differences between groups were for reports of vomiting and somnolence in the comparison of atomoxetine (V12 TMX) and methylphenidate (V12 MPH) in the initial open label phase of the study. Differences in reporting frequencies did not reach statistical significance in the comparisons between atomoxetine (V21/22 TMX) and placebo (V21/22 PBO). The comparison of EMs to PMs treated with atomoxetine is of interest, but hampered by the low number of PMs and the fact that the PMs were treated at lower doses. Although individual differences are seen, there is no pattern to suggest that the adverse event profiles in EMs and PMs differ. Anorexia (typically captured as “decreased appetite”) was commonly reported in the initial phase of therapy with atomoxetine (19%), but declined over time. There were no deaths and no serious adverse events attributable to atomoxetine. Discontinuations of atomoxetine therapy due to adverse events did not fall into a particular pattern.

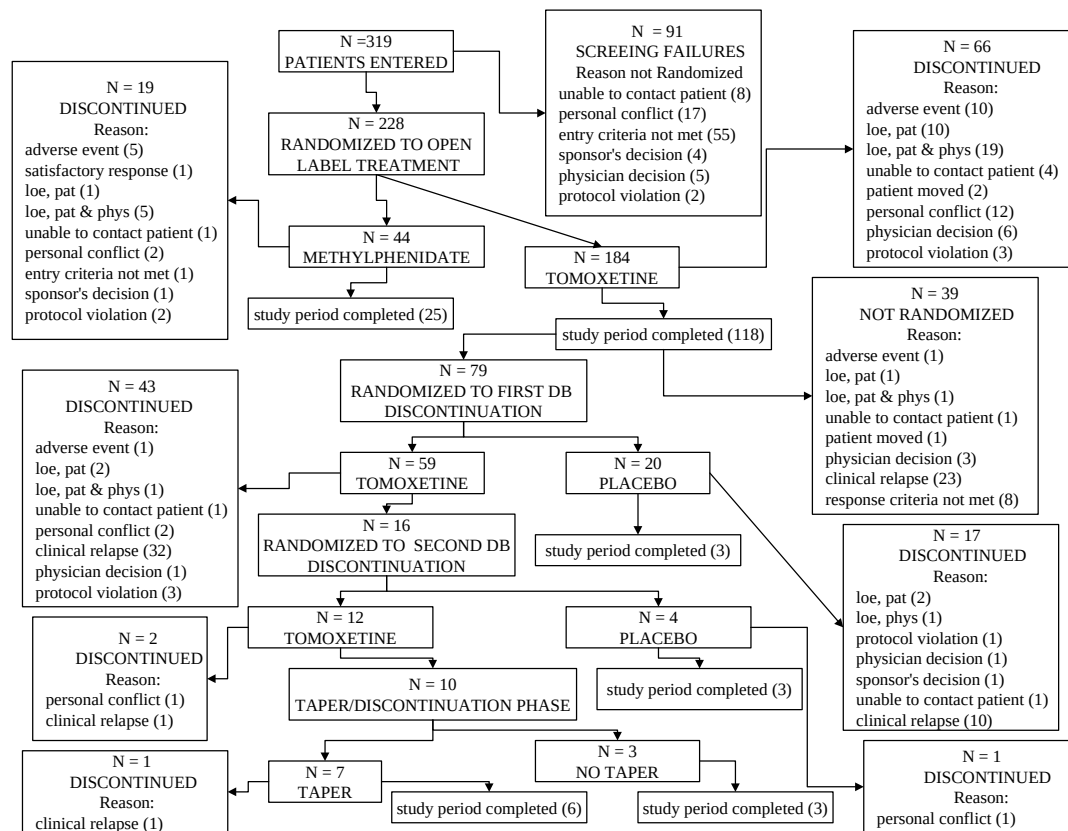
Table HFBE.8 shows mean baseline and change values for vital signs for the various treatment groups and comparisons. Similar to methylphenidate, treatment with atomoxetine tends to be associated with a mean increase in diastolic and systolic blood pressure, and in pulse (see change [C] values in the V12 TMX and V12 MPH column). During the initial 10 weeks of therapy, patients taking atomoxetine tended to lose an average of 0.6 kg, while those taking methylphenidate lost about 0.1 kg. Mean changes in vital sign values in the atomoxetine group were not statistically significantly different from those in the methylphenidate group.

When patients switched from atomoxetine to placebo (V21/22 PBO and V26 TMX-PBO) diastolic blood pressure tended to decrease, and these differences were statistically significant when compared to those who stayed on atomoxetine (V21/22 TMX and V26 TMX-TMX). Overall, diastolic blood pressure increased an average of 1.9 mm Hg for the pool of all atomoxetine-treated patients by the end of therapy (TMX-Entire Exposure-All).

In patients who switched from atomoxetine to placebo (V21/22 PBO), pulse tended to decrease by 3.6 beats per minute (bpm), while for those continuing on atomoxetine (V21/22 TMX) it tended to increase by 4.0 bpm, and this difference was statistically significant. Thus, pulse tended to increase in association with atomoxetine treatment over a period of about 9 months (Visit 2 to 21). However, this increase was not sustained, and pulse decreased an average of 4.9 bpm (V26 TMX-TMX), even as patients were maintained on atomoxetine for another 4 to 5 months. When all exposure to atomoxetine is considered (TMX-Entire Exposure -All), pulse increased by an average of 6.1 BPM.

Weight lost during the initial open-label phase of the study (V12 TMX - 0.6 kg) tended to be regained even as treatment with atomoxetine was continued. Relative to their previous treatment phase, those randomized to continue with atomoxetine (V21/22 TMX) gained an average of 0.9 kg, while those

randomized to placebo (V21/22 PBO) gained an average of 4.3 kg, a statistically significant difference. A similar pattern of weight gain was seen during the second potential therapy change, where patients continuing on atomoxetine gained an average of 1.7 kg (V26 TMX-TMX), which was significantly less than the 5.3 kg gained by those who switched to placebo (V26 TMX-PBO). By the end of therapy, patients taking atomoxetine lost an average of 0.1 kg (TMX-Entire Exposure -All).



Source Data: RMP.B4ZO.HFBECTR (RD1A200P), RMP.B4ZO.HFBECTR (RD1A1042), RMP.B4ZSHFBE.SASPGM (DSPDBE01)

Figure HFBE.1. Disposition of patients in Study B4Z-MC-HFBE.

Table HFBE.1. Selected Demographic and Baseline Characteristics
Open-Label Phase
All Randomized Patients
B4Z-MC-HFBE

Variable	Tomoxetine (N=184)	Methylphenidate (N=44)	Total (N=228)	p-value
Sex: No. (%)				
No. Patients	184	44	228	.036 ^a
Female	17 (9.2)	0	17 (7.5)	
Male	167 (90.8)	44 (100)	211 (92.5)	
Origin: No. (%)				
No. Patients	184	44	228	.274 ^a
African Descent	20 (10.9)	6 (13.6)	26 (11.4)	
Western Asian	2 (1.1)	0	2 (0.9)	
Caucasian	139 (75.5)	36 (81.8)	175 (76.8)	
Hispanic	17 (9.2)	0	17 (7.5)	
Other	6 (3.3)	2 (4.5)	8 (3.5)	
Age: yrs.				
No. Patients	184	44	228	.904 ^b
Mean	10.45	10.41	10.44	
Median	10.16	10.17	10.16	
Standard Dev.	2.15	2.12	2.14	
Minimum	7.01	7.01	7.01	
Maximum	15.82	14.77	15.82	
WISC IQ				
No. Patients	181	44	225	.308 ^b
Mean	103.92	106.55	104.43	
Median	101.00	104.50	101.00	
Standard Dev.	14.59	17.97	15.30	
Minimum	73.00	81.00	73.00	
Maximum	144.00	147.00	147.00	
Baseline ADHDRS- IV-Parent:Inv (Total)				
No. Patients	184	44	228	.320 ^b
Mean	39.24	37.77	38.95	
Median	39.50	37.00	39.00	
Standard Dev.	8.60	9.42	8.76	
Minimum	18.00	9.00	9.00	
Maximum	54.00	53.00	54.00	

(continued)

Table HFBE.1. Selected Demographic and Baseline Characteristics
Open-Label Phase
All Randomized Patients
B4Z-MC-HFBE (concluded)

Variable	Tomoxetine (N=184)	Methylphenidate (N=44)	Total (N=228)	p-value
Baseline CGI-ADHD-S				
No. Patients	184	44	228	.411 ^b
Mean	4.82	4.70	4.79	
Median	5.00	5.00	5.00	
Standard Dev.	0.79	0.85	0.80	
Minimum	3.00	2.00	2.00	
Maximum	7.00	6.00	7.00	

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CGI-ADHD-S = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity; WISC = Weschler Intelligence Scale for Children

^a Frequencies analyzed using a Chi-Square Test.

^b Means analyzed using a Type III Sums of Squares analysis of variance.

Source Data: RMP.B4ZO.HFBECTR(MDE1CD043);

RMP.B4ZSHFBE.SASPGM(BSEDBE01).

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Table HFBE.2. ADHDRS-IV-Parent:Inv Total and Subscale Scores and CGI-ADHD-S Mean Changes from Baseline to Endpoint, Open-Label Phase B4Z-MC-HFBE

Variable	n	Baseline		Endpoint		Change		Change p-value ^a
		Mean	SD	Mean	SD	Mean	SD	
ADHD Total Score								
Tomoxetine	178	39.43	8.51	19.99	13.86	-19.44	13.31	<.001
Methylphenidate	40	37.60	9.67	19.83	16.65	-17.78	14.69	<.001
p-value ^b = .484								
ADHD Hyperactivity / Impulsivity Subscale								
Tomoxetine	178	17.77	6.31	8.26	7.44	- 9.50	6.99	<.001
Methylphenidate	40	16.95	7.07	8.48	8.24	- 8.48	7.08	<.001
p-value ^b = .403								
ADHD Inattention Subscale								
Tomoxetine	178	21.66	4.23	11.72	7.65	- 9.94	7.73	<.001
Methylphenidate	40	20.65	4.77	11.35	9.18	- 9.30	8.89	<.001
p-value ^b = .647								
CGI-ADHD-S								
Tomoxetine	178	4.83	0.79	3.16	1.26	- 1.67	1.30	<.001
Methylphenidate	40	4.70	0.88	3.00	1.55	- 1.70	1.51	<.001
p-value ^b = .912								

Abbreviations: ADHD = Attention-Deficit/Hyperactivity Disorder; ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CGI-ADHD-S = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity

^a Within-treatment-group p-values are from Wilcoxon Signed-Rank test on mean change from baseline to endpoint (last-observation-carried-forward) scores.

^b Between-treatment-group p-values are from ANOVA (analysis of variance) models (with treatment effect) on mean change from baseline to endpoint (last-observation-carried-forward) scores.

Source Data: RMP.B4ZSHFBE.SASPGM(EFYDBE01)

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Table HFBE.3. **CGI-ADHD-I**
 Mean Endpoint Values
 Open-Label Phase
 B4Z-MC-HFBE

		Endpoint		
Variable	N	Mean	SD	p-value ^a
CGI-ADHD-I				
Tomoxetine	178	2.40	1.23	.193
Methylphenidate	40	2.13	1.20	

Abbreviations: CGI-ADHD-I = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Improvement

^a Between treatment group p-values are from ANOVA on mean endpoint (last-observation-carried-forward) scores.

Source Data: RMP.B4ZSHFBE.SASPGM (EFYDBE01)

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Table HFBE.4. Conners' Parent Rating Scale
Mean Changes from Baseline to Endpoint
Open-Label Phase
B4Z-MC-HFBE

Variable	n	Baseline		Endpoint		Change		Change p-value ^a
		Mean	SD	Mean	SD	Mean	SD	
ADHD Index								
Tomoxetine	178	27.37	6.30	16.01	9.93	-11.36	10.23	<.001
Methylphenidate	40	25.92	6.94	13.95	10.83	-11.97	10.64	<.001
p-value ^b = .737								
Cognitive								
Tomoxetine	149	13.94	3.73	7.77	5.21	- 6.17	5.33	<.001
Methylphenidate	39	13.44	4.06	7.74	6.17	- 5.69	6.03	<.001
p-value ^b = .629								
Hyperactive								
Tomoxetine	149	10.25	4.39	4.69	4.55	- 5.56	4.74	<.001
Methylphenidate	39	10.05	5.35	5.18	5.33	- 4.78	4.49	<.001
p-value ^b = .417								

Abbreviations: ADHD = Attention-Deficit/Hyperactivity Disorder; SD = standard deviation.

^a Within-treatment-group p-values are from Wilcoxon Signed-Rank test on mean change from baseline to endpoint (last-observation-carried-forward) scores.

^b Between-treatment-group p-values are from ANOVA models (with treatment effect) on mean change from baseline to endpoint (last-observation-carried-forward) scores.

Source Data: RMP.B4ZSHFBE.SASPGM(EFYDBE01)

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**Table HFBE.5. CGI-ADHD-S and CGI-ADHD-I
 Categorical Analysis
 Open-Label Phase
 B4Z-MC-HFBE**

Variable	Treatment	N	n	Percent ^a	p-value ^b
CGI-ADHD-S	Tomoxetine	178	64	36.0%	.286
	Methylphenidate	40	18	45.0%	
CGI-ADHD-I	Tomoxetine	178	115	64.6%	.962
	Methylphenidate	40	26	65.0%	

Abbreviations: CGI-ADHD-I = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Improvement; CGI-ADHD-S = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity

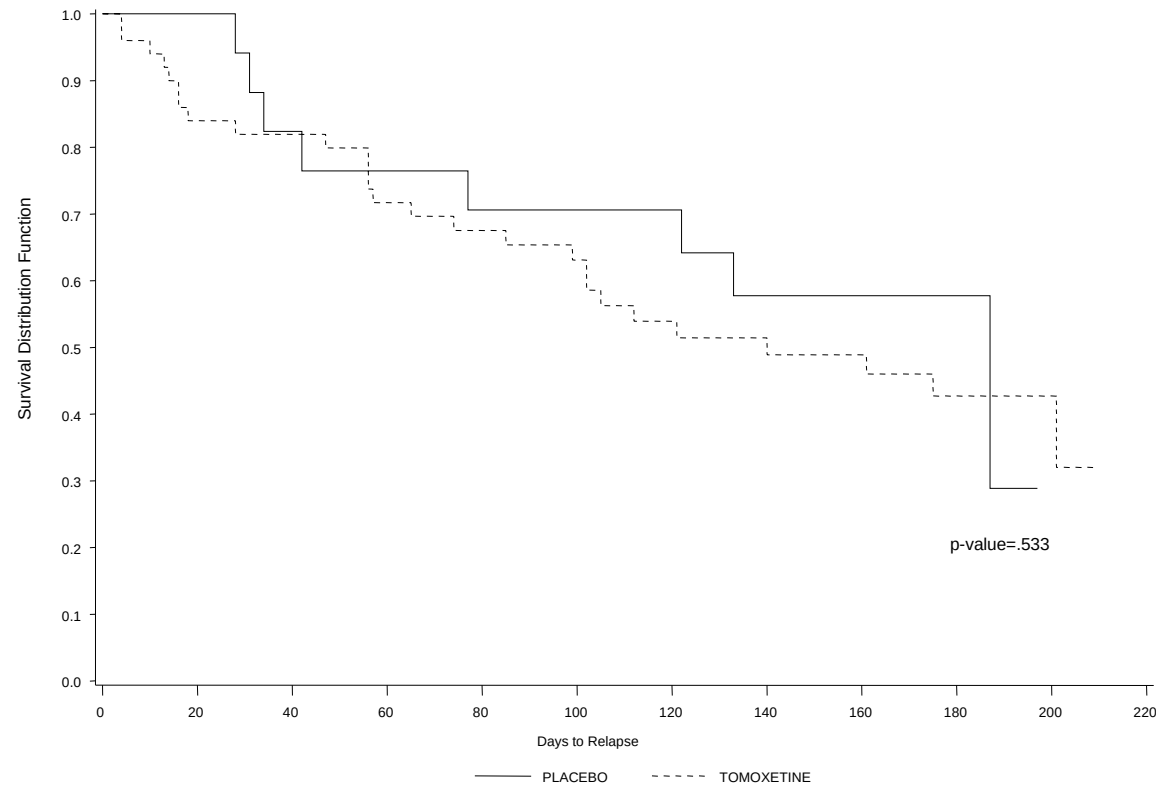
^a Percentage of patients with CGI-ADHD scores of 1 or 2 at endpoint (last-observation-carried-forward).

^b Frequencies analyzed using a Chi-Square Test

Source Data: RMP.B4ZSHFBE.SASPGM(EFYDBE01)

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Source Data: eagle:\programs_g\rmplb4zs\hfbe\final analysis\time to relapse.sas

Figure HFBE.2. Time to relapse by treatment for tomoxetine and placebo, B4Z-MC-HFBE.

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**Table HFBE.6. ADHDRS-IV-Parent: Inv Total Score and CGI-ADHD-S
 Mean Changes from Baseline to Endpoint
 Variable-Discontinuation Phase
 B4Z-MC-HFBE**

Variable	N	Baseline		Endpoint		Change		Change p-value ^a
		Mean	SD	Mean	SD	Mean	SD	
ADHD Total Score								
Tomoxetine	51	16.73	9.11	28.02	15.68	11.29	14.63	<.001
Placebo	19	11.84	8.16	26.32	15.23	14.47	15.51	.001
p-value ^b = .428								
CGI-ADHD-S								
Tomoxetine	51	2.92	0.98	3.90	1.63	0.98	1.39	<.001
Placebo	19	2.21	1.03	3.68	1.29	1.47	1.61	.001
p-value ^b = .211								

Abbreviations: ADHD = Attention-Deficit/Hyperactivity Disorder; ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored.

^a Within-treatment-group p-values are from Wilcoxon Signed-Rank test on mean change from baseline to endpoint (last-observation-carried-forward) scores.

^b Between-treatment-group p-values are from ANOVA models (with treatment effect) on mean change from baseline to endpoint (last-observation-carried-forward) scores.

Source Data: RMP.B4ZSHFBE.SASPGM(EFYDBE02)

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Table HFBE.7. Treatment-Emergent Adverse Events
Percent of Patients Reporting Event (≥5% in TMX-Entire Exposure-All)
B4Z-MC-HFBE

	V12 TMX	V12 MPH	V14/15 TMX	V21/22 TMX	V21/22 PBO	V26 TMX- TMX	V26 TMX- PBO	V28 TMX- TAP	V28 TMX- noTAP	TMX – Entire Exposure			V40 MPH
										All	EM	PM	
Event	184	40	109	54	19	12	4	7	3	184	174	10	24
At least 1	81.5	77.5	39.4	59.3	36.8	91.7	50.0	14.3	33.3	83.2	82.8	90.0	4.2
headache	31.0	32.5	3.7	9.3	10.5	16.7	0	0	0	36.4	37.4	20.0	0
abdominal pain	23.4	17.5	1.8	1.9	0	8.3	0	0	0	25.5	24.7	40.0	0
anorexia	19.0	15.0	0	1.9	0	0	0	0	0	19.6	19.0	30.0	0
rhinitis	17.9	20.0	2.8	13.0	0	25.0	25.0	0	0	23.9	21.8	60.0	0
nervousness	15.8	10.0	0.9	3.7	0	0	0	0	0	17.4	18.4	0	0
vomiting	12.0 ^a	0	3.7	3.7	5.3	0	0	0	0	15.2	14.4	30.0	0
fever	10.9	10.0	0.9	5.6	0	8.3	25.0	14.3	0	13.6	14.4	0	0
somnolence	10.9 ^a	0	0.9	1.9	0	0	0	0	0	12.0	12.6	0	0
nausea	10.3	5.0	2.8	5.6	0	0	0	0	0	13.6	13.8	10.0	0
insomnia	9.2	17.5	2.8	1.9	0	0	0	0	0	11.4	12.1	0	0
asthenia	7.6	2.5	0	3.7	5.3	0	0	0	0	8.2	8.6	0	0
diarrhea	7.1	2.5	0.9	0	0	8.3	25.0	0	0	7.6	8.0	0	0

(continued)

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Table HFBE.7. Treatment-Emergent Adverse Events
Percent of Patients Reporting Event (≥5% in TMX-Entire Exposure-All)
B4Z-MC-HFBE (continued)

	V12	V12	V14/15	V21/22	V21/22	V26	V26	V28	V28	TMX – Entire Exposure			V40
	TMX	MPH	TMX	TMX	PBO	TMX- TMX	TMX- PBO	TMX- TAP	TMX- no TAP	All	EM	PM	MPH
n	184	40	109	54	19	12	4	7	3	184	174	10	24
Event													
emotional lability	6.0	5.0	0	3.7	0	0	0	0	0	7.1	6.9	10.0	0
pharyngitis	6.0	7.5	2.8	3.7	0	8.3	25.0	0	0	9.2	9.8	0	0
tachycardia	6.0	5.0	0	1.9	0	0	0	0	0	6.5	6.9	0	0
accidental injury	5.4	12.5	1.8	0	5.3	0	0	0	0	6.5	6.9	0	0
cough increased	5.4	5.0	1.8	7.4	0	8.3	25.0	0	0	9.2	9.8	0	0
dyspepsia	5.4	5.0	0	0	0	16.7	0	0	0	6.5	5.2	30.0	0
pain	5.4	2.5	0	5.6	0	0	0	0	0	7.1	7.5	0	0
allergic reaction	4.9	0	0.9	1.9	5.3	0	0	0	0	6.0	6.3	0	0
flu syndrome	4.9	10.0	1.8	3.7	0	16.7	25.0	0	0	8.2	7.5	20.0	0
infection	4.3	7.5	0.9	0	0	8.3	0	0	0	5.4	5.2	10.0	0

(continued)

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Table HFBE.7. Treatment-Emergent Adverse Events
Percent of Patients Reporting Event (≥5% in TMX-Entire Exposure-All)
B4Z-MC-HFBE (concluded)

	V12 TMX	V12 MPH	V14/15 TMX	V21/22 TMX	V21/22 PBO	V26 TMX- TMX	V26 TMX- PBO	V28 TMX- TAP	V28 TMX- no TAP	TMX – Entire Exposure			V40 MPH
										All	EM	PM	
Event	n												
	184	40	109	54	19	12	4	7	3	184	174	10	24
sinusitis	3.8	2.5	2.8	1.9	0	0	0	0	0	6.0	6.3	0	0
rash	3.8	7.5	2.8	7.4	0.0	0.0	0.0	0.0	0.0	7.6	8.0	0.0	0.0
dizziness	3.3	0	1.8	3.7	0.0	8.3	0.0	0.0	0.0	6.0	6.3	0.0	0.0

Abbreviations: EM = extensive metabolizer; MPH = methylphenidate; PBO = placebo; PM = poor metabolizer; TAP = tapered; TMX = tomoxetine; TMX –Entire Exposure = captures patients' tomoxetine exposure throughout the study; V = visit; V12 =Study Period II (open-label phase); V14/15 = pre-variable discontinuation phase of Study Period III; V21/22 = 1st potential therapy change to 2nd potential therapy change of Study Period III; V26 = 2nd potential therapy change to end of Study Period III; V28 = Study Period IV; V40 = Discontinuation phase for methylphenidate patients (Study Period IIIM).

^a Statistically significantly different between groups (p.<.05).

Source Data: RMP.B4ZO.HFBECTR (AE2D102Z), RMP.B4ZO.HFBECTR (AE2D103P), RMP.B4ZO.HFBECTR (AE2D503T), RMP.B4ZO.HFBECTR (AE2D603V), RMP.B4ZO.HFBECTR (AE2D703X), RMP.B4ZO. HFBECTR (AE2D1057), RMP.B4ZO.HFBECTR (AE2D1055), RMP.B4ZO.HFBECTR (AE2D1056), RMP.B4ZO.HFBECTR (AE2D203\$)

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**Table HFBE.8. Mean Changes in Vital Signs
 Baseline to Endpoint
 All Study Phases
 B4Z-MC-HFBE**

Variable		V12	V12	V14/15	V21/22	V21/22	V26	V26	V28	V28	TMX – Entire Exposure			V40
		TMX	MPH	TMX	TMX	PBO	TMX- TMX	TMX -PBO	TMX- TAP	TMX -no TAP	All	EM	PM	MPH
Diastolic BP Average (mm Hg)	n	180	40	108	51	19	11	4	7	3	180	170	10	23
	B	65.4	63.5	68.6	67.6	69.2	68.3	76.8	68.5	72.2	65.4	65.5	63.9	65.4
	C	+2.6 ^a	+3.0 ^a	-1.3	+0.2 ^b	-5.3	+1.7 ^b	-8.4	-2.6	-2.2	+1.9 ^a	+1.9 ^a	+1.0	-0.1
Systolic BP Average (mm Hg)	n	180	40	108	51	19	11	4	7	3	180	170	10	23
	B	103.4	102.2	106.3	106.2	109.3	109.5	115.6	109.6	110.7	103.4	103.3	104.6	104.2
	C	+2.7 ^a	+3.4 ^a	-0.4	+1.0	-0.5	+0.9	-1.3	+0.1	-0.8	+2.8 ^a	+2.9 ^a	+0.7	+0.3
Pulse (BPM)	n	180	40	108	51	19	11	4	7	3	180	170	10	23
	B	82.5	80.4	89.2	88.8	89.7	93.9	93.8	95.9	78.3	82.5	82.7	78.0	88.5
	C	+6.1 ^a	+5.7 ^a	-0.9	+4.0 ^b	-3.6	-4.9	-8.8	-9.0 ^{a,b}	+4.3	+6.1 ^a	+6.1 ^a	+6.9	-3.3
Weight (kg)	n	179	40	108	51	19	11	4	7	3	179	169	10	23
	B	41.4	40.7	41.1	39.9	47.8	38.2	63.8	38.9	41.5	41.4	41.4	39.9	40.4
	C	-0.6 ^a	-0.1	+0.1	+0.9 ^{a,b}	+4.3 ^a	+1.7 ^{a,b}	+5.3	+1.6 ^a	+1.7	-0.1	-0.13	-0.21	+0.5 ^a

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**Table HFBE.8. Mean Changes in Vital Signs
 Baseline to Endpoint
 All Study Phases
 B4Z-MC-HFBE (concluded)**

Variable		V12 TMX	V12 MPH	V14/15 TMX	V21/22 TMX	V21/22 PBO	V26 TMX- TMX	V26 TMX -PBO	V28 TMX- TAP	V28 TMX -no TAP	TMX – Entire Exposure			V40 MPH
											All	EM	PM	
Height (cm)	n	145	35	29	50	17	11	4	7	3	149	141	8	12
	B	142.9	143.7	143.4	145.1	150.3	142.7	160.8	147.0	141.8	142.8	143.0	139.3	151.1
	C	+1.4 ^a	+0.7 ^a	+0.7 ^a	+1.3 ^a	+1.1	+3.8 ^a	+2.6	-0.9	+0.2	+2.1 ^a	+2.1 ^a	+3.2 ^a	+0.8 ^a
Temp (°C)	n	180	40	108	51	19	11	4	7	3	180	170	10	23
	B	36.7	36.7	36.7	36.6	36.6	36.8	36.5	36.6	36.4	36.7	36.7	36.6	36.7
	C	-0.01	-0.06	-0.08 ^a	+0.03	-0.14	-0.13	-0.17	+0.07	+0.47	-0.06	-0.06	0.00	+0.02

Abbreviations: B = baseline, C = change; EM = extensive metabolizer; MPH = methylphenidate; PBO = placebo; PM = poor metabolizer; TAP = tapered; TMX = tomoxetine; TMX –Entire Exposure = captures patients' tomoxetine exposure throughout the study; V = visit; V12 =Study Period II (open-label phase); V14/15 = pre-variable discontinuation phase of Study Period III; V21/22 = 1st potential therapy change to 2nd potential therapy change of Study Period III; V26 = 2nd potential therapy change to end of Study Period III; V28 = Study Period IV; V40 = Discontinuation phase for methylphenidate patients (Study Period IIIM);

^a Statistically significant change within group (p <.05).

^b Statistically significantly different between groups (p <.05).

Source Data: RMP.B4ZO.HFBECTR(M(VI3L302Z), RMP.B4ZO.HFBECTR(M(VI3L303P), RMP.B4ZO.HFBECTR(M(VI3L303T), RMP.B4ZO.HFBECTR(M(VI3L303V), RMP.B4ZO.HFBECTR(M(VI3L303X), RMP.B4ZO.HFBECTR(M(VI3L303\$), RMP.B4ZO.HFBECTR(M(VI3L3055), RMP.B4ZO.HFBECTR(M(VI3L3056), RMP.B4ZO.HFBECTR(M(VI3L3057)

Summary ID#2097

Clinical Study Summary: Study B4Z-MC-HFBB

Title of Study: Long-Term, Open-Label, Safety Study of Atomoxetine Hydrochloride in Patients, 6 Years and Older	
Investigators: This multicenter study included 36 principal investigators (PIs).	
Study Centers: This study was conducted at 24 study centers in the United States. (Ten sites had two PIs each and one site had three PIs; hence the seeming discrepancy of 36 PIs at 24 study centers.)	
Length of Study: Approximately 2 years, 7 months Date first patient enrolled: 15 September 1998 Date last patient completed: 30 April 2001	Phase of Development: 2
Objectives: The primary objective of Study B4Z-MC-HFBB (HFBB) was to assess long-term (6 months and longer) safety and tolerability of atomoxetine (formerly called tomoxetine) in patients aged 6 years and older (but less than 18 years of age at the time of entry into their prior study). The secondary objective of this study was to assess the long-term efficacy of patients treated with atomoxetine.	
Study Design: Study HFBB was an open-label investigation of the long-term safety and tolerability of atomoxetine (5 mg to 90 mg, usually given in divided doses) taken for up to 96 weeks. The maximum allowable dose for all patients was 1.8 mg/kg/day or 120 mg/day, whichever was less. Patients were aged 6 years and older (but aged less than 18 years at the time of entry into their prior study). There were 325 patients diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD) at entry into their previous study who participated in Study HFBB. Study HFBB comprised four study periods: • Study Period I, Evaluation and Medication Washout: A 0- to 16-day washout period (if necessary). • Study Period II, Acute, Open-Label, Safety Study of Atomoxetine: During this 2- to 8-week period, each patient's dose of atomoxetine was titrated and the dose schedule was adjusted to achieve efficacy. • Study Period III, Long-Term Safety Study of Atomoxetine Responders: During this approximately 70-week period, patients remained on the same dose and dosing schedule they were taking at their final visit in Study Period II. • Study Period IV, Discontinuation of Treatment with Atomoxetine: During this approximately 1-week (2- to 10-day interval) period, atomoxetine treatment could be tapered and/or discontinued over a period of up to 10 days.	
Number of Patients: Planned: The sample size for this study was determined by the number of eligible patients from previous atomoxetine studies who chose to enroll in this study. The sample size was not based on any statistical power calculations. Enrolled: 325 Completed: 66	
Diagnosis and Main Criteria for Inclusion: For the purposes of this study, patients met criteria for <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)</i> ADHD at the time of entry into Study HFBB, or at the time of entry into their previous atomoxetine study.	
Test Product, Dose, and Mode of Administration: Atomoxetine: 5 mg, 10 mg, and 20 mg capsules; 5 mg/day to 90 mg/day, given orally and usually given in divided doses twice daily.	
Duration of Treatment: Up to 96 weeks.	
Reference Therapy, Dose, and Mode of Administration: None.	

Variables:

Efficacy: The primary efficacy measures for this study were the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) and the Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity (CGI-ADHD-S).

Safety: Adverse events, vital signs, routine laboratory tests, pharmacokinetic blood sampling, and electrocardiogram. Adverse events were collected through open-ended discussion, followed by the Barkley Behavioral Adverse Event Questionnaire-Modified (BBAEQ-M).

Evaluation Methods:

Statistical Analysis of Efficacy: Descriptive statistics reported include sample size; mean baseline, endpoint, and change scores; standard deviations of baseline, endpoint, and change scores. Wilcoxon's signed-rank test provided the primary analysis on the changes from baseline for each of the primary efficacy measures.

Statistical Analysis of Safety: Descriptive statistics reported include sample size, mean, standard deviation, minimum, median, and maximum for baseline, endpoint, and change measures. T-tests and Wilcoxon's signed-rank test provided analyses on the changes in continuous safety measures.

Summary:

Patient Disposition: Twelve (12; 3.7%) of the 325 patients enrolled in Study HFBF discontinued due to an adverse event and 103 (31.7%) patients discontinued due to lack of efficacy or relapse.

Patient Demographics: Table HFBF.1 summarizes demographic and other patient characteristics. The population of patients treated with atomoxetine in this study is similar to those of other studies in that most were males (81.8%) and the mean age was 10 years.

Efficacy: As Table HFBF.2 illustrates, the ADHDRS-IV-Parent:Inv scores in this study demonstrated significant ($p < .001$) mean change from baseline for the Total score (-13.8) as well as for the scores on both the hyperactive/impulsive sub-scale (-7.3) and the inattentive sub-scale (-6.5). Table HFBF.3 presents the results of the CGI-ADHD-S which rates severity of illness on a seven point scale (1 = normal through 7 = among the most extremely ill patients). Consistent with the ADHDRS-IV-Parent:Inv, the CGI-ADHD-S scores showed a statistically significant mean decrease in severity ratings (-1.2; $p < .001$) falling from a baseline mean score of 4.3 to an endpoint mean score of 3.0.

Safety: There were no deaths in this study. In the course of this study, 12 of 325 patients (3.7%) discontinued due to an adverse event. One patient discontinued due to overdose associated with lightheadedness, and one patient discontinued due to being hospitalized for suicidal ideation. These two adverse events met regulatory criteria for "serious." In addition to the 12 patients who discontinued due to an adverse event, six were reported to have a serious event, but did not discontinue. Table HFBF.4 presents a summary of adverse events occurring in 5% or more of patients. Events did not increase over time.

In addition to adverse events collected through open-ended discussion, adverse events were solicited using the BBAEQ-M. Mean change scores (baseline to endpoint) for events found to be statistically significantly decreased were "difficulty falling asleep," "stares a lot (daydreams)," "talks less with others," "uninterested in others," "irritable (grouchy, fussy)," "anxious/nervous," "bites fingernails," "unusually happy/euphoric," and "talks too much/nonstop talking." For none of the 24 items on the BBAEQ-M was a statistically significant mean increase detected.

Laboratory evaluations revealed statistically significant mean increases from baseline for calcium, phosphorus, total protein, albumin, uric acid, creatinine, hemoglobin, sodium, potassium, chloride, and UA specific gravity. Statistically significant mean decreases from baseline were detected for AST/SGOT, creatine phosphokinase, and bilirubin (total).

Mean changes from baseline to endpoint, minimum, and maximum values were statistically significant for all vital sign measurements. Consistent with the pharmacology of atomoxetine, an increase in mean baseline to endpoint diastolic blood pressure (3.6 mm Hg; $p < .001$) and heart rate (3.9 bpm; $p < .001$) were

observed in this trial. In this study, an increase in mean baseline to endpoint systolic blood pressure (3.5 mm Hg; $p < .001$) was detected. In contrast to acute studies, where a mean weight decrease was found, a mean weight increase (2.6 kg; $p < .001$) from baseline to endpoint was observed in this long-term trial. Over the duration of this trial, mean change from baseline to endpoint height was 4.4 cm ($p < .001$). Table HFBF.5 shows the number and percent of patients meeting specified categorical changes in heart rate and weight at any time during the study.

Consistent with an increase in pulse, mean RR interval and QT interval were decreased (-0.033 and -9.690, respectively; $p < .001$ for both), but there was no statistically significant mean change in QRS intervals. QT intervals corrected by both the Bazett and Fridericia methods were decreased from baseline to endpoint (-1.919 [$p = .115$] and -4.825 [$p < .001$], respectively). Electrocardiogram data confirmed an increase in pulse, with a mean baseline to endpoint increase of 3.9 bpm ($p < .001$). Table HFBF.6 shows the number and percent of patients meeting specified categorical changes in ECG parameters at any time during the study. The large percentage of patients meeting categorical criteria for heart rate increases is consistent with mean baseline to endpoint changes discussed above.

Table HFBF.1. **Summary of Demographics and Other Patient Characteristics**
B4Z-MC-HFBF

Variable	ATOMOX (N=325)
Sex: No. (%)	
No. Patients	325
Female	59 (18.2)
Male	266 (81.8)
Origin: No. (%)	
No. Patients	325
African Descent	19 (5.8)
Western Asian	1 (0.3)
Caucasian	278 (85.5)
East/Southeast A	1 (0.3)
Hispanic	16 (4.9)
Other	10 (3.1)
Age: yrs.	
No. Patients	325
Mean	10.42
Median	10.32
Standard Dev.	1.80
Minimum	7.19
Maximum	17.10
Height: cm	
No. Patients	218
Mean	142.14
Median	141.00
Standard Dev.	12.02
Minimum	122.00
Maximum	194.50
Unspecified	107
Weight: kg	
No. Patients	323
Mean	39.35
Median	36.00
Standard Dev.	13.34
Minimum	23.70
Maximum	131.00
Unspecified	2
DSM-IV ADHD Subtype	
No. Patients	325
HYP/IMP	4 (1.2)
INATTV	62 (19.1)
MIXED	259 (79.7)
Fam Hist of ADHD Mother	
No. Patients	325
N	257 (79.6)
U	33 (10.2)
Y	33 (10.2)
Unspecified	2
Fam Hist of ADHD Father	
No. Patients	325
N	212 (65.6)
U	48 (14.9)
Y	63 (19.5)
Unspecified	2

(continued)

Table HFBF.1. **Summary of Demographics and Other Patient Characteristics**
B4Z-MC-HFBF (concluded)

Variable	ATOMOX (N=325)

Fam Hist of ADHD Grandparents	
No. Patients	325
N	256 (79.3)
U	47 (14.6)
Y	20 (6.2)
Unspecified	2
Fam Hist of ADHD Siblings	
No. Patients	325
N	193 (59.8)
N/A	23 (7.1)
U	26 (8.0)
Y	81 (25.1)
Unspecified	2
Prior Stimulant Exposure	
No. Patients	325
N	303 (93.2)
Y	22 (6.8)
DRD4 Allele	
No. Patients	325
Unspecified	325
Grade in School	
No. Patients	325
1	3 (0.9)
2	39 (12.0)
3	58 (17.9)
4	74 (22.8)
5	54 (16.7)
6	47 (14.5)
7	31 (9.6)
8	10 (3.1)
9	3 (0.9)
10	4 (1.2)
11	1 (0.3)
Unspecified	1

Population: Randomized patients who took at least 1 dose of study drug.

Initial Visit ONLY

Input data from RMP.SAS.B4ZM.MCHFBFSW

Output stored as RMP.B4Z0.HFBFCTRM.FINAL(DE10801L)

XDES0001

Atomoxetine hydrochloride
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Approved: 11 November 2004

**Table HFBF.2. Summary of Change From Baseline to Endpoint
 ADHDRS-IV-Parent:Inv Total Score B4Z-MC-HFBF**

Variable analyzed: ADHDRS-IV Parent/Inv Imputed Total (AD4PITLI)

No.	Therapy	n	Baseline			Endpoint			Change		
			Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	ATOMOX	321	32.548	34.000	13.984	18.725	18.000	11.329	-13.823	-13.000	14.230

p-Values

No.	Therapy	Within Group*1
1)	ATOMOX	<.001

(continued)

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Table HFBF.2. Summary of Change From Baseline to Endpoint
ADHDRS-IV-Parent:Inv Total Score B4Z-MC-HFBF (continued)

Variable analyzed: ADHDRS-IV Parent/Inv Imputed Hyp/Imp (AD4PIHII)

No.	Therapy	n	Baseline			Endpoint			Change		
			Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	ATOMOX	321	14.362	15.000	7.975	7.027	6.000	5.919	-7.335	-6.000	7.380

p-Values

No.	Therapy	Within Group*1
1)	ATOMOX	<.001

(continued)

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Table HFBF.2. Summary of Change From Baseline to Endpoint
ADHDRS-IV-Parent:Inv Total Score B4Z-MC-HFBF (concluded)

Variable analyzed: ADHDRS-IV Parent/Inv Imputed Inatten (AD4PIINI)

No.	Therapy	n	Baseline			Endpoint			Change		
			Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	ATOMOX	321	18.187	19.000	7.228	11.698	11.000	6.631	-6.489	-6.000	8.039

p-Values

No.	Therapy	Within Group*1
1)	ATOMOX	<.001

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.

Population: Randomized patients who took at least 1 dose of study drug.

Baseline: Visits 1-2, Endpoint: Visits 3-24

Input data from RMP.SAS.B4ZM.MCHFBFSW

Output stored as RMP.B4Z0.HFBFCTRM.FINAL(EF3LK01F)

XLAS0003

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Approved: 11 November 2004

**Table HFBF.3. Summary of Change From Baseline to Endpoint
 CGI-ADHD-S B4Z-MC-HFBF**

Variable analyzed: CGI ADHD Severity (CGIADS)

No.	Therapy	n	Baseline			Endpoint			Change		
			Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	ATOMOX	321	4.255	4.000	1.295	3.022	3.000	1.236	-1.234	-1.000	1.491

p-Values

No.	Therapy	Within Group*1
1)	ATOMOX	<.001

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.

Population: Randomized patients who took at least 1 dose of study drug.

Baseline: Visits 1-2, Endpoint: Visits 3-24

Input data from RMP.SAS.B4ZM.MCHFBSW

Output stored as RMP.B4Z0.HFBFCTRM.FINAL(EF3LJ01F)

XLAS0003

Table HFBF.4. **Summary of Treatment-Emergent Adverse Events**
Incidence $\geq$ 5% B4Z-MC-HFBF

Event Classification	ATOMOX (N=322)	
	n	(%)

PATIENTS WITH $\geq$ 1 TESS	303	(94.1)
PATIENTS WITH NO TESS	19	(5.9)
HEADACHE	171	(53.1)
RHINITIS	142	(44.1)
ABDOMINAL PAIN	115	(35.7)
PHARYNGITIS	100	(31.1)
VOMITING	87	(27.0)
COUGH INCREASED	75	(23.3)
FEVER	72	(22.4)
ACCIDENTAL INJURY	65	(20.2)
FLU SYNDROME	58	(18.0)
ANOREXIA	53	(16.5)
NAUSEA	50	(15.5)
NERVOUSNESS	45	(14.0)
INSOMNIA	42	(13.0)
PAIN	42	(13.0)
INFECTION	40	(12.4)
ALLERGIC REACTION	39	(12.1)
RASH	35	(10.9)
DIARRHEA	34	(10.6)
ASTHENIA	30	(9.3)
CONSTIPATION	30	(9.3)
SOMNOLENCE	29	(9.0)
DIZZINESS	28	(8.7)
SINUSITIS	27	(8.4)
DYSPEPSIA	25	(7.8)
EMOTIONAL LABILITY	23	(7.1)
CONTACT DERMATITIS	21	(6.5)
DRY MOUTH	20	(6.2)
ECCHYMOSIS	20	(6.2)
MYALGIA	20	(6.2)
GASTROENTERITIS	19	(5.9)
UNEXPECTED BENEFIT	18	(5.6)
WEIGHT LOSS	18	(5.6)
CHEST PAIN	16	(5.0)

Population: Randomized patients who took at least 1 dose of study drug.

Baseline: Visits 1-2, Endpoint: Visits 3-24

Input data from RMP.SAS.B4ZM.MCHFBFSW

Output stored as RMP.B4Z0.HFBFCTRM.FINAL(AE20501F)

XAES0002

Table HFBF.5. Summary of Vital Signs Changes
Categorical Analysis – Heart Rate and Weight
B4Z-MC-HFBF

Variable	N	Atomoxetine n	%
Heart Rate			
Maximum Value $\geq 110^a$	320	110	34.4
Change to Maximum of ≥ 25	320	98	30.6
Change of ≥ 25 to Max of $\geq 110^a$	320	67	20.9
Weight			
Percent of patients with $\geq 3.5\%$ decrease to minimum weight	321	131	40.8

^aTreatment emergent values of 110 only. Patients were not included if baseline heart rate was 110 or greater.

Source Data: Eagle:\programs._g\RMP\B4ZS\HFBF\Final Analysis\vitcat.sas

Table HFBF.6. Summary of ECG Changes
Categorical Analysis -Fredericia's QTc Interval and Heart
Rate B4Z-MC-HFBF

Variable	N	Atomoxetine n	%
QTc interval			
Maximum Value $\geq 435^a$	287	23	8.0
Change to Maximum of ≥ 30	297	48	16.2
Change of ≥ 30 to Max of $\geq 435^a$	287	15	5.2
Heart Rate			
Maximum Value $\geq 100^b$	277	141	50.9
Change to Maximum of ≥ 20	297	124	41.8
Change of ≥ 20 to Max of $\geq 100^b$	277	91	32.9

^aTreatment emergent values of 435 only. Patients were not included if baseline QTc score was 435 or greater.

^bTreatment emergent values of 100 only. Patients were not included if baseline heart rate was 100 or greater.

Source Data: Eagle:\programs._g\RMP\B4ZS\HFBF\Final Analysis\ecgcat.sas

Summary ID#2552

Clinical Study Summary: Study B4Z-MC-LYAF (9-Month Interim Report, Study Period I – Study Period III Visit Group I)

Relapse Prevention after 10-Week and 52-Week Treatment with Tomoxetine Hydrochloride in Children with Attention-Deficit/Hyperactivity Disorder

Date summary approved by Lilly: 09 July 2007

Brief Summary of Results

The primary objective of Study B4Z-MC-LYAF (LYAF) was to test the hypothesis that pediatric outpatients who achieved a satisfactory initial response to acute treatment (approximately 10 weeks, Study Period II) with tomoxetine hydrochloride (hereafter referred to as atomoxetine) and who continued treatment with atomoxetine, would have a superior response when compared with placebo-treated patients as measured by the number of days until relapse during a 9-month, randomized treatment period (Study Period III). There were no deaths in this study. A total of 33 patients discontinued from the study due to an adverse event (AE).

Results for Study Period II through Study Period III Visit Group I are as follows (Study Period I was a screening period only).

Primary Efficacy Results: Study Period III Visit Group I

- All qualified patients on atomoxetine were statistically significantly less likely to relapse than patients assigned to placebo as assessed by the Wilcoxon test ($p=.013$).
- All randomized patients on atomoxetine were statistically significantly less likely to relapse than patients assigned to placebo as assessed by the Wilcoxon test ($p<.001$).

Secondary Efficacy Results: Study Period II

- Statistically significant ($p<.001$) improvement from baseline to endpoint was observed for the following measures: Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Inventory (ADHDRS-IV-Parent:Inv) (Total score, T-score, and subscales), Conners Ratings Scales-Revised: Short Form (CPRS-R:S) and Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity (CGI-ADHD-S), Conners Teachers Rating Scale-Revised: Short Form (CTRS-R:S), Children's Depression Inventory (CDI), and Conners Depression Rating Scale-Revised (CDRS-R), Multidimensional Anxiety Scale for Children (MASC) Total, and 9 of the 13 components of the Child Health Questionnaire (CHQ). From baseline to endpoint, 247 (41%) patients showed marked improvement without any side effects, and 6 (1%) patients who had side effects that outweighed the perceived therapeutic effects.

Secondary Efficacy Results: Study Period III Visit Group I

- Statistically significant improvement was observed in atomoxetine- compared to placebo-treated patients for the following measures: ADHDRS-IV:Inv (Total score and subscales) and CGI-ADHD-S (Table 10), CPRS-R:S (Table 11), and 5 of the 13 components of the CHQ (Table 30). No statistically significant differences were observed for the remaining secondary efficacy measures (Tables 12 through 15).
- On 14 January 2005, the FDA requested Lilly to undertake a comprehensive reexamination of the coding of AEs and patient hospitalizations in Study LYAF. That post hoc analysis is presented separately in this document; it was not integrated into any of the analyses performed prior to unblinding.

Title of Study: Relapse Prevention after 10-Week and 52-Week Treatment with Tomoxetine Hydrochloride in Children with Attention-Deficit/Hyperactivity Disorder	
Investigator(s): This multicenter study included 33 principal investigators.	
Study Center(s): This study was conducted at 33 study centers in 14 countries.	
Length of Study: 2 years Date of first patient enrolled: 28 November 2000 Date of last patient completed, (Study Period III Visit Group I): 20 Nov 2002	Phase of Development: 2/3
Objectives: <u>Primary:</u> The primary objective of Study LYAF was to test the hypothesis that among pediatric outpatients who achieve a satisfactory initial response to acute (approximately 10 weeks) treatment with atomoxetine and who continued treatment with atomoxetine, would have a superior response when compared with placebo-treated patients as measured by the number of days until relapse. <u>Secondary:</u> Secondary objectives of the study were to assess: the long-term safety of atomoxetine; the effects of atomoxetine on measures of cognitive and neuropsychological function during long-term treatment; teacher evaluations of the effects of atomoxetine on symptoms associated with impaired performance at school; and health outcomes during long-term treatment with atomoxetine.	
Study Design: Double-blind, randomized, placebo-controlled, outpatient, relapse-prevention study. (See Figure 1 for illustration of study design.)	
Number of Patients: Planned: 500 patients Enrolled (and Entered Study Period II): 604 patients Randomized/Entered: 292 atomoxetine, 124 placebo Continuing: 160 atomoxetine, 45 placebo	
Diagnosis and Main Criteria for Inclusion: Patients 6 through 15 years of age (inclusive) at Visit 1, who met <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition™</i> (DSM-IV™) diagnostic criteria for Attention-Deficit/Hyperactivity Disorder (ADHD). Each patient's score from the ADHDRS-IV-Parent:Inv was at least 1.5 standard deviations above the age/gender norm for their diagnostic subtype.	
Test Product/Study Drug, Dose, and Mode of Administration: Atomoxetine: 0.5 mg/kg/day to 1.8 mg/kg/day, given twice daily; atomoxetine capsules, 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, and 40 mg.	
Reference Therapy/Comparator, Dose, and Mode of Administration: Placebo, given twice daily.	
Duration of Treatment: Maximum of 78 weeks of treatment.	
Measures: <u>Efficacy:</u> ADHDRS-IV-Parent:Inv Total score, Inattention subscale scores and Hyperactivity-Impulsivity subscale score; CGI-ADHD-S score; CPRS-R:S Oppositional score, Cognitive Problems/Inattention score, Hyperactivity score, and ADHD Index; CTRS-R:S Oppositional score, Cognitive Problems/Inattention score, Hyperactivity score, and ADHD Index; CDI total score; CDRS-R total score; MASC total score, Physical Symptom Scale, Harm Avoidance Scale, Social Anxiety Scale, and Separation/Panic Scale score; Stroop Color Word Test (Stroop) interference score; Dual Verbal Working Memory Task (DUAL-VWM) score; Trail Making Test (Trails A and Trails B) scores; Wechsler Intelligence Scale for Children® – Third Edition (WISC-III®) Working Memory Arithmetic and Digit Span test scores, Mazes subtest score, Block Design score, Picture Arrangement score, Similarities, and Vocabulary score; and the CGI-Efficacy Index (CGI-EI) score. <u>Safety:</u> Treatment-emergent adverse events (TEAEs), vital signs, height and weight, laboratory analytes, and electrocardiograms (ECGs). <u>Health Outcomes:</u> Physical and psychosocial well being using the CHQ.	

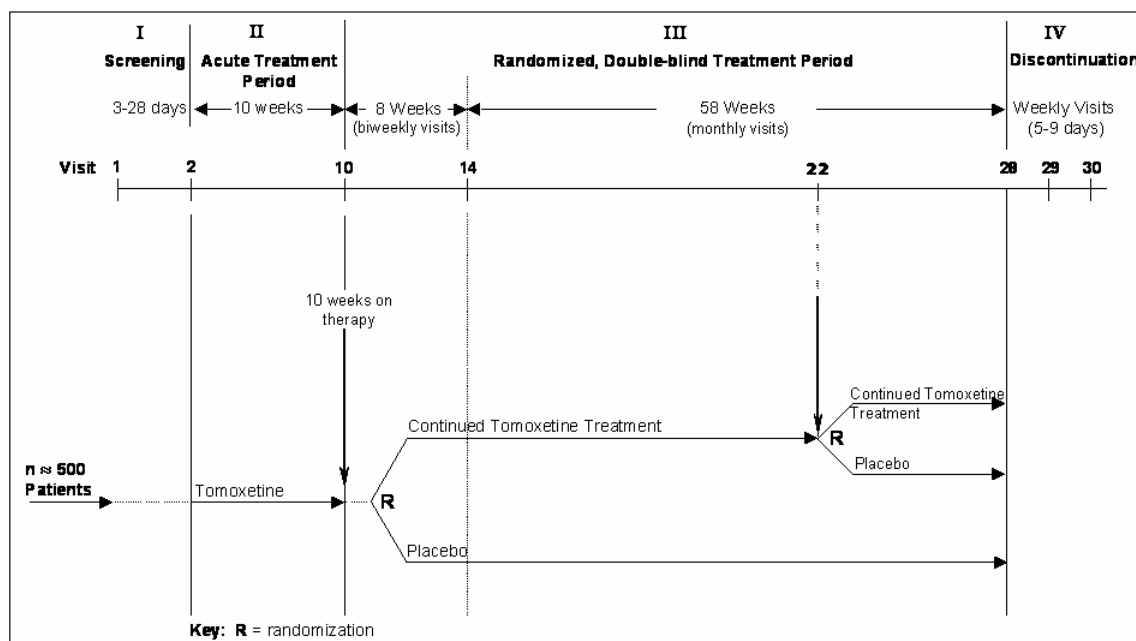
Evaluation Methods:

Statistical Methods: The primary efficacy variable was days-to-relapse and was analyzed using Kaplan-Meier analysis, a Wilcoxon test was used to assess the treatment difference in the distribution. Secondary analysis using primary efficacy variables included log-rank test and proportional hazard analyses.

Secondary Efficacy Measures and Safety Measures: Changes from baseline-to-endpoint values were computed for each secondary efficacy measures, vital sign, continuous laboratory measures, and continuous ECG parameters by treatment group. Last-observation-carried-forward (LOCF) approach was used to handle missing data. For continuous variables, treatment effect was assessed by analysis of variance (ANOVA) model. Within-treatment-group changes were assessed using Wilcoxon signed-rank test. Mean, standard deviation (SD) and 2-sided 95% confidence intervals were also calculated for selected measures. The percentage of patients meeting categorical criteria was also computed for abnormal labs, vital signs, and ECG intervals by treatment group. For categorical variables, Fisher's exact test was used to assess treatment effect.

Study Design

Figure 1 shows the study design for Study LYAF. This report summarizes results for Study Period II and Study Period III Visit Group I. Study Period I was used for screening. Study Period II comprised 10 weeks of acute, open-label treatment with atomoxetine 0.5 mg/kg titrated up to 1.2 mg/kg. Patients who tolerated doses up to 0.8 mg/kg/day and met response criteria at the end of Study Period II were randomized at Visit 11 into the double-blind, placebo-controlled Study Period III Visit Group I lasting about 9 months. Patients randomized to atomoxetine were rerandomized (at Visit 22, after approximately 1 year of blinded therapy), into Study Period III Visit Group II, to placebo or atomoxetine, which they continued at the same dose they received at the end of Study Period III Visit Group I. In Study Period IV, which consisted of 2 visits, patients who completed all Study Period III visits were randomized to a double-blind, placebo-controlled, dose-reduction period during which study drug was either abruptly discontinued, or tapered and discontinued.



Study Period III Visit Group I = Visits 11 to 22; Study Period III Visit Group II = Visits 22 to 28.

Figure 1. Illustration of study design for Study B4Z-MC-LYAF.

Results:

Patient Demographics

Table 1 summarizes demographic characteristics at baseline for all entered patients in this study. Of the 604 enrolled patients, 89.6% were male; 96.7% were Caucasian; 43.5% had no prior stimulant exposure, 45.5% had comorbid Oppositional Defiant Disorder (ODD), 1.5% had comorbid depression disorder, and 39 (6.5%) were determined to be poor cytochrome P450 2D6 (CYP2D6) metabolizer patients. The mean age was 10.2 years (range of 5.9 years to 15.7 years).

Table 2 summarizes demographic characteristics for randomized patients in Study Period III Visit Group I (visits from first randomization to the second randomization of Study Period III). Of the 416 randomized patients, 89.7% were male, and 97.4% were Caucasian. The mean age for patients randomized in Study Period III Visit Group I (at study entry) was 10.4 years (range of 6.0 years to 15.7 years). Other baseline characteristics included: 47.4% had no prior stimulant exposure, 43% had comorbid ODD, 1.9% had comorbid depression disorder, 73.1% met criteria for the combined ADHD subtype, with 22.4% classified as predominantly inattentive and 4.6% as predominantly hyperactive-impulsive, and 5.4% were determined to be poor metabolizers (PM) of cytochrome P450 2D6 (CYP2D6). Statistically significantly more poor CYP2D6 metabolizer patients were assigned to the atomoxetine treatment group (n=21, 7.3%) than to placebo (n=1, 0.8%) (p=.008). There were no statistically significant

differences between treatment groups in any of the other patient characteristics examined at baseline.

**Table 1. Summary of Patient Demographics and Other Characteristics
All Entered Patients**

Variable	ATOMOX (N=604)	NO DRUG (N=40)	Total (N=644)

Sex: No. (%)			
No. Patients	604	40	644
Female	63 (10.4)	6 (15.0)	69 (10.7)
Male	541 (89.6)	34 (85.0)	575 (89.3)
Origin: No. (%)			
No. Patients	604	40	644
African Descent	4 (0.7)	0	4 (0.6)
Western Asian	1 (0.2)	0	1 (0.2)
Caucasian	584 (96.7)	38 (95.0)	622 (96.6)
East/Southeast A	1 (0.2)	0	1 (0.2)
Hispanic	1 (0.2)	0	1 (0.2)
Other	13 (2.2)	2 (5.0)	15 (2.3)
Age: yrs.			
No. Patients	604	40	644
Mean	10.24	10.13	10.23
Median	10.21	10.31	10.22
Standard Dev.	2.25	2.61	2.28
Minimum	5.91	6.13	5.91
Maximum	15.72	15.37	15.72
Height: cm			
No. Patients	600	37	637
Mean	141.71	143.78	141.83
Median	141.00	145.00	141.00
Standard Dev.	14.44	16.73	14.58
Minimum	110.00	114.50	110.00
Maximum	191.50	187.00	191.50
Unspecified	4	3	7
Weight: kg			
No. Patients	604	39	643
Mean	37.31	38.48	37.38
Median	34.45	35.20	34.50
Standard Dev.	12.64	14.32	12.74
Minimum	19.20	17.00	17.00
Maximum	97.00	71.30	97.00
Unspecified	0	1	1

(continued)

**Table 1. Summary of Patient Demographics and Other Characteristics
All Entered Patients (Concluded)**

Variable	ATOMOX (N=604)	NO_DRUG (N=40)	Total (N=644)
ADHD Subtype			
No. Patients	604	40	644
HYP/IMP	30 (5.0)	2 (6.3)	32 (5.0)
INATTV	124 (20.5)	7 (21.9)	131 (20.6)
MIXED	450 (74.5)	23 (71.9)	473 (74.4)
Unspecified	0	8	8
Family History of ADHD-Mother			
No. Patients	604	40	644
N	454 (77.2)	30 (78.9)	484 (77.3)
U	62 (10.5)	4 (10.5)	66 (10.5)
Y	72 (12.2)	4 (10.5)	76 (12.1)
Unspecified	16	2	18
Family History of ADHD-Father			
No. Patients	604	40	644
N	398 (67.7)	25 (65.8)	423 (67.6)
U	86 (14.6)	8 (21.1)	94 (15.0)
Y	104 (17.7)	5 (13.2)	109 (17.4)
Unspecified	16	2	18
Family History of ADHD-Grandparents			
No. Patients	604	40	644
N	398 (67.7)	27 (71.1)	425 (67.9)
U	145 (24.7)	10 (26.3)	155 (24.8)
Y	45 (7.7)	1 (2.6)	46 (7.3)
Unspecified	16	2	18
Family History of ADHD-Siblings			
No. Patients	604	40	644
N	374 (63.6)	19 (50.0)	393 (62.8)
N/A	35 (6.0)	5 (13.2)	40 (6.4)
U	59 (10.0)	2 (5.3)	61 (9.7)
Y	120 (20.4)	12 (31.6)	132 (21.1)
Unspecified	16	2	18
Prior Stimulant Exposure			
No. Patients	604	40	644
N	263 (43.5)	21 (52.5)	284 (44.1)
Y	341 (56.5)	19 (47.5)	360 (55.9)
Grade Level			
No. Patients	604	40	644
0	18 (3.0)	2 (5.1)	20 (3.1)
1	51 (8.5)	6 (15.4)	57 (8.9)
10	3 (0.5)	1 (2.6)	4 (0.6)
2	78 (13.0)	2 (5.1)	80 (12.5)
3	91 (15.1)	4 (10.3)	95 (14.8)
4	94 (15.6)	5 (12.8)	99 (15.4)
5	87 (14.5)	9 (23.1)	96 (15.0)
6	73 (12.1)	5 (12.8)	78 (12.2)
7	55 (9.1)	3 (7.7)	58 (9.0)
8	35 (5.8)	2 (5.1)	37 (5.8)
9	17 (2.8)	0	17 (2.7)
Unspecified	2	1	3

Population: Enrolled patients who took at least 1 dose of study drug.
Visits 1-10

(continued)

**Table 2. Patient Demographics and Other Characteristics
Comparison of Treatment Groups at Baseline
All Randomized Patients in Double-Blind Continuation
Therapy Phase
Study Period III Visit Group I**

Variable	ATOMOX (N=292)	PLACEBO (N=124)	Total (N=416)	p-Value
Sex: No. (%)				
No. Patients	292	124	416	.774*
Female	31 (10.6)	12 (9.7)	43 (10.3)	
Male	261 (89.4)	112 (90.3)	373 (89.7)	
Origin: No. (%)				
No. Patients	292	124	416	.450*
African Descent	3 (1.0)	0	3 (0.7)	
Western Asian	1 (0.3)	0	1 (0.2)	
Caucasian	283 (96.9)	122 (98.4)	405 (97.4)	
East/Southeast A	1 (0.3)	0	1 (0.2)	
Hispanic	0	1 (0.8)	1 (0.2)	
Other	4 (1.4)	1 (0.8)	5 (1.2)	
Age: yrs.				
No. Patients	292	124	416	.124**
Mean	10.57	10.12	10.44	
Median	10.50	10.32	10.45	
Standard Dev.	2.28	2.28	2.28	
Minimum	6.02	6.01	6.01	
Maximum	15.69	15.72	15.72	
CYP2D6				
No. Patients	292	124	416	.008*
EXTN	268 (92.7)	120 (99.2)	388 (94.6)	
SLOW	21 (7.3)	1 (0.8)	22 (5.4)	
Unspecified	3	3	6	

Population: Randomized Patients in Study Period III
Visit Group I

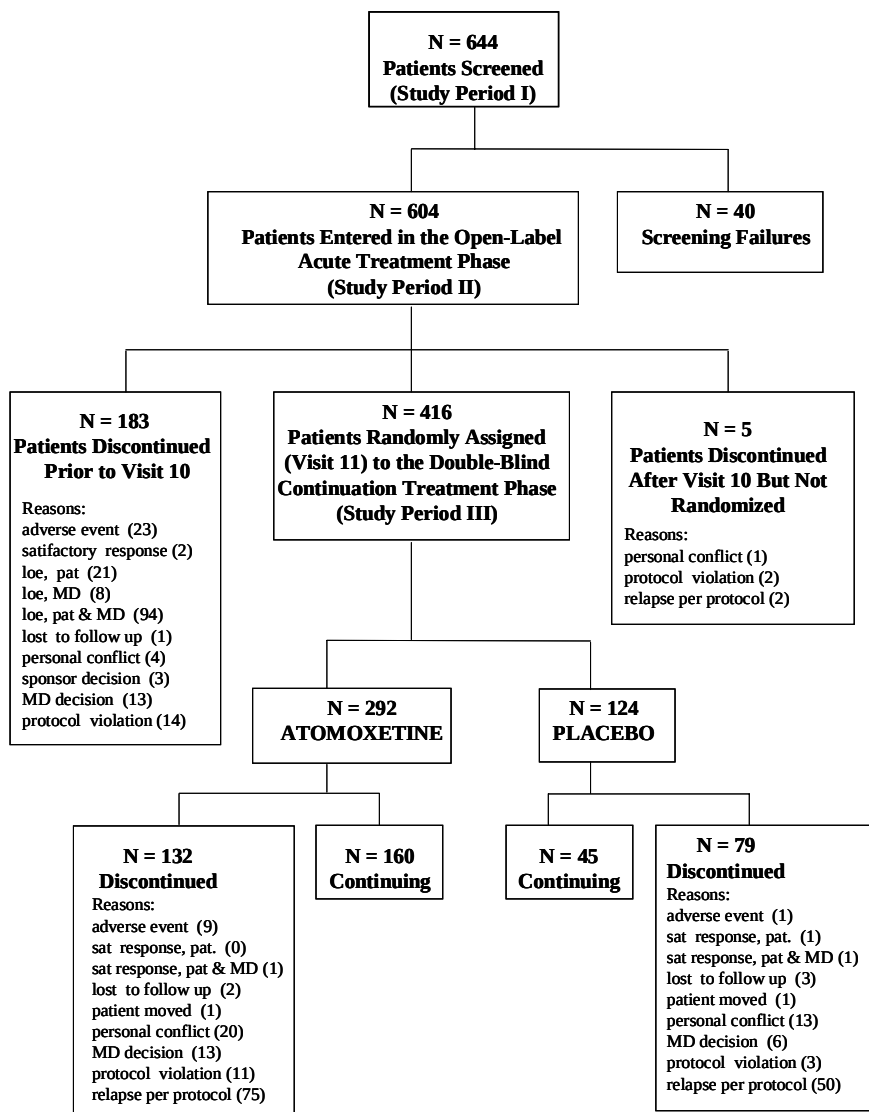
Initial Visit ONLY

* Frequencies are analyzed using a Chi-Square test.

** Means are analyzed using a Type III Sum of Squares analysis of variance
(ANOVA): PROC GLM model=investigator and treatment.

Patient Disposition

Figure 2 shows an overview of patient disposition for Study Period I, Study Period II, and Study Period III Visit Group I. Of the 644 patients who entered the study at Visit 1, 604 patients received open-label atomoxetine treatment at Visit 2. At Visit 11, 416 patients were randomized to the double-blind treatment phase (124 patients received placebo and 292 patients received atomoxetine). Two patients were randomized at Visit 11 and then discontinued by the site on the same day due to AEs (1 patient discontinued due to somnolence and the other discontinued due to relapse).



Abbreviations: loe=lack of efficacy; MD=physician decision; pat=patient decision; sat=satisfactory.

Figure 2. Overview of patient disposition.

Discontinuation of Patients

Discontinuation from Study Period II

Of the 604 enrolled patients, 421 (69.7%) completed Study Period II. The most common reason for discontinuation was due to the perception of a lack of efficacy, which was reported by 123 (20.4%) patients. Twenty-three (3.8%) patients discontinued from Study Period II due to AEs.

Discontinuation from Study Period III Visit Group I

A total of 5 patients were discontinued in Study Period III before they were randomized to a treatment group. Two patients discontinued due to protocol violation, another 2 discontinued due to relapse per-protocol definition and 1 discontinued due to personal conflict or other patient decision. Of the 416 patients who entered Study Period III, 205 (49.3%) completed Study Period III up to the second randomization. The most common reasons for patient discontinuation were relapse per-protocol definition (n=125, 30.0%), personal conflict or other patient decision (n=33, 7.9%), and physician decision (n=19, 4.6%). Ten (2.4%) patients discontinued from Study Period III Visit Group I due to AEs. Study discontinuations and study period completion rates were compared and relapse per-protocol definition as judged by investigator was statistically significant between groups because more placebo patients discontinued the study for this reason (p=.003). There was a statistically significant difference between the number of atomoxetine patients (160, 54.8%) and placebo patients (45, 36.3%) continuing in the study (p=.001).

Primary Efficacy Measures

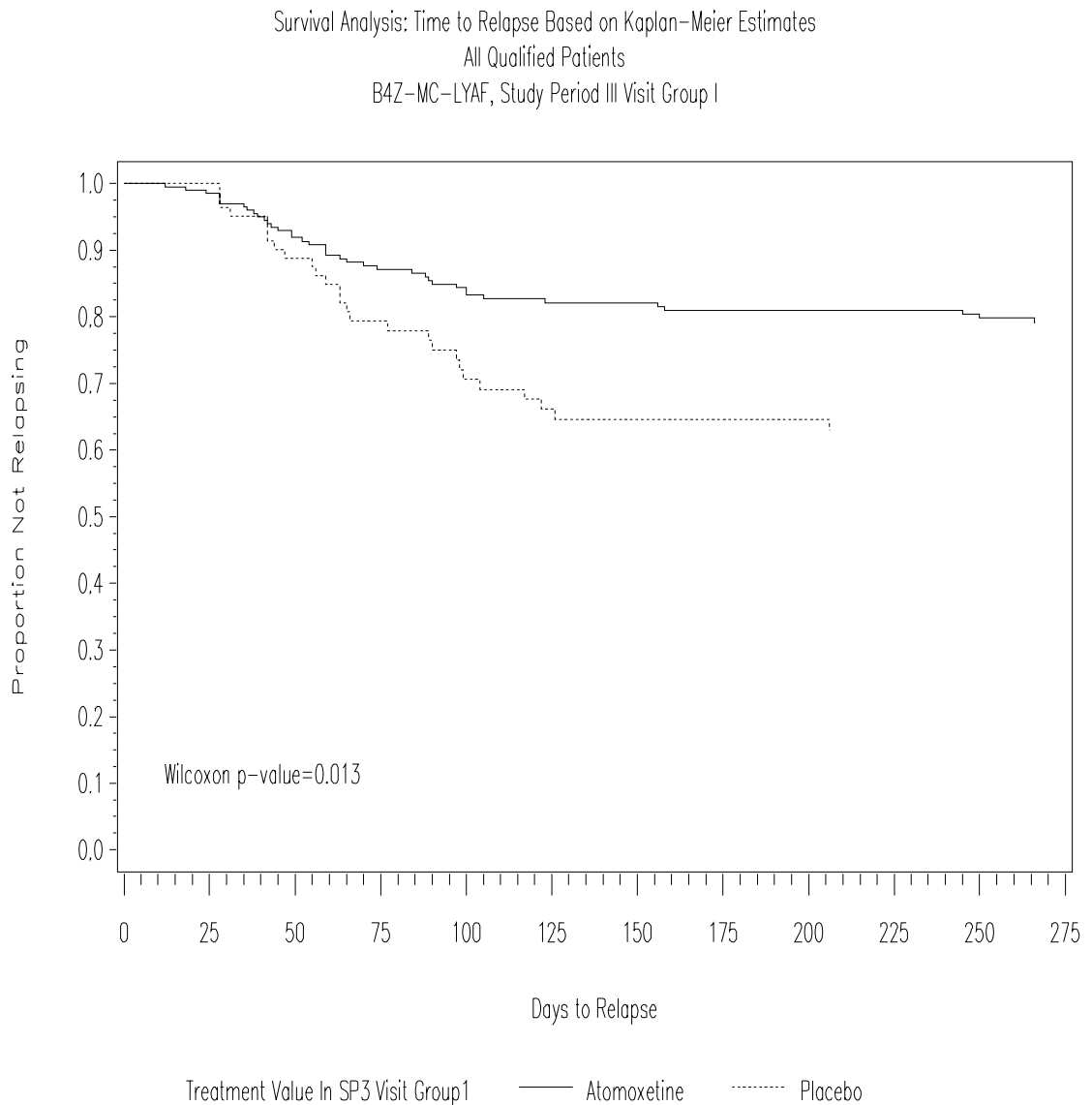
Results for All Qualified Patients

The primary efficacy analysis for this summary was a test of time to relapse following the first randomization during Study Period III and up to, but not including, the second randomization. Patients were considered qualified if they did not a) meet either the CGI-ADHD-S or ADHDRS-IV-Parent:Inv criteria for relapse at either the visit before or the visit of the first randomization, or b) have any increase in CGI-ADHD-S score to above their Study Period III baseline score at either the visit before or the visit of the first randomization.

The protocol defined relapse as follows: “During Study Period III, if at 2 consecutive visits a patient’s CGI-ADHD-S score increases by 2 or more categories from their score at the end of Study Period II (Visit 10) **and** their ADHDRS-IV-Parent:Inv total score returns to 90% or more of their Study Period II baseline score, the patient will be considered to be a relapser and must be discontinued from the study. If a patient shows evidence of a return of symptoms at one visit that meet the severity criteria described above, and because of worsening symptoms is unwilling to remain in the study, or does not return for a second visit, the patient will also be considered to have relapsed.”

Of the 416 patients randomized, 295 met the criteria to be included in the primary efficacy analysis. The Kaplan-Meier plot illustrated in Figure 3 shows the proportion of patients not relapsing on the vertical axis, and time (days on therapy) on the horizontal axis. There was a statistically significant treatment difference in the distribution as assessed by the Wilcoxon test ($p=.013$).

Table 3 summarizes the Kaplan-Meier estimates for the 2 treatment groups for all qualified patients. Patients on atomoxetine were less likely to relapse than patients assigned to placebo. Mean time to relapse in days (SD) was 227.65 (5.88) for patients on atomoxetine and 158.11 (7.92) for patients on placebo. The atomoxetine relapse rate was statistically significantly lower after 84 days postrandomization (the confidence interval of difference between atomoxetine and placebo was above zero) with an estimated relapse rate at end of Study Period III Visit Group I of 19% for the atomoxetine group and 36.9% for the placebo group.



Relapse Definition: Relapse per protocol definition within study period III visit group I

Abbreviation: SP3 = Study Period 3

Figure 3. Relapse rates among treatment groups based on protocol defined relapse for all qualified patients.

Atomoxetine

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Table 3. **Time to Relapse by Visit**
Based on Kaplan-Meier Estimates
Double-Blind Continuation Treatment Phase
Study Period III Visit Group I

Days to Relapse	----- Atomoxetine -----			----- Placebo -----			Difference between Atomoxetine and Placebo Diff (LCI , UCI)
	N at Risk	Prop. Nonrelapse	SE	N at Risk	Prop. Nonrelapse	SE	
0	209	1.000	0.000	85	1.000	0.000	0.000 (0.000 , 0.000)
14	203	0.995	0.005	84	1.000	0.000	-0.005 (-0.014 , 0.005)
28	193	0.970	0.012	80	0.964	0.020	0.006 (-0.040 , 0.053)
42	183	0.940	0.017	73	0.914	0.031	0.025 (-0.044 , 0.095)
56	171	0.908	0.021	64	0.862	0.039	0.047 (-0.039 , 0.133)
70	165	0.876	0.024	55	0.794	0.046	0.082 (-0.019 , 0.184)
84	160	0.866	0.025	53	0.780	0.047	0.086 (-0.019 , 0.191)
98	153	0.844	0.026	49	0.721	0.052	0.123 (0.008 , 0.237)
112	148	0.827	0.027	46	0.691	0.054	0.136 (0.017 , 0.255)
126	145	0.822	0.028	43	0.646	0.056	0.175 (0.052 , 0.299)
140	143	0.822	0.028	42	0.646	0.056	0.175 (0.052 , 0.299)
154	142	0.822	0.028	41	0.646	0.056	0.175 (0.052 , 0.299)
168	139	0.810	0.029	41	0.646	0.056	0.164 (0.040 , 0.288)
182	139	0.810	0.029	41	0.646	0.056	0.164 (0.040 , 0.288)
196	138	0.810	0.029	41	0.646	0.056	0.164 (0.040 , 0.288)
210	138	0.810	0.029	40	0.631	0.057	0.179 (0.054 , 0.305)
224	136	0.810	0.029	39	0.631	0.057	0.179 (0.054 , 0.305)
238	136	0.810	0.029	38	0.631	0.057	0.179 (0.054 , 0.305)

Log-Rank p-value = 0.008

TIME(DAYS) TO EVENT/CENSOR

MEAN(SE) Atomoxetine: 227.65(5.88)

Placebo: 158.11(7.92)

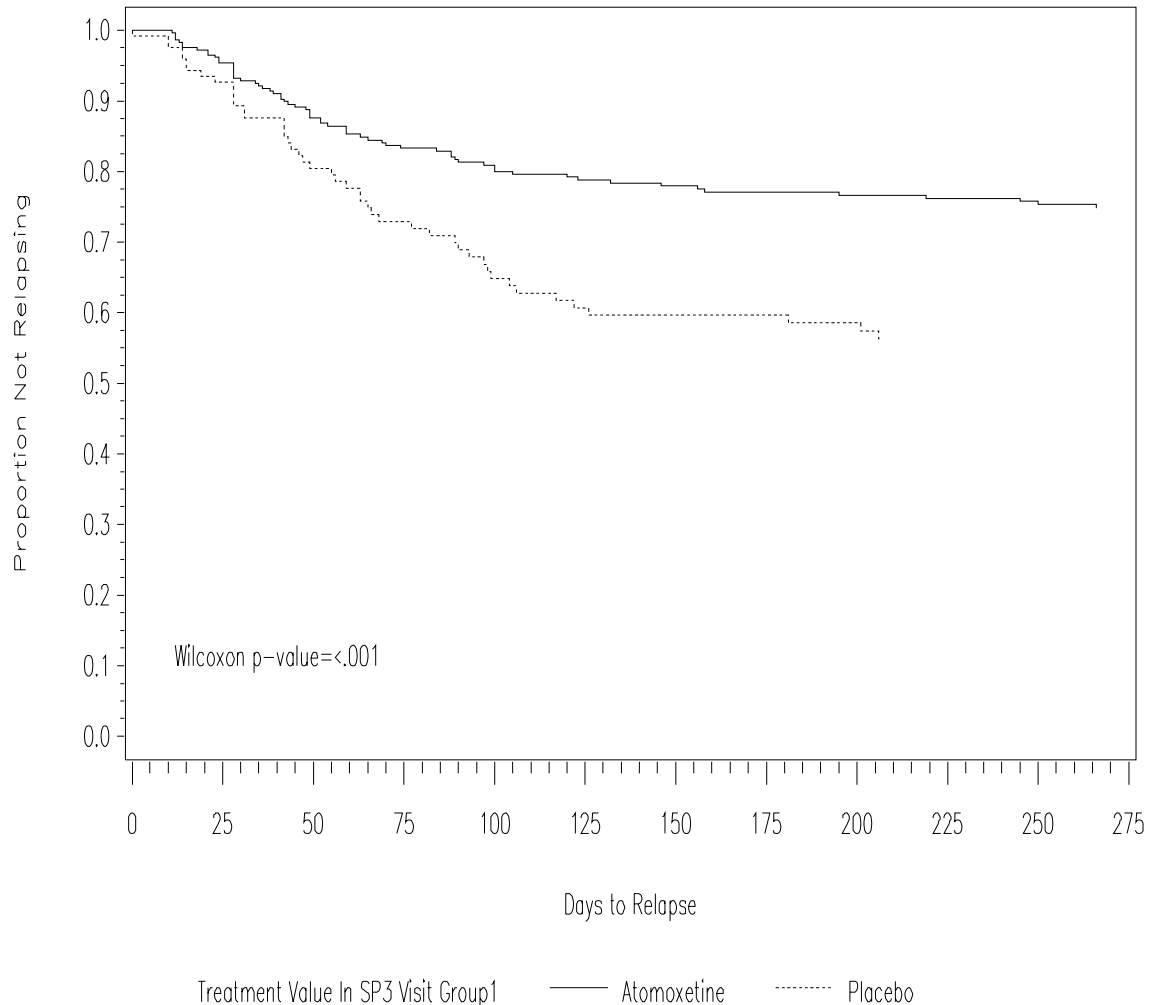
Abbreviations: SE=Standard Error

Relapse Definition: Relapse per protocol definition within study period III visit group I

Results for All Randomized Patients

Figure 4 contains the results from the survival analysis per-protocol definition for all randomized patients. The analysis using all randomized patients showed that patients on atomoxetine were statistically significantly less likely to relapse than patients assigned to placebo as assessed by the Wilcoxon test ($p < .001$). Table 4 shows that the estimated relapse rate at end of Study Period III Visit Group I was 23.8% for atomoxetine group and 43.7% for placebo group. Mean time to relapse in days (SD) for patients on atomoxetine was statistically significantly longer ($p < .001$) than for patients on placebo (atomoxetine 217.67 [5.52] days; placebo 146.09 [7.24] days).

Survival Analysis: Time to Relapse Based on Kaplan-Meier Estimates
All Randomized Patients
B4Z-MC-LYAF, Study Period III Visit Group I



Relapse Definition: Relapse per protocol definition within study period III visit group I

Figure 4. Relapse rates among treatment groups based on protocol defined relapse for all randomized patients.

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Table 4. **Time to Relapse**
Based on Kaplan-Meier Estimates
All Randomized Patients
Study Period III Visit Group I

Days to Relapse	----- Atomoxetine -----			----- Placebo -----			Difference between Atomoxetine and Placebo Diff (LCI , UCI)
	N at Risk	Prop. Nonrelapse	SE	N at Risk	Prop. Nonrelapse	SE	
0	292	1.000	0.000	122	0.992	0.008	0.008 (-0.008 , 0.024)
14	279	0.976	0.009	117	0.959	0.018	0.017 (-0.023 , 0.056)
28	256	0.932	0.015	107	0.893	0.028	0.040 (-0.023 , 0.102)
42	240	0.899	0.018	97	0.849	0.033	0.049 (-0.024 , 0.123)
56	220	0.864	0.021	84	0.786	0.038	0.079 (-0.007 , 0.164)
70	213	0.837	0.023	73	0.729	0.042	0.108 (0.014 , 0.201)
84	206	0.829	0.023	70	0.709	0.043	0.120 (0.024 , 0.215)
98	198	0.808	0.024	65	0.659	0.045	0.150 (0.049 , 0.251)
112	191	0.796	0.025	60	0.628	0.047	0.169 (0.065 , 0.272)
126	187	0.788	0.025	57	0.596	0.048	0.192 (0.086 , 0.297)
140	184	0.784	0.026	56	0.596	0.048	0.187 (0.081 , 0.293)
154	182	0.779	0.026	55	0.596	0.048	0.183 (0.077 , 0.289)
168	178	0.771	0.026	54	0.596	0.048	0.174 (0.068 , 0.281)
182	178	0.771	0.026	53	0.585	0.048	0.185 (0.078 , 0.293)
196	175	0.766	0.026	53	0.585	0.048	0.181 (0.074 , 0.289)
210	175	0.766	0.026	51	0.563	0.049	0.203 (0.094 , 0.312)
224	172	0.762	0.027	50	0.563	0.049	0.199 (0.090 , 0.308)
238	171	0.762	0.027	49	0.563	0.049	0.199 (0.090 , 0.308)

Log-Rank p-value = <.001

TIME(DAYS) TO EVENT/CENSOR

MEAN(SE) Atomoxetine: 217.67(5.52)

Placebo: 146.09(7.24)

Abbreviations: SE=Standard Error

Relapse Definition: Relapse per protocol definition within study period III visit group I

Secondary Efficacy Measures

Secondary objectives of the study were to assess the effects of atomoxetine on measures of cognitive and neuropsychological function during long-term treatment, teacher evaluations of the effects of atomoxetine on symptoms associated with impaired performance at school, and health outcomes during long-term treatment with atomoxetine. Results were as follows:

Study Period II

Analysis of the ADHDRS-IV-Parent:Inv Total score, T-score, and subscales demonstrated a reduction in mean total and subscale scores, and showed evidence of patients' improvements in both Inattention and Hyperactivity-Impulsivity symptom domains. At baseline, patients' mean Total ADHDRS-IV-Parent:Inv scores were approximately 3 SDs above the age and gender norms for United States (US) patients (mean T-score 80.3). However, at endpoint the ADHDRS-IV-Parent:Inv Total scores were found to have decreased by an average of 56.6%, with mean overall scores <1 standard deviation above the age and gender norms (mean T-scores at endpoint <60). Table 5 summarizes the LOCF change from baseline-to-endpoint analysis of the ADHDRS-IV-Parent:Inv Total score, T-score and subscales.

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**Table 5. ADHDRS-IV-Parent:Inv
Change from Baseline to Endpoint
Study Period II**

Variable / Treatment Group	N	-- Baseline --		-- Endpoint --		----- Change -----				Within Group p-value (a)
		Mean	SD	Mean	SD	Mean	SD	LCI	UCI	

Total										
Atomoxetine	603	41.32	7.85	17.95	11.86	-23.37	12.68	-24.38	-22.36	<.001
Total T-score										
Atomoxetine	603	80.29	9.22	56.73	12.28	-23.56	13.04	-24.60	-22.52	<.001
Hyp/Imp Subscale										
Atomoxetine	603	19.87	5.55	8.35	6.48	-11.52	7.04	-12.08	-10.95	<.001
Inatt. Subscale										
Atomoxetine	603	21.45	4.08	9.60	6.25	-11.85	6.73	-12.39	-11.31	<.001

Abbreviations: N = number of patients with a baseline and at least one postbaseline measurement;
SD=Standard Deviation; Change = endpoint-baseline; LCI=Lower bound of 95% CI; UCI=Upper bound of 95% CI;
Baseline visits: 1-2; Endpoint visits: 3-10.
(a) Within Groups p-values obtained from Wilcoxon's Signed-rank Test for mean change from baseline to endpoint.
Population: all enrolled patients with baseline and at least one postbaseline measurement.

Table 6 summarizes the Clinical Global Impresssion-Efficacy Index (CGI-EI) endpoint. There were 247 (41%) patients who showed marked improvement without any side effects, and 6 (1.0%) patients had side effects that outweighed the perceived therapeutic effect.

Table 7 summarizes the CPRS-R:S and CGI-ADHD-S change from baseline to endpoint, and Table 8 summarizes CTRS-R:S, CDI, and CDRS-R changes from baseline to endpoint; there was a statistically significant within-group improvement compared to study baseline ($p < .001$) in all the measures. Table 9 summarizes MASC changes from baseline to endpoint; there was a statistically significant within-group improvement compared to study baseline ($p < .001$) in the total scores and all subscale scores except for the MASC/Harm/Imputed subscore ($p = .200$).

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Table 6.
Summary of CGI-EI
Endpoint Only
All Enrolled Patients
Study Period II

Therapeutic Effect	-----Side Effects-----				Total
	None	Do Not Significantly Interfere with Patients functioning	Significantly Interferes with Patients functioning	Outweighs therapeutic effect	
MARKED IMPROVEMENT	247 (40.96%)	54 (8.96%)	9 (1.49%)	6 (1.00%)	316 (52.40%)
MODERATE IMPROVEMENT	109 (18.08%)	35 (5.80%)	2 (0.33%)	4 (0.66%)	150 (24.88%)
MINIMAL IMPROVEMENT	45 (7.46%)	14 (2.32%)	3 (0.50%)	5 (0.83%)	67 (11.11%)
UNCHANGED OR WORSE	44 (7.30%)	11 (1.82%)	10 (1.66%)	5 (0.83%)	70 (11.61%)
TOTAL	445 (73.80%)	114 (18.91%)	24 (3.98%)	20 (3.32%)	603 (100.00%)

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**Table 7. Summary of CPRS-R:S and CGI-ADHD-S
Change from Baseline to Endpoint
All Enrolled Patients
Study Period II**

Variable / Treatment Group	N	-- Baseline -- Mean SD	-- Endpoint -- Mean SD	----- Change ----- Mean SD LCI UCI	Within Group p-value (a)
CGI-ADHD-S Atomoxetine	603	5.21 0.79	2.56 1.33	-2.65 1.46 -2.77 -2.54	<.001
CPRS ADHD Index Atomoxetine	572	28.37 5.70	15.54 8.24	-12.83 8.91 -13.56 -12.10	<.001
CPRS Cognitive Subscale Atomoxetine	571	14.34 3.63	7.90 4.73	-6.44 5.13 -6.86 -6.02	<.001
CPRS Hyperactive Subscale Atomoxetine	577	12.00 4.36	5.63 4.41	-6.37 4.96 -6.78 -5.97	<.001
CPRS Oppositional Subscale Atomoxetine	578	10.98 4.29	7.15 4.71	-3.83 4.98 -4.23 -3.42	<.001
CPRS Total Score Atomoxetine	561	58.46 12.82	32.43 17.76	-26.03 19.06 -27.61 -24.46	<.001

Abbreviations: N = number of patients with a baseline and at least one postbaseline measurement;
SD=Standard Deviation; Change = endpoint-baseline; LCI=Lower bound of 95% CI; UCI=Upper bound of 95% CI;
Baseline visits: 1-2; Endpoint visits: 3-10.
(a) Within Groups p-values obtained from Wilcoxon's Signed-rank Test for mean change from baseline to endpoint.
Population: all enrolled patients with baseline and at least one postbaseline measurement.

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**Table 8. Summary of CTRS-R:S, CDI, and CDRS-R Change from Baseline to Endpoint
All Enrolled Patients on Atomoxetine
Study Period II**

Variable analyzed	n	Baseline			Endpoint			Change			p-values within group *1
		Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	
CTRS Total (CTRSTL)	438	47.050	49.000	17.075	35.834	35.000	17.604	-11.217	-10.000	15.749	<.001
CTRS Oppositional/Subscale (CTRSOPP)	467	5.653	5.000	4.442	4.259	3.000	4.068	-1.395	-1.000	3.848	<.001
CTRS Cognitive/Prob/Subscale (CTRSCOG)	453	7.108	7.000	4.044	6.106	6.000	3.803	-1.002	-1.000	2.986	<.001
CTRS Hyperactivity/Subscale (CTRSHYP)	462	12.034	13.000	5.761	8.648	8.500	5.520	-3.386	-3.000	4.915	<.001
CTRS/ADHD Index/Subscale (CTRSADI)	458	24.04	25.000	8.017	18.060	18.000	8.429	-5.980	-5.000	7.700	<.001
CDI TOTAL/Score/Imputed (CDITLI)	541	12.332	12.000	6.372	8.674	7.000	6.747	-3.659	-4.000	5.962	<.001
CDRS /T-Score (CDRSTOTT)	601	48.935	46.854	8.665	45.538	42.360	8.852	-3.397	-3.371	9.425	<.001
CDRS /Raw Total/Score (CDRSTOTR)	601	26.852	25.000	7.712	23.829	21.000	7.878	-3.023	-3.000	8.388	<.001

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.

Population: Enrolled patients who took at least 1 dose of study drug. Baseline: Visits 1-2, Endpoint: visits 3-10

Abbreviations: CDRS = Children's Depression Rating Scale-Revised; CDI = Children's Depression Inventory; CTRS = Conners' Teacher Rating Scale-Revised: Short Form; n = number of patients;
SD = standard deviation.

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Table 9. **Summary of MASC**
Change from Baseline to Endpoint
All Enrolled Patients on Atomoxetine
Study Period II

Variable analyzed	n	Baseline			Endpoint			Change			p-values within group *1
		Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	
MASC/Total Score/Imputed (MASCTLI)	538	42.865	41.500	16.536	35.184	33.000	16.142	-7.681	-7.000	14.459	<.001
MASC/Total/T-Score (MASCTLT)	531	50.909	49.960	10.444	45.974	44.906	10.365	-4.934	-4.422	9.244	<.001
MASC/Physical/Imputed (MASCPHYI)	540	10.869	10.000	5.991	8.204	7.000	5.839	-2.665	-3.000	5.993	<.001
MASC/Harm/Imputed (MASCHMRI)	540	14.123	14.000	4.877	13.883	14.000	5.387	-0.241	0.000	5.026	.200
MASC/Social/Imputed (MASC SOCI)	539	10.083	9.000	6.255	6.686	6.000	5.704	-3.397	-3.000	5.614	<.001
MASC/Separation/Imputed (MASCSEPI)	541	7.757	7.000	5.164	6.388	6.000	4.741	-1.369	-1.000	4.030	<.001
MASC/Anxiety/Imputed (MASCAIDI)	540	11.304	11.000	4.844	9.448	9.000	4.387	-1.856	-2.000	4.563	<.001

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.

Population: Enrolled patients who took at least 1 dose of study drug. Baseline: Visits 1-2, Endpoint: visits 3-10

Abbreviations: MASC = Multidimensional Anxiety Scale for Children; n = number of patients; SD = standard deviation.

Study Period III Visit Group I

Postrandomization, mean ADHDRS-IV-Parent:Inv Total scores and subscale scores increased statistically significantly more in the placebo treatment group than in the atomoxetine treatment group (p-values <.001 for all 3 variables) (Table 10).

Statistically significant differences between treatment groups were also noted in the CGI-ADHD-S score (p=.003) (Table 10).

**Table 10. ADHDRS-IV-Parent:Inv and CGI-ADHD-S
Change from Baseline to Endpoint
All Randomized Patients
Study Period III Visit Group I**

		-----Baseline-----		Change to -----Endpoint-----		p-Values	
Variables Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy
AD4PITLI	ATOMOX	290	15.774	9.589	6.799	13.642	<.001
	PLACEBO	123	15.712	9.957	12.270	14.305	
AD4PIHII	ATOMOX	290	7.204	5.519	3.103	7.049	<.001
	PLACEBO	123	7.106	5.453	5.861	7.414	
AD4PIINI	ATOMOX	290	8.570	5.068	3.696	7.389	<.001
	PLACEBO	123	8.607	5.369	6.410	7.714	
CGIADS	ATOMOX	290	2.266	1.016	0.862	1.594	.003
	PLACEBO	123	2.195	0.929	1.358	1.584	

Population: Randomized Patients in Study Period III
Visit Group I

Baseline: Visits 1-11, Endpoint: Visits 12-22

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDUC1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Note: Each investigator has at least one patient in each treatment group.

Abbrev.	Description
-----	-----
AD4PIHII	ADHDRS-IV Par/Inv Hyp/Imp Impute Score
AD4PIINI	ADHDRS-IV Par/Inv Inatt. Impute Score
AD4PITLI	ADHDRS-IV Par/Inv Imputation Total
CGIADS	CGI ADHD Severity

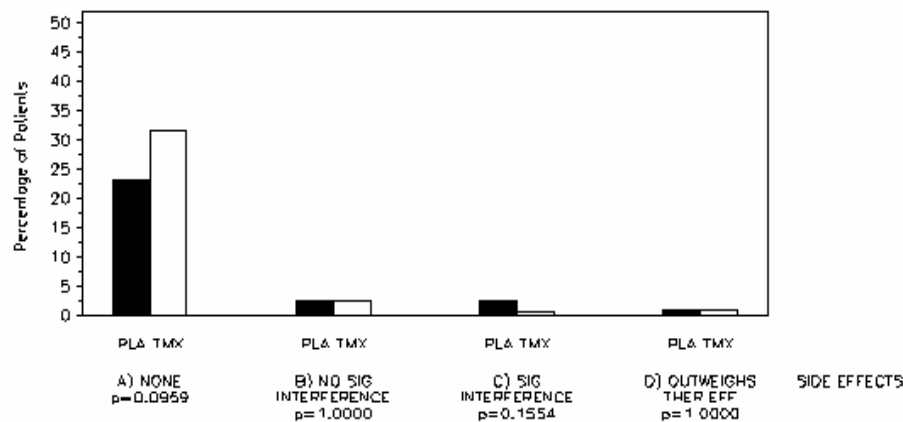
There was no statistically significant difference between the atomoxetine group and the placebo group as measured by patient frequency in each of the 16 categories of CGI-EI rating scales (Figure 5).

Table 11 summarizes the LOCF change from baseline to endpoint in the following subscales of the CPRS-R:S: ADHD Index, Cognitive Problems/Inattention, Hyperactivity, and Oppositional. The placebo treatment group showed statistically significantly greater worsening compared with the atomoxetine treatment group on each of the CPRS-R:S subscales.

PRODUCTION DATA – PRODUCTION MODE

Summary of CGI Efficacy Index
 All Randomized Patients – LAST NONMISSING CGI Observation
 BAZ-MC-LY&F, Study Period III Visit Group I

THERAPEUTIC EFFECT=A) MARKED IMPROVEMENT

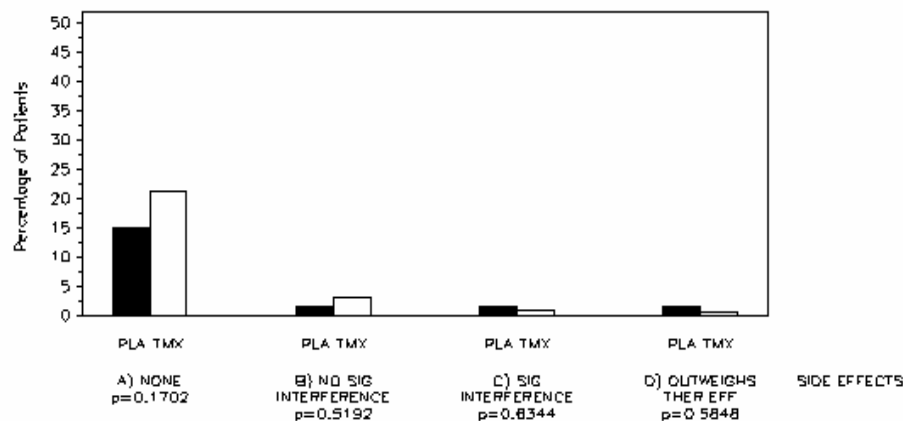


p = P-value from Fishers Exact Test comparing treatments

PRODUCTION DATA – PRODUCTION MODE

Summary of CGI Efficacy Index
 All Randomized Patients – LAST NONMISSING CGI Observation
 BAZ-MC-LY&F, Study Period III Visit Group I

THERAPEUTIC EFFECT=B) MODERATE IMPROVEMENT



p = P-value from Fishers Exact Test comparing treatments

(continued)

Figure 5. Frequency of CGI-EI endpoints, all randomized patients.

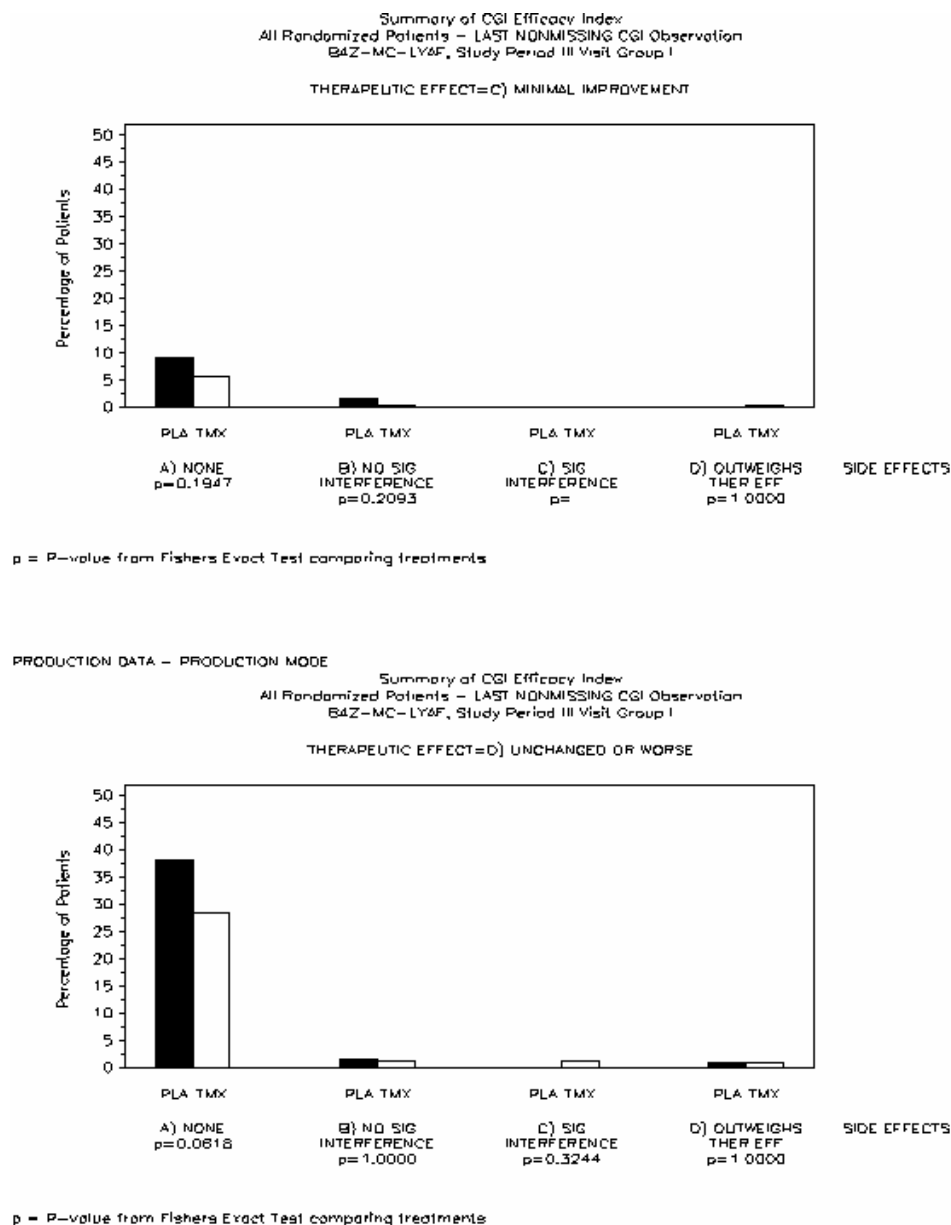


Figure 5. Frequency of CGI-EI endpoints, all randomized patients (Concluded).

Table 11. **CPRS-R:S**
Change from Baseline to Endpoint
Study Period III Visit Group I

		-----Baseline-----		Change to -----Endpoint-----		p-Values	
Variables	Therapy	n	Mean	SD	Mean	SD	Therapy
CPRSOPP	ATOMOX	291	6.505	4.413	1.594	4.916	.027
	PLACEBO	123	5.431	4.245	2.675	4.294	
CPRSCOG	ATOMOX	290	7.263	4.496	1.914	5.211	<.001
	PLACEBO	123	6.798	4.451	3.714	4.942	
CPRSHYP	ATOMOX	291	4.525	3.796	1.489	4.707	.001
	PLACEBO	123	4.618	4.152	3.127	4.870	
CPRSADI	ATOMOX	291	13.740	7.238	3.690	8.984	<.001
	PLACEBO	123	13.331	7.572	6.889	8.577	

Population: Randomized Patients in Study Period III
Visit Group I

Baseline: Visits 1-11, Endpoint: Visits 12-22

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDUCL - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for
error.

Note: Each investigator has at least one patient in each treatment group.

Abbrev.	Description
-----	-----
CPRSADI	CPRS ADHD Index Subscale Score
CPRSCOG	CPRS Cognitive Problems Subscale Score
CPRSHYP	CPRS Hyperactivity Subscale Score
CPRSOPP	CPRS Oppositional Subscale Score

Table 12 summarizes the LOCF change from baseline to endpoint in the following subscales of the CTRS-R:S: ADHD Index, Cognitive Problems/Inattention, Hyperactivity, and Oppositional. Both the atomoxetine and placebo treatment groups showed mean baseline-to-endpoint increases on each of the CTRS-R:S subscales. The differences between treatment groups were not statistically significant.

Table 12. **CTRS-R:S**
Change from Baseline to Endpoint
Study Period III Visit Group I

		-----Baseline-----		Change to -----Endpoint-----		p-Values	
Variables	Therapy	n	Mean	SD	Mean	SD	Therapy
CTRSOPP	ATOMOX	228	3.947	3.766	0.532	3.721	.903
	PLACEBO	94	3.537	3.644	0.519	3.777	
CTRSCOG	ATOMOX	225	6.188	3.892	0.260	2.876	.176
	PLACEBO	90	5.728	4.027	0.864	3.338	
CTRSHYP	ATOMOX	228	7.730	5.084	0.365	5.239	.079
	PLACEBO	93	8.095	5.533	1.443	4.575	
CTRSADI	ATOMOX	227	16.700	7.898	0.867	8.378	.426
	PLACEBO	92	17.220	8.026	1.686	7.879	

Population: Randomized Patients in Study Period III
Visit Group I

Baseline: Visits 1-11, Endpoint: Visits 12-22

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDUC2 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for
error.

Note: At least one investigator does not have patients in every treatment group.

Abbrev.	Description
-----	-----
CTRSADI	CTRS ADHD Index Subscale Score
CTRSCOG	CTRS Cognitive Problems Subscale Score
CTRSHYP	CTRS Hyperactivity Subscale Score
CTRSOPP	CTRS Oppositional Subscale Score

Table 13 summarizes the LOCF change from baseline to endpoint for the CDI, CDRS-R, and MASC. There were no statistically significant differences between treatment groups for any of these subscales.

Table 13. **CDI, CDRS-R, MASC**
Change from Baseline to Endpoint
Study Period III Visit Group I

		-----Baseline-----				Change to -----Endpoint-----		- p-Values -	
Variables	Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy	Model
MASCTLI		ATOMOX	263	34.143	16.002	-1.687	13.347	.621	RDUC2
		PLACEBO	106	34.414	14.316	-1.301	12.300		
MASCPHYI		ATOMOX	265	7.548	5.507	-0.097	4.958	.684	RDUC1
		PLACEBO	107	7.757	5.460	-0.028	4.967		
MASCHRM		ATOMOX	264	13.958	5.310	-0.928	4.502	.609	RDUC1
		PLACEBO	107	14.099	5.457	-0.651	4.712		
MASC SOCI		ATOMOX	265	6.615	5.833	0.036	4.864	.527	RDUC1
		PLACEBO	107	6.333	5.261	0.312	4.883		
MASCSEPI		ATOMOX	264	6.048	4.737	-0.645	3.754	.699	RDUC2
		PLACEBO	106	6.217	4.172	-0.915	3.633		
MASC AIDI		ATOMOX	265	9.311	4.313	-0.209	4.335	.958	RDUC1
		PLACEBO	107	9.271	3.913	-0.243	3.502		
CDITLI		ATOMOX	264	7.914	6.330	0.755	5.897	.484	RDUC1
		PLACEBO	107	7.847	6.417	1.114	5.633		
CDRSTOTR		ATOMOX	281	21.554	4.741	2.126	6.667	.684	RDUC1
		PLACEBO	116	21.657	5.442	2.317	5.400		
CDRSTOTT		ATOMOX	281	42.982	5.327	2.389	7.491	.684	RDUC1
		PLACEBO	116	43.098	6.114	2.604	6.067		

Population: Randomized Patients in Study Period III
Visit Group I

Baseline: Visits 1-11, Endpoint: Visits 12-22

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDUC1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Note: Each investigator has at least one patient in each treatment group.

RDUC2 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Note: At least one investigator does not have patients in every treatment group.

Abbrev.	Description
CDITLI	CDI Total Imputed Score
CDRSTOTR	CDRS Raw Total Score
CDRSTOTT	CDRS T-Score
MASCAIDI	MASC Anxiety Disorders Index Imputed
MASCHRM	MASC Harm Avoidance Score Imputed
MASC PHYI	MASC Physical Symptoms Score Imputed
MASCSEPI	MASC Separation Score Imputed
MASC SOCI	MASC Social Anxiety Score Imputed
MASCTLI	MASC Total Score Imputed

No statistically significant differences were found between the treatment groups (from baseline to endpoint) on any of the following scales: the WISC-III® (Table 14), DUAL-VWM, Stroop Color and Word Test (Stroop), Trail Making Part A (Trails A), and Trail Making Part B (Trails B) (Table 15). Stop Signal Test (SST) data were not analyzed due to SST program errors that generated incorrect data.

Table 14. **WISC**
Change from Baseline to Endpoint
Study Period III Visit Group I

Research Project Code: B4Z

				Change to					
		-----Baseline-----		-----Endpoint-----		- p-Values -			
Variables	Therapy	n	Mean	SD	Mean	SD	Therapy	Model	
WISCPARS	ATOMOX	173	10.948	3.536	0.873	3.332	.234	RDUC2	
	PLACEBO	63	10.889	3.606	1.540	2.994			
WISCSIMS	ATOMOX	175	10.977	3.173	0.011	2.215	.671	RDUC1	
	PLACEBO	63	10.476	3.306	0.095	2.115			
WISCVOCs	ATOMOX	175	11.080	3.366	-0.057	2.261	.536	RDUC1	
	PLACEBO	63	10.667	3.473	-0.222	2.768			
WISCBDSs	ATOMOX	173	10.358	3.125	0.486	2.309	.868	RDUC2	
	PLACEBO	63	10.683	3.325	0.587	2.728			
WISCRMSS	ATOMOX	179	10.117	4.096	0.514	3.972	.133	RDUC2	
	PLACEBO	77	10.312	3.510	-0.351	3.493			
WISCRMTs	ATOMOX	174	20.718	7.353	1.994	5.211	.089	RDUC2	
	PLACEBO	74	20.338	5.770	0.635	4.244			
WISCARS	ATOMOX	213	8.892	3.443	-0.235	2.442	.690	RDUC2	
	PLACEBO	82	8.732	3.147	0.037	2.627			
WISCDSS	ATOMOX	227	8.859	2.979	-0.048	2.604	.629	RDUC2	
	PLACEBO	87	8.759	2.654	0.080	2.407			

Population: Randomized Patients in Study Period III, Visit Group I

Baseline: Visits 1-11, Endpoint: Visits 12-22

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDUC1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for
error.

Note: Each investigator has at least one patient in each treatment group.

RDUC2 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for
error.

Note: At least one investigator does not have patients in every treatment group.

Legend of Variable Abbreviations:

Abbrev.	Description
-----	-----
WISCARS	WISC ARITHMETIC SCALED SCORE
WISCBDSs	WISC BLOCK DESIGN SCALED SCORE
WISCDSS	WISC DIGITAL SPAN SCALED SCORE
WISCPARS	WISC PIC ARRANGEMENT SCALED SCORE
WISCRMSS	WISC MAZES SCALED SCORE
WISCRMTs	WISC MAZES TOTAL SUBSET SCORE
WISCSIMS	WISC SIMILARITIES SCALED SCORE
WISCVOCs	WISC VOCABULARY SCALED SCORE

**Table 15. Cognitive Measurement –DUAL-VWM, Stroop, Trails A, and Trails B
Change from Baseline to Endpoint
Study Period III Visit Group I**

				Change to		-----Baseline-----		-----Endpoint-----		- p-Values -	
Variables	Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy	Model		
INTERFT		ATOMOX	243	51.700	8.605	0.471	9.205	.585	RDUC2		
		PLACEBO	95	51.291	7.381	-0.373	8.738				
DWMTCR		ATOMOX	252	4.397	2.878	0.663	3.160	.509	RDUC1		
		PLACEBO	105	3.943	2.499	0.790	3.435				
TMASCR		ATOMOX	259	25.988	13.386	-4.239	11.889	.450	RDUC2		
		PLACEBO	105	26.438	16.035	-5.467	12.369				
TMBSCORE		ATOMOX	248	59.157	36.403	-13.286	27.205	.848	RDUC2		
		PLACEBO	100	56.850	27.791	-15.750	23.533				

Population: Randomized Patients in Study Period III

Visit Group I

Baseline: Visits 1-11, Endpoint: Visits 12-22

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDUC1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Note: Each investigator has at least one patient in each treatment group.

RDUC2 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Note: At least one investigator does not have patients in every treatment group.

Legend of Variable Abbreviations:

Abbrev.	Description
DWMTCR	DUAL WORK MEMORY TOTAL SCORE
INTERFT	INTERFERENCE T-SCORE
TMASCR	TM TRAILS A TIME
TMBSCORE	TM TRAILS B TIME

Safety

Adverse Events (AEs)

There were no deaths in this study. A total of 33 patients discontinued from the study due to an AE (Study Period II, n=23; Study Period III Visit Group I, n=9 on atomoxetine, n=1 on placebo). Table 16 contains an overview of AEs reported during Study Period II and Study Period III Visit Group I. A total of 19 patients with at least 1 serious adverse

event (SAE) were reported during this study (Study Period II, n=12; Study Period III Visit Group I, n=7). Of these, 6 SAEs were classified as possibly related to study drug (on atomoxetine, fever and chills in 1 patient, acute confusional state and elevated liver function tests in a second, suspected Wolff-Parkinson-White syndrome in a third, and peripheral shut down in a fourth; on atomoxetine/placebo, diabetes mellitus in 1 patient). There was no statistically significant difference between treatment groups in the percentage of patients who discontinued due to an AE during Study Period III Visit Group I (atomoxetine 9 [3.1%]; placebo 1 [0.8%], p=.293).

**Table 16. Overview of Adverse Events
Study Period II and Study Period III Visit Group I**

Adverse Event ^a	Number (%) of Patients		
	SPII (Visits 2-11)	SPIII VGI (Visits 12-22)	
	ATX n=604	ATX n=292	PBO n=124
Deaths	0 (0)	0 (0)	0 (0)
Serious adverse events	12 (2.0%)	5 (1.7%)	2 (1.6%)
Discontinuations due to an adverse event	23 (3.8%)	9 (3.1%)	1 (0.8)
Treatment-emergent adverse events	485 (80.3%)	191 (65.6%)	66 (53.7%)

Abbreviations: ATX = atomoxetine; PBO = placebo; SPII = Study Period II; SPIII VGI = Study Period III Visit Group I.

^a Patients may be counted in more than 1 category.

Table 17 summarizes TEAEs in Study Period II by system organ class and the Medical Dictionary for Regulatory Activities Terminology (MedDRA®) Preferred Term in order of decreasing frequency. The summary includes TEAEs that occurred in ≥5% of drug-treated patients. The most common TEAEs were headache (n=120; 19.9%), appetite decreased not otherwise specified (NOS) (N=110; 18.2%) and unexpected therapeutic drug effect (N=75; 12.4%).

**Table 17. Summary of Treatment-Emergent Adverse Events (≥5%)
by System Organ Class Using MedDRA Preferred Terms
All Enrolled Patients
Study Period II**

Preferred Term	ATOMOX (N=604)	
	n	(%)
PATIENTS WITH ≥ 1 TESS	485	(80.3)
PATIENTS WITH NO TESS	119	(19.7)
Headache	120	(19.9)
Appetite decreased NOS	110	(18.2)
Unexpected therapeutic drug effect	75	(12.4)
Anorexia	64	(10.6)
Nausea	63	(10.4)
Nasopharyngitis	56	(9.3)
Irritability	52	(8.6)
Vomiting NOS	46	(7.6)
Abdominal pain upper	45	(7.5)
Abdominal pain NOS	44	(7.3)
Fatigue	43	(7.1)

Population: Enrolled patients who took at least 1 dose of study drug.

Baseline: Visits 1-2, Endpoint: visits 3-10

MEDDRA VERSION: 5.1

Table 18 summarizes TEAEs in Study Period III Visit Group I using MedDRA Preferred Terms for events that occurred in ≥5% of drug-treated patients. A statistically significantly greater percentage of patients on atomoxetine treatment reported at least 1 TEAE compared with patients on placebo (65.6% versus 53.7%; p=.027). Among individual AEs reported by 5% or greater of either group, a statistically significantly greater percentage of atomoxetine-treated patients compared with placebo-treated patients reported gastroenteritis NOS (7.9% versus 2.4%; p=.044) and pharyngitis (6.2% versus 1.6%; p=.048). Appetite increased NOS was reported at a statistically significantly greater rate in the placebo treatment group compared with the atomoxetine treatment group (6.5% versus 1.4%; p=.008).

**Table 18. Summary of Treatment-Emergent Adverse Events (≥5%)
Using MedDRA Preferred Terms
All Randomized Patients
Study Period III Visit Group I**

Preferred Term	ATOMOX (N=291) n (%)	PLACEBO (N=123) n (%)	Total (N=414) n (%)	p-Value*
PATIENTS WITH ≥ 1 TESS	191 (65.6)	66 (53.7)	257 (62.1)	.027
PATIENTS WITH NO TESS	100 (34.4)	57 (46.3)	157 (37.9)	.027
Headache	37 (12.7)	12 (9.8)	49 (11.8)	.506
Nasopharyngitis	31 (10.7)	15 (12.2)	46 (11.1)	.732
Influenza	20 (6.9)	8 (6.5)	28 (6.8)	1.00
Gastroenteritis NOS	23 (7.9)	3 (2.4)	26 (6.3)	.044
Vomiting NOS	22 (7.6)	4 (3.3)	26 (6.3)	.122
Irritability	17 (5.8)	4 (3.3)	21 (5.1)	.334
Pharyngitis	18 (6.2)	2 (1.6)	20 (4.8)	.048
Appetite increased NOS	4 (1.4)	8 (6.5)	12 (2.9)	.008

Population: Randomized Patients in Study Period III
Visit Group I

Baseline: Visit 11, Endpoint: Visits 12-22

* Frequencies are analyzed using a Fisher's Exact test.

MEDDRA VERSION: 5.1

Post Hoc Analysis of Adverse Events after Unblinding per FDA Request

On 14 January 2005, the FDA asked Lilly to undertake a comprehensive reexamination of the coding of AEs in Study LYAF. As part of the comprehensive reexamination, Lilly reviewed the investigator comments for all enrolled patients, comparing them to the AE data to ensure all AEs were accurately captured in the Lilly database. The following tables describe these additional data from comments fields that were not collected as AEs during the trial reporting.

The review identified 252 potentially missed AEs from comments in all visits in Study Period I, Study Period II, and Study Period III Visit Group I for all patients. Tables 19 to 22 summarize these additional events from the comments field section of the case report forms (CRFs). Adverse events (AEs) identified in this review were consistent with those already reported.

Table 19. **Frequency of Potentially Missed Adverse Events from**
Comments Field
Visits 1 to 2

Preferred Term	Atomoxetine
Aggression	2
Blood Pressure Increased	1
Electrocardiogram Abnormal	3
Eosinophil Count Increased	1
Fatigue	1
Headache	1
Increased Appetite	1
Irritability	1
Laboratory Test Abnormal	1
Nightmare	1
Pain in Extremity	2
Pharyngitis	1
Pyrexia	1
Suicidal Ideation	1
Syncope	1
Upper Respiratory Tract Infection	1
Urine Analysis Abnormal	1
Ventricular hypertrophy	1
Vomiting	1
Weight Increased	2

Table 20. Frequency of Potentially Missed Adverse Events from Comments Field Visits 3 to 11

Preferred Term	Atomoxetine
Haemoglobin Decreased	1
Lymphadenopathy	1
Myalgia	1
Weight Decreased	1
Abdominal Discomfort	1
Abdominal Pain	1
Abdominal Pain Upper	1
Abdominal pain	1
Accommodation Disorder	1
Affect Lability	1
Aggression	13
Alanine Amniotransferase Increased	1
Anemia	1
Anger	1
Anorexia	1
Anxiety	3
Apathy	1
Appendectomy	1
Appetite Disorder	1
Asthena	1
Asthenia	2
Attention Seeking Behavior	1
Behavior Abnormal	2
Behavior Disorder	1
Biopsy Stomach	1
Blood Pressure Increased	3
Blood Thyroid Stimulating Hormone Increased	2
Bradycardia	1
Decreased Appetite	6
Depressed Mood	4
Dermatitis	1
Diarrhea	1
Disturbance in Attention	1
Disturbance in Social Behavior	2
Dizziness	3
Dysphagia	1
Dysthymic Disorder	1
Electrocardiogram Abnormal	1
Electrocardiogram Change	2
Electrocardiogram abnormal	1
Enuresis	1
Fatigue	2

(continued)

Table 20. Frequency of Potentially Missed Adverse Events from Comments Field Visits 3 to 11 (Concluded)

Preferred Term	Atomoxetine
Feeling Sick	1
Feeling of Despair	1
Headache	5
Hypertension	1
Impulsive Behavior	3
Increased Appetite	1
Increased Tendency to bruise	1
Initial Insomnia	1
Insomnia	2
Irritability	5
Logorrhoea	1
Malaise	1
Mean Cell Volume Decreased	2
Middle Insomnia	1
Mood Swings	1
Morbid Thoughts	1
Nausea	4
Nervousness	2
Nightmares	1
Nocturnal Waking	1
Ovarian Enlargement	1
Ovarian Lesion Excision	1
Pharyngitis Streptococcal	1
Pharyngolaryngeal Pain	1
Psychomotor Retardation	1
Pyrexia	4
Rash	1
Restlessness	1
Sedation	1
Sinus Arrhythmia	1
Sinus Tachycardia	1
Sleep Disorder	1
Stress	2
Suicidal Ideation	2
Syncope	1
Tachycardia	2
Therapeutic Response Unexpected	6
Vasovagal Syncope	1
Viral Infection	2
Vomiting	2
Weight Decreased	16
Weight Increased	6

Table 21. Frequency of Potentially Missed Adverse Events from
Comments Field
Visits 12 to 22

Preferred Term	PLA	TMX
Abdominal pain	0	1
Abnormal behavior	1	0
Accidental Overdose	0	1
Affect Lability	0	1
Aggression	3	4
Agitation	1	0
Alanine Amniotransferase Increased	0	1
Anger	1	2
Behavior Abnormal	1	1
Behavior Disorder	0	1
Blood Bilirubin Increased	1	0
Blood Calcium Increased	1	0
Blood Pressure Increased	0	1
Blood Uric Acid Increased	0	1
Cough	0	1
Decreased Appetite	1	0
Depressed Mood	0	1
Disturbance In Attention	0	2
Dyspepsia	0	1
Dysphagia	0	1
Electrocardiogram Abnormal	0	1
Electrocardiogram QT Corrected Interval Prolonged	0	1
Electrocardiogram QRS complex Prolonged	0	1
Hiatus Hernia	0	1
Hostility	0	2
Hyperventilation	0	1
Impatience	0	1
Increased Appetite	1	0
Inguinal Hernia Repair	0	1
Irritability	0	3
Nervousness	0	1
Psychomotor Hyperactivity	0	2
Pyrexia	1	0
Restlessness	0	2
Sleep Disorder	0	1
Suicidal Ideation	1	0
Tachycardia	1	0
Therapeutic Response Unexpected	1	0
Tourette's Disorder	0	1
Weight Decreased	0	3
Weight Increased	3	2

Abbreviations: PLA = placebo; TMX = atomoxetine.

On January 14, 2005, the FDA asked Lilly to verify that study sites did not inappropriately hospitalize patients during the trial.

In response, Lilly has thoroughly investigated the hospitalizations that occurred at any site during Study LYAF that were not previously reported as SAEs in the LYAF clinical study reports. Through this process, 56 hospitalizations for 39 patients were identified during Study Period I, Study Period II, and Study Period III Visit Group I.

This study was conducted in Europe under several socialized medical systems. Hospitalizations are permitted in some countries and even encouraged for better observation of the patient by the investigator. Additionally, in some countries, hospitalizations also occur for a number of “social” reasons, such as the need for brief boarding of the patient, or to separate the patient from an undesirable family situation. Fifty-one of the 56 hospitalizations identified in the post hoc review are considered social hospitalizations. Five hospitalizations were categorized as SAEs.

Most hospitalizations occurred in a country where hospitalizations are more common as a result of their medical system. Two hospitalizations in another country were discovered through a CRF comment text search. Due to misinterpretation of the protocol, the 2 patients were in the hospital at time of enrollment and remained hospitalized during their course in the study.

Table 22 below presents a listing of the 5 hospitalizations for SAEs that occurred in Study LYAF Study Period I, Study Period II, and Study Period III Visit Group I.

Table 22. Listing of Hospitalizations for Serious Adverse Events Occurring in Study B4Z-MC-LYAF

Patient	Reason	Visit	Serious AE	Comments	Discontinue Visit & Reason
A	Medical condition, non-psychiatric	V3	Yes	Chronic Otitis Media (surgical procedure). Two days after starting study drug, the patient was hospitalized for chronic otitis media and underwent a bilateral myringotomy tube insertion.	DC at V10 due to LOE
B	ADHD	V21	Yes	ADHD and Conduct Disorder. While the patient was away from home, he developed severe conduct problems (date unknown). Patient was hospitalized 22 days after stopping study drug for conduct disorder and ADHD.	DC at V21 due to Protocol Violation (non-compliance)
C	ADHD	V18	Yes	Worsening of ADHD Symptoms. Patient was hospitalized to assess whether the mother's assessment of worsening of symptoms could be confirmed by clinical tests. Site could not confirm worsening of symptoms during observation. The event was considered a serious adverse event because the investigator did not state that it was for observation only.	DC at V18 due to personal conflict

(continued)

Table 22. Listing of Hospitalizations for Serious Adverse Events Occurring in Study B4Z-MC-LYAF (Concluded)

Site-Patient	Reason	Visit	Serious AE	Comments	Discontinue Visit & Reason
D	ADHD	V18	Yes	Learning and behavioral issues. ADHD progression. Patient was hospitalized for observation and status, and for learning and behavioral issues. It was concluded that there was progression of ADHD during the hospitalization. Study drug was discontinued.	DC at V18 due to relapse
E	Medical condition, non-psychiatric	V3	Yes	Viral Infection and High Fever. Eight days after starting study drug, the patient experienced a high fever and was hospitalized for a viral infection. Patient was withdrawn from the study.	DC at V3 due to physician decision

Abbreviations: ADHD = Attention-Deficit/Hyperactivity Disorder; AE = adverse event; CGI = Clinical Global Impressions; DC = discontinued; ECG = electrocardiogram; LOE = lack of efficacy; N/A = not applicable; V = visit.

As part of the comprehensive reexamination of the coding of AEs, for patients that discontinued, a Lilly physician who had not previously worked on Study LYAF reviewed the CRF comments fields from the last 2 visits and compared the comments to the AE data to verify that the “Reason for Discontinuation” was appropriately recorded. The review determined that a potentially inappropriate “Reason for Discontinuation” was listed for 11 of 439 discontinued patients in Study Period I, Study Period II and Study Period III Visit Group I. A summary of information on these 11 patients is presented in Table 23.

Table 23. Summary of Patients with a Potentially Inappropriate Reason for Discontinuation Recorded in Study LYAF

Patient #	Information/ Reason for Discontinuation Recorded by the Investigator	Sponsor Determined Reason for Discontinuation
F	Parents felt “too many side effects;” stopped drug early; Abdominal pain Nausea Anxiety Coded as Protocol violation (V8)	Adverse Event
G	2 nd episode of noncompliance in 6 months; patient felt “out of sorts” and “uncomfortable” on medication; better off meds Coded as Protocol Violation (V14)	Adverse Event
H	Mother discontinued treatment because of psychomotor agitation Coded as Personal Conflict or Patient Decision (V10)	Adverse Event
J	Increasing behavioral difficulties and worsening ADHD symptoms Coded as Personal Conflict or Patient Decision (V21)	Adverse Event
K	Stopped medication because of tachycardia Coded as Physician Decision (V7)	Adverse Event
L	D/C because of Clinically significant rise in TSH Coded as Physician Decision (V10)	Adverse Event
M	Withdrawn because of exacerbation of sinusitis; coughing at night when Seretide inhaler had to be stopped Coded as Physician Decision (V3)	Adverse Event
N	Increasing behavior problems, worsening oppositional behavior; depression Physician Decision (V22)	Adverse Event
P	Withdrawn due to lack of response and worsening oppositional and aggressive behavior while on medication Coded as Physician Decision (V7)	Adverse Event
Q	Discontinued because of diabetes and start of hospitalization Coded as Physician Decision (V12)	Adverse Event
R	Increased irritability (reported as excitability) Coded as Lack of Efficacy, Patient Perception (V7)	Adverse Event

Abbreviations: ADHD = Attention-Deficit/Hyperactivity Disorder; D/C = discontinued; TSH = thyroid-stimulating hormone; V = visit.

Clinical Laboratory

Mean change from baseline to endpoint in Study Period II was computed for each analyte for each patient who received at least 1 dose of study drug and who had a baseline and at least 1 postbaseline measurement. No clinically significant changes were observed for

any analyte from baseline to endpoint for Study Period II. Analytes that were found to be outside of the normal range in >5% of Study Period II patients included: hematocrit (below normal range, 24 [5.1%] patients), mean cell volume (below normal, 49 [11.1%]), platelet count (above normal, 30 [6.4%]), albumin (above normal, 35 [6.9%]), and cholesterol (above normal, 34 [7.1%]).

In Study Period III Visit Group I, there was a statistically significant treatment difference between atomoxetine and placebo for the frequency of: hematocrit above normal range (atomoxetine 0.4%, placebo 5.7%, $p=.003$), hemoglobin below normal (atomoxetine 1.2%, placebo 5.7%, $p=.021$), calcium above normal (atomoxetine 5.7%, placebo 12.4%, $p=.042$), inorganic phosphorous above normal (atomoxetine 0.8%, placebo 6.6%, $p=.003$), uric acid above normal (atomoxetine 0.7%, placebo 5.4%, $p=.009$), and cholesterol above normal (atomoxetine 8.6% versus placebo 2.3%; $p=.047$).

Table 24 summarizes the mean change by treatment group during Study Period III Visit Group I. Statistically significant ($p<.05$) treatment differences in mean change were observed for creatine phosphokinase, alkaline phosphatase, chloride, total protein, uric acid, and bicarbonate.

Table 25 shows the percentage of Study Period III Visit Group I patients whose laboratory values were normal at the baseline, but were found to be above or below the normal range at anytime after randomization.

Table 24. Summary of Laboratory Data
Mean Change from Baseline to Endpoint by Analyte
Study Period III Visit Group I

Lab Test	Lab Unit	Therapy	n	Change to				p-Values
				-----Baseline-----		-----Endpoint-----		
				Mean	SD	Mean	SD	Therapy
HCT	l	ATOMOX	267	0.384	0.025	0.005	0.025	.293
		PLACEBO	109	0.385	0.026	0.003	0.028	
HGB	mmL/L-Fe	ATOMOX	268	8.417	0.571	-0.021	0.427	.208
		PLACEBO	109	8.460	0.607	-0.075	0.503	
RBC	TI/L	ATOMOX	268	4.871	0.340	-0.037	0.254	.244
		PLACEBO	109	4.859	0.343	-0.058	0.281	
WBC	GI/L	ATOMOX	268	6.885	1.805	0.023	2.219	.560
		PLACEBO	109	7.040	1.855	-0.134	1.774	
BANDS	GI/L	ATOMOX	268	0.000	0.000	0.000	0.000	*
		PLACEBO	109	0.000	0.000	0.000	0.000	
POLYS	GI/L	ATOMOX	268	3.447	1.272	0.156	1.850	.243
		PLACEBO	109	3.589	1.256	-0.032	1.407	
LYMPHS	GI/L	ATOMOX	268	2.741	0.866	-0.133	0.729	.670
		PLACEBO	109	2.739	0.756	-0.097	0.618	
MONOS	GI/L	ATOMOX	268	0.390	0.127	0.008	0.152	.494
		PLACEBO	109	0.400	0.131	0.012	0.133	
EOSN	GI/L	ATOMOX	268	0.250	0.212	-0.006	0.211	.613
		PLACEBO	109	0.249	0.205	-0.003	0.137	
BASO	GI/L	ATOMOX	268	0.052	0.028	0.002	0.032	.081
		PLACEBO	109	0.059	0.035	-0.006	0.032	
MCV	fL	ATOMOX	267	79.195	4.551	1.783	3.330	.881
		PLACEBO	109	79.615	4.708	1.606	3.493	
PLTCT	GI/L	ATOMOX	268	303.246	65.949	6.407	51.874	.225
		PLACEBO	108	307.102	75.670	-3.500	64.314	
U-SPGR	NO UNITS	ATOMOX	273	1.025	0.007	-0.001	0.009	.827
		PLACEBO	113	1.025	0.007	-0.001	0.008	
AST	U/L	ATOMOX	273	27.125	5.931	-0.604	4.675	.783
		PLACEBO	112	29.348	9.363	-0.804	6.320	
ALT	U/L	ATOMOX	273	16.850	6.188	0.363	5.914	.069
		PLACEBO	112	18.536	13.970	0.063	11.539	
CPK	U/L	ATOMOX	274	127.657	55.939	-2.788	50.684	.014
		PLACEBO	112	124.241	48.886	9.848	57.573	
ALKPH	U/L	ATOMOX	274	224.620	69.294	-2.281	47.853	<.001
		PLACEBO	112	235.955	70.346	21.616	43.543	
GGT	U/L	ATOMOX	274	11.321	3.542	0.423	2.941	.822
		PLACEBO	112	12.339	5.793	0.152	4.391	
BUN	mmol/L	ATOMOX	273	4.619	1.013	-0.008	1.040	.941
		PLACEBO	112	4.816	1.094	-0.041	1.071	
CALC	mmol/L	ATOMOX	274	2.452	0.085	-0.007	0.092	.854
		PLACEBO	112	2.459	0.095	-0.008	0.099	

(continued)

**Table 24. Summary of Laboratory Data
Mean Change from Baseline to Endpoint by Analyte
Study Period III Visit Group I (Continued)**

Lab Test	Lab Unit	Therapy	n	-----Baseline-----		Change to -----Endpoint-----		p-Values
				Mean	SD	Mean	SD	
PHOS	mmol/L	ATOMOX	273	1.574	0.168	-0.013	0.180	.054
		PLACEBO	111	1.613	0.162	0.028	0.199	
SODIUM	mmol/L	ATOMOX	274	140.609	1.990	0.142	2.778	.741
		PLACEBO	111	140.694	2.161	0.252	3.391	
POTAS	mmol/L	ATOMOX	274	4.259	0.351	0.034	0.430	.970
		PLACEBO	112	4.313	0.376	0.039	0.439	
CHLOR	mmol/L	ATOMOX	274	102.620	2.245	-0.131	2.801	.020
		PLACEBO	111	102.523	1.995	0.613	3.046	
TPROT	g/L	ATOMOX	274	72.880	4.027	-0.376	3.975	.048
		PLACEBO	112	73.179	4.790	-1.241	4.402	
ALBUM	g/L	ATOMOX	274	43.865	2.466	-0.044	2.777	.532
		PLACEBO	112	43.518	3.090	0.366	2.870	
NFGLU	mmol/L	ATOMOX	274	4.985	0.845	0.005	1.110	.440
		PLACEBO	111	5.162	1.286	0.082	1.403	
UR AC	umol/L	ATOMOX	274	227.609	58.158	5.861	39.586	<.001
		PLACEBO	112	220.820	61.265	32.077	46.041	
CHOL	mmol/L	ATOMOX	274	4.368	0.735	-0.016	0.441	.285
		PLACEBO	112	4.302	0.814	-0.093	0.503	
BICARB	mmol/L	ATOMOX	274	22.192	2.015	-0.114	2.386	.008
		PLACEBO	112	22.091	1.925	-0.874	2.410	
CREAT	umol/L	ATOMOX	274	50.233	9.164	0.290	7.912	.848
		PLACEBO	112	50.199	10.628	0.395	9.297	
T.BILI	umol/L	ATOMOX	266	7.541	4.123	0.026	3.217	.258
		PLACEBO	106	7.518	4.476	0.339	2.933	

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks:

PROC GLM model=treatment.

Least-squares mean option in PROC GLM from the ANOVA on the ranks using the

CPK CREATINE PHOSPHOKINASE
ALKPH ALKALINE PHOSPHATASE
GGT GGT (GGPT/SGGT/YGGT)
BUN UREA NITROGEN
CALC CALCIUM

(continued)

Table 24. **Summary of Laboratory Data**
Mean Change from Baseline to Endpoint by Analyte
Study Period III Visit Group I (Concluded)

Legend of Lab Test Code Abbreviations:

Abbrev.	Description
-----	-----
HCT	HEMATOCRIT
HGB	HEMOGLOBIN
RBC	ERYTHROCYTE COUNT
WBC	LEUKOCYTE COUNT
BANDS	BANDS
POLYS	NEUTROPHILS, SEGMENTED
LYMPHS	LYMPHOCYTES
MONOS	MONOCYTES
EOSN	EOSINOPHILS
BASO	BASOPHILS
MCV	MEAN CELL VOLUME (MCV)
PLTCT	PLATELET COUNT
U-SPGR	UA-SPECIFIC GRAVITY
AST	AST/SGOT
ALT	ALT/SGPT
Abbrev.	Description
-----	-----
PHOS	INORGANIC PHOSPHORUS
SODIUM	SODIUM
POTAS	POTASSIUM
CHLOR	CHLORIDE
TPROT	TOTAL PROTEIN
ALBUM	ALBUMIN
NFGLU	GLUCOSE, NON-FASTING
UR AC	URIC ACID
CHOL	CHOLESTEROL
BICARB	BICARBONATE, HCO ₃
CREAT	CREATININE
T.BILI	BILIRUBIN, TOTAL

**Table 25. Summary of Laboratory (SI) Data
Frequency of Patients with Abnormal Laboratory Values
with Treatment Emergent Adverse Events (TESS) Option
Study Period III Visit Group I**

Incidence Group	ATOMOX (1) (Total=291)			PLACEBO (2) (Total=123)			-- p-Value * --
	N	n	(%)	N	n	(%)	Overall

Lab Test: HEMATOCRIT							

LOW	228	17	(7.5)	98	8	(8.2)	.823
HIGH	260	1	(0.4)	106	6	(5.7)	.003
Lab Test: HEMOGLOBIN							

LOW	257	3	(1.2)	106	6	(5.7)	.021
HIGH	263	0		107	2	(1.9)	.083
Lab Test: ERYTHROCYTE COUNT							

LOW	263	4	(1.5)	109	2	(1.8)	1.00
HIGH	265	0		108	1	(0.9)	
Lab Test: LEUKOCYTE COUNT							

LOW	246	12	(4.9)	99	4	(4.0)	1.00
HIGH	266	5	(1.9)	108	1	(0.9)	.677
Lab Test: BANDS							

LOW	268	0		109	0		
HIGH	268	0		109	0		
Lab Test: NEUTROPHILS, SEGMENTED							

LOW	262	9	(3.4)	105	2	(1.9)	.735
HIGH	264	4	(1.5)	107	1	(0.9)	1.00
Lab Test: LYMPHOCYTES							

LOW	266	1	(0.4)	108	1	(0.9)	.495
HIGH	267	0		109	0		
Lab Test: MONOCYTES							

LOW	268	3	(1.1)	109	0		.560
HIGH	265	3	(1.1)	109	0		.559

(continued)

**Table 25. Summary of Laboratory (SI) Data
Frequency of Patients with Abnormal Laboratory Values
with Treatment Emergent Adverse Events (TESS) Option
Study Period III Visit Group I (Continued)**

Incidence Group	ATOMOX (1) (Total=291)			PLACEBO (2) (Total=123)			-- p-Value * --
	N	n	(%)	N	n	(%)	Overall

Lab Test: EOSINOPHILS							

LOW	268	0		109	0		
HIGH	242	14	(5.8)	98	2	(2.0)	.168
Lab Test: BASOPHILS							

LOW	268	0		109	0		
HIGH	267	1	(0.4)	108	0		
Lab Test: MEAN CELL VOLUME (MCV)							

LOW	195	15	(7.7)	89	6	(6.7)	1.00
HIGH	267	0		108	2	(1.9)	.082
Lab Test: PLATELET COUNT							

LOW	267	0		108	0		
HIGH	236	23	(9.7)	94	4	(4.3)	.121
Lab Test: UA-SPECIFIC GRAVITY							

LOW	250	11	(4.4)	107	5	(4.7)	1.00
HIGH	247	11	(4.5)	104	2	(1.9)	.359
Lab Test: AST/SGOT							

LOW	273	1	(0.4)	112	0		
HIGH	259	3	(1.2)	105	3	(2.9)	.361
Lab Test: ALT/SGPT							

LOW	273	0		112	0		
HIGH	267	3	(1.1)	106	1	(0.9)	1.00
Lab Test: CREATINE PHOSPHOKINASE							

LOW	274	0		112	0		
HIGH	261	5	(1.9)	108	3	(2.8)	.697

(continued)

**Table 25. Summary of Laboratory (SI) Data
Frequency of Patients with Abnormal Laboratory Values
with Treatment Emergent Adverse Events (TESS) Option
Study Period III Visit Group I (Continued)**

Incidence Group	ATOMOX (1) (Total=291)			PLACEBO (2) (Total=123)			-- p-Value * --
	N	n	(%)	N	n	(%)	Overall
Lab Test: ALKALINE PHOSPHATASE							

LOW	274	2	(0.7)	112	0		1.00
HIGH	247	3	(1.2)	100	3	(3.0)	.360
Lab Test: GGT (GGPT/SGGT/YGGT)							

LOW	274	0		112	0		
HIGH	273	2	(0.7)	110	0		1.00
Lab Test: UREA NITROGEN							

LOW	273	0		112	0		
HIGH	273	0		112	0		
Lab Test: CALCIUM							

LOW	274	0		112	0		
HIGH	247	14	(5.7)	97	12	(12.4)	.042
Lab Test: INORGANIC PHOSPHORUS							

LOW	273	1	(0.4)	111	0		
HIGH	262	2	(0.8)	106	7	(6.6)	.003
Lab Test: SODIUM							

LOW	273	0		111	0		
HIGH	271	2	(0.7)	110	2	(1.8)	.328
Lab Test: POTASSIUM							

LOW	274	0		112	0		
HIGH	273	5	(1.8)	110	0		.327
Lab Test: CHLORIDE							

LOW	274	0		111	1	(0.9)	
HIGH	274	1	(0.4)	111	0		

(continued)

**Table 25. Summary of Laboratory (SI) Data
Frequency of Patients with Abnormal Laboratory Values
with Treatment Emergent Adverse Events (TESS) Option
Study Period III Visit Group I (Continued)**

Incidence Group	ATOMOX (1) (Total=291)			PLACEBO (2) (Total=123)			-- p-Value * --
	N	n	(%)	N	n	(%)	Overall

Lab Test: TOTAL PROTEIN							

LOW	274	0		112	1	(0.9)	
HIGH	270	1	(0.4)	110	0		
Lab Test: ALBUMIN							

LOW	274	0		112	0		
HIGH	244	20	(8.2)	94	4	(4.3)	.245
Lab Test: GLUCOSE, NON-FASTING							

LOW	268	1	(0.4)	111	0		
HIGH	274	0		110	0		
Lab Test: URIC ACID							

LOW	267	2	(0.7)	109	1	(0.9)	1.00
HIGH	267	2	(0.7)	111	6	(5.4)	.009
Lab Test: CHOLESTEROL							

LOW	248	6	(2.4)	101	8	(7.9)	.030
HIGH	220	19	(8.6)	88	2	(2.3)	.047
Lab Test: BICARBONATE, HCO3							

LOW	268	4	(1.5)	111	4	(3.6)	.240
HIGH	274	0		112	0		
Lab Test: CREATININE							

LOW	274	0		112	0		
HIGH	258	19	(7.4)	102	5	(4.9)	.488
Lab Test: BILIRUBIN, TOTAL							

LOW	274	0		112	0		
HIGH	269	5	(1.9)	108	0		.327

(continued)

Table 25. **Summary of Laboratory (SI) Data**
Frequency of Patients with Abnormal Laboratory Values
with Treatment Emergent Adverse Events (TESS) Option
Study Period III Visit Group I (Concluded)

Population: Randomized Patients in Study Period III
 Visit Group I
 Baseline: Visits 1-11, Endpoint: Visits 12-22

No. of

Treatment	Patients	Test Name	Test Code
Group	OBS Excluded		
	1	HEMATOCRIT	A01
ATOMOX	2		
	2	HEMOGLOBIN	A02
ATOMOX	2		
	3	ERYTHROCYTE COUNT	A03
ATOMOX	2		
	4	LEUKOCYTE COUNT	A10
ATOMOX	2		
	5	BANDS	A12
ATOMOX	2		
	6	NEUTROPHILS, SEGMENTED	A13
ATOMOX	2		
	7	LYMPHOCYTES	A14
ATOMOX	2		
	8	MONOCYTES	A15
ATOMOX	2		
	9	EOSINOPHILS	A16
ATOMOX	2		
	10	BASOPHILS	A17
ATOMOX	2		
	11	MEAN CELL VOLUME (MCV)	A19
ATOMOX	2		
	12	PLATELET COUNT	A20
ATOMOX	1		
	13	HYPOCHROMIA	A65
ATOMOX	1		
	14	LYMPHOCYTES, ATYPICAL	A87
ATOMOX	5		

*Frequencies are analyzed using a Fisher's Exact test.

Note: Total = Total number of patients in the treatment group having both baseline and endpoint visits.

N = Total number of at risk patients with the lab test.

N = Total number of at risk patients with the specific lab result (e.g. HIGH).

Vital Signs

In Study Period II, for all enrolled patients who took at least 1 dose of study drug, the data showed a statistically significant ($p < .001$) baseline-to-endpoint mean decrease (0.78 kg) in weight for atomoxetine-treated patients. There were also statistically significant baseline-to-endpoint changes in average diastolic blood pressure ($p < .001$), average systolic blood pressure ($p < .001$), average heart rate ($p < .001$), and height ($p < .001$).

In Study Period III Visit Group I, there were statistically significant differences between atomoxetine and placebo for mean weight change ($p < .001$), average diastolic blood pressure ($p = .002$), and average heart rate ($p < .001$) when analyzed for all randomized patients (Table 26). There was no statistically significant difference in height between treatment groups ($p = .088$ for all randomized patients).

Electrocardiograms (ECG)

For Study Period II, Table 27 summarizes the mean change from baseline to endpoint in Study Period II for ECG variables. Statistically significant differences between atomoxetine and placebo were found for heart rate and the RR, PR, QRS, QT, Bazett corrected QT (QTcB), and Fridericia corrected QT (QTcF) intervals. Table 28 summarizes the mean change from Study Period III Visit Group I baseline-to-endpoint ECG intervals and heart rate. Statistically significant differences between atomoxetine and placebo were found for heart rate and the RR, QRS, QT, QTcB, and QTcF intervals.

Table 26. Summary of Vital Sign Data Change from Baseline to Endpoint Study Period III Visit Group I

		-----Baseline-----		Change to -----Endpoint-----		p-Values	
Variables Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy
DIASAVG	ATOMOX	290	67.669	8.444	0.893	10.163	.002
	PLACEBO	123	67.528	9.036	-2.508	10.311	
PULSAVG	ATOMOX	290	87.016	11.250	-1.121	12.808	<.001
	PLACEBO	123	88.732	13.852	-8.402	13.474	
WEIGHT	ATOMOX	290	38.339	13.093	1.248	2.383	<.001
	PLACEBO	123	36.518	11.847	3.316	3.587	
HEIGHT	ATOMOX	279	144.286	14.350	2.462	2.163	.088
	PLACEBO	112	142.707	14.412	2.896	2.504	

Abbreviations: DIASAVG = diastolic BP average, HEIGHT = height in CM, PULSAVG = Heart rate average, WEIGHT = weight in KG

Population: Randomized Patients in Study Period III
Visit Group I

Baseline: Visits 1-11, Endpoint: Visits 12-22

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models: FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM. model=treatment. Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Atomoxetine

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**Table 27. Summary of ECG Changes
Baseline to Endpoint
Study Period II**

Variable analyzed: RR Interval (RR)

			Baseline			Endpoint			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	ATOMOX	576	802.457	800.000	132.014	694.992	681.818	111.879	-107.465	-100.334	115.835

p-Values

No.	Therapy	Within Group*1
1)	ATOMOX	<.001

Variable analyzed: PR Interval (PR)

			Baseline			Endpoint			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	ATOMOX	570	136.193	132.000	18.739	132.874	132.000	16.289	-3.319	-4.000	13.283

p-Values

No.	Therapy	Within Group*1
1)	ATOMOX	<.001

Variable analyzed: QRS Interval (QRS)

			Baseline			Endpoint			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	ATOMOX	576	84.365	84.000	11.208	84.757	84.000	10.553	0.392	0.000	10.185

(continued)

Atomoxetine

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**Table 27. Summary of ECG Changes
Baseline to Endpoint
Study Period II (Continued)**

			p-Values								

No.	Therapy		Within								
---	-----		Group*1								
---	-----		-----								
1)	ATOMOX		.002								
Variable analyzed:			QT Interval (QT)								
			Baseline			Endpoint			Change		
			-----			-----			-----		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
1)	ATOMOX	575	371.085	372.000	27.940	351.068	352.000	26.239	-20.017	-20.000	25.000

			p-Values								

No.	Therapy		Within								
---	-----		Group*1								
---	-----		-----								
1)	ATOMOX		<.001								
Variable analyzed:			Bazett QTC Interval (QTCB)								
			Baseline			Endpoint			Change		
			-----			-----			-----		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
---	-----	---	-----	-----	-----	-----	-----	-----	-----	-----	-----
1)	ATOMOX	575	415.701	415.000	18.298	422.503	422.000	17.347	6.802	7.000	19.513

(continued)

Atomoxetine

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**Table 27. Summary of ECG Changes
Baseline to Endpoint
Study Period II (Continued)**

Variable analyzed: Fridericia QTC Interval (QTCF)

No.	Therapy	n	Baseline			Endpoint			Change		
			Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	ATOMOX	575	400.287	399.827	16.450	397.248	396.667	15.939	-3.039	-3.933	16.761

p-Values

No.	Therapy	Within Group*1
1)	ATOMOX	<.001

Variable analyzed: Data Corrected QTC Interval (QTCD)

No.	Therapy	n	Baseline			Endpoint			Change		
			Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	ATOMOX	575	405.595	404.430	16.245	405.792	405.059	15.635	0.197	-0.163	17.020

p-Values

No.	Therapy	Within Group*1
1)	ATOMOX	.906

Variable analyzed: Data Corrected QTR Interval (QTCR)

No.	Therapy	n	Baseline			Endpoint			Change		
			Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
1)	ATOMOX	575	403.709	402.943	16.221	402.752	401.636	15.655	-0.957	-1.275	16.848

(continued)

Atomoxetine

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Table 27. **Summary of ECG Changes**
Baseline to Endpoint
Study Period II (Concluded)

		p-Values									

		Within									
		Group*1									

No.	Therapy										
---	-----										
1)	ATOMOX	.066									
Variable analyzed: ECG Heart Rate (HR)											
			Baseline			Endpoint			Change		
			-----			-----			-----		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
---	-----	---	-----	-----	-----	-----	-----	-----	-----	-----	-----
1)	ATOMOX	576	76.811	75.000	12.747	88.486	88.000	13.732	11.675	11.000	12.466
		p-Values									

		Within									
		Group*1									

No.	Therapy										
---	-----										
1)	ATOMOX	<.001									

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.
 Population: Enrolled patients who took at least 1 dose of study drug.
 Baseline: Visits 1-2, Endpoint: visits 3-10

Table 28. Summary of Changes from Baseline ECG Study Period III Visit Group I

				Change to		p-Values	
		-----Baseline-----		-----Endpoint-----			
Variables							
Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy
RR	ATOMOX	284	701.364	104.990	9.959	92.213	<.001
	PLACEBO	115	682.093	107.433	142.470	118.421	
PR	ATOMOX	281	132.441	16.148	1.295	16.600	.242
	PLACEBO	113	135.991	24.392	3.407	15.128	
QRS	ATOMOX	284	86.324	12.539	0.394	12.458	.023
	PLACEBO	115	84.209	9.593	3.687	14.336	
QT	ATOMOX	283	353.159	25.484	2.742	21.655	<.001
	PLACEBO	115	349.043	26.273	29.774	26.086	
QTCB	ATOMOX	283	422.883	18.117	0.332	18.176	.019
	PLACEBO	115	423.835	17.023	-4.861	23.802	
QTCF	ATOMOX	283	398.298	16.679	1.200	15.920	<.001
	PLACEBO	115	397.306	16.144	7.799	20.474	
QTCD	ATOMOX	283	406.623	16.517	0.906	16.192	.165
	PLACEBO	115	406.257	15.697	3.633	21.084	
HR	ATOMOX	284	87.394	12.636	-1.021	10.977	<.001
	PLACEBO	115	90.078	13.844	-15.104	11.115	

Population: Randomized Patients in Study Period III
Visit Group I

Baseline: Visits 1-11, Endpoint: Visits 12-22

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Condensed Summary of ECG Data

Research Project Code: B4Z

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Abbrev.	Description
-----	-----
HR	ECG Heart Rate
PR	PR Interval
QRS	QRS Interval
QT	QT Interval
QTCB	Bazett QTC Interval
QTCD	Data Corrected QTC Interval
QTCF	Fridericia QTC Interval
RR	RR Interval

Health Outcomes

The CHQ was administered at baseline and at the end of Study Period II. Table 29 summarizes change from baseline to endpoint on the 13 subscales of the measure in Study Period II. Changes were statistically significant ($p < .001$) for behavior, family activities, mental health, parent impact-emotion, physical summary score, psychosocial summary score, parent time impact, role-emotion/behavior, and self esteem. Reductions in core ADHD symptoms were accompanied by improvement in psychosocial and family functioning (mean change [SD] of psychosocial summary score: 10.47 [12.14]; mean change [SD] of family activities score: 16.86 [24.64]).

Atomoxetine

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Table 29. **Summary of CHQ**
Change from Baseline to Endpoint
All Enrolled Patients
Study Period II

Variable / Treatment Group	N	-- Baseline -- Mean SD	-- Endpoint -- Mean SD	----- Change ----- Mean SD LCI UCI	Within Group p-value (a)
Behavior					
Atomoxetine	488	40.80 17.33	58.66 18.58	17.86 19.89 16.09 19.62	<.001
Bodily Pain					
Atomoxetine	488	80.20 21.20	80.41 19.74	0.20 22.91 -1.83 2.24	0.997
Family Activities					
Atomoxetine	487	49.31 25.33	66.17 23.21	16.86 24.64 14.67 19.05	<.001
General Health					
Atomoxetine	488	76.52 17.28	77.48 16.02	0.96 15.88 -0.45 2.37	0.211
Mental Health					
Atomoxetine	489	62.04 16.95	70.69 16.29	8.65 18.36 7.02 10.28	<.001
Parent Imapct-Emotion					
Atomoxetine	488	43.28 18.82	56.77 23.22	13.49 24.12 11.35 15.63	<.001
Physical Functioning					
Atomoxetine	488	97.40 8.18	96.92 9.71	-0.49 11.52 -1.51 0.54	0.526
Physical Summary Score					
Atomoxetine	481	55.81 6.96	54.30 6.95	-1.51 7.76 -2.21 -0.82	<.001
Psychosocial Summary Score					
Atomoxetine	481	30.06 10.27	40.53 11.13	10.47 12.14 9.38 11.55	<.001
Parent Time Impact					
Atomoxetine	485	62.85 24.64	75.09 22.60	12.24 27.16 9.83 14.66	<.001

(continued)

Atomoxetine

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Table 29. **Summary of CHQ**
Change from Baseline to Endpoint
All Enrolled Patients
Study Period II (Concluded)

Variable / Treatment Group	N	-- Baseline --		-- Endpoint --		----- Change -----				Within Group p-value (a)
		Mean	SD	Mean	SD	Mean	SD	LCI	UCI	

Role-Emotion/Behavior Atomoxetine	488	55.70	35.05	77.21	29.09	21.52	37.32	18.21	24.83	<.001
Role-Physical Atomoxetine	487	94.06	17.82	94.26	16.70	0.20	21.50	-1.71	2.11	0.851
Self-Esteem Atomoxetine	489	61.65	18.06	71.58	17.42	9.93	19.02	8.25	11.62	<.001

Abbreviations: N = number of patients with a baseline and at least one postbaseline measurement;
SD=Standard Deviation; Change = endpoint-baseline; LCI=Lower bound of 95% CI; UCI=Upper bound of 95% CI;
Baseline visits: 1-2; Endpoint visits: 3-10
(a) Within Groups p-values obtained from Wilcoxon Signed-rank Test for mean change from baseline to endpoint.
Population: All Enrolled patients with baseline and at least one postbaseline measurement.

Table 30 summarizes change from baseline (end of Study Period II) to endpoint on the 13 concepts of the CHQ measure in Study Period III Visit Group I. There were statistically significant differences between the atomoxetine treatment group and the placebo treatment group on the following CHQ subscales: Psychosocial Summary ($p=.016$), Behavior ($p=.007$), Family Activities ($p=.016$), Role-Emotional/Behavior ($p=.011$), and Self-Esteem ($p=.005$).

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Table 30. CHQ
Change from Baseline to Endpoint
Study Period III Visit Group I

Variable / Treatment Group	N	-- Baseline -- Mean SD	-- Endpoint -- Mean SD	Change Mean SD	LSMean (a)	Within Group p-value (b)	Between Group p-value (a)
Behavior							
Placebo	98	64.38 13.13	47.69 19.63	-16.68	18.73	<.001	0.007
Atomoxetine	235	64.37 16.63	54.13 22.11	-10.23	20.31	<.001	—
LSMean Difference(95%CI) = -6.51(-11.18 , -1.83)							
Bodily Pain							
Placebo	98	82.86 16.18	80.00 19.90	-2.86	21.49	0.180	0.190
Atomoxetine	235	83.06 18.19	83.53 19.08	0.47	22.63	0.758	—
LSMean Difference(95%CI) = -3.53(-8.83 , 1.76)							
Family Activities							
Placebo	98	74.12 17.67	58.37 28.39	-15.76	23.88	<.001	0.016
Atomoxetine	235	71.46 21.07	62.80 26.86	-8.66	23.44	<.001	—
LSMean Difference(95%CI) = -6.86(-12.43 , -1.28)							
General Health							
Placebo	97	77.98 14.67	76.60 16.73	-1.38	12.04	0.215	0.424
Atomoxetine	235	79.00 16.03	76.03 15.73	-2.97	14.20	<.001	—
LSMean Difference(95%CI) = 1.31(-1.91 , 4.54)							
Mental Health							
Placebo	98	74.77 13.49	64.59 19.83	-10.17	18.23	<.001	0.163
Atomoxetine	235	73.62 14.61	66.62 18.28	-7.00	17.52	<.001	—
LSMean Difference(95%CI) = -3.01(-7.25 , 1.23)							
Parent Imapct-Emotion							
Placebo	98	59.32 22.91	49.80 21.79	-9.52	23.51	<.001	0.197
Atomoxetine	235	62.35 22.33	57.25 22.49	-5.11	25.19	0.001	—
LSMean Difference(95%CI) = -3.75(-9.46 , 1.96)							

(continued)

Atomoxetine

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Table 30. **CHQ**
Change from Baseline to Endpoint
Study Period III Visit Group I (Continued)

Variable / Treatment Group	N	-- Baseline --		-- Endpoint --		----- Change -----			Within Group p-value (b)	Between Group p-value (a)
		Mean	SD	Mean	SD	Mean	SD	LSMean (a)		

Physical Functioning										
Placebo	98	97.41	6.97	94.39	14.25	-3.02	12.63	-3.41	0.032	0.221
Atomoxetine	235	97.44	10.09	96.29	10.69	-1.14	14.74	-1.27	0.058	—
LSMean Difference(95%CI) = -2.14(-5.58 , 1.30)										
Physical Summary Score										
Placebo	96	54.20	5.93	53.78	9.72	-0.42	8.68	-0.40	0.360	0.484
Atomoxetine	235	54.86	6.26	54.95	7.07	0.10	7.94	0.30	0.269	—
LSMean Difference(95%CI) = -0.70(-2.68 , 1.28)										
Psychosocial Summary Score										
Placebo	96	43.96	8.56	34.45	13.71	-9.51	11.97	-9.88	<.001	0.016
Atomoxetine	235	43.41	9.97	37.85	12.80	-5.56	13.24	-6.16	<.001	—
LSMean Difference(95%CI) = -3.71(-6.74 , -0.69)										
Parent Time Impact										
Placebo	97	81.25	19.24	71.05	25.38	-10.20	25.41	-10.47	<.001	0.354
Atomoxetine	235	78.26	21.01	71.26	23.89	-7.01	27.62	-7.46	<.001	—
LSMean Difference(95%CI) = -3.00(-9.37 , 3.36)										
Role-Emotion/Behavior										
Placebo	98	84.02	22.52	63.52	36.39	-20.50	34.40	-22.58	<.001	0.011
Atomoxetine	235	84.97	22.49	74.63	29.89	-10.34	31.79	-12.69	<.001	—
LSMean Difference(95%CI) = -9.89(-17.51 , -2.27)										
Role-Physical										
Placebo	97	94.60	14.07	88.92	25.31	-5.68	26.87	-5.33	0.051	0.163
Atomoxetine	235	96.77	12.54	94.18	15.83	-2.59	17.25	-1.79	0.017	—
LSMean Difference(95%CI) = -3.55(-8.53 , 1.44)										

(continued)

Atomoxetine

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Table 30. **CHQ**
Change from Baseline to Endpoint
Study Period III Visit Group I (Concluded)

Variable / Treatment Group	N	-- Baseline --		-- Endpoint --		----- Change -----			Within Group p-value (b)	Between Group p-value (a)
		Mean	SD	Mean	SD	Mean	SD	LSMean (a)		

Self-Esteem										
Placebo	98	76.05	15.65	63.64	21.20	-12.41	16.08	-11.89	<.001	0.005
Atomoxetine	235	74.34	16.63	67.93	18.11	-6.41	17.97	-5.97	<.001	—
LSMean Difference(95%CI) = -5.93(-10.10 , -1.76)										

(a) LSMeans and Between Groups p-values are from ANOVA model with terms for Treatment and Investigator.

(b) Within Groups p-values obtained from Wilcoxon's Signed-rank Test for mean change from baseline to endpoint.

Population: All randomized patient with at least one baseline and postbaseline measurement

Summary ID#2552

Clinical Study Summary: Study B4Z-MC-LYAF (Final Report, Study Period III Visit Group II – Study Period IV)

Relapse Prevention after 10-Week and 52-Week Treatment with Atomoxetine Hydrochloride in Children with Attention-Deficit/Hyperactivity Disorder

Date summary approved by Lilly: 14 June 2007

Brief Summary of Results

The results for Study Periods I, II, and III Visit Group I (10-week, acute treatment plus 9-month, double-blind, placebo-controlled treatment) are reported in a separate CTR summary (CT Registry ID#2552, Clinical Study Summary Study B4Z-MC-LYAF [LYAF]) (9-month interim report for Study Period I through Study Period III Visit Group I). The current summary contains data for the last 2 periods of Study LYAF, in which investigators tested the hypothesis that pediatric outpatients who achieved and maintained a satisfactory response to approximately 52 weeks of treatment with atomoxetine (previously called tomoxetine hydrochloride and hereafter referred to as atomoxetine), and continued treatment with atomoxetine, would have a superior response when compared with placebo-treated patients as measured by the number of days until relapse. The results for Study Period III Visit Group II and Study Period IV are as follows:

- After 1 year of active atomoxetine treatment, patients who continued atomoxetine for 6 additional months (taper group) were statistically significantly less likely to relapse or to experience partial symptom return compared with patients who discontinued active treatment and switched to placebo (nontaper group). The p-value from the Wilcoxon test for qualified patients was not statistically significant ($p=.055$), but the p-value for all randomized patients was ($p=.008$).

- At the end of Study Period III Visit Group II, all randomized patients who were treated with atomoxetine showed statistically significantly less symptom worsening than patients on placebo as assessed by: the Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHDRS-IV-Parent:Inv) Total Score and Subscale Score ($p < .001$ for Total Score and Hyperactivity-Impulsivity Subscale, $p = .002$ for Inattentive Subscale), Clinical Global Impressions-Attention Deficit/Hyperactivity Disorder–Severity (CGI-ADHD-S) Scale ($p = .005$), Conners’ Parent Rating Scale-Revised: Short Form (CPRS-R:S) Scale (Hyperactivity Subscale $p = .018$; Cognitive Problems/Inattention Subscale $p = .050$), and the Conners’ Teacher Rating Scale-Revised: Short Form (CTRS R:S) Scale (Attention-Deficit/Hyperactivity Disorder [ADHD] Index $p < .001$, Hyperactivity Subscale $p = .027$).
- There were no statistically significant differences among treatment groups in any of the patient characteristics examined at baseline (for example, gender, age, and ADHD subtype) for patients randomized in Study Period III Visit Group II.
- There were no deaths in Study LYAF. During this reporting period, 1 atomoxetine patient discontinued due to an adverse event (AE), ST segment depression, and 1 placebo patient discontinued due to depression. A total of 7 serious adverse events (SAEs) were reported by 5 placebo patients during this portion of the study. Of these, 1 SAE, incomplete right bundle branch block (RBBB), was classified as possibly related to the study drug (the patient was on atomoxetine therapy at RBBB onset, but was randomized to placebo group at Visit 22 and discontinued while on placebo).
- There were no statistically significant differences between all randomized patient treatment groups in the incidence of treatment-emergent abnormal laboratory values during Study Period III Visit Group II.
- There were statistically significant differences between the 2 treatment groups for mean change in weight ($p < .001$), pulse ($p < .001$), and temperature ($p = .038$) when analyzed for all randomized patients during Study Period III Visit Group II.
- Statistically significant differences between atomoxetine and placebo were found for heart rate ($p < .001$), RR interval ($p < .001$), PR interval ($p = .014$), QT interval ($p < .001$), and Bazett corrected QT interval (QTcB) ($p = .003$), but not for Fridericia corrected QT (QTcF), when analyzed for all randomized patients during Study Period III Visit Group II.
- There was a statistically significant difference ($p = .029$) between atomoxetine taper and nontaper groups for mean diastolic blood pressure when analyzed for all randomized patients during Study Period IV (discontinuation phase).
- On 14 January 2005, the Food and Drug Administration (FDA) requested Eli Lilly and Company (Lilly) to undertake a comprehensive reexamination of the

coding of AEs, reasons for discontinuation, and patients with hospitalizations in Study LYAF. That post hoc analysis is presented separately in this document; it was not integrated into any of the analyses done prior to unblinding.

Title of Study: Relapse Prevention after 10-Week and 52-Week Treatment with Atomoxetine Hydrochloride in Children with Attention-Deficit/Hyperactivity Disorder	
Investigator(s): This multicenter study included 33 principal investigators.	
Study Center(s): This study was conducted at 33 study centers in 14 countries.	
Length of Study: 2 years 5 months Date of first patient enrolled: 28 November 2000 Date of last patient completed: 03 June 2003	Phase of Development: 2/3
Objectives: <u>Primary:</u> The primary objective of Study LYAF was to test the hypothesis that pediatric outpatients who achieved a satisfactory initial response to acute (approximately 10 weeks) treatment with atomoxetine hydrochloride continued treatment with atomoxetine would have a superior response when compared with placebo-treated patients as measured by the number of days until relapse. Since atomoxetine proved to be superior to placebo in the above analysis (as shown in this study's interim study report, the summary of which appears in CT Registry Synopsis ID#2552, Clinical Study Summary Study LYAF (9-Month Interim Report for Study Periods I through Study Period III Visit Group I), the following hypothesis was also tested: among pediatric outpatients who achieve and maintain a satisfactory response to approximately 52 weeks of treatment with atomoxetine, continued treatment with atomoxetine would be superior to placebo as measured by the number of days until relapse. <u>Secondary:</u> Secondary objectives of the study were to assess: the long-term safety of atomoxetine; the effects of atomoxetine on measures of cognitive and neuropsychological function during long-term treatment; teacher evaluations of the effects of atomoxetine on symptoms associated with impaired performance at school; and health outcomes during long-term treatment with atomoxetine.	
Methodology: Double-blind, randomized, placebo-controlled, relapse-prevention study (see Figure 1 for illustration of study design).	
Number of Patients: Planned: 500 patients Enrolled: 604 patients Randomized in Study Period III Visit Group I: 416 (292 atomoxetine, 124 placebo) Randomized in Study Period III Visit Group II: 81 atomoxetine, 82 placebo; 46 continuing on placebo (not randomized) Randomized Study Period IV: 34 atomoxetine tapered discontinuation, 31 atomoxetine nontapered discontinuation; 91 continuing on placebo (not randomized) Completed: 33 atomoxetine tapered discontinuation, 31 atomoxetine nontapered discontinuation; 90 continuing on placebo	
Diagnosis and Main Criteria for Inclusion: Patients 6 through 15 years of age (inclusive) at Visit 1, who met <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</i> TM (DSM-IV TM) diagnostic criteria for ADHD. Each patient's score from the ADHDRS-IV-Parent:Inv was at least 1.5 standard deviations above the age/gender norm for their diagnostic subtype.	
Test Product/Study Drug, Dose, and Mode of Administration: Atomoxetine: 0.5 mg/kg/day to 1.8 mg/kg/day, given twice daily; atomoxetine capsules, 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, and 40 mg.	
Reference Therapy/Comparator, Dose, and Mode of Administration: Placebo, given twice daily.	
Duration of Treatment: Maximum of 78 weeks treatment.	

Variables:

Criteria for Evaluation

Efficacy: Days to relapse, relapse rate, ADHDRS-IV-Parent:Inv Total Score, Inattention Subscale Scores and Hyperactivity-Impulsivity Subscale Score; CGI-ADHD-S Score; CPRS-R:S Oppositional Subscale Score, Cognitive Problems/Inattention Subscale Score, Hyperactivity Subscale Score, and ADHD Index; CTRS-R:S Oppositional Subscale Score, Cognitive Problems/Inattention Subscale Score, Hyperactivity Subscale Score, and ADHD Index; Children's Depression Inventory Total Score; Children's Depression Rating Scale-Revised Total Score; Multidimensional Anxiety Scale for Children Total Score, Physical Symptoms Scale, Harm Avoidance Scale, Social Anxiety Scale, and Separation/Panic Scale Score; Stroop Color Word Test interference Score; Dual Verbal Working Memory Task Score; Trail Making Test (A and B) Scores; Mazes Subtest Score, Block Design Score, Wechsler Intelligence Scale for Children® – Third Edition Working Memory Arithmetic and Digit Span Test Scores, Picture Arrangement Score, Similarities, and Vocabulary Score; and the CGI-Efficacy Index Score.

Safety: Treatment-emergent adverse events (TEAEs), vital signs, height and weight, laboratory analytes, and electrocardiograms (ECGs).

Health Outcomes: Physical and psychosocial well-being using the Child Health Questionnaire (CHQ).

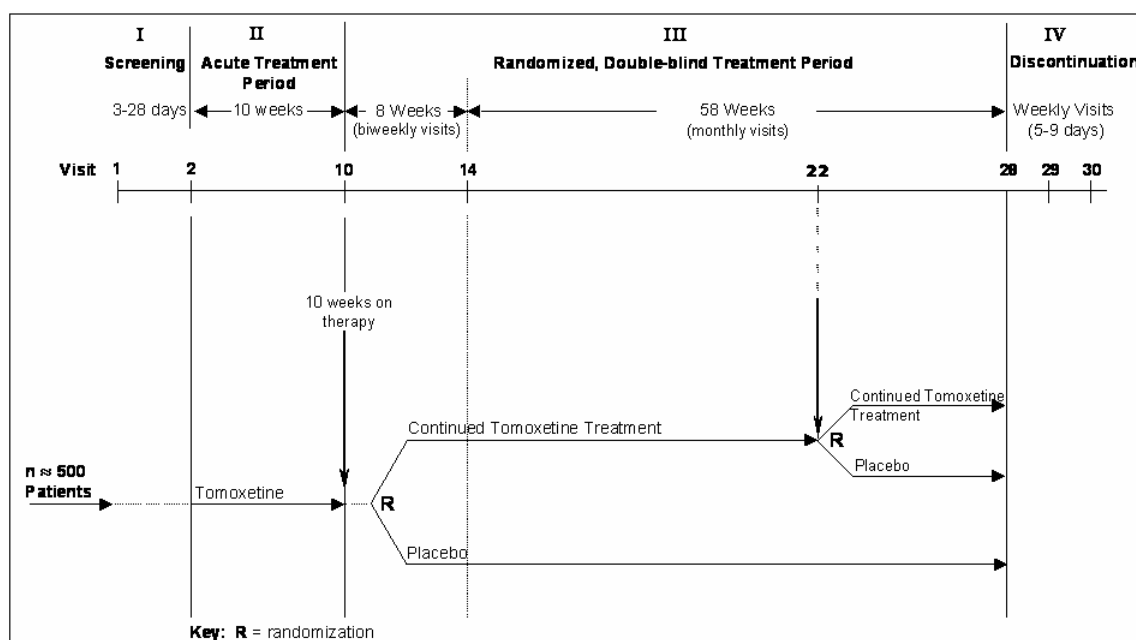
Evaluation Methods:

Statistical Methods: The primary efficacy variable was days to relapse and was analyzed using Kaplan-Meier analysis; Wilcoxon test was used to assess the treatment difference in the distribution. Secondary analysis using primary efficacy variable included log-rank test and proportional hazard analyses.

Secondary efficacy measures and safety measures: Changes from baseline to endpoint values were computed for each vital sign, continuous laboratory measures, and continuous ECG parameters by treatment group. Last-observation-carried-forward (LOCF) approach was used to handle missing data. For continuous variables, treatment effect was assessed by analysis of variance (ANOVA) model. Within-treatment-group changes were assessed using Wilcoxon signed rank test. Mean standard deviation and 2-sided 95% confidence intervals were also calculated for selected measures. The percentage of patients meeting categorical criteria was also computed for abnormal labs, vital signs, and ECG intervals by treatment group. For categorical variables, Fisher's Exact test was used to assess treatment effect.

Study Design

Figure 1 shows the study design for Study LYAF. Study Period I was used for screening. Study Period II comprised 10 weeks of acute open-label treatment with atomoxetine 0.5 mg/kg titrated up to 1.2 mg/kg. Patients who tolerated doses up to 0.8 mg/kg/day and met response criteria at the end of Study Period II were randomized at Visit 11 into the double-blind, placebo-controlled Study Period III Visit Group I. Patients randomized to atomoxetine were rerandomized (at Visit 22, after approximately 1 year of blinded therapy) into Study Period III Visit Group II, to placebo or atomoxetine, which they continued at the same dose that they received at the end of Study Period III Visit Group I. In Study Period IV, which consisted of 2 visits, patients who completed all Study Period III visits were randomized to a double-blind, placebo-controlled, dose-reduction period, during which study drug was either abruptly discontinued, or tapered and discontinued.



Study period III Visit Group I = Visits 11 to 22; Study period III Visit Group II = Visits 22 to 28.

Figure 1. Illustration of study design for Study B4Z-MC-LYAF.

Results:

Patient Demographics

Table 1 summarizes demographic characteristics for randomized patients in Study Period III Visit Group II (visits from the second randomization to the end of Study Period III). Of the 163 randomized patients, 89.6% were male, and 96.3% were Caucasian. The mean age for patients randomized in Study Period III Visit Group II (at study entry) was 10.83 years (range of 6.07 years to 15.4 years). Other baseline characteristics included:

47.9% had no prior stimulant exposure, 74.2% met criteria for the combined ADHD subtype, with 20.9% classified as predominantly inattentive and 4.9% as hyperactive-impulsive, and 7.4% were determined to be poor cytochrome P450 2D6 (CYP2D6) metabolizer (PM) patients. There were no statistically significant differences between treatment groups in any of the patient characteristics examined at baseline.

**Table 1. Patient Demographics
Comparison of Treatment Groups at Baseline
All Randomized Patients in Double-Blind Continuation
Therapy Phase
Study Period III Visit Group II**

Variable	TMX_TMX (N=81)	TMX_PLA (N=82)	Total (N=163)	p-Value
Sex: No. (%)				
No. Patients	81	82	163	.777a
Female	9 (11.1)	8 (9.8)	17 (10.4)	
Male	72 (88.9)	74 (90.2)	146 (89.6)	
Origin: No. (%)				
No. Patients	81	82	163	.343a
African Descent	2 (2.5)	1 (1.2)	3 (1.8)	
Western Asian	1 (1.2)	0	1 (0.6)	
Caucasian	78 (96.3)	79 (96.3)	157 (96.3)	
Other	0	2 (2.4)	2 (1.2)	
Age: yrs.				
No. Patients	81	82	163	.670b
Mean	10.70	10.96	10.83	
Median	10.63	10.80	10.71	
Standard Dev.	2.40	2.03	2.22	
Minimum	6.07	6.15	6.07	
Maximum	14.96	15.40	15.40	

Population: ALL Randomized Patients in SPIII VG2

Initial Visit ONLY

a Frequencies are analyzed using a Chi-Square test.

b Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=investigator and treatment.

Abbreviations: Dev = deviation; No. = number; PLA = placebo; TMX = atomoxetine; yrs. = years.

Table 2 summarizes demographic characteristics for all patients in Study Period IV. There were no statistically significant differences among treatment groups in any of the patient characteristics examined at baseline.

**Table 2. Patient Demographics
Comparison of Treatment Groups at Baseline
All Patients Entered
Study Period IV**

Variable	TMX TAP (N=34)	TMX NTAP (N=31)	PLACEBO (N=92)	Total (N=157)	p-Value
Sex: No. (%)					
No. Patients	34	31	92	157	.462 ^a
Female	4 (11.8)	2 (6.5)	5 (5.4)	11 (7.0)	
Male	30 (88.2)	29 (93.5)	87 (94.6)	146 (93.0)	
Origin: No. (%)					
No. Patients	34	31	92	157	.053 ^a
African Descent	2 (5.9)	0	0	2 (1.3)	
Western Asian	1 (2.9)	0	0	1 (0.6)	
Caucasian	31 (91.2)	31 (100)	90 (97.8)	152 (96.8)	
Other	0	0	2 (2.2)	2 (1.3)	
Age: yrs.					
No. Patients	34	31	92	157	.848 ^b
Mean	10.82	10.54	10.82	10.76	
Median	10.76	10.12	10.69	10.67	
Standard Dev.	2.43	2.41	2.14	2.25	
Minimum	6.07	7.23	6.01	6.01	
Maximum	14.74	14.96	15.46	15.46	

Population: All Patients in Study Period IV

Initial Visit ONLY

^a Frequencies are analyzed using a Chi-Square test.

^b Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=investigator and treatment.

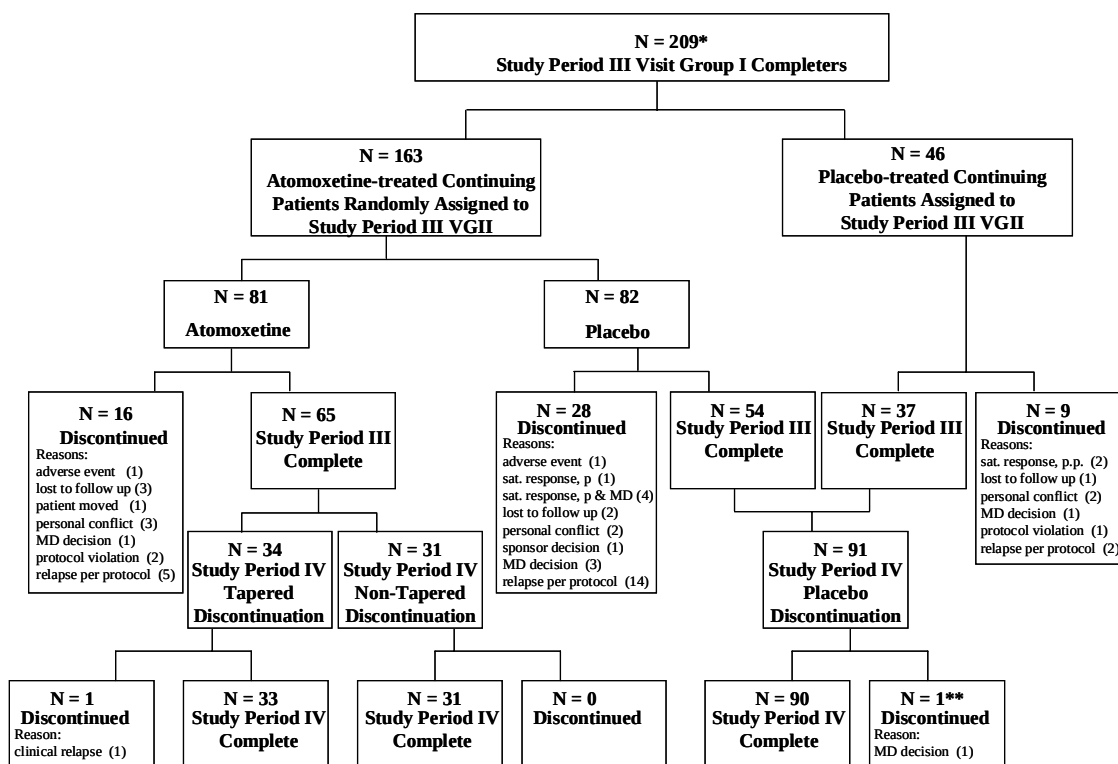
Abbreviations: Dev = deviation; N/No. = number; NTAP = nontapered; PLA = placebo; TAP = tapered; TMX = atomoxetine; yrs = years.

Patient Disposition

Figure 2 shows an overview of patient disposition for Study Period III Visit Group II and Study Period IV. A total of 209 patients entered Study Period III Visit Group II. Four patients actually discontinued in Study Period III Visit Group I, but were entered into Study Period III Visit Group II inappropriately. At Visit 22, the 163 patients who received atomoxetine treatment in Study Period III Visit Group I were rerandomized to continued atomoxetine treatment (n=81) or to placebo treatment (n=82). The continuing placebo-treated patients (n=46) remained on placebo treatment throughout the study. Sixty-five atomoxetine-atomoxetine-treated patients (80.2%), 54 atomoxetine-placebo-treated patients (65.9%), and 37 placebo-placebo-treated patients (80.4%) completed Study Period III Visit Group II.

Study Period IV was a randomized, double-blind, placebo-controlled, tapering, and discontinuation of study drug phase. Patients who received atomoxetine treatment during Study Period III Visit Group II were randomized to placebo treatment by either an abrupt discontinuation of study drug (nontapered discontinuation, n=31) or to a gradual discontinuation of study drug (tapered discontinuation, n=34). Patients who received placebo treatment during Study Period III Visit Group II remained on placebo treatment

throughout Study Period IV (n=91). A total of 154 patients (98.7%) successfully completed the discontinuation phase (Study Period IV).



Abbreviations: MD = physician; N = number of patients; p = patient;
 sat. = satisfactory.

* Four patients discontinued in Study Period III Visit Group I but were randomized into Study Period III Visit Group II.

** One patient was randomized into Study Period IV but actually discontinued in Study Period III Visit Group II due to physician decision.

Figure 2. Patient disposition for Study Period III Visit Group II and Study Period IV.

Table 3 shows the number of patients with data at each visit of Study Period III Visit Group II and Study Period IV, and the number of patients from each treatment group who completed the study.

**Table 3. Patient Disposition by Visit, All Entered Patients
Study Period III Visit Group II and Study Period IV**

Study Period	Visit	Number of Patients			
SPIII VGI Completers	22	ATX n=163			PBO n=46
SPIII VGII Randomization		ATX-ATX 81 (100%)	ATX-PBO 82 (100%)	PBO 46 (100%)	
SPIII VGII	22	79 (97.5)	81 (98.8)	45 (97.8)	
	23	76 (93.8)	74 (90.2)	43 (93.5)	
	24	73 (90.1)	66 (80.5)	40 (87.0)	
	25	71 (87.7)	59 (72.0)	39 (84.8)	
	26	69 (85.2)	57 (69.5)	38 (82.6)	
	27	66 (81.5)	56 (68.3)	38 (82.6)	
	28	65 (80.2)	54 (65.9)	37 (80.4)	
SPIV Randomization	28	Tapered 34	Nontapered 31	54	37
SPIV	29	34	31	54	37
Protocol Complete	30	33	31	54	36

Abbreviations: ATX = atomoxetine; PBO = placebo; SPIII VGI = Study Period III Visit Group I; SPIII VGII = Study Period III Visit Group II; SPIV = Study Period IV; Tapered = tapered study drug discontinuation; Nontapered = abrupt study drug discontinuation.

Discontinuation of Patients

Discontinuation from Study Period III Visit Group II

Table 4 shows the percentage of randomized patients who discontinued from Study Period III Visit Group II by their primary reason for discontinuation. A total of 163 patients who received atomoxetine treatment in Study Period III Visit Group I were randomized in Study Period III Visit Group II to either continued atomoxetine treatment (atomoxetine-atomoxetine, n=81) or to placebo (atomoxetine-placebo, n=82) (NOTE: the total of 163 patients includes 3 patients who were inappropriately randomized into this study period after being discontinued from the study. These patients are not shown in the data tables). Study Period III Visit Group II was completed by 119 randomized patients (74.4%). Statistically significantly more atomoxetine-treated patients than placebo-treated patients completed Study Period III Visit Group II (atomoxetine-atomoxetine: 82.3%; atomoxetine-placebo: 66.7%; p=.030). The most common reason for discontinuation was due to relapse per the protocol definition, which was reported by 19 patients (11.9%). Statistically significantly more placebo-treated patients than atomoxetine-treated patients relapsed during this study period (atomoxetine-atomoxetine n=5; atomoxetine-placebo n=14; p=.049). Two randomized patients (1.3%) discontinued from Study Period III Visit Group II due to AEs.

**Table 4. Summary of Primary Reasons for Study Discontinuation
Comparison of Treatment Groups
All Randomized Patients
Study Period III Visit Group II**

Primary Reason for Discontinuation	TMX (N=79) n (%)	TMX (N=81) n (%)	PLA (N=81) n (%)	Total (N=160) n (%)	p-Value*
Adverse event	1 (1.3)	1 (1.2)		2 (1.3)	1.00
Satisfactory response, patient perception	0	1 (1.2)		1 (0.6)	
Satisfactory response, patient and physician perception	0	4 (4.9)		4 (2.5)	.120
Unable to contact patient (lost to follow-up)	3 (3.8)	2 (2.5)		5 (3.1)	.680
Patient moved	1 (1.3)	0		1 (0.6)	
Personal conflict or other patient decision	3 (3.8)	2 (2.5)		5 (3.1)	.680
Sponsor's decision	0	1 (1.2)		1 (0.6)	
Physician decision	0	2 (2.5)		2 (1.3)	.497
Protocol Violation	1 (1.3)	0		1 (0.6)	
Relapse per protocol definition	5 (6.3)	14 (17.3)		19 (11.9)	.049
Study Period III completed	65 (82.3)	54 (66.7)		119 (74.4)	.030

Population: ALL Randomized Patients in SPIII VG2
Subjects in SP3VG2: Visits 23-28

- Frequencies are analyzed using a Fisher's Exact test.

Abbreviations: N = total sample size; n = number of patients who discontinued; PLA = placebo; TMX = atomoxetine.

Discontinuation from Study Period IV

Table 5 shows the percentage of all randomized patients who discontinued from Study Period IV by their primary reason for discontinuation by treatment. A total of 64 patients (98.5%) completed Study Period IV. One patient was randomized into Study Period IV, but actually discontinued in Study Period III Visit Group II due to physician decision. One patient from the atomoxetine-atomoxetine-tapered treatment group discontinued in Study Period IV due to clinical relapse.

**Table 5. Summary of Primary Reasons for Study Discontinuation
Comparison of Treatment Groups
All Randomized Patients
Study Period IV**

Primary Reason for Discontinuation	TMX TAP (N=34)	TMX NTAP (N=31)	Total (N=65)	p-Value*
	n (%)	n (%)	n (%)	
Protocol completed	33 (97.1)	31 (100)	64 (98.5)	1.00
Clinical relapse	1 (2.9)	0	1 (1.5)	

Population: Randomized Patients in Study Period IV
Subjects in SP4: Visits 29-30

- Frequencies are analyzed using a Fisher's Exact test.

Abbreviations: N = total sample size; n = number of patients who discontinued; NTAP = nontapered;

TAP = TAPERED; TMX = atomoxetine.

Note: Relapse as defined by investigator.

Primary Efficacy Measures

The protocol defined relapse as follows: “During Study Period III, if at 2 consecutive visits a patient’s CGI-ADHD-S score increases by 2 or more categories from their score at the end of Study Period II (Visit 10) **and** their ADHDRS-IV-Parent:Inv total score returns to 90% or more of their Study Period II baseline score, the patient will be considered to be a relapser and must be discontinued from the study. If a patient shows evidence of a return of symptoms at 1 visit that meets the severity criteria described above, and because of worsening symptoms is unwilling to remain in the study, or does not return for a second visit, the patient will also be considered to have relapsed.”

Figure 3 contains the results from the survival analysis based on protocol-defined relapse for all randomized patients. The Kaplan-Meier plot’s vertical axis shows the proportion of patients not relapsing, and the horizontal axis shows time (days on therapy). Based on the Kaplan-Meier estimates, for all randomized patients, the mean time to relapse in days (and standard error) for patients on atomoxetine was 160.5 days (0.71), compared with 130.8 days (3.09) for patients on placebo (Table 6). The analysis using all randomized patients showed that patients on atomoxetine treatment were statistically significantly less likely to relapse than patients assigned to placebo as assessed by the Wilcoxon test (p=.008).

Figure 4 contains the results from the survival analysis based on protocol-defined relapse for qualified patients only. Treatment differences in the distribution were assessed using the Wilcoxon test (p=.055). In qualified patients, based on Kaplan-Meier estimates, time to relapse in days (and standard error) for patients on atomoxetine was 160.21 days (1.11), compared with 131.81 days (3.42) for patients on placebo (Table 7).

Atomoxetine

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Table 6. **Time-to-Relapse**
Based on Kaplan-Meier Estimates (Relapse per Protocol)
All Randomized Patients
Study Period III Visit Group II

		----- Relapse -----				Total		Fishers Exact p-Value
		Placebo N	n (%)	Atomoxetine N	n (%)	N	n (%)	
Relapse		82	10 (12.2%)	81	2 (2.5%)	163	12 (7.4%)	0.0319
Days to Relapse	----- Atomoxetine -----			----- Placebo -----			Difference between Atomoxetine and Placebo Diff (LCI , UCI)	
	N at Risk	Prop. Nonrelapse	SE	N at Risk	Prop. Nonrelapse	SE		
0	78	1.000	0.000	81	1.000	0.000	0.000 (0.000 , 0.000)	
14	78	1.000	0.000	79	1.000	0.000	0.000 (0.000 , 0.000)	
28	77	1.000	0.000	78	1.000	0.000	0.000 (0.000 , 0.000)	
42	76	1.000	0.000	74	0.987	0.013	0.013 (-0.013 , 0.039)	
56	76	1.000	0.000	70	0.959	0.023	0.041 (-0.004 , 0.086)	
70	73	1.000	0.000	64	0.932	0.029	0.068 (0.010 , 0.125)	
84	71	1.000	0.000	61	0.888	0.037	0.112 (0.039 , 0.185)	
98	70	1.000	0.000	59	0.874	0.039	0.126 (0.049 , 0.203)	
112	70	1.000	0.000	58	0.874	0.039	0.126 (0.049 , 0.203)	
126	67	1.000	0.000	57	0.874	0.039	0.126 (0.049 , 0.203)	
140	63	0.985	0.015	55	0.858	0.042	0.127 (0.040 , 0.214)	
154	59	0.985	0.015	50	0.858	0.042	0.127 (0.040 , 0.214)	
168	48	0.968	0.022	40	0.858	0.042	0.110 (0.017 , 0.202)	
182	23	0.968	0.022	19	0.858	0.042	0.110 (0.017 , 0.202)	
196	4	0.968	0.022	3	0.858	0.042	0.110 (0.017 , 0.202)	
210	0	.	.	0	.	.	.	(. , .)
224	0	.	.	0	.	.	.	(. , .)
238	0	.	.	0	.	.	.	(. , .)
Log-Rank p-value = 0.013								
TIME(DAYS) TO EVENT/CENSOR		MEAN(SE)		Atomoxetine: 160.49(0.71)		Placebo: 130.80(3.09)		

Abbreviations: LCI = Lower limit of Confidence Interval; N = total number in sample; n = sample subset; Prop. = proportion; SE = Standard Error; UCI = Upper limit of Confidence Interval.

Relapse Definition: Relapse per protocol definition within study period III visit Group II

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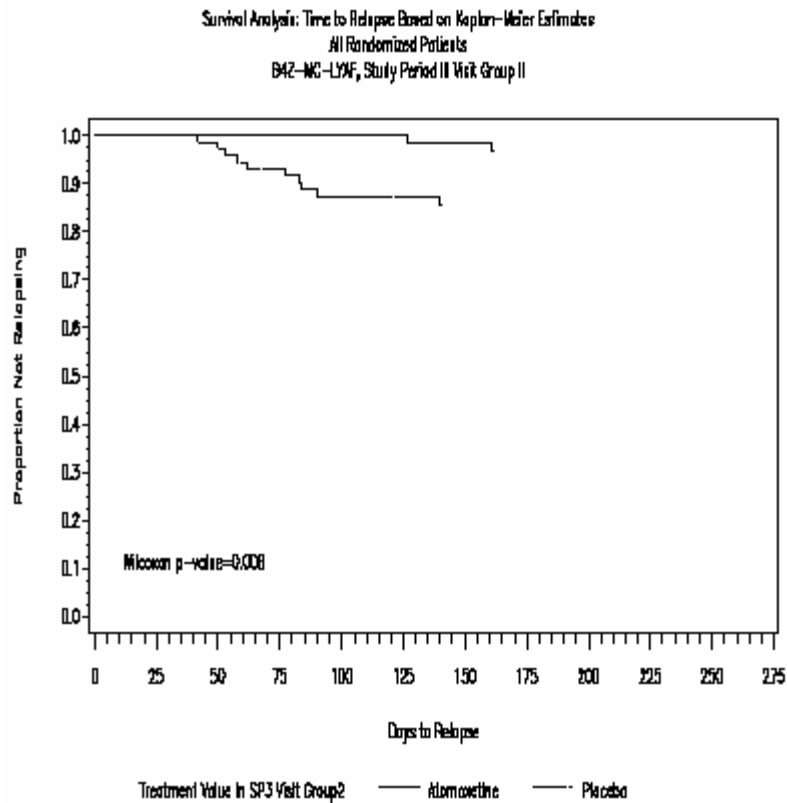
Table 7. Time-to-Relapse by Visit
Based on Kaplan-Meier Estimates (Relapse per Protocol)
Qualified Patients Only
Study Period III Visit Group II

		----- Relapse -----				Total		Fishers Exact p-Value
		Placebo		Atomoxetine		N	n (%)	
		N	n (%)	N	n (%)			
Relapse		54	7 (13%)	48	2 (4.2%)	102	9 (8.8%)	0.1670
Days to Relapse	----- Atomoxetine -----			----- Placebo -----			Difference between Atomoxetine and Placebo Diff (LCI , UCI)	
	N at Risk	Prop. Nonrelapse	SE	N at Risk	Prop. Nonrelapse	SE		
0	48	1.000	0.000	54	1.000	0.000	0.000 (0.000 , 0.000)	
14	48	1.000	0.000	53	1.000	0.000	0.000 (0.000 , 0.000)	
28	48	1.000	0.000	52	1.000	0.000	0.000 (0.000 , 0.000)	
42	48	1.000	0.000	50	1.000	0.000	0.000 (0.000 , 0.000)	
56	48	1.000	0.000	49	1.000	0.000	0.000 (0.000 , 0.000)	
70	47	1.000	0.000	44	0.959	0.028	0.041 (-0.015 , 0.096)	
84	45	1.000	0.000	41	0.894	0.045	0.106 (0.018 , 0.194)	
98	44	1.000	0.000	40	0.872	0.049	0.128 (0.032 , 0.224)	
112	44	1.000	0.000	39	0.872	0.049	0.128 (0.032 , 0.224)	
126	43	1.000	0.000	38	0.872	0.049	0.128 (0.032 , 0.224)	
140	40	0.977	0.023	36	0.848	0.053	0.128 (0.015 , 0.241)	
154	38	0.977	0.023	34	0.848	0.053	0.128 (0.015 , 0.241)	
168	29	0.950	0.034	27	0.848	0.053	0.102 (-0.022 , 0.226)	
182	16	0.950	0.034	13	0.848	0.053	0.102 (-0.022 , 0.226)	
196	3	0.950	0.034	2	0.848	0.053	0.102 (-0.022 , 0.226)	
210	0	.	.	0	.	.	.	(. , .)
224	0	.	.	0	.	.	.	(. , .)
238	0	.	.	0	.	.	.	(. , .)
Log-Rank p-value = 0.077								
TIME(DAYS) TO EVENT/CENSOR		MEAN(SE)		Atomoxetine: 160.21(1.11)			Placebo: 131.81(3.42)	

Relapse Definition: Relapse per protocol definition within study period III visit Group II

Abbreviations: N = total number in sample; n = sample subset; Prop. = proportion; SE = Standard Error

LCI = Lower limit of Confidence Interval; UCI = Upper limit of Confidence Interval



Relapse Definition: Relapse per protocol definition within study period II visit Group II

Figure 3. Relapse rates among treatment groups based on protocol-defined relapse for all randomized patients.

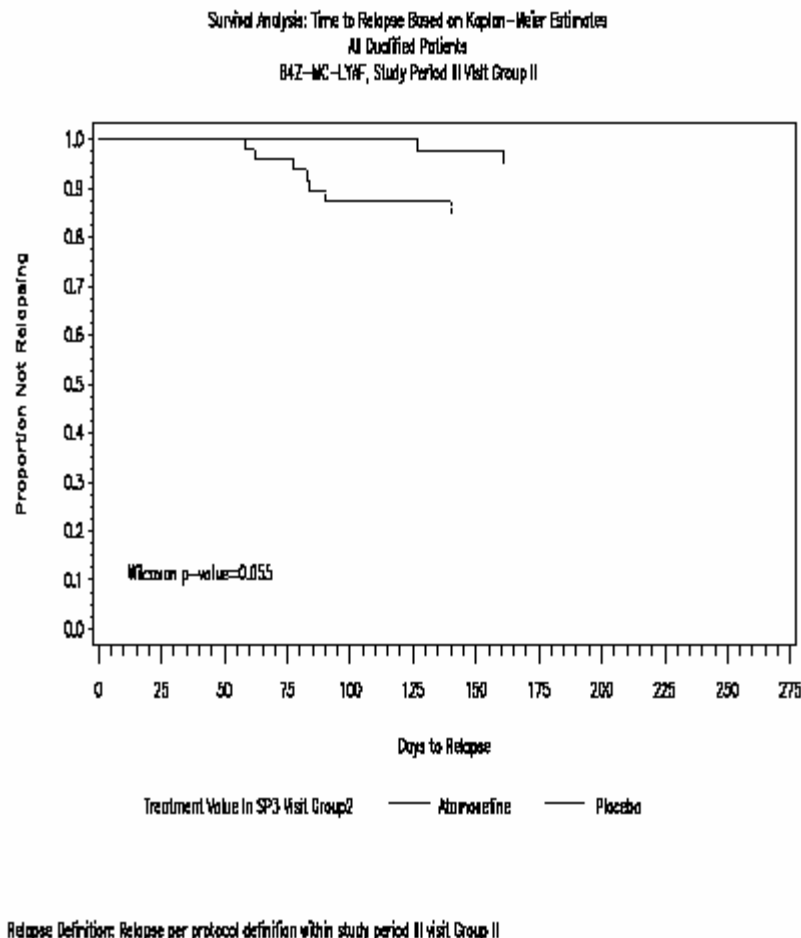


Figure 4. Relapse rates among treatment groups based on protocol defined relapse for qualified patients.

Secondary Efficacy Measures

Study Period III Visit Group II

Secondary objectives of the study were to assess the long-term safety of atomoxetine, the effects of atomoxetine on measures of cognitive and neuropsychological function during long-term treatment, teacher evaluations of the effects of atomoxetine on symptoms associated with impaired performance at school, and health outcomes during long-term treatment with atomoxetine. Results were as follows:

- Postrandomization mean ADHDRS-IV-Parent:Inv Total Scores, Total T-Score and 2 subscale scores showed statistically significantly greater worsening in the placebo treatment group than in the atomoxetine treatment group ($p=.002$ for the Inattentive Subscale and $p<.001$ for all other variables) (see Table 8).

- Statistically significant differences between treatment groups were also noted in the CGI-ADHD-S Score ($p=.005$) (see Table 8).
- There was a statistically significant difference between treatment groups when patients showed an unchanged or worse therapeutic effect without experiencing any side effects (atomoxetine: 5 [6.41%], placebo: 15 [18.52%]; $p=.03$) for the Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Efficacy Index (CGI-ADHD-EI) Rating Scale. There was no statistically significant difference between the atomoxetine group and the placebo group as measured by patient frequency in any of the other 15 categories of CGI-ADHD-EI Rating Scales.
- The placebo treatment group showed statistically significantly greater worsening compared with the atomoxetine treatment group on the CPRS-R:S Cognitive Subscale ($p=.050$) and Hyperactive Subscale ($p=.018$). There was no statistically significant difference between the 2 treatment groups on the ADHD Index Score ($p=.054$), or on the Oppositional Subscale ($p=.575$) (see Table 9).
- There was a statistically significant difference between the 2 treatment groups on the CTRS-R:S ADHD Index Subscale ($p<.001$) and the Hyperactive Subscale ($p=.027$). The placebo treatment group showed symptom worsening while the atomoxetine treatment group showed symptom improvement. There was no statistically significant difference between the 2 treatment groups on the Cognitive Subscale, ($p=.056$) and on the Oppositional Subscale ($p=.195$) (see Table 10).
- The differences between treatment groups for the Children's Depression Inventory (CDI), Children's Depression Rating Scale-Revised (CDRS-R) and Multidimensional Anxiety Scale for Children (MASC) were not statistically significant for any of the measurements (see Table 11).
- There was a statistically significant difference between the 2 treatment groups on the Wechsler Intelligence scale (WISC) IQ ($p=.038$) and WISC Vocabulary Scaled Score ($p=.049$). No statistically significant differences were found between the treatment groups on the other WISC Scales, or on the Cognitive Measurement Dual Verbal Working Memory Task (DUAL-VWM), Stroop Color and Word Test (Stroop), Trail Making Part A (Trails A), and Trail Making Part B (Trails B). Tables 12 and 13 present the summaries of efficacy scores for a subset of efficacy measures, which includes all patients in Study Period III Visit Group II by visit.

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Table 8. **ADHDRS-IV-Parent:Inv and CGI-ADHD-S**
Change from Baseline to Endpoint
All Randomized Patients
Study Period III Visit Group II

Variable / Treatment Group	N	-- Baseline -- Mean	SD	-- Endpoint -- Mean	SD	----- Mean	Change SD	----- LSMean (a)	Within Group p-value (b)	Between Group p-value (a)

ADHDRS-PI Total Score										
Placebo	81	12.54	6.52	20.31	12.55	7.77	12.35	6.92	<.001	<.001
Atomoxetine	77	13.42	9.01	15.10	9.74	1.69	9.14	0.92	0.232	—
Treatment LSMean Difference(95%CI) = 6.00(2.76 , 9.24)										
ADHDRS-PI Total T-score										
Placebo	81	51.34	7.12	59.38	13.63	8.05	13.08	7.20	<.001	<.001
Atomoxetine	77	52.29	8.99	53.95	9.89	1.66	9.20	0.89	0.235	—
Treatment LSMean Difference(95%CI) = 6.31(2.95 , 9.67)										
ADHDRS-PI Hyp/Imp Subscale										
Placebo	81	5.21	4.01	8.85	6.73	3.64	6.80	3.25	<.001	<.001
Atomoxetine	77	6.19	5.74	6.70	5.36	0.51	4.75	0.14	0.285	—
Treatment LSMean Difference(95%CI) = 3.11(1.37 , 4.85)										
ADHDRS-PI Inatt. Subscale										
Placebo	81	7.33	4.24	11.46	6.88	4.12	6.14	3.67	<.001	0.002
Atomoxetine	77	7.22	4.70	8.40	6.09	1.18	5.44	0.79	0.164	—
Treatment LSMean Difference(95%CI) = 2.89(1.09 , 4.68)										
CGI ADHD Severity										
Placebo	81	1.91	0.67	2.77	1.36	0.85	1.34	0.72	<.001	0.005
Atomoxetine	78	2.00	0.91	2.24	1.11	0.24	1.21	0.17	0.085	—
Treatment LSMean Difference(95%CI) = 0.56(0.17 , 0.95)										

(a) LSMeans and Between Groups p-value are from ANOVA model with terms for Treatment and Investigator.
(b) Within Groups p-values obtained from Wilcoxon's Signed-rank Test for mean change from baseline to endpoint.
Population: All randomized patients with at least one baseline and postbaseline measurement.
Baseline visits: 1-22, Endpoint visits: 23-28.

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Table 9. **CPRS-R:S**
Change from Baseline to Endpoint
All Randomized Patients
Study Period III Visit Group II

Variable / Treatment Group	N	-- Baseline -- Mean	SD	-- Endpoint -- Mean	SD	----- Mean	Change SD	----- LSMean (a)	Within Group p-value (b)	Between Group p-value (a)
CPRS ADHD Index										
Placebo	81	12.18	6.89	15.65	8.47	3.47	7.60	3.00	<.001	0.054
Atomoxetine	77	11.38	7.05	12.61	7.46	1.23	6.04	0.82	0.133	—
Treatment LSMean Difference(95%CI) = 2.18(-0.04 , 4.41)										
CPRS Oppositional Score										
Placebo	81	5.81	4.11	6.58	4.62	0.77	4.35	0.38	0.229	0.575
Atomoxetine	77	5.75	4.51	6.26	4.43	0.51	3.40	0.04	0.141	—
Treatment LSMean Difference(95%CI) = 0.34(-0.86 , 1.55)										
CPRS Cognitive Problems										
Placebo	81	6.36	4.47	8.58	4.75	2.22	4.35	2.05	<.001	0.050
Atomoxetine	77	5.74	4.02	6.61	4.35	0.87	3.89	0.68	0.064	—
Treatment LSMean Difference(95%CI) = 1.37(0.00 , 2.73)										
CPRS Hyperactive Score										
Placebo	81	2.99	2.87	4.72	4.28	1.73	4.05	1.43	<.001	0.018
Atomoxetine	77	3.75	3.88	4.14	3.78	0.39	2.75	0.06	0.264	—
Treatment LSMean Difference(95%CI) = 1.38(0.24 , 2.51)										

(a) LSMeans and Between Groups p-value are from ANOVA model with terms for Treatment and Investigator.
(b) Within Groups p-values obtained from Wilcoxon's Signed-rank Test for mean change from baseline to endpoint.
Population: All randomized patients with at least one baseline and postbaseline measurement.
Baseline visits: 1-22, Endpoint visits: 23-28.

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Table 10. **CTRS-R:S**
Change from Baseline to Endpoint
All Randomized Patients
Study Period III Visit Group II

Variable / Treatment Group	N	-- Baseline -- Mean	SD	-- Endpoint -- Mean	SD	----- Mean	Change SD	----- LSMean (a)	Within Group p-value (b)	Between Group p-value (a)

CTRS ADHD Index Subscale										
Placebo	67	16.15	8.42	19.48	8.77	3.33	9.00	3.80	0.011	<.001
Atomoxetine	64	15.80	9.03	13.98	8.44	-1.82	9.01	-2.27	0.155	—
Treatment LSMean Difference(95%CI) = 6.08(2.85 , 9.30)										
CTRS Cognitive Problems Subscale										
Placebo	67	6.38	4.15	6.88	3.80	0.50	3.11	0.25	0.187	0.056
Atomoxetine	64	6.39	4.21	5.72	4.28	-0.67	3.67	-0.98	0.293	—
Treatment LSMean Difference(95%CI) = 1.24(-0.03 , 2.51)										
CTRS Hyperactive Subscale										
Placebo	67	7.61	5.26	8.53	5.60	0.92	5.07	0.95	0.207	0.027
Atomoxetine	63	7.33	5.57	6.04	4.79	-1.30	5.83	-1.36	0.191	—
Treatment LSMean Difference(95%CI) = 2.31(0.27 , 4.34)										
CTRS Oppositional Subscale										
Placebo	67	3.91	3.90	4.37	4.37	0.47	3.29	0.43	0.137	0.195
Atomoxetine	64	3.66	3.82	3.14	3.89	-0.52	3.80	-0.45	0.436	—
Treatment LSMean Difference(95%CI) = 0.87(-0.46 , 2.20)										

(a) LSMeans and Between Groups p-value are from ANOVA model with terms for Treatment and Investigator.
(b) Within Groups p-values obtained from Wilcoxon's Signed-rank Test for mean change from baseline to endpoint.
Population: All randomized patients with at least one baseline and postbaseline measurement.
Baseline visits: 1-22, Endpoint visits: 23-28.

Study Period IV

- During the discontinuation phase, there were no statistically significant differences between treatment groups (tapered atomoxetine discontinuation versus nontapered discontinuation) on any of the following scales (that is, ADHDRS-IV-Parent:Inv Total Score, Total T-Scores, Subscale Scores, and CGI-ADHD-Scores) (see Table 14).
- During the discontinuation phase (2 weeks), no tapered discontinuation patients relapsed, and 1 nontapered discontinuation patient relapsed ($p=.4769$) based on the protocol definition of relapse (see Table 15). This differs from the investigator's clinical judgment of relapse as the reason for disposition (shown in Table 5).

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Table 11. **CDI, CDRS-R, MASC**
Change from Baseline to Endpoint
All Randomized Patients
Study Period III Visit Group II

Variable / Treatment Group	N	-- Baseline -- Mean SD	-- Endpoint -- Mean SD	----- Mean	Change SD	----- LSMean (a)	Within Group p-value (b)	Between Group p-value (a)
MASC Total Score								
Placebo	74	31.78 15.32	32.33 15.57	0.55	10.01	0.52	0.590	0.559
Atomoxetine	68	31.86 15.41	31.37 16.74	-0.49	10.26	-0.48	0.343	—
Treatment LSMean Difference(95%CI) = 1.01(-2.39 , 4.41)								
MASC Physical Symptoms Score								
Placebo	75	7.07 5.67	7.35 6.14	0.28	4.15	0.41	0.485	0.564
Atomoxetine	68	6.88 5.06	6.68 5.42	-0.20	3.73	0.01	0.367	—
Treatment LSMean Difference(95%CI) = 0.40(-0.97 , 1.77)								
MASC Harm Avoidance Score								
Placebo	75	13.36 4.74	12.65 5.27	-0.71	3.76	-1.00	0.130	0.298
Atomoxetine	68	13.22 5.80	13.01 5.83	-0.21	3.73	-0.34	0.514	—
Treatment LSMean Difference(95%CI) = -0.66(-1.91 , 0.59)								
MASC Social Anxiety Score								
Placebo	74	6.35 5.96	7.59 6.09	1.24	4.62	1.32	0.009	0.069
Atomoxetine	68	6.91 5.33	6.91 5.78	0.00	4.21	-0.05	0.908	—
Treatment LSMean Difference(95%CI) = 1.37(-0.11 , 2.86)								
MASC Separation Score								
Placebo	75	5.00 4.28	4.76 3.88	-0.24	2.82	-0.17	0.356	0.881
Atomoxetine	68	4.84 4.07	4.76 4.97	-0.08	3.13	-0.10	0.609	—
Treatment LSMean Difference(95%CI) = -0.08(-1.12 , 0.97)								

(continued)

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Table 11. **CDI, CDRS-R, MASC**
Change from Baseline to Endpoint
All Randomized Patients
Study Period III Visit Group II (Concluded)

Variable / Treatment Group	N	-- Baseline -- Mean SD	-- Endpoint -- Mean SD	----- Change ----- Mean SD LSMean (a)	Within Group p-value (b)	Between Group p-value (a)
MASC Anxiety Disorders Index						
Placebo	75	8.89 3.63	9.26 4.01	0.37 3.45 0.45	0.350	0.131
Atomoxetine	68	9.24 4.40	8.79 4.05	-0.45 3.33 -0.41	0.228	—
Treatment LSMean Difference(95%CI) = 0.86 (-0.26 , 1.99)						
CDI Total Score						
Placebo	74	8.27 6.52	8.62 6.21	0.35 5.24 0.17	0.433	0.668
Atomoxetine	65	7.03 5.76	7.11 5.63	0.08 4.01 -0.20	0.755	—
Treatment LSMean Difference(95%CI) = 0.37 (-1.35 , 2.09)						
CDRS Total Score						
Placebo	77	21.25 5.12	22.36 4.97	1.12 5.46 1.07	0.076	0.838
Atomoxetine	73	21.37 4.48	22.27 5.75	0.90 4.41 0.90	0.209	—
Treatment LSMean Difference(95%CI) = 0.17 (-1.43 , 1.76)						

(a) LSMeans and Between Groups p-value are from ANOVA model with terms for Treatment and Investigator.

(b) Within Groups p-values obtained from Wilcoxon's Signed-rank Test for mean change from baseline to endpoint.

Population: All randomized patients with at least one baseline and postbaseline measurement.

Baseline visits: 1-22, Endpoint visits: 23-28.

Abbreviations: ANOVA = analysis of variance; CDI = Children's Depression Inventory; CI = confidence interval; LSMean = least-squares mean; MASC = Multidimensional Anxiety Scale for Children; N = number of patients; SD = standard deviation.

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Table 12. **WISC**
Change from Baseline to Endpoint
All Randomized Patients
Study Period III Visit Group II

Variable / Treatment Group	N	-- Baseline -- Mean	-- Baseline -- SD	-- Endpoint -- Mean	-- Endpoint -- SD	----- Change ----- Mean	----- Change ----- SD	----- Change ----- LSMean (a)	Within Group p-value (b)	Between Group p-value (a)
WISC Block Design Scaled Score										
Placebo	49	10.41	4.02	10.45	4.16	0.04	2.06	0.35	0.948	0.391
Atomoxetine	49	10.63	3.17	10.94	3.60	0.31	2.32	0.72	0.407	—
Treatment LSMean Difference(95%CI) = -0.37(-1.24 , 0.49)										
WISC IQ										
Placebo	62	108.23	21.23	107.29	21.62	-0.94	9.30	-0.88	0.411	0.038
Atomoxetine	61	105.82	17.70	107.85	17.45	2.03	8.14	2.53	0.096	—
Treatment LSMean Difference(95%CI) = -3.41(-6.63 , -0.19)										
WISC Pic Arrangement Scaled Score										
Placebo	49	11.67	3.54	12.06	3.91	0.39	3.17	0.44	0.365	0.760
Atomoxetine	49	11.76	4.45	12.22	3.91	0.47	3.48	0.66	0.467	—
Treatment LSMean Difference(95%CI) = -0.22(-1.63 , 1.19)										
WISC Similarities Scaled Score										
Placebo	49	10.67	4.16	10.53	3.88	-0.14	2.57	-0.11	0.452	0.457
Atomoxetine	48	10.83	3.14	11.15	3.08	0.31	2.18	0.25	0.268	—
Treatment LSMean Difference(95%CI) = -0.36(-1.30 , 0.59)										
WISC Vocabulary Scaled Score										
Placebo	49	10.67	3.43	9.90	3.44	-0.78	1.83	-0.90	0.007	0.049
Atomoxetine	49	11.08	3.06	10.88	3.14	-0.20	1.94	-0.13	0.442	—
Treatment LSMean Difference(95%CI) = -0.77(-1.53 , -0.00)										

(continued)

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Table 12. **WISC**
Change from Baseline to Endpoint
All Randomized Patients
Study Period III Visit Group II (Concluded)

Variable / Treatment Group	N	-- Baseline -- Mean SD	-- Endpoint -- Mean SD	----- Change ----- Mean SD LSMean (a)	Within Group p-value (b)	Between Group p-value (a)
WISC Arithmetic Scaled Score						
Placebo	59	8.54 3.53	8.83 3.51	0.29 2.39 0.14	0.377	0.326
Atomoxetine	61	8.70 3.60	8.34 4.35	-0.36 2.84 -0.35	0.263	—
Treatment LSMean Difference(95%CI) = 0.48(-0.49 , 1.46)						
WISC Mazes Scaled Score						
Placebo	45	11.13 3.34	10.64 3.34	-0.49 3.42 -0.76	0.422	0.576
Atomoxetine	45	10.18 3.52	9.71 3.90	-0.47 3.12 -0.37	0.463	—
Treatment LSMean Difference(95%CI) = -0.39(-1.77 , 0.99)						
WISC Mazes Total Subset Score						
Placebo	44	24.89 6.00	24.36 6.11	-0.52 4.07 -0.76	0.493	0.336
Atomoxetine	43	23.00 6.93	22.93 7.41	-0.07 3.55 0.05	0.963	—
Treatment LSMean Difference(95%CI) = -0.81(-2.48 , 0.86)						
WISC Digital Span (Total) Scaled Score						
Placebo	62	8.73 3.45	8.92 3.61	0.19 3.09 0.09	0.494	0.550
Atomoxetine	61	8.51 2.87	8.84 3.24	0.33 2.53 0.39	0.249	—
Treatment LSMean Difference(95%CI) = -0.30(-1.29 , 0.69)						

(a) LSMeans and Between Groups p-value are from ANOVA model with terms for Treatment and Investigator.

(b) Within Groups p-values obtained from Wilcoxon Signed-rank Test for mean change from baseline to endpoint.

Population: All randomized patient with at least one baseline and postbaseline measurement.

Baseline visits: 1-22, Endpoint visits: 23-28.

Abbreviations: CI = confidence interval; LSMean = least-squares mean; N = number of patients; SD = standard deviation; WISC = Wechsler Intelligence scale.

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**Table 13. Cognitive Measurement – DUAL-VWM, Stroop, Trails A, and Trails B
Change from Baseline to Endpoint
All Randomized Patients
Study Period III Visit Group II**

Variable / Treatment Group	N	-- Baseline -- Mean	SD	-- Endpoint -- Mean	SD	----- Change ----- Mean	SD	----- LSMean (a)	Within Group p-value (b)	Between Group p-value (a)

Stroop CW test Interference T Score										
Placebo	67	52.03	6.27	53.13	8.77	1.10	8.37	0.93	0.179	0.877
Atomoxetine	67	52.89	6.24	53.33	7.80	0.43	7.13	0.70	0.238	—
Treatment LSMean Difference(95%CI) = 0.23 (-2.69 , 3.15)										
Dual Working Memory Total Score										
Placebo	68	5.37	2.22	5.40	2.68	0.03	1.97	0.01	0.991	0.305
Atomoxetine	67	4.81	2.17	5.18	2.18	0.37	2.05	0.37	0.125	—
Treatment LSMean Difference(95%CI) = -0.36 (-1.06 , 0.33)										
Trail Making Trials A Time										
Placebo	69	19.97	8.75	19.28	9.93	-0.70	6.88	-1.42	0.111	0.269
Atomoxetine	68	22.19	10.10	19.85	8.27	-2.34	8.78	-2.86	0.012	—
Treatment LSMean Difference(95%CI) = 1.44 (-1.13 , 4.01)										
Trail Making Trials B Time										
Placebo	67	41.66	23.01	38.57	17.97	-3.09	16.16	-2.89	0.203	0.613
Atomoxetine	66	45.74	24.82	43.97	22.56	-1.77	18.90	-1.36	0.496	—
Treatment LSMean Difference(95%CI) = -1.53 (-7.51 , 4.45)										

(a) LSMeans and Between Groups p-value are from ANOVA model with terms for Treatment and Investigator.

(b) Within Groups p-values obtained from Wilcoxon's Signed-rank Test for mean change from baseline to endpoint.

Population: All randomized patient with at least one baseline and postbaseline measurement.

Baseline visits: 1-22, Endpoint visits: 23-28.

Abbreviations: CI = confidence interval; CW = color-word; LSMean = least-squares mean; N = number of patients; SD = standard deviation.

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**Table 14. ADHDRS-IV-Parent:Inv and CGI-ADHD-S
Change from Baseline to Endpoint
Study Period IV**

Variable / Treatment Group	N	-- Baseline -- Mean	SD	-- Endpoint -- Mean	SD	----- Mean	Change SD	----- LSMean (a)	Group p-value (b)	Group p-value (a)
ADHDRS-PI Total Score										
Atomoxetine - No Tape	31	13.74	7.09	17.97	12.57	4.23	11.65	4.37	0.123	0.334
Atomoxetine - Taper	33	12.91	9.53	15.94	12.38	3.03	8.94	1.45	0.055	—
Treatment LSMean Difference(95%CI) = 2.92(-3.13 , 8.97)										
ADHDRS-PI Total T-score										
Atomoxetine - No Tape	31	52.00	6.87	56.20	12.11	4.20	11.44	4.24	0.108	0.393
Atomoxetine - Taper	33	51.99	9.37	55.21	13.20	3.22	9.50	1.60	0.065	—
Treatment LSMean Difference(95%CI) = 2.64(-3.56 , 8.84)										
ADHDRS-PI Hyp/Imp Subscale										
Atomoxetine - No Tape	31	6.42	4.10	8.42	7.07	2.00	5.76	2.01	0.116	0.433
Atomoxetine - Taper	33	5.61	5.36	7.24	7.25	1.64	4.76	0.86	0.122	—
Treatment LSMean Difference(95%CI) = 1.15(-1.79 , 4.08)										
ADHDRS-PI Inatt. Subscale										
Atomoxetine - No Tape	31	7.32	5.17	9.55	6.85	2.23	6.75	2.37	0.147	0.312
Atomoxetine - Taper	33	7.30	5.34	8.70	5.99	1.39	4.53	0.60	0.069	—
Treatment LSMean Difference(95%CI) = 1.77(-1.74 , 5.28)										
CGI ADHD Severity										
Atomoxetine - No Tape	31	1.97	0.66	2.55	1.36	0.58	1.18	0.52	0.011	0.274
Atomoxetine - Taper	34	1.91	0.87	2.24	1.28	0.32	0.98	0.17	0.094	—
Treatment LSMean Difference(95%CI) = 0.35(-0.29 , 0.98)										

(a) LSMeans and Between Groups p-value are from ANOVA model with terms for Treatment and Investigator.
(b) Within Groups p-values obtained from Wilcoxon's Signed-rank Test for mean change from baseline to endpoint.
Population: All randomized patients with at least one baseline and postbaseline measurement.
Baseline visits: 1-28, Endpoint visits: 29-30.

Abbreviations: ADHD = Attention-Deficit/Hyperactivity disorder; ADHDRS-PI = Attention-Deficit/Hyperactivity Disorder Rating Scale; Inatt. = inattention;
LSMean = least-squares mean; N = number of patients; SD = standard deviation.

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Table 15. **Summary of Relapse Rate**
Relapse per Protocol
Randomized Patients
Study Period IV

	----- Relapse -----				Total		Fishers Exact
	ATX-No Taper		ATX-Taper				p-Value
	N	n (%)	N	n (%)	N	n (%)	
Relapse	31	1 (3.2%)	34	0 (0%)	65	1 (1.5%)	0.4769

 Relapse per protocol definition within study Period IV

Note: Relapse as defined by protocol.

Safety

Adverse Events Analysis per Protocol

In Study Period III Visit Group II, 2 TEAEs had >5% incidence rate (headache [n=15, 9.4%] and nasopharyngitis [n=13, 8.1%]). There were no statistically significant differences between the treatment groups (see Table 16).

Table 16. Summary of Treatment-Emergent Adverse Events (≥5%) by System Organ Class Using MedDRA Preferred Terms All Randomized Patients Study Period III Visit Group II

Preferred Term	TMX_TMX (N=79) n (%)	TMX_PLA (N=81) n (%)	Total (N=160) n (%)	p-Value*
PATIENTS WITH ≥ 1 TESS	42 (53.2)	47 (58.0)	89 (55.6)	.633
PATIENTS WITH NO TESS	37 (46.8)	34 (42.0)	71 (44.4)	.633
Headache	8 (10.1)	7 (8.6)	15 (9.4)	.792
Nasopharyngitis	6 (7.6)	7 (8.6)	13 (8.1)	1.00

Population: ALL Randomized Patients in SPIII VG2

Baseline: Visit 22, Endpoint: Visits 23-28

Abbreviations: N = number of patients; n = number of patients in subgroup; PLA = placebo; TESS = treatment-emergent signs and symptoms; TMX = tomoxetine.

In Study Period IV, 1 class of TEAEs had more than a 5% incidence in either treatment group (mood swings: atomoxetine taper n=2 [5.9%]; atomoxetine nontaper n=0 [0.0%]) (see Table 17).

Table 17. Summary of Treatment-Emergent Adverse Events (≥5%) by System Organ Class Using MedDRA Preferred Terms All Randomized Patients Study Period IV

Preferred Term	TMX_TAP (N=34) n (%)	TMX_NTAP (N=31) n (%)	Total (N=65) n (%)	p-Value*
PATIENTS WITH ≥ 1 TESS	8 (23.5)	9 (29.0)	17 (26.2)	.778
PATIENTS WITH NO TESS	26 (76.5)	22 (71.0)	48 (73.8)	.778
Mood swings	2 (5.9)	0	2 (3.1)	

Population: Randomized Patients in Study Period IV

Baseline: Visit 28, Endpoint: Visits 29-30

• Frequencies are analyzed using a Fisher's Exact test.

Abbreviations: N = number of patients; n = number of patients in subgroup; NTAP = nontaper ; TAP = taper; TESS = treatment-emergent signs and symptoms; TMX = tomoxetine.

A total of 7 SAEs were reported by 5 patients (placebo group) during Study Periods III and IV. Of these, 1 SAE was classified as possibly related to study drug. This patient experienced the SAE of incomplete RBBB, which began after 365 days of atomoxetine therapy; the patient was randomized to placebo group at Visit 22 after the onset of this SAE. The patient was discontinued from the study 9 days after Visit 22, 374 days after first receiving study drug. Fourteen days after the SAE was discovered at Visit 22 the patient recovered and an ECG confirmed the disappearance of the incomplete RBBB.

See Table 18 for a listing of all patients who experienced an SAE.

Table 18. **Listing of Serious Adverse Events**
All Patients
Visit 23 Through Visit 30

Obs	VISIT	TRTP3VG1	TRTP3VG2	TRTSP4	ACTTERM
1	23	TMX	PLA		INCOMPLETE RIGHT BUNDLE BRANCH BLOCK
2	28	PLA	OPLA	PLA	INJURY IN ARM CAUSED BY DOG BITE
3	28	PLA	OPLA	PLA	INFECTION IN LEFT ARM
4	28	PLA	OPLA	PLA	MOTOR ACCIDENT
5	29	PLA	OPLA	PLA	MOTOR ACCIDENT
6	24	PLA	OPLA	PLA	SINOVITIS
7	23	TMX	PLA		DEPRESSIVE ILLNESS

Obs	SEREVNT	STDRGRLX
1	Y	YES
2	Y	NO
3	Y	NO
4	Y	NO
5	Y	NO
6	Y	NO
7	Y	NO

trtp3vg1=treatment in SPIII VG1, actterm=actual event term, trtp3vg2=treatment in SPIII VG2, trtsp4=treatment in SP4, serevnt=event serious flag, stdrgrlx=possible related to drug flag

Abbreviations: OPLA = ; PLA = placebo; SP = study period; TMX = tomoxetine; VG = visit group.

Post Hoc Analysis of Hospitalization After Unblinding per FDA Request

On 14 January 2005, the FDA asked Lilly to verify that study sites did not inappropriately hospitalize patients during the trial.

In response, Lilly has thoroughly investigated the hospitalizations that occurred at any site during Study LYAF that were not previously reported as SAEs in the LYAF clinical study reports. Through this process, 5 hospitalizations for 5 patients were identified during Study Period III Visit Group II and Study Period IV.

This study was conducted in Europe under several socialized medical systems. Hospitalizations are permitted in some countries and even encouraged for better observation of the patient by the investigator. Additionally, in some countries, hospitalizations also occur for a number of “social” reasons, such as the need for brief boarding of the patient, or to separate the patient from an undesirable family situation. Of the 5 hospitalizations identified in the post hoc review, 3 were considered observational, 1 was considered social, and 1 was categorized as an SAE.

Hospitalizations Occurring in Study LYAF

Table 19 presents a listing of all 5 hospitalizations that occurred during Study Period III Visit Group II and Study Period IV.

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Table 19. Listing of Hospitalizations Occurring during LYAF Study Period III Visit Group II and Study Period IV

Site-Patient	Reason	Visit	Serious AE	Comments	Discontinue Visit & Reason
C	Social	V29	No	Patient was hospitalized due to social reasons. The patient presented no signs of ADHD and no concomitant disorders. CGI was 1.	Completed
D	Observation	V23	No	Patient was hospitalized for observation due to symptoms of ADHD (attention and learning issues) noted at school and for some family conflicts. The site stated that based on the observation the patient's symptoms have not relapsed. When queried, the site stated that the hospitalization was for observation only, not due to worsening of symptoms.	Completed
E	Observation	V23	No	Patient was hospitalized due to behavioral issues but according to the site personnel, not due to increase in symptoms. The patient was withdrawn from the study due to ECG deviation (ST depression). Since stopping medication and related to the adaptation to the hospital environment, the patient symptoms increased. The investigator commented that the hospitalization was for observation only.	DC at V23 due to adverse event

(continued)

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Table 19. Listing of Hospitalizations Occurring during LYAF Study Period III Visit Group II and Study Period IV (Concluded)

Site-Patient	Reason	Visit	Serious AE	Comments	Discontinue Visit & Reason
F	Observation	V26 – V27	No	Patient was hospitalized for observation. The school and mother noted that the patient was more irritable and less concentrated. These observations were not confirmed and no worsening of symptoms was observed during the hospitalization.	Completed
G	Medical condition, non-psychiatric	V27-V28	Yes	Maxillary Sinusitis and Bilateral Eustachitis. Adverse event was previously reported. However, hospitalization for event was discovered at a follow-up monitoring visit to the site.	Completed

Abbreviations: ADHD = Attention-Deficit/Hyperactivity Disorder; AE = adverse event; CGI = Clinical Global Impressions; DC = discontinued; ECG = electrocardiogram; LOE = lack of efficacy; N/A = not applicable; V = visit.

Post Hoc Analysis of Adverse Events After Unblinding per FDA Request

On 14 January 2005, the FDA asked Lilly to undertake a comprehensive reexamination of the coding of AEs in Study LYAF. As part of the comprehensive reexamination for patients who discontinued, a Lilly physician, who had not previously worked on Study LYAF, reviewed the case report form (CRF) comments fields from the last 2 visits and compared the comments to the AE data to verify that the reason for discontinuation was appropriately recorded. The review determined that a potentially inappropriate reason for discontinuation was listed for 2 discontinued patients in Study Period III Visit Group II and Study Period IV (between Visit 23 and Visit 30). A summary of information on these 2 patients is presented in Table 20. Both were in the atomoxetine treatment group.

Table 20. Summary of Patients with a Potentially Inappropriate Reason for Discontinuation Recorded in Study LYAF – Study Period III Visit Group II and Study Period IV

Patient	Information/Reason for Discontinuation Recorded by the Investigator	Sponsor Determined Reason for Discontinuation
A	Patient stopped study at V23; mother claimed [child] did “life threatening things” Coded as Personal conflict or Other Patient Decision (V23)	Adverse Event
B	Decision to withdraw due to “extreme anxiety” Coded as Personal Conflict or Patient Decision (V25)	Adverse Event

Abbreviations: V23 = Visit 23; V25 = Visit 25.

Adverse Events Analysis per Protocol, Continued

There were no deaths in this study. A total of 2 patients discontinued from the study due to an AE (Study Period III Visit Group II, n=1 on atomoxetine, n=1 on placebo). The patient on atomoxetine discontinued due to ST segment depression; the patient on placebo discontinued due to depression. No patients discontinued due to an AE in Study Period IV. See Tables 21 and 22 for an overview of AEs in Study Period III Visit Group II and Study Period IV.

**Table 21. Overview of Adverse Events
Study Period III Visit Group II**

Adverse Event ^a	Number (%) of Patients	
	Atomoxetine n=79	Placebo n=81
Deaths	0 (0)	0 (0)
Serious adverse events	0 (0)	5 (6.2%)
Discontinuations due to an adverse event	1 (1.3%)	1 (1.2%)
Other clinically significant adverse events	0 (0)	0 (0)
Treatment-emergent adverse events	42 (53.2%)	47 (58.0%)

Abbreviation: n = number of patients.

^a Patients may be counted in more than 1 category.

**Table 22. Overview of Adverse Events
Study Period IV**

Adverse Event ^a	Number (%) of Patients		
	Atomoxetine Taper n=34	Atomoxetine Nontaper n=31	Placebo n=91
Deaths	0 (0)	0 (0)	0 (0)
Serious adverse events	0 (0)	0 (0)	1 (1.1%)
Discontinuations due to an adverse event	0 (0)	0 (0)	0 (0)
Other clinically significant adverse events	0 (0)	0 (0)	0 (0)
Treatment-emergent adverse events	8 (23.5%)	9 (29.0%)	23 (25.3%)

Abbreviation: n = number of patients.

^a Patients may be counted in more than 1 category.

An additional part of the FDA-requested comprehensive reexamination of AE coding was Lilly's review of the investigator comments for all enrolled patients and comparison to the investigator-reported AEs to ensure all AEs were accurately captured in the Lilly database. This review of investigators' comments revealed 29 potentially missed AEs for all patients in Study Period III Visit Group II and Study Period IV. Tables 23 and 24 summarize these additional events from the comments field section of the CRFs.

Table 23. Frequency of Potentially Missed Adverse Events from Comments Field, Visit 23 – Visit 28

Preferred Term	PLA-PLA	TMX-PLA	TMX-TMX
Abnormal Behavior	0	1	0
Behavior Disorder	0	0	2
Blood Bilirubin Increased	0	1	0
Feeling of Despair	0	0	1
Increased Appetite	1	1	0
Insomnia	0	0	1
Irritability	0	0	1
Memory Impairment	0	1	0
Nervousness	1	0	0
Pyrexia	1	0	0
Suicidal Ideation	0	1	0
Synovitis	1	0	0
Weight Increased	1	2	0

Abbreviations: PLA=placebo, TMX=atomoxetine.

Table 24. Frequency of Potentially Missed Adverse Events from Comments Field, Visit 29 – Visit 30

Preferred Term	TMX-Nontaper	PLA	TMX-Taper
Blood Alkaline Phosphate Increased	0	1	0
Blood Bilirubin Increased	0	2	0
Blood Thyroid Stimulating Hormone Abnormal	0	1	0
Blood Thyroid Stimulating Hormone Decreased	1	0	0
Electrocardiogram Abnormal	0	1	1
Electrocardiogram PR Shortened	1	0	0
Initial Insomnia	0	0	1
Laboratory Test Abnormal	0	0	1
Restlessness	0	0	1
White Blood Cell Count Increased	0	0	1

Abbreviations: PLA = placebo; PR = PR interval; TMX = tomoxetine.

Clinical Laboratory

Table 25 summarizes the mean change by treatment group during Study Period III Visit Group II. Statistically significant ($p < .05$) treatment differences in mean change scores were observed for: hemoglobin, alkaline phosphatase, total protein, and uric acid.

Table 25. Summary of Laboratory Data
Mean Change from Baseline to Endpoint by Analyte
Study Period III Visit Group II

Lab Test	Lab Unit	Therapy	n	--Baseline--		Change to --Endpoint--		p-Values
				Mean	SD	Mean	SD	
HCT	l	TMX_TMX	68	0.399	0.032	0.009	0.030	.133
		TMX_PLA	73	0.395	0.026	0.002	0.028	
HGB	mm1/L-Fe	TMX_TMX	69	8.528	0.656	0.132	0.516	.029
		TMX_PLA	73	8.480	0.475	-0.045	0.338	
RBC	TI/L	TMX_TMX	69	4.899	0.439	0.057	0.289	.424
		TMX_PLA	73	4.875	0.329	0.018	0.218	
WBC	GI/L	TMX_TMX	69	6.611	1.670	-0.014	1.445	.583
		TMX_PLA	73	6.857	2.787	-0.082	2.640	
BANDS	GI/L	TMX_TMX	69	0.000	0.000	0.000	0.000	*
		TMX_PLA	73	0.000	0.000	0.000	0.000	
POLYS	GI/L	TMX_TMX	69	3.371	1.236	-0.052	1.131	.486
		TMX_PLA	73	3.634	2.158	-0.134	2.215	
LYMPHS	GI/L	TMX_TMX	69	2.588	0.634	0.022	0.675	.617
		TMX_PLA	73	2.525	0.784	-0.012	0.624	
MONOS	GI/L	TMX_TMX	69	0.386	0.130	0.003	0.103	.260
		TMX_PLA	73	0.408	0.167	0.019	0.140	
EOSN	GI/L	TMX_TMX	69	0.211	0.195	0.016	0.149	.539
		TMX_PLA	73	0.236	0.218	0.051	0.598	
BASO	GI/L	TMX_TMX	69	0.053	0.024	-0.002	0.032	.605
		TMX_PLA	73	0.050	0.030	-0.001	0.028	
MCV	fL	TMX_TMX	68	82.059	5.866	0.485	3.945	.287
		TMX_PLA	73	81.521	5.276	-0.315	4.209	
PLTCT	GI/L	TMX_TMX	69	309.884	75.263	-0.130	68.132	.935
		TMX_PLA	72	306.986	78.864	1.097	58.886	
U-SPGR	NO UNITS	TMX_TMX	69	1.024	0.006	0.000	0.008	.269
		TMX_PLA	73	1.025	0.006	-0.001	0.007	
AST	U/L	TMX_TMX	69	26.188	5.470	0.058	4.348	.247
		TMX_PLA	71	26.338	6.050	0.901	4.926	
ALT	U/L	TMX_TMX	70	17.771	7.850	0.343	5.808	.086
		TMX_PLA	71	17.282	5.509	2.493	8.267	

(continued)

Table 25. **Summary of Laboratory Data**
Mean Change from Baseline to Endpoint by Analyte
Study Period III Visit Group II (Continued)

Lab Test	Lab Unit	Therapy	n	--Baseline--		Change to --Endpoint--		p-Values
				Mean	SD	Mean	SD	
CPK	U/L	TMX_TMX	71	121.803	51.950	12.592	66.591	.198
		TMX_PLA	71	122.803	55.964	19.690	68.297	
ALKPH	U/L	TMX_TMX	71	225.423	69.207	7.211	47.355	.028
		TMX_PLA	71	219.380	60.780	22.577	42.804	
GGT	U/L	TMX_TMX	71	12.507	3.585	0.620	2.717	.697
		TMX_PLA	71	11.986	2.866	0.648	2.678	
BUN	mmol/L	TMX_TMX	70	4.519	1.175	0.189	1.187	.191
		TMX_PLA	71	4.576	1.058	0.448	1.069	
CALC	mmol/L	TMX_TMX	71	2.440	0.085	0.011	0.109	.077
		TMX_PLA	71	2.452	0.090	-0.032	0.133	
PHOS	mmol/L	TMX_TMX	71	1.534	0.179	0.032	0.177	.543
		TMX_PLA	71	1.554	0.189	0.051	0.203	
SODIUM	mmol/L	TMX_TMX	70	140.929	2.228	-0.443	2.641	.660
		TMX_PLA	70	140.786	1.985	-0.157	2.641	
POTAS	mmol/L	TMX_TMX	70	4.259	0.305	0.059	0.420	.299
		TMX_PLA	71	4.296	0.403	0.085	0.389	
CHLOR	mmol/L	TMX_TMX	70	102.443	2.338	0.757	3.104	.730
		TMX_PLA	70	102.357	2.252	0.786	2.864	
TPROT	g/L	TMX_TMX	71	72.634	4.317	0.183	4.955	.032
		TMX_PLA	71	73.296	4.012	-1.479	3.710	
ALBUM	g/L	TMX_TMX	71	44.070	3.150	-0.042	3.100	.316
		TMX_PLA	71	44.141	2.706	-0.592	2.786	
NFGLU	mmol/L	TMX_TMX	71	5.134	0.967	-0.054	1.050	.969
		TMX_PLA	71	4.994	0.811	-0.035	1.031	
UR AC	umol/L	TMX_TMX	71	236.496	72.594	8.629	39.974	<.001
		TMX_PLA	71	237.752	57.360	31.248	45.240	
CHOL	mmol/L	TMX_TMX	71	4.265	0.842	-0.121	0.418	.540
		TMX_PLA	71	4.326	0.711	-0.147	0.474	
BICARB	mmol/L	TMX_TMX	70	22.229	1.792	-0.777	2.231	.326
		TMX_PLA	69	21.884	2.361	-0.246	2.747	
CREAT	umol/L	TMX_TMX	71	50.176	9.184	-1.121	7.897	.902
		TMX_PLA	71	51.048	10.156	-0.996	6.607	
T.BILI	umol/L	TMX_TMX	68	7.368	3.609	0.402	2.153	.179
		TMX_PLA	68	7.745	4.225	1.056	2.724	

(continued)

**Table 25. Summary of Laboratory Data
Mean Change from Baseline to Endpoint by Analyte
Study Period III Visit Group II (Concluded)**

Population: ALL Randomized Patients in SPIII VG2

Baseline: Visits 1-22, Endpoint: Visits 23-28

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks:
PROC GLM model=treatment.

Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.

Legend of Lab Test Code Abbreviations:

Abbrev.	Description
HCT	HEMATOCRIT
HGB	HEMOGLOBIN
RBC	ERYTHROCYTE COUNT
WBC	LEUKOCYTE COUNT
BANDS	BANDS
POLYS	NEUTROPHILS, SEGMENTED
LYMPHS	LYMPHOCYTES
MONOS	MONOCYTES
EOSN	EOSINOPHILS
BASO	BASOPHILS
MCV	MEAN CELL VOLUME (MCV)
PLTCT	PLATELET COUNT
U-SPGR	UA-SPECIFIC GRAVITY
AST	AST/SGOT
ALT	ALT/SGPT
CPK	CREATINE PHOSPHOKINASE
ALKPH	ALKALINE PHOSPHATASE
GGT	GGT (GGPT/SGGT/YGGT)
BUN	UREA NITROGEN
CALC	CALCIUM
PHOS	INORGANIC PHOSPHORUS
SODIUM	SODIUM
POTAS	POTASSIUM
CHLOR	CHLORIDE
TPROT	TOTAL PROTEIN
ALBUM	ALBUMIN
NFGLU	GLUCOSE, NON-FASTING
UR AC	URIC ACID
CHOL	CHOLESTEROL
BICARB	BICARBONATE, HCO ₃
CREAT	CREATININE
T.BILI	BILIRUBIN, TOTAL

In Study Period IV, using the last nonmissing values from Visits 1 to 28 as the baseline, statistically significant treatment differences between the tapered atomoxetine discontinuation, nontapered atomoxetine discontinuation, and placebo groups in mean change scores ($p < .05$) were observed for: hemoglobin, red blood cell count, basophils, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, creatinine, and uric acid (Table 26).

Using the last nonmissing values from Visits 1 to 2 as the baseline, statistically significant treatment differences in Study Period IV's mean change scores ($p < .05$) were observed for: AST, ALT, alkaline phosphatase, and cholesterol (Table 27).

For the percentage of patients in Study Period III Visit Group II whose laboratory values were normal at the respective baseline, but were found to be above or below the normal range at any time after randomization, there was no statistically significant treatment difference (that is, $p \leq .05$) between the atomoxetine and placebo treatment groups for any of the analytes examined.

There were no statistically significant treatment differences (that is, $p \leq .05$) in Study Period IV between the tapered atomoxetine discontinuation and nontapered discontinuation groups for any lab analytes examined.

**Table 26. Condensed Summary of Lab Data
Change from Baseline (Visit 28)
Randomized Patients
Study Period IV**

Research Project Code: B4Z

Lab Test	Lab Unit	Therapy	n	-----Baseline-----		Change to -----Endpoint-----		p-Values
				Mean	SD	Mean	SD	
HGB	mmol/L-Fe	TMX_TAP	30	8.554	0.614	-0.203	0.401	.008
		TMX_NTAP	28	8.717	0.547	-0.277	0.324	
		PLACEBO	76	8.510	0.630	-0.047	0.397	
RBC	TI/L	TMX_TAP	30	4.897	0.446	-0.110	0.243	.028
		TMX_NTAP	28	4.911	0.326	-0.150	0.205	
		PLACEBO	76	4.924	0.397	-0.038	0.221	
BASO	GI/L	TMX_TAP	30	0.048	0.032	0.017	0.041	.044
		TMX_NTAP	28	0.049	0.026	0.004	0.030	
		PLACEBO	76	0.052	0.029	-0.000	0.031	
AST	U/L	TMX_TAP	28	26.500	6.101	0.679	5.838	<.001
		TMX_NTAP	28	24.786	4.483	11.429	38.705	
		PLACEBO	74	26.716	6.420	-0.919	4.788	
ALT	U/L	TMX_TAP	29	18.207	6.516	4.207	14.698	<.001
		TMX_NTAP	28	17.857	5.746	19.500	67.411	
		PLACEBO	77	18.052	5.760	-0.636	4.763	
ALKPH	U/L	TMX_TAP	30	229.300	60.948	5.433	30.606	.003
		TMX_NTAP	28	238.429	104.764	-12.929	27.417	
		PLACEBO	78	259.051	80.497	-4.628	27.224	
UR AC	umol/L	TMX_TAP	30	231.972	70.464	20.818	46.278	.004
		TMX_NTAP	28	248.541	73.659	7.435	52.547	
		PLACEBO	78	280.624	72.410	-7.397	39.758	
CREAT	umol/L	TMX_TAP	30	49.209	8.896	4.125	7.952	.031
		TMX_NTAP	28	49.567	8.102	-1.263	7.499	
		PLACEBO	78	52.360	10.447	1.587	7.899	

Population: All Patients in Study Period IV

Baseline: Visits 1-28, Endpoint: Visits 29-30

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULLL1 - Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks:
PROC GLM model=treatment.

Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.

Legend of Lab Test Code Abbreviations:

Abbrev.	Description
HGB	HEMOGLOBIN
RBC	ERYTHROCYTE COUNT
BASO	BASOPHILS
AST	AST/SGOT
ALT	ALT/SGPT
ALKPH	ALKALINE PHOSPHATASE
UR AC	URIC ACID
CREAT	CREATININE

**Table 27. Condensed Summary of Lab Data
Change from Baseline (Visit 2)
Randomized Patients
Study Period IV**

Research Project Code: B4Z

Lab Test	Lab Unit	Therapy	n	-----Baseline-----		Change to -----Endpoint-----		p-Values
				Mean	SD	Mean	SD	
AST	U/L	TMX_TAP	27	29.185	5.414	-1.963	5.977	.007
		TMX_NTAP	28	27.571	4.290	8.643	41.157	
		PLACEBO	74	28.838	6.413	-3.041	6.049	
ALT	U/L	TMX_TAP	28	21.857	14.015	0.893	6.903	.005
		TMX_NTAP	28	18.929	6.283	18.429	70.349	
		PLACEBO	77	19.623	7.638	-2.208	7.494	
ALKPH	U/L	TMX_TAP	29	264.172	68.384	-29.517	71.290	.008
		TMX_NTAP	28	246.464	76.421	-20.964	87.344	
		PLACEBO	77	254.260	67.341	1.156	66.774	
CHOL	mmol/L	TMX_TAP	29	4.311	0.918	-0.257	0.366	.005
		TMX_NTAP	28	4.153	0.809	0.082	0.507	
		PLACEBO	78	4.384	0.781	-0.322	0.539	

Population: All Patients in Study Period IV

Baseline: Visits 1-2, Endpoint: Visits 29-30

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks:
PROC GLM model=treatment.

Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.

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Legend of Lab Test Code Abbreviations:

Abbrev.	Description
AST	AST/SGOT
ALT	ALT/SGPT
ALKPH	ALKALINE PHOSPHATASE
CHOL	CHOLESTEROL

Vital Signs

Table 28 summarizes the mean change from baseline to endpoint in vital sign measures from Study Period III Visit Group II. There were statistically significant differences between the atomoxetine and placebo treatment groups for: mean weight change, average heart rate, and temperature when analyzed for all randomized patients. Patients in the placebo group tended to gain more weight, and had a decrease in heart rate and temperature. There was no statistically significant difference in height change between the 2 treatment groups.

Table 28. **Summary of Vital Sign Data**
Change from Baseline to Endpoint
All Randomized Patients
Study Period III Visit Group II

			-----Baseline-----		Change to -----Endpoint-----		p-Values
Variables							
Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy
DIASAVG	TMX_TM	77	69.058	9.632	-0.234	10.452	.275
	TMX_PLA	81	69.975	8.546	-1.975	9.513	
SYSAVG	TMX_TM	77	106.416	11.975	1.201	10.039	.784
	TMX_PLA	81	108.309	10.968	0.741	11.014	
PULSAVG	TMX_TM	77	84.740	11.415	0.273	12.245	<.001
	TMX_PLA	81	87.389	11.731	-7.525	11.883	
WEIGHT	TMX_TM	77	42.282	15.373	2.218	1.795	<.001
	TMX_PLA	81	42.844	14.314	4.936	3.864	
HEIGHT	TMX_TM	74	148.895	15.796	3.057	2.239	.928
	TMX_PLA	76	150.114	13.802	3.024	2.260	
TEMP	TMX_TM	77	36.379	0.480	0.147	0.495	.038
	TMX_PLA	81	36.526	0.448	-0.011	0.450	

Population: ALL Randomized Patients in SPIII VG2

Baseline: Visits 1-22, Endpoint: Visits 23-28

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.

Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Legend of Variable Abbreviations:

Abbrev.	Description
-----	-----
DIASAVG	Diastolic BP Average
HEIGHT	Height in CM
PULSAVG	Heart Rate Average
SYSAVG	Systolic BP Average
TEMP	Temperature in Centigrade
WEIGHT	Weight in KG

Table 29 summarizes the mean change from baseline (Visit 28) to endpoint in vital sign measures from Study Period IV. There was a statistically significant difference between atomoxetine taper and nontaper groups for mean diastolic blood pressure when analyzed for all randomized patients. Tapered patients had a decrease in diastolic blood pressure, while patients who discontinued atomoxetine abruptly had an increase in diastolic blood pressure (p=.029).

Table 29. **Summary of Vital Sign Data**
Change from Baseline to Endpoint
All Randomized Patients
Study Period IV

			-----Baseline-----		Change to -----Endpoint-----		p-Values
Variables							
Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy
DIASAVG	TMX_TAP	34	69.750	8.530	-2.956	8.336	.029
	TMX_NTAP	31	68.016	7.714	1.323	7.005	
SYSAVG	TMX_TAP	34	108.691	12.815	-1.132	8.468	.388
	TMX_NTAP	31	106.855	12.659	0.581	7.313	
PULSAVG	TMX_TAP	34	86.426	10.604	-2.735	8.850	.898
	TMX_NTAP	31	85.823	11.787	-3.032	9.712	
WEIGHT	TMX_TAP	34	44.491	13.422	0.426	0.759	.146
	TMX_NTAP	31	41.881	16.418	0.726	0.881	
HEIGHT	TMX_TAP	34	153.559	15.977	0.568	1.262	.469
	TMX_NTAP	31	150.087	16.459	0.377	0.752	
TEMP	TMX_TAP	34	36.606	0.480	-0.144	0.405	.759
	TMX_NTAP	31	36.477	0.418	-0.113	0.410	

Population: Randomized Patients in Study Period IV

Baseline: Visits 1-28, Endpoint: Visits 29-30

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.

Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Legend of Variable Abbreviations:

Abbrev.	Description
-----	-----
DIASAVG	Diastolic BP Average
HEIGHT	Height in CM
PULSAVG	Heart Rate Average
SYSAVG	Systolic BP Average
TEMP	Temperature in Centigrade
WEIGHT	Weight in KG

In regard to the mean change from baseline (Visit 2) to endpoint in vital sign measures from Study Period IV there were no statistically significant differences between atomoxetine taper and nontaper groups for any of the vital signs analyzed for all randomized patients (Table 30).

Table 30. **Condensed Summary of Vital Sign Data**
Change from Baseline (Visit 2)
Randomized Patients
Study Period IV

		-----Baseline-----		Change to -----Endpoint-----		p-Values		
Variables	Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy
DIASAVG		TMX_TAP	34	65.265	8.667	1.529	9.803	.198
		TMX_NTAP	31	64.661	7.523	4.677	9.689	
SYSAVG		TMX_TAP	34	103.206	12.842	4.353	15.813	.664
		TMX_NTAP	31	104.532	9.272	2.903	9.984	
PULSAVG		TMX_TAP	34	80.074	9.752	3.618	10.370	.346
		TMX_NTAP	31	76.742	8.872	6.048	10.223	
WEIGHT		TMX_TAP	34	42.053	13.090	2.865	3.788	.255
		TMX_NTAP	31	38.584	14.764	4.023	4.336	
HEIGHT		TMX_TAP	34	146.112	15.576	8.015	2.656	.443
		TMX_NTAP	31	142.974	16.139	7.490	2.823	
TEMP		TMX_TAP	34	36.471	0.363	-0.009	0.397	.326
		TMX_NTAP	31	36.477	0.337	-0.113	0.451	

Population: Randomized Patients in Study Period IV

Baseline: Visits 1-2, Endpoint: Visits 29-30

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
 model=treatment.
 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Abbrev.	Description
-----	-----
DIASAVG	Diastolic BP Average
HEIGHT	Height in CM
PULSAVG	Heart Rate Average
SYS AVG	Systolic BP Average
TEMP	Temperature in Centigrade
WEIGHT	Weight in KG

Electrocardiograms (ECGs)

Table 31 summarizes the mean change from Study Period III Visit Group II baseline-to-endpoint ECG intervals and heart rate. Statistically significant differences between atomoxetine and placebo were found for: RR, PR, QT, and QTcB intervals, and heart rate, but not for QTcF.

**Table 31. Summary of Changes from Baseline ECG
All Randomized Patients
Study Period III Visit Group II**

Variables Analyzed	Therapy	n	-----Baseline-----		Change to -----Endpoint-----		p-Values
			Mean	SD	Mean	SD	
RR	TMX_TMX	73	725.276	116.947	8.864	115.158	<.001
	TMX_PLA	72	705.256	97.623	137.529	115.817	
PR	TMX_TMX	73	132.137	18.792	-0.685	11.087	.014
	TMX_PLA	72	133.111	17.263	4.458	13.686	
QRS	TMX_TMX	73	85.973	9.455	0.329	7.565	.208
	TMX_PLA	72	86.056	14.936	-1.944	13.343	
QT	TMX_TMX	73	357.589	24.862	1.973	23.853	<.001
	TMX_PLA	72	355.444	25.926	24.000	23.688	
QTCB	TMX_TMX	73	421.425	18.776	-0.055	16.043	.003
	TMX_PLA	72	424.125	19.340	-9.625	22.139	
QTCF	TMX_TMX	73	398.974	15.910	0.633	13.637	.464
	TMX_PLA	72	399.937	18.493	2.600	18.331	
QTCD	TMX_TMX	73	406.578	16.141	0.402	13.663	.507
	TMX_PLA	72	408.120	18.272	-1.431	19.097	
HR	TMX_TMX	73	84.712	12.687	-0.534	11.925	<.001
	TMX_PLA	72	86.681	11.910	-14.056	12.077	

Population: ALL Randomized Patients in SPIII VG2

Baseline: Visits 1-22, Endpoint: Visits 23-28

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM

model=treatment.

Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

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Legend of Variable Abbreviations:

Abbrev.	Description
HR	ECG Heart Rate
PR	PR Interval
QRS	QRS Interval
QT	QT Interval
QTCB	Bazett QTC Interval
QTCD	Data Corrected QTC Interval
QTCF	Fridericia QTC Interval
RR	RR Interval

Table 32 summarizes the mean change from Study Period IV baseline (Visit 28) to endpoint ECG intervals and heart rate. A statistically significant difference (p=.014) between tapered atomoxetine discontinuation and nontapered discontinuation was found for the PR interval.

**Table 32. Summary of Changes from Baseline ECG
All Randomized Patients
Study Period IV**

Variables Analyzed	Therapy	n	-----Baseline-----		Change to -----Endpoint-----		p-Values
			Mean	SD	Mean	SD	
RR	TMX_TAP	33	725.777	132.787	43.869	124.569	.864
	TMX_NTAP	29	713.985	97.815	38.994	93.526	
PR	TMX_TAP	33	134.424	20.855	-1.455	13.410	.014
	TMX_NTAP	29	128.690	13.387	5.931	8.610	
QRS	TMX_TAP	33	86.545	13.335	0.000	8.185	.098
	TMX_NTAP	29	87.724	11.209	-3.310	7.177	
QT	TMX_TAP	33	358.061	31.735	10.182	25.516	.318
	TMX_NTAP	29	356.414	22.661	4.414	18.434	
QTCB	TMX_TAP	33	421.970	17.359	-0.758	18.169	.290
	TMX_NTAP	29	422.621	14.929	-5.414	15.896	
QTCF	TMX_TAP	33	399.422	17.346	3.335	15.147	.151
	TMX_NTAP	29	399.390	13.618	-1.827	12.408	
QTCD	TMX_TAP	33	407.058	16.367	2.015	15.357	.174
	TMX_NTAP	29	407.273	13.388	-3.006	13.046	
HR	TMX_TAP	33	85.333	15.286	-5.030	12.729	.741
	TMX_NTAP	29	85.483	11.005	-4.034	10.588	

Population: Randomized Patients in Study Period IV

Baseline: Visits 1-28, Endpoint: Visits 29-30

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.

Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Legend of Variable Abbreviations:

Abbrev.	Description
-----	-----
HR	ECG Heart Rate
PR	PR Interval
QRS	QRS Interval
QT	QT Interval
QTCB	Bazett QTC Interval
QTCD	Data Corrected QTC Interval
QTCF	Fridericia QTC Interval
RR	RR Interval

In regard to the mean change from baseline (Visit 2) to endpoint in ECG measures from Study Period IV, no statistically significant difference was observed between the 2 treatment groups (Table 33).

**Table 33. Condensed Summary of ECG Data
Change from Baseline (Visit 2) to Endpoint
Randomized Patients
Study Period IV**

Variables Analyzed	Therapy	n	Change to				p-Values
			-----Baseline-----	-----Endpoint-----	Mean	SD	
RR	TMX_TAP	33	810.297	114.111	-40.651	121.644	.425
	TMX_NTAP	29	819.008	125.000	-66.029	127.186	
PR	TMX_TAP	33	136.606	24.023	-3.636	11.330	.306
	TMX_NTAP	29	135.034	13.842	-0.414	13.238	
QRS	TMX_TAP	33	85.333	10.661	1.212	7.175	.551
	TMX_NTAP	29	84.276	8.137	0.138	6.885	
QT	TMX_TAP	33	372.485	26.415	-4.242	29.697	.112
	TMX_NTAP	29	376.690	30.651	-15.862	26.629	
QTCB	TMX_TAP	33	414.727	16.823	6.485	20.184	.220
	TMX_NTAP	29	416.897	13.216	0.310	18.830	
QTCF	TMX_TAP	33	400.187	16.238	2.570	19.708	.084
	TMX_NTAP	29	403.111	16.281	-5.548	16.205	
QTCD	TMX_TAP	33	405.185	15.792	3.888	19.302	.106
	TMX_NTAP	29	407.881	14.600	-3.614	16.295	
HR	TMX_TAP	33	75.515	10.869	4.788	11.327	.566
	TMX_NTAP	29	74.862	11.057	6.586	13.238	

Population: Randomized Patients in Study Period IV

Baseline: Visits 1-2, Endpoint: Visits 29-30

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Abbrev.	Description
HR	ECG Heart Rate
PR	PR Interval
QRS	QRS Interval
QT	QT Interval
QTCB	Bazett QTC Interval
QTCD	Data Corrected QTC Interval
QTCF	Fridericia QTC Interval
RR	RR Interval

Health Outcomes

Quality of life was assessed during the study using the CHQ.

There were no statistically significant differences between the 2 treatment groups on any of the subscales for the CHQ at the end of Study Period III Visit Group II (see Table 34).

Table 35 summarizes the mean change from baseline to endpoint for the CHQ quality-of-life variables during Study Period IV. There was a statistically significant difference between the tapered atomoxetine discontinuation group and the nontapered atomoxetine discontinuation group on the Psychosocial Summary Subscale ($p=.032$). There was no statistically significant difference between the 2 discontinuation groups on the Behavior Subscale ($p=.059$). The tapered atomoxetine discontinuation group showed symptom worsening while the nontapered atomoxetine discontinuation group had symptom improvement on these 2 subscales (see Table 35).

Atomoxetine

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Table 34. **Child Health Questionnaire (CHQ)**
Change from Baseline to Endpoint
Study Period III Visit Group II

Variable / Treatment Group	N	-- Baseline -- Mean SD	-- Endpoint -- Mean SD	----- Change ----- Mean SD	----- LSMean (a)	Within Group p-value (b)	Between Group p-value (a)
Behavior							
Placebo	62	66.68 16.67	59.60 19.79	-7.08 19.40	-6.34	0.012	0.235
Atomoxetine	60	66.15 16.16	63.78 15.74	-2.37 16.27	-2.32	0.348	—
LSMean Difference(95%CI) = -4.03(-10.72 , 2.66)							
Bodily Pain							
Placebo	62	79.84 20.36	78.71 21.08	-1.13 22.77	-0.76	0.533	0.594
Atomoxetine	60	86.17 18.51	83.33 19.63	-2.83 22.25	-3.02	0.391	—
LSMean Difference(95%CI) = 2.26(-6.13 , 10.65)							
Family Activities							
Placebo	62	75.98 21.54	70.50 24.21	-5.48 22.16	-4.01	0.048	0.831
Atomoxetine	60	76.13 19.78	71.62 21.68	-4.52 19.99	-3.12	0.090	—
LSMean Difference(95%CI) = -0.89(-9.11 , 7.34)							
General Health							
Placebo	62	75.45 15.80	76.42 15.78	0.97 15.35	0.03	0.600	0.628
Atomoxetine	60	77.92 17.30	77.55 15.33	-0.37 12.59	-1.29	0.858	—
LSMean Difference(95%CI) = 1.32(-4.07 , 6.71)							
Mental Health							
Placebo	62	72.66 14.70	73.23 15.74	0.56 13.73	-0.03	0.677	0.423
Atomoxetine	60	74.50 14.78	73.75 14.37	-0.75 14.75	-2.20	0.737	—
LSMean Difference(95%CI) = 2.18(-3.20 , 7.55)							
Parent Impact-Emotion							
Placebo	62	66.23 19.83	59.90 23.38	-6.32 21.39	-4.68	0.022	0.843
Atomoxetine	60	67.17 22.16	61.75 25.02	-5.42 27.17	-3.74	0.184	—
LSMean Difference(95%CI) = -0.94(-10.31 , 8.43)							

(a) LSMeans and Between Groups p-values are from ANOVA model with terms for Treatment and Investigator.
(b) Within Groups p-values obtained from Wilcoxon's Signed-rank Test for mean change from baseline to endpoint.
Population: All randomized patient with at least one baseline and postbaseline measurement.

(continued)

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Table 34. **Child Health Questionnaire (CHQ)**
Change from Baseline to Endpoint
Study Period III Visit Group II (Continued)

Variable / Treatment Group	N	-- Baseline -- Mean SD	-- Endpoint -- Mean SD	----- Change ----- Mean SD LSMean (a)	Within Group p-value (b)	Between Group p-value (a)
Physical Functioning						
Placebo	62	98.48 5.22	93.90 17.22	-4.58 17.81 -4.55	0.037	0.070
Atomoxetine	60	96.63 7.96	96.75 9.75	0.12 12.82 0.77	0.576	—
LSMean Difference(95%CI) = -5.32(-11.09 , 0.44)						
Physical Summary Score						
Placebo	62	54.47 5.55	52.97 9.54	-1.50 9.20 -1.30	0.631	0.341
Atomoxetine	59	54.93 6.37	54.58 6.02	-0.36 8.02 0.28	0.788	—
LSMean Difference(95%CI) = -1.58(-4.87 , 1.70)						
Psychosocial Summary Score						
Placebo	62	44.32 10.00	41.44 11.27	-2.89 10.86 -2.77	0.077	0.354
Atomoxetine	59	45.63 8.86	44.76 7.78	-0.86 10.06 -0.91	0.736	—
LSMean Difference(95%CI) = -1.86(-5.81 , 2.10)						
Parent Time Impact						
Placebo	62	81.81 19.19	75.50 23.45	-6.31 24.85 -5.59	0.093	0.097
Atomoxetine	60	82.72 18.21	84.68 16.98	1.97 24.83 2.56	0.653	—
LSMean Difference(95%CI) = -8.14(-17.79 , 1.50)						
Role-Emotion/Behavior						
Placebo	62	86.84 22.11	80.02 29.06	-6.82 30.09 -5.55	0.079	0.255
Atomoxetine	60	89.42 19.78	89.38 19.56	-0.03 24.65 0.45	0.916	—
LSMean Difference(95%CI) = -6.01(-16.42 , 4.41)						
Role-Physical						
Placebo	62	95.92 13.17	92.69 20.46	-3.23 25.55 -2.33	0.383	0.473
Atomoxetine	59	96.25 10.50	95.14 14.68	-1.12 17.97 0.69	0.781	—
LSMean Difference(95%CI) = -3.02(-11.35 , 5.30)						

(a) LSMeans and Between Groups p-values are from ANOVA model with terms for Treatment and Investigator.
(b) Within Groups p-values obtained from Wilcoxon's Signed-rank Test for mean change from baseline to endpoint.
Population: All randomized patient with at least one baseline and postbaseline measurement.

(continued)

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**Table 34. Child Health Questionnaire (CHQ)
Change from Baseline to Endpoint
Study Period III Visit Group II (Concluded)**

Variable / Treatment Group	N	-- Baseline --		-- Endpoint --		----- Change -----			Within Group p-value (b)	Between Group p-value (a)
		Mean	SD	Mean	SD	Mean	SD	LSMean (a)		

Self-Esteem										
Placebo	62	70.56	17.91	67.87	15.31	-2.69	18.42	-4.14	0.125	0.822
Atomoxetine	59	75.02	16.39	72.80	14.68	-2.22	19.01	-3.33	0.555	—
LSMean Difference(95%CI) = -0.82(-8.03 , 6.39)										
Single Item Family Cohesion										
Placebo	62	60.81	28.32	57.90	28.25	-2.90	23.09	-1.34	0.488	0.680
Atomoxetine	60	63.92	22.94	62.25	22.24	-1.67	22.03	0.44	0.702	—
LSMean Difference(95%CI) = -1.78(-10.31 , 6.75)										
Change in Health Item										
Placebo	61	3.64	0.86	3.43	0.81	-0.21	0.90	-0.31	0.065	0.195
Atomoxetine	60	3.65	0.90	3.68	0.87	0.03	0.86	-0.09	0.758	—
LSMean Difference(95%CI) = -0.22(-0.55 , 0.11)										

(a) LSMeans and Between Groups p-values are from ANOVA model with terms for Treatment and Investigator.

(b) Within Groups p-values obtained from Wilcoxon's Signed-rank Test for mean change from baseline to endpoint.

Population: All randomized patient with at least one baseline and postbaseline measurement.

Abbreviations: CI = confidence interval; LSMean = least-squares mean; N = number of patients; SD = standard deviation.

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**Table 35. Child Health Questionnaire (CHQ)
Change from Baseline to Endpoint
Study Period IV**

Variable / Treatment Group	N	-- Baseline -- Mean SD	-- Endpoint -- Mean SD	Change Mean SD	LSMean (a)	Within Group p-value (b)	Between Group p-value (a)
Behavior							
Atomoxetine - No Taper	25	60.88 13.94	63.20 16.55	2.32 13.98	4.02	0.371	0.059
Atomoxetine - Taper	28	66.79 16.84	64.29 19.31	-2.50 12.35	-5.43	0.513	—
LSMean Difference(95%CI) = 9.45(-0.39 , 19.28)							
Bodily Pain							
Atomoxetine - No Taper	25	86.00 15.55	87.60 16.40	1.60 20.14	1.22	0.665	0.826
Atomoxetine - Taper	28	81.43 21.21	78.21 18.27	-3.21 20.38	-0.21	0.318	—
LSMean Difference(95%CI) = 1.43(-11.81 , 14.67)							
Family Activities							
Atomoxetine - No Taper	25	69.04 20.59	73.20 21.19	4.16 18.72	2.62	0.353	0.425
Atomoxetine - Taper	28	73.75 24.99	74.07 19.61	0.32 13.78	-2.12	0.893	—
LSMean Difference(95%CI) = 4.73(-7.26 , 16.72)							
General Health							
Atomoxetine - No Taper	25	77.24 18.80	78.32 19.07	1.08 12.17	-0.25	0.556	0.877
Atomoxetine - Taper	28	79.54 11.65	80.61 11.27	1.07 11.26	-0.91	0.576	—
LSMean Difference(95%CI) = 0.66(-8.01 , 9.33)							
Mental Health							
Atomoxetine - No Taper	25	73.00 15.14	78.00 17.74	5.00 12.33	3.85	0.029	0.390
Atomoxetine - Taper	28	76.25 12.95	76.61 13.88	0.36 9.32	0.82	0.816	—
LSMean Difference(95%CI) = 3.04(-4.10 , 10.18)							
Parent Impact-Emotion							
Atomoxetine - No Taper	25	58.96 24.74	57.72 23.63	-1.24 21.75	-0.95	0.839	0.277
Atomoxetine - Taper	28	69.32 24.24	62.14 23.29	-7.18 18.32	-8.64	0.073	—
LSMean Difference(95%CI) = 7.70(-6.56 , 21.95)							

(a) LSMeans and Between Groups p-values are from ANOVA model with terms for Treatment and Investigator.
(b) Within Groups p-values obtained from Wilcoxon's Signed-rank Test for mean change from baseline to endpoint.
Population: All randomized patient with at least one baseline and postbaseline measurement.

(continued)

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**Table 35. Child Health Questionnaire (CHQ)
Change from Baseline to Endpoint
Study Period IV (Continued)**

Variable / Treatment Group	N	-- Baseline -- Mean SD	-- Endpoint -- Mean SD	Change Mean SD	LSMean (a)	Within Group p-value (b)	Between Group p-value (a)
Physical Functioning							
Atomoxetine - No Taper	25	96.16 13.66	97.88 4.73	1.72	11.22	1.30	1.000
Atomoxetine - Taper	28	96.68 6.24	98.32 4.45	1.64	6.40	1.14	0.285
LSMean Difference(95%CI) = 0.16(-7.83 , 8.15)							
Physical Summary Score							
Atomoxetine - No Taper	25	54.44 7.79	56.00 4.93	1.56	6.47	0.83	0.602
Atomoxetine - Taper	28	54.89 4.41	55.21 4.18	0.32	4.17	0.21	0.530
LSMean Difference(95%CI) = 0.62(-3.37 , 4.62)							
Psychosocial Summary Score							
Atomoxetine - No Taper	25	42.48 8.76	43.24 11.52	0.76	9.34	0.70	0.380
Atomoxetine - Taper	28	47.07 6.86	44.18 9.89	-2.89	6.89	-4.94	0.059
LSMean Difference(95%CI) = 5.64(0.54 , 10.75)							
Parent Time Impact							
Atomoxetine - No Taper	25	82.16 19.12	84.08 21.67	1.92	19.30	2.01	0.511
Atomoxetine - Taper	28	86.00 15.41	82.07 17.43	-3.93	13.94	-7.41	0.198
LSMean Difference(95%CI) = 9.43(-2.03 , 20.89)							
Role-Emotion/Behavior							
Atomoxetine - No Taper	25	86.92 24.08	86.52 26.37	-0.40	34.18	-2.05	0.923
Atomoxetine - Taper	28	89.75 16.85	85.86 25.33	-3.89	17.67	-10.64	0.404
LSMean Difference(95%CI) = 8.59(-9.91 , 27.08)							
Role-Physical							
Atomoxetine - No Taper	25	91.92 20.06	97.28 9.41	5.36	20.99	2.86	0.375
Atomoxetine - Taper	28	96.96 9.32	98.79 4.46	1.82	10.69	0.24	0.438
LSMean Difference(95%CI) = 2.62(-9.49 , 14.74)							

(a) LSMeans and Between Groups p-values are from ANOVA model with terms for Treatment and Investigator.

(b) Within Groups p-values obtained from Wilcoxon's Signed-rank Test for mean change from baseline to endpoint.
Population: All randomized patient with at least one baseline and postbaseline measurement.

(continued)

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**Table 35. Child Health Questionnaire (CHQ)
Change from Baseline to Endpoint
Study Period IV (Concluded)**

Variable / Treatment Group	N	-- Baseline --		-- Endpoint --		----- Change -----			Within Group p-value (b)	Between Group p-value (a)
		Mean	SD	Mean	SD	Mean	SD	LSMean (a)		
Self-Esteem										
Atomoxetine - No Taper	25	68.20	15.55	66.28	24.10	-1.92	23.20	-4.41	0.813	0.620
Atomoxetine - Taper	28	75.57	12.25	72.00	16.87	-3.57	14.69	-6.96	0.289	—
LSMean Difference(95%CI) = 2.55(-7.89 , 13.00)										
Single Item Family Cohesion										
Atomoxetine - No Taper	25	58.60	23.70	60.80	25.03	2.20	24.24	1.48	0.778	0.695
Atomoxetine - Taper	28	65.36	21.94	65.71	24.67	0.36	18.15	-1.64	0.934	—
LSMean Difference(95%CI) = 3.13(-13.06 , 19.31)										
Change in Health Item										
Atomoxetine - No Taper	25	3.68	0.85	3.80	0.82	0.12	0.67	0.14	0.563	0.635
Atomoxetine - Taper	28	3.79	0.88	3.79	0.83	0.00	0.77	0.02	1.000	—
LSMean Difference(95%CI) = 0.13(-0.41 , 0.66)										

(a) LSMeans and Between Groups p-values are from ANOVA model with terms for Treatment and Investigator.

(b) Within Groups p-values obtained from Wilcoxon's Signed-rank Test for mean change from baseline to endpoint.

Population: All randomized patient with at least one baseline and postbaseline measurement.

Abbreviations: CI = confidence interval; LSMean = least-squares mean; N = number of patients; SD = standard deviation.

Summary ID#2553

Clinical Study Summary: Study B4Z-MC-LYAD

Title of Study: A Randomized, Double-Blind, Placebo- and Comparator-Controlled Study of Atomoxetine Hydrochloride in Recreational Drug Users	
Investigator: This single-center study included 1 principal investigator.	
Study Center: This study was conducted at 1 study center in the United States	
Length of Study: 3 months Date first patient enrolled: February 2000 Date last patient completed: May 2000	Phase of Development: 3
Objectives: The primary objective of study B4Z-MC-LYAD (LYAD) was to compare and discriminate the behavioral effects of atomoxetine (formerly called tomoxetine) hydrochloride in experienced recreational drug users with the behavioral effects of methylphenidate hydrochloride (hereafter referred to as methylphenidate) and placebo. These behavioral effects were assessed by evaluating treatment differences in the scores of the Visual Analog Scale (VAS; primary measure), the Addiction Research Center Inventory: Short Form (ARCI:SF; secondary measure), and the Adjective Rating Scale (ARS; secondary measure). This study had two secondary objectives: to demonstrate that atomoxetine has no adverse effect on measures of associative ability and performance through the Digit Symbol Substitution Test (DSST), and to compare the safety of atomoxetine, methylphenidate, and placebo in the subject population.	
Study Design: Study LYAD was a single-site, randomized, double-blind investigation of the safety and abuse potential of atomoxetine in 16 enrolled subjects. Subjects were male or female experienced recreational drug users aged 18 through 36 years. (For the purposes of this study, a “recreational drug user” was defined as someone who used recreational drugs [but not daily], did not meet the <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</i> [DSM-IV] criteria for drug dependency [caffeine and tobacco use were permitted], and had no medical, social, or other adverse consequences resulting from using drugs.) Study LYAD comprised two study periods. Study Period I was a screening and washout period of 2 to 31 days (Visits 1 and 2). Study Period II was a double-blind, multiple-dose treatment and evaluation period of approximately 10 to 50 days (Visits 3 through 8). Only subjects who were identified as cytochrome P450 2D6 (CYP2D6) extensive metabolizer (EM) subjects participated in the treatment phase of the study. At Visit 3, qualified subjects were randomized to a blinded treatment sequence according to a Latin-square design.	
Number of Patients: Planned: 12 Randomized: 16 (all subjects were randomized to receive all treatments over the 5-week treatment phase) Completed: 14	
Diagnosis and Main Criteria for Inclusion: Subjects were volunteer male and female recreational drug users aged 18 through 36 years who did not meet the DSM-IV criteria for drug dependency. They did not use drugs daily and had no known medical, social, or other adverse consequences resulting from using drugs.	
Test Product, Dose, and Mode of Administration: Atomoxetine: 20 mg/day, 45 mg/day, and 90 mg/day, each given as a single-dose capsule as dictated by the Latin Square.	

Duration of Treatment:

Atomoxetine: Single dose of appropriate amount on 3 separate, weekly test days over the six-session testing phase.

Methylphenidate: Single dose of appropriate amount on 2 separate weekly test days over the six-session testing phase.

Placebo: Single dose on 1 weekly test day over the six-session testing phase.

Reference Therapy, Dose, and Mode of Administration:

Methylphenidate: 20 mg/day and 40 mg/day, each given as a single-dose capsule as dictated by the Latin Square.

Placebo: Given as a single-dose capsule as dictated by the Latin Square.

Variables:

Safety: Safety was assessed by spontaneous and elicited reports of adverse events, changes in vital signs, laboratory values, and electrocardiogram (ECG) intervals.

Behavioral: A VAS questionnaire was the primary abuse potential measure. There were two other secondary abuse potential measures: the ARCI:SF and the ARS. The DSST was used to assess effects on performance and associative ability.

Evaluation Methods:

Statistical: Changes from baseline to maximum postbaseline score and changes from baseline to average postbaseline score were computed for each subject at each visit. Analysis of variance (ANOVA), utilizing the SAS Mixed procedure, was used to determine the significance of treatment differences. The ANOVA model included terms for treatment, visit, square (block of 6 subjects), and subject within square. Pairwise comparisons with placebo were performed using the least squares means procedure for each of the treatment groups from the ANOVA model and were considered the primary analyses. Dunnett's procedure was used to control the overall significance level to 0.05 for each analysis variable in the presence of the multiple (5) pairwise comparisons with placebo. Other pairwise comparisons were considered secondary analyses.

Summary:

Patient Disposition: Initially, 22 subjects entered LYAD. Of those, 6 subjects were not randomized (that is, were discontinued prior to randomization at Visit 3). Subjects were not randomized for the following reasons: personal conflict or other subject decision (N = 1); protocol entry criteria not met (N = 4); and protocol violation (N = 1). Of the 22 patients entered, 16 were subsequently randomized to a sequence group at Visit 3. Of the 16 randomized subjects, 14 (87.5%) completed the protocol and 2 (12.5%) discontinued due to a time conflict or for personal reasons.

Patient Demographics: Table LYAD.1 shows subject characteristics and demographics. Of the 16 randomized subjects, 11 (68.8%) were female, 15 (93.8%) were Caucasian, and the mean age was 22.3 years (range 18 through 36 years). Regarding the subjects' recreational drug use history: 100% had used marijuana, 68.8% hallucinogens, 50.0% stimulants, 18.8% opioids, and 12.5% sedatives.

Efficacy: The primary objective of Study LYAD was to compare and discriminate the behavioral effects of atomoxetine with methylphenidate in experienced recreational drug users. Treatment differences in abuse potential were evaluated using scores on the following tests: VAS (primary measure), ARCI:SF (secondary measure), and ARS questionnaire (secondary measure). Secondary objectives were to demonstrate that atomoxetine had no adverse effect on measures of associative ability and performance through the use of the DSST, and to compare the safety of atomoxetine, methylphenidate, and placebo in the study population.

The analyses compared treatment effects on mean change from baseline to maximum of the scores of the VAS, ARCI:SF, ARS, and DSST using an ANOVA model. The primary abuse potential measure was the VAS, which consisted of 7 items: "bad," "liking," "sick," "good," "sedated," "stimulated," and "would take again." The "stimulated," "liking," and "good" items were considered the primary variables. Each item was scored on a 0 (not at all) to 100 (extremely) scale. As Table LYAD.2 shows, for all randomized

subjects, mean change to maximum “stimulated” scores on the VAS were approximately 18 points higher on high-dose methylphenidate than placebo (34.4 versus 16.1; $p=.003$). Also, the scores on the Benzedrine Group (BG) or “stimulant,” “amphetamine,” and Morphine-Benzedrine Group (MBG) or “euphoria” subscales of the ARCI:SF following methylphenidate 40 mg were all statistically significantly greater than those measured after placebo (Table LYAD.3, Table LYAD.4, and Table LYAD.5, respectively). That profile of scores for methylphenidate was consistent with the previous literature and with the profiles of other stimulant drugs. The change scores on the same stimulant subscales following atomoxetine treatment were not statistically different from placebo. Compared with placebo, significant change scores for atomoxetine 90 mg were found on the “bad” and “sick” subscales of the VAS (Table LYAD.6 and Table LYAD.7) and the “sedative” subscale of the ARS (Table LYAD.8). Those results suggested that atomoxetine was not perceived as pleasurable.

Both atomoxetine and methylphenidate were significantly different from placebo, but not from each other in the ARCI:SF Lysergic Acid Diethylamide (LSD) or “dysphoria” grouping (Table LYAD.9).

No subjects discontinued due to drug effects. There were no changes seen for either drug in the DSST (a measure of associative ability and performance).

The results of this study provided evidence that atomoxetine was not subjectively experienced as a stimulant. The nonpleasurable profile of effects provided evidence that atomoxetine would not be a drug of abuse.

Safety: The safety of single-dose treatment exposure to atomoxetine was assessed by unsolicited adverse events, laboratory values, changes in vital signs, and ECG intervals. All 16 enrolled patients took at least one dose of study drugs and were included in adverse event analyses. No patients were genotypically CYP2D6 poor metabolizer (PM) patients.

No serious adverse events occurred in the study. Two of the 16 subjects (12.5%) were discontinued for non-drug-related personal problems. Table LYAD.10 summarizes the percentages of subjects reporting specific treatment-emergent adverse events by treatment group. Other than nausea (reported by 4 subjects while taking atomoxetine 90 mg, and 3 subjects taking atomoxetine 45 mg), no specific treatment-emergent event was reported more than twice following any atomoxetine dose.

Only 2 subjects had a treatment-emergent out-of-range laboratory value: 1 had a low lymphocyte value and the other an out-of-range potassium value. One patient had an elevated creatine phosphokinase (CPK) value at Visit 8. Twenty-nine days after the last dose of medication the subject with the elevated CPK value returned for a repeat test. The physician interviewed the patient and did not uncover any apparent explanations for the elevated value. The subject was in good health. The CPK value at this follow-up visit was 291. A final follow-up CPK value (taken 56 days after the last medication dose) was 161. Because there were no apparent explanations for the elevation, the physician indicated this elevation could be due to one of the study drugs (either methylphenidate or atomoxetine).

As Table LYAD.11 shows, there were statistically significant increases from baseline to maximum in systolic blood pressure with atomoxetine at the highest dose (15.1 mm Hg versus 3.7 mm Hg, $p=.005$). As compared with placebo, statistically significant greater mean changes to average value were noted for methylphenidate 20 mg and 40 mg as well as atomoxetine 45 mg and 90 mg. The mean change to average postbaseline value for the placebo group was a decrease of 9.3 mm Hg. Statistically significant dose response relationships were noted for both methylphenidate and atomoxetine. As Table LYAD.12 illustrates, changes to maximum in heart rate were statistically significant for methylphenidate (20 mg and 40 mg) and atomoxetine (45 mg and 90 mg).

Analysis of ECG data found no evidence for an increase in corrected QT interval (QTc) with atomoxetine treatment.

Table LYAD.1. Subject Characteristics and Demographics
B4Z-MC-LYAD

Variable	All TRTs (N=16)

Sex: No. (%)	
No. Patients	16
Female	11 (68.8)
Male	5 (31.3)
Origin: No. (%)	
No. Patients	16
Caucasian	15 (93.8)
East/Southeast A	1 (6.3)
Age: yrs.	
No. Patients	16
Mean	22.25
Median	20.16
Standard Dev.	5.32
Minimum	18.41
Maximum	36.23
Height: cm	
No. Patients	16
Mean	167.84
Median	168.50
Standard Dev.	10.91
Minimum	152.00
Maximum	186.50
Weight: kg	
No. Patients	16
Mean	65.52
Median	63.35
Standard Dev.	14.00
Minimum	50.40
Maximum	95.30
Body Mass Index	
No. Patients	16
Mean	23.13
Median	22.40
Standard Dev.	3.61
Minimum	18.32
Maximum	32.59
RDUH Sedatives (Y/N)	
No. Patients	16
N	14 (87.5)
Y	2 (12.5)
RDUH Stimulants (Y/N)	
No. Patients	16
N	8 (50.0)
Y	8 (50.0)

(continued)

Table LYAD.1 **Subject Characteristics and Demographics**
B4Z-MC-LYAD (Concluded)

Variable	All TRTs (N=16)
----------	--------------------

RDUH Hallucinogens (Y/N)

No. Patients	16
N	5 (31.3)
Y	11 (68.8)

RDUH Marijuana (Y/N)

No. Patients	16
Y	16 (100)

RDUH Opioids (Y/N)

No. Patients	16
N	13 (81.3)
Y	3 (18.8)

Population: All Randomized Patients.

Initial Visit ONLY

RDUH - Recreational Drug Use History

Input data from RMP.SAS.B4ZM.MCLYADSW

Output stored as RMP.B4Z0.LYADCTRM(DE102003)

XDES0001

Table LYAD.2. VAS-Stimulated Score
Summary Statistics on Baseline, Change to Average and
Change to Maximum
Scores by Treatment, All Randomized Subjects
B4Z-MC-LYAD

Treatment	N	Baseline		Change to Average			Change to Maximum		
		Mean	SD	Mean	SD	p-value ^a	Mean	SD	p-value ^a
PLA	15	12.3	19.0	3.7	15.4	-----	16.1	23.9	-----
MPH 20	16	16.5	20.3	2.4	17.0	0.988	14.9	24.2	1.000
40	14	17.4	26.6	12.9	16.9	0.001*	34.4	27.9	0.003*
TMX 20	14	12.5	19.9	2.5	17.8	1.000	7.5	19.3	0.502
45	14	12.1	19.8	0.2	12.8	0.850	12.2	16.6	0.923
90	15	14.6	29.3	4.3	18.7	0.940	17.3	23.3	0.983

Linear Trend MPH				p-value ^b =	<0.001*		<0.001*		
Linear Trend TMX				p-value ^b =	0.366		0.060		
Linear Trend MPH (with placebo)				p-value ^b =	<0.001*		<0.001*		
Linear Trend TMX (with placebo)				p-value ^b =	0.534		0.329		
Abbreviations: MPH = methylphenidate; PLA = placebo; SD = standard deviation; TMX = tomoxetine.									
* p<.05.									
^a Pairwise treatment comparison versus placebo, adjusted for multiple comparisons (Dunnett).									
Analysis of variance model: change to average change to maximum = baseline treatment visit subject.									
^b Test for linear dose effect from the analysis of variance model using contrast of least squares means.									
Source Data: eagle:\programs._g\rmp\b4zs\lyad\final analysis\latsqanova.sas									

Table LYAD.3. ARCI:SF-BG Score
Summary Statistics on Baseline, Change to Average and
Change to Maximum
Scores by Treatment, All Randomized Subjects
B4Z-MC-LYAD

Treatment	N	<u>Baseline</u>		<u>Change to Average</u>			<u>Change to Maximum</u>		
		Mean	SD	Mean	SD	p-value ^a	Mean	SD	p-value ^a
PLA	15	5.9	1.5	-0.2	0.5	-----	0.6	0.8	-----
MPH 20	16	5.9	1.9	-0.1	0.9	0.546	0.9	1.1	0.693
40	14	6.1	2.2	0.2	0.9	0.173	1.4	1.5	0.056
TMX 20	14	5.9	1.6	-0.2	0.9	1.000	0.5	1.1	0.993
45	14	6.1	1.9	-0.3	0.4	0.999	0.4	0.6	0.989
90	15	5.8	1.4	-0.4	1.2	0.842	0.5	1.3	0.967

Linear Trend MPH				p-value ^b =	0.455		0.146		
Linear Trend TMX				p-value ^b =	0.271		0.870		
Linear Trend MPH (with placebo)				p-value ^b =	0.047*		0.014*		
Linear Trend TMX (with placebo)				p-value ^b =	0.336		0.598		

Abbreviations: MPH = methylphenidate; PLA = placebo; SD = standard deviation; TMX = tomoxetine.

* p<.05.

^a Pairwise treatment comparison versus placebo, adjusted for multiple comparisons (Dunnett).

Analysis of variance model: change to average change to maximum = baseline treatment visit subject.

^b Test for linear dose effect from the analysis of variance model using contrast of least squares means.

Source Data: eagle:\programs._g\rm\p\b4zs\lyad\final analysis\latsqanova.sas

Table LYAD.4. ARCI:SF-Amphetamine Score
Summary Statistics on Baseline, Change to Average and
Change to Maximum
Scores by Treatment, All Randomized Subjects
B4Z-MC-LYAD

Treatment	N	<u>Baseline</u>		<u>Change to Average</u>			<u>Change to Maximum</u>		
		Mean	SD	Mean	SD	p-value ^a	Mean	SD	p-value ^a
PLA	15	2.3	1.7	0.2	1.2	-----	0.9	1.5	-----
MPH 20	16	2.6	2.5	0.5	1.1	0.302	1.5	1.9	0.428
40	14	2.8	2.5	0.6	0.9	0.113	2.3	2.0	0.005*
TMX 20	14	2.6	2.1	-0.3	1.1	0.882	0.4	1.5	0.970
45	14	2.5	2.0	-0.0	0.8	1.000	0.9	1.2	1.000
90	15	2.1	1.5	0.1	1.0	0.967	1.2	1.4	0.996

Linear Trend MPH				p-value ^b =	0.568		0.049*		
Linear Trend TMX				p-value ^b =	0.894		0.383		
Linear Trend MPH (with placebo)				p-value ^b =	0.028*		0.001*		
Linear Trend TMX (with placebo)				p-value ^b =	0.737		0.536		

Abbreviations: MPH = methylphenidate; PLA = placebo; SD = standard deviation; TMX = tomoxetine.

* p<.05

^a Pairwise treatment comparison versus placebo, adjusted for multiple comparisons (Dunnett).

Analysis of variance model: change to average change to maximum = baseline treatment visit subject.

^b Test for linear dose effect from the analysis of variance model using contrast of least squares means.

Source Data: eagle:\programs._g\rmp\b4zs\lyad\final analysis\latsqanova.sas

Table LYAD.5. ARCI:SF-MBG Score
Summary Statistics on Baseline, Change to Average and
Change to Maximum
Scores by Treatment, All Randomized Subjects
B4Z-MC-LYAD

Treatment	N	<u>Baseline</u>		<u>Change to Average</u>			<u>Change to Maximum</u>		
		Mean	SD	Mean	SD	p-value ^a	Mean	SD	p-value ^a
PLA	15	3.2	4.0	-0.5	1.3	-----	0.5	1.2	-----
MPH 20	16	3.4	4.3	-0.1	2.1	0.673	1.6	3.0	0.295
40	14	3.9	5.1	-0.2	2.7	0.497	2.3	3.9	0.012*
TMX 20	14	3.4	4.3	-0.7	1.9	0.997	0.4	1.4	1.000
45	14	2.8	3.8	-0.1	2.0	0.998	1.5	2.2	0.759
90	15	2.1	2.8	-0.3	1.1	0.796	0.7	1.5	0.974
Linear Trend MPH				p-value ^b =	0.769		0.149		
Linear Trend TMX				p-value ^b =	0.432		0.455		
Linear Trend MPH (with placebo)				p-value ^b =	0.162		0.003*		
Linear Trend TMX (with placebo)				p-value ^b =	0.384		0.654		

Abbreviations: MPH = methylphenidate; PLA = placebo; SD = standard deviation; TMX = tomoxetine.

* p<.05.

^a Pairwise treatment comparison versus placebo, adjusted for multiple comparisons (Dunnett).

Analysis of variance model: change to average change to maximum = baseline treatment visit subject.

^b Test for linear dose effect from the analysis of variance model using contrast of least squares means.

Source Data: eagle:\programs._g\rm\p\b4zs\lyad\final analysis\latsqanova.sas

Table LYAD.6. VAS-Bad Score
Summary Statistics on Baseline, Change to Average and
Change to Maximum
Scores by Treatment, All Randomized Subjects
B4Z-MC-LYAD

Treatment	N	<u>Baseline</u>		<u>Change to Average</u>			<u>Change to Maximum</u>		
		Mean	SD	Mean	SD	p-value ^a	Mean	SD	p-value ^a
PLA	15	3.9	5.8	3.6	8.7	-----	13.1	16.7	-----
MPH 20	16	4.8	6.8	2.7	7.7	1.000	15.4	18.2	0.938
40	14	2.4	5.5	4.4	4.8	1.000	15.9	14.1	1.000
TMX 20	14	5.4	8.7	0.5	7.7	0.997	5.5	11.1	0.928
45	14	5.1	6.6	4.9	7.3	0.527	27.9	24.3	0.052
90	15	4.1	8.0	11.7	19.2	0.014*	33.9	31.3	0.017*
.....									
Linear Trend MPH				p-value ^b =		0.891	0.626		
Linear Trend TMX				p-value ^b =		0.002*	0.002*		
Linear Trend MPH (with placebo)				p-value ^b =		0.973	0.850		
Linear Trend TMX (with placebo)				p-value ^b =		<0.001*	<0.001*		

Abbreviations: MPH = methylphenidate; PLA = placebo; SD = standard deviation; TMX = tomoxetine.

* p<.05.

^a Pairwise treatment comparison versus placebo, adjusted for multiple comparisons (Dunnett).

Analysis of variance model: change average change to maximum = baseline treatment visit subject.

^b Test for linear dose effect from the analysis of variance model using contrast of least squares means.

Source Data: eagle:\programs._g\rmp\b4zs\lyad\final analysis\latsqanova.sas

Table LYAD.7. VAS-Sick Score
Summary Statistics on Baseline, Change to Average and
Change to Maximum
Scores by Treatment, All Randomized Subjects
B4Z-MC-LYAD

Treatment	N	<u>Baseline</u>		<u>Change to Average</u>			<u>Change to Maximum</u>		
		Mean	SD	Mean	SD	p-value ^a	Mean	SD	p-value ^a
PLA	15	9.0	14.3	-5.5	14.7	-----	1.0	19.5	-----
MPH 20	16	7.8	13.6	-1.2	15.5	0.740	10.1	25.8	0.721
40	14	3.9	5.9	6.0	13.7	0.082	22.5	29.2	0.137
TMX 20	14	3.0	3.7	1.7	5.7	0.778	8.1	11.5	0.997
45	14	7.9	14.6	2.8	9.6	0.048*	17.9	23.5	0.115
90	15	3.2	4.9	11.4	15.0	0.005*	30.3	29.5	0.025*

Linear Trend MPH				p-value ^b =		0.163	0.257		
Linear Trend TMX				p-value ^b =		0.027*	0.023*		
Linear Trend MPH (with placebo)				p-value ^b =		0.021*	0.037*		
Linear Trend TMX (with placebo)				p-value ^b =		<0.001*	0.002*		

Abbreviations: MPH = methylphenidate; PLA = placebo; SD = standard deviation; TMX = tomoxetine.

* p<.05.

^a Pairwise treatment comparison vs. placebo, adjusted for multiple comparisons (Dunnett).

Analysis of variance model: change to average change to maximum = baseline treatment visit subject.

^b Test for linear dose effect from the ANOVA model using contrast of least squares means.

Source Data: eagle:\programs._g\rmp\b4zs\lyad\final analysis\latsqanova.sas

Table LYAD.8. ARS-Sedative Score
Summary Statistics on Baseline, Change to Average and
Change to Maximum
Scores by Treatment. All Randomized Subjects
B4Z-MC-LYAD

Treatment	N	<u>Baseline</u>		<u>Change to Average</u>			<u>Change to Maximum</u>		
		Mean	SD	Mean	SD	p-value ^a	Mean	SD	p-value ^a
PLA	15	13.7	19.4	-1.7	5.6	-----	3.0	5.6	-----
MPH 20	16	11.3	13.6	0.9	3.7	0.826	8.8	12.1	0.541
40	14	7.3	5.3	3.7	5.5	0.175	10.7	11.9	0.134
TMX 20	14	6.9	8.7	2.5	6.3	0.420	6.7	9.1	0.662
45	14	9.0	14.9	3.6	5.3	0.095	9.9	10.4	0.148
90	15	11.6	12.1	4.6	9.1	0.031*	14.5	15.4	0.011*
Linear Trend MPH				p-value ^b =		0.247	0.373		
Linear Trend TMX				p-value ^b =		0.277	0.066		
Linear Trend MPH (with placebo)				p-value ^b =		0.049*	0.036*		
Linear Trend TMX (with placebo)				p-value ^b =		0.009*	0.002*		

Abbreviations: MPH = methylphenidate; PLA = placebo; SD = standard deviation; TMX = tomoxetine.

* p<.05.

^a Pairwise treatment comparison versus placebo, adjusted for multiple comparisons (Dunnett).

Analysis of variance model: change to average change to maximum = baseline treatment visit subject.

^b Test for linear dose effect from the analysis of variance model using contrast of least squares means.

Source Data: eagle:\programs._g\rmp\b4zs\lyad\final analysis\ latsqanova.sas

Table LYAD.9. ARCI:SF-LSD (Dysphoria)Score
Summary Statistics on Baseline, Change to Average and
Change to Maximum
Scores by Treatment, All Randomized Subjects
B4Z-MC-LYAD

Treatment	N	<u>Baseline</u>		<u>Change to Average</u>			<u>Change to Maximum</u>		
		Mean	SD	Mean	SD	p-value ^a	Mean	SD	p-value ^a
PLA	15	2.8	1.1	0.2	0.8	-----	0.8	1.1	-----
MPH 20	16	2.8	1.5	0.5	1.3	0.603	1.4	1.9	0.663
40	14	2.6	1.3	1.2	1.3	0.015*	2.5	1.9	0.006*
TMX 20	14	2.9	1.1	-0.1	0.5	1.000	0.4	0.8	1.000
45	14	3.1	1.0	0.4	0.8	0.323	1.1	0.9	0.590
90	15	3.0	0.8	0.7	1.0	0.081	2.5	2.1	0.001*

Linear Trend MPH				p-value ^b =	0.069		0.029*		
Linear Trend TMX				p-value ^b =	0.035*		<0.001*		
Linear Trend MPH (with placebo)				p-value ^b =	0.004*		0.002*		
Linear Trend TMX (with placebo)				p-value ^b =	0.008*		<0.001*		

Abbreviations: MPH = methylphenidate; PLA = placebo; SD = standard deviation; TMX = tomoxetine.

* p<.05

^a Pairwise treatment comparison versus placebo, adjusted for multiple comparisons (Dunnett).

Analysis of variance model: change to average change to maximum = baseline treatment visit subject.

^b Test for linear dose effect from the analysis of variance model using contrast of least squares means.

Source Data: eagle:\programs._g\rm\p\b4zs\lyad\final analysis\latsqanova.sas

**Table LYAD.10. Treatment-Emergent Adverse Events^a by Incidence
BZ-MC-LYAD**

	TMX 20 mg (N=14)	TMX 45 mg (N=15)	TMX 90 mg (N=15)	MPH 20 mg (N=16)	MPH 40 mg (N=14)	PLA (N=15)	TOTAL
Event	n	n	n	n	n	n	n (%)
Nausea	1	3	4	2	4	0	14 (15.7)
Somnolence	0	2	2	3	1	0	8 (9.0)
Euphoria	1	1	0	1	1	0	4 (4.5)
Chills	0	0	2	0	1	0	3 (3.4)
Dizziness	0	1	2	0	0	0	3 (3.4)
Headache	0	0	0	1	1	1	3 (3.4)
Nervousness	0	0	0	0	3	0	3 (3.4)
Asthenia	1	0	0	1	0	0	2 (2.2)
Dyspepsia	0	0	1	0	1	0	2 (2.2)
Hyperkinesia	0	0	0	1	1	0	2 (2.2)
Palpitation	0	0	1	0	1	0	2 (2.2)
Sweating	0	0	2	0	0	0	2 (2.2)
Thinking Abnorm.	0	0	0	0	2	0	2 (2.2)
Tremor	0	0	0	2	0	0	2 (2.2)
Unexpected Benef.	1	1	0	0	0	0	2 (2.2)
Confusion	0	0	0	0	1	0	1 (1.1)
Mydriasis	0	0	1	0	0	0	1 (1.1)
Taste Perversion	0	0	0	1	0	0	1 (1.1)
Vomiting	0	0	1	0	0	0	1 (1.1)

Population: All Randomized Patients.

^aBaseline: Predose In Office; Endpoint: From Time of Dose through End of Office Visit

For each treatment, N represents the number of patients taking the treatment. The denominator for the

Total column (89) is the number of patient visits on a study treatment during the study.

Source Data: RMP.B4ZO.LYADCTRM(AE201002)

**Table LYAD.11. Systolic Blood Pressure
 Summary Statistics on Baseline, Change to Average and Change to Maximum
 Scores by Treatment, All Randomized Patients
 B4Z-MC-LYAD**

Treatment	N	<u>Baseline</u>		<u>Change to Average</u>			<u>Change to Maximum</u>		
		Mean	SD	Mean	SD	p-value ^a	Mean	SD	p-value ^a
PLA	15	123.4	13.0	-9.3	9.0	-----	3.7	10.0	-----
MPH 20	16	125.4	16.3	-4.0	14.5	0.006*	6.2	16.5	0.351
40	14	125.4	11.2	-1.6	11.2	<0.001*	8.0	13.8	0.255
TMX 20	14	122.1	11.7	-5.3	9.5	0.498	6.3	11.1	0.995
45	15	119.7	12.7	2.0	10.1	<0.001*	12.9	10.8	0.082
90	15	121.0	11.3	4.0	7.8	<0.001*	15.1	8.4	0.005*

Linear Trend MPH				p-value ^b =	0.293	0.813			
Linear Trend TMX				p-value ^b =	<0.001*	0.006*			
Linear Trend MPH (with placebo)				p-value ^b =	<0.001*	0.071			
Linear Trend TMX (with placebo)				p-value ^b =	<0.001*	<0.001*			

Abbreviations: MPH = methylphenidate; PLA = placebo; SD = standard deviation; TMX = tomoxetine.

* p<.05.

^a Pairwise treatment comparison vs. placebo, adjusted for multiple comparisons (Dunnett).

ANOVA model: change average change maximum = baseline treatment visit patient.

^b Test for linear dose effect from the ANOVA model using contrast of least squares means.

Source Data: eagle:\programs._g\rmp\b4zs\lyad\final analysis\latsqanova.sas

Atomoxetine hydrochloride
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Approved: 11 November 2004

Table LYAD.12.

Heart Rate

Summary Statistics on Baseline, Change to Average and Change to Maximum Scores by Treatment, All Randomized Patients

B4Z-MC-LYAD

Treatment	N	<u>Baseline</u>		<u>Change to Average</u>			<u>Change to Maximum</u>		
		Mean	SD	Mean	SD	p-value ^a	Mean	SD	p-value ^a
PLA	15	78.8	14.3	-11.5	9.5	-----	-3.3	9.8	-----
MPH 20	16	79.3	15.2	-4.4	10.0	<0.001*	3.8	10.7	0.011*
40	14	78.1	11.2	0.2	9.3	<0.001*	8.4	9.1	<0.001*
TMX 20	14	81.3	13.2	-8.3	10.4	0.004*	0.4	13.2	0.142
45	15	80.8	14.5	-5.3	11.0	<0.001*	3.5	11.7	0.007*
90	15	79.9	13.5	-1.3	8.7	<0.001*	11.8	9.5	<0.001*

Linear Trend MPH				p-value ^b =		0.014*	0.194		
Linear Trend TMX				p-value ^b =		<0.001*	<0.001*		
Linear Trend MPH (with placebo)				p-value ^b =		<0.001*	<0.001*		
Linear Trend TMX (with placebo)				p-value ^b =		<0.001*	<0.001*		

Abbreviations: MPH = methylphenidate; PLA = placebo; SD = standard deviation; TMX = tomoxetine.

* p<.05.

^a Pairwise treatment comparison vs. placebo, adjusted for multiple comparisons (Dunnett).

ANOVA model: change average change maximum = baseline treatment visit patient

^b Test for linear dose effect from the ANOVA model using contrast of least squares means.

Source Data: eagle:\programs._g\rmpl\b4zs\lyad\final analysis\latsqanova.sas

Summary ID#2556

Clinical Study Summary: Study B4Z-MC-LYAA

Title of Study: A Phase III Randomized, Double-Blind Comparison of Placebo and Atomoxetine Hydrochloride in Adult Outpatients with DSM-IV Attention-Deficit/Hyperactivity Disorder.	
Investigators: This multicenter study included 17 principal investigators.	
Study Centers: This study was conducted at 17 study centers in two countries.	
Length of Study: 9 months Date first patient enrolled: 28 July 2000 Date last patient completed: 30 April 2001	Phase of Development: 3
Objectives: The primary objective of this study was to test the hypothesis that, compared with placebo, administration of atomoxetine (formerly called tomoxetine) at total daily doses of 60 mg to 120 mg for up to 10 weeks would result in a statistically significantly greater reduction in mean Total Attention-Deficit/Hyperactivity Disorder (ADHD) Symptom Score on the investigator-administered and scored Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV). The secondary objectives of this study were as follows: • To compare percentages of responders among atomoxetine-treated and placebo-treated patients who had completed a minimum of three visits following randomization. Determination of clinical response was based on the CAARS-Inv:SV and the Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) scores. • To compare improvement of neurocognitive function during treatment with atomoxetine to improvement during treatment with placebo using the Stroop Color Word Test (Stroop). • To compare the safety of atomoxetine with placebo in a population of adult patients who met <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</i> (DSM-IV) criteria for ADHD. • To assess changes in health outcomes.	
Study Design: Study B4Z-MC-LYAA (LYAA) was a Phase 3, randomized, double-blind, placebo-controlled study in which 280 adult outpatients were enrolled. Patients were at least 18 years old at the time of entry into this study and met DSM-IV CAARS-Inv:SV criteria for ADHD, in addition to all enrollment criteria. After an initial washout, screening, and entry period, patients completed a 2-week placebo lead-in period followed by randomization to study drug or placebo at Visit 3. During the 10-week acute treatment phase of Study LYAA, patients were titrated to a maximum tolerated dose, not to exceed 120 mg/day. After completing the acute treatment phase, patients proceeded to Study Period III, and were randomized to one of two groups. One group had study drug abruptly discontinued; the other group had study drug tapered and discontinued over a 4-week period.	
Number of Patients: Planned: 95 atomoxetine hydrochloride, 95 placebo Randomized: 141 atomoxetine hydrochloride, 139 placebo Completed: 93 active drug, 97 placebo	

Diagnosis and Main Criteria for Inclusion: Patients had to meet DSM-IV diagnostic criteria for ADHD on the Conner's Adult ADHD Diagnostic Interview for DSM-IV (CAAR-D) at Visit 1 for both childhood and current symptoms, as well as meeting criteria based on the investigator's clinical assessment. In addition, the patient's score on either the inattentive or hyperactive subsections of CAARS-Inv:SV screening instrument had to have at least 6 of the symptoms in either subsection rated 2 ('pretty much/often') or greater and a Total ADHD Symptom Score ≥ 20 . At Visit 1 patients also had to have a CGI-ADHD-S score of 4 (moderate symptoms) or greater.

Test Product, Dose, and Mode of Administration: Atomoxetine hydrochloride; 2.5-mg, 5-mg, 10-mg, 20-mg, 25-mg, and 40-mg capsules; 60 mg/day to 120 mg/day, given twice daily.

Duration of Treatment: Up to approximately 10 weeks.

Reference Therapy, Dose, and Mode of Administration: Placebo capsules.

Variables:

Efficacy: The primary efficacy analysis was a comparison of the CAARS-Inv:SV Total ADHD Symptom Scores between atomoxetine and placebo during Study Period II.

Safety: Adverse events were collected by open-ended discussion and by the Association for Methodology and Documentation in Psychiatry-5: Somatic Signs (AMDP-5) questionnaire. Electrocardiograms (ECGs) and vital signs, cytochrome P450 2D6 (CYP2D6) genotype characterization and clinical laboratory tests were also performed. Safety analyses included all patients who took at least one dose of study drug.

Pharmacokinetic: Patients provided blood samples for assessment of plasma concentrations of atomoxetine, 4-hydroxyatomoxetine, and N-desmethyldatomoxetine to evaluate the relationship, if any, between QTc and atomoxetine plasma concentration.

Evaluation Methods:

Statistical: The primary efficacy analysis was an F-test for a treatment difference between atomoxetine and placebo at Visit 8 (the last Study Period II visit) from a repeated measures mixed model analysis of the CAARS-Inv:SV Total ADHD Symptom score. The repeated measures mixed model included terms for treatment, investigational site, visit, CYP2D6 metabolism status, and an interaction between treatment and visit. The model also included baseline CAARS-Inv:SV Total ADHD Symptom score as a covariate. For secondary efficacy and safety assessments, treatment differences in mean change scores from continuous measures were assessed using analysis of variance (ANOVA), while the Fisher's exact test was used to assess treatment differences in binary data.

Summary:

Patient Disposition: Table LYAA.1 shows demographic characteristics for all randomized patients. Four hundred forty-eight (448) patients entered Study B4Z-MC-LYAA (LYAA). Of those, 168 were not randomized (that is, were discontinued prior to randomization at Visit 3). Patients were not randomized for the following reasons: adverse event (N = 3); lack of efficacy, patient perception (N = 1); lost to follow-up (N = 13); personal conflict (N = 21); entry criteria not met (N = 119); sponsor's decision (N = 2); physician's decision (N = 4), and protocol violation (N = 5). Of the 280 patients enrolled, all were screened in Study Period I (Medication Washout, Screening, and Assessment) and were subsequently randomized to Study Period II (Randomized, Double-Blind, Acute Treatment) at Visit 3. At Visit 3, 141 patients were randomized to atomoxetine and 139 to placebo. Of the 280 patients who enrolled in this study, 209 (74.6%) completed Study Period II, and proceeded to Study Period III. One hundred ninety (190) of the 209 patients (90.9%) randomized in Study Period III completed the protocol.

Patient Demographics: Of the 280 enrolled patients, 63.6% were male; 87.5% were Caucasian, 53.6% had no prior stimulant exposure, and 6.8% were determined to be poor metabolizer (PM) patients. The mean age for these patients was 40.3 years (range of 18.2 to 67.5). Patients were required to meet DSM-IV diagnostic criteria for current ADHD as well as meeting criteria for a historical diagnosis of ADHD during childhood, both assessed by the Conner's Adult ADHD Diagnostic Interview for DSM-IV(CAAR-D). The most common diagnosis was the combined ADHD subtype (71.8%), followed by the predominantly inattentive subtype (27.5%), and hyperactive/impulsive subtype (0.7%). Comorbid DSM-IV diagnoses were assessed using the Structured Clinical Interview for DSM-IV Axis Disorders – Modified (SCID). All comorbid diagnoses were reported as either absent or unspecified for this patient population.

Efficacy: Symptom reduction in the atomoxetine group was numerically superior compared to placebo as assessed by both repeated measures analysis and mean change on the primary outcome measure, the CAARS-Inv:SV Total ADHD Symptom Score. As Table LYAA.2 shows, the mean score for atomoxetine-treated patients for the repeated measures analysis at Visit 8 was 23.88 and the mean score for placebo-treated patients was 27.60, giving a mean treatment difference of -3.72 (p=.004). As Table LYAA.3 shows, the mean change from baseline to endpoint for atomoxetine-treated patients was -9.5 compared to a mean change of -6.0 for placebo-treated patients (p=.006).

The significance of the outcomes on the primary efficacy measure are supported by the outcomes on the secondary measures, including the CAARS-Inv:SV subscale scores (Table LYAA.4), Conners' Adult ADHD Rating Scale – Self-Administered (CAARS-Self) Total ADHD Symptom Score and subscale scores (Table LYAA.5), CGI-ADHD-S (Table LYAA.6), and Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS; Table LYAA.7), which was intended to measure the severity of the target symptoms (from the Utah Criteria) of adults with ADHD. Results on the Hamilton Depression Rating Scale (HAMD-17) and the Hamilton Anxiety Rating Scale (HAMA) show that these efficacy results were specific for ADHD symptoms, as opposed to affective or anxiety symptoms (Table LYAA.8). Atomoxetine treatment did not result in either a dependence or withdrawal syndrome since there were no significant differences between groups when atomoxetine was discontinued with or without a taper, and no symptom rebound was observed (Table LYAA.9).

A significantly higher percentage of patients meeting the CAARS-Inv:SV Total ADHD Symptom score and Clinical Global Impressions-Efficacy Index (CGI-EI) responder criteria was observed for the atomoxetine treatment group compared to the placebo treatment group. The percentage of patients meeting responder criteria in the atomoxetine treatment group was not statistically significantly different from the placebo treatment group using the CGI-ADHD-S definition. For the CAARS-Inv:SV Total ADHD Symptom score response criterion, 51.9% of the atomoxetine-treated and 38.8% of the placebo-treated patients met response criterion (p=.037). Lower percentages of patients in both treatment groups met response criteria for the CGI-EI (atomoxetine 37.9%, placebo 20.9%) and the CGI-ADHD-S (atomoxetine 29.3%, placebo 21.6%), although the difference between groups was only statistically significant for the CGI-EI (p=.003), not for the CGI-ADHD-S (p=.162).

There were no statistically significant differences between the atomoxetine-treated patients compared to placebo-treated patients for any of the Stroop T-scores.

The Arizona Sexual Experiences Scale (ASEX), the Psychological General Well-Being (PGWB), and the Sheehan Disability Scale and Habits Questionnaire were administered to assess changes in health outcomes. Atomoxetine treatment resulted in no significant statistical differences on scores for either gender version of the ASEX. There were no statistically significant differences between atomoxetine and placebo on the PGWB. Atomoxetine treatment resulted in a significantly lower score compared to placebo on the work life subscale of the Sheehan Disability scale (mean change for atomoxetine = -1.6, mean change for placebo = -1.0, $p=.007$). Changes on the family life and social life subscales of the Sheehan Disability scale did not reach statistical significance ($p=.090$ and $p=.123$, respectively).

Safety: There were no deaths in this study. Adverse events resulted in discontinuation for 12 patients treated with atomoxetine, and were most commonly related to the cardiovascular system, nervous system, and the urogenital system. No single event was reported by more than one patient as the reason for discontinuation. Table LYAA.10 summarizes the treatment-emergent adverse events by incidence during Study Period II. Unsolicited (spontaneous) adverse events reported statistically significantly more often by patients taking atomoxetine than by those taking placebo were dry mouth, insomnia, nausea, constipation, sweating, and dysuria. Differences that approached statistical significance were detected for anorexia (typically captured as “decreased appetite”) ($p=.086$), libido decreased ($p=.085$), and palpitation ($p=.067$). For some adverse events (dry mouth, insomnia, nausea, and constipation), reporting rates initially increased in frequency, then plateaued or rose gradually throughout this 10-week study. Reports of libido decreased occurred mainly during the first few weeks. Anorexia (typically captured as “decreased appetite”), sweating, and dysuria were reported at a relatively constant rate throughout the trial. Analysis of CYP2D6 subgroups revealed that adult poor metabolizer (PM) patients tended to report adverse events more frequently than did extensive metabolizer (EM) patients; however, these differences did not reach statistical significance. Females reported nausea more often, and males were more likely to report libido decreased and dysuria. Younger patients tended to report anorexia (typically captured as “decreased appetite”) more often, and older patients were more likely to report decreased libido and dysuria.

Analysis of laboratory data showed that alkaline phosphatase increased in adults taking atomoxetine. The mean change from baseline to endpoint for alkaline phosphatase was +3.055 U/L in atomoxetine-treated patients versus -1.881 U/L in placebo-treated patients ($p<.001$); no abnormally high values were recorded in either group, although one abnormally low value was recorded in the placebo group.

Table LYAA.11 summarizes the mean change from baseline to endpoint in vital sign measures for Study Period II, the acute treatment period. A statistical comparison for the mean change in the atomoxetine (all patients) group compared to the mean change for patients taking placebo is shown. Mean changes for EMs and PMs taking atomoxetine are provided, but no statistical comparison is given because the number of PMs is so small. Use of atomoxetine was found to be associated with an elevation of heart rate (a mean change of 6.657 beats per minute [bpm] for atomoxetine-treated patients versus -0.545 bpm for placebo-treated patients; $p<.001$). In this trial, the mean change in systolic blood pressure was statistically significantly increased in the atomoxetine group (2.321 mm Hg) when compared to the mean change in the placebo group (-0.791 mm Hg, $p=.015$). The mean change in diastolic blood pressure was increased in the atomoxetine group (2.313 mm Hg) when compared to the mean change in the placebo group (0.0493 mm Hg, $p=.063$). Mean weight was statistically significantly decreased in the atomoxetine group (-1.290 kg) versus the placebo group (0.246 kg, $p<.001$). Effects on the ECG were consistent with an increase in heart rate. The QT interval was not prolonged.

Pharmacokinetic: There was no relationship between baseline to endpoint changes in the QTc interval relative to plasma atomoxetine concentrations. This was true for EMs ($p=.464$) and PMs ($p=.639$).

Table LYAA.1. Summary of Demographics and Other Patient Characteristics
All Randomized Patients
B4Z-MC-LYAA

Variable	ATOMOX (N=141)	PLACEBO (N=139)	Total (N=280)	p-Value

Sex: No. (%)				
No. Patients	141	139	280	.804*
Female	50 (35.5)	52 (37.4)	102 (36.4)	
Male	91 (64.5)	87 (62.6)	178 (63.6)	
Origin: No. (%)				
No. Patients	141	139	280	.459*
African Descent	3 (2.1)	7 (5.0)	10 (3.6)	
Western Asian	3 (2.1)	0	3 (1.1)	
Caucasian	124 (87.9)	121 (87.1)	245 (87.5)	
East/Southeast A	3 (2.1)	3 (2.2)	6 (2.1)	
Hispanic	6 (4.3)	7 (5.0)	13 (4.6)	
Other	2 (1.4)	1 (0.7)	3 (1.1)	
Age: yrs.				
No. Patients	141	139	280	.976**
Mean	40.23	40.27	40.25	
Median	40.91	40.12	40.34	
Standard Dev.	11.69	11.61	11.63	
Minimum	18.74	18.22	18.22	
Maximum	65.40	67.46	67.46	
Height: cm				
No. Patients	137	138	275	.980**
Mean	172.38	172.35	172.36	
Median	174.00	172.50	173.00	
Standard Dev.	11.67	9.39	10.57	
Minimum	122.00	150.00	122.00	
Maximum	195.50	193.00	195.50	
Unspecified	4	1	5	
Weight: kg				
No. Patients	141	138	279	.332**
Mean	82.97	85.17	84.06	
Median	83.20	83.60	83.60	
Standard Dev.	17.71	20.17	18.96	
Minimum	47.20	52.30	47.20	
Maximum	131.00	157.50	157.50	
Unspecified	0	1	1	
Family History of ADHD-Mother				
No. Patients	141	139	280	.936*
N	91 (64.5)	92 (66.2)	183 (65.4)	
U	31 (22.0)	28 (20.1)	59 (21.1)	
Y	19 (13.5)	19 (13.7)	38 (13.6)	
Family History of ADHD-Father				
No. Patients	141	139	280	.899*
N	87 (61.7)	82 (59.0)	169 (60.4)	
U	35 (24.8)	36 (25.9)	71 (25.4)	
Y	19 (13.5)	21 (15.1)	40 (14.3)	
Family History of ADHD-Grandparents				
No. Patients	141	139	280	.466*
N	74 (52.5)	62 (44.6)	136 (48.6)	
U	63 (44.7)	73 (52.5)	136 (48.6)	
Y	4 (2.8)	4 (2.9)	8 (2.9)	

(continued)

Table LYAA.1. Summary of Demographics and Other Patient Characteristics
All Randomized Patients
B4Z-MC-LYAA (Concluded)

Variable	ATOMOX (N=141)	PLACEBO (N=139)	Total (N=280)	p-Value
Family History of ADHD-Siblings				
No. Patients	141	139	280	.964*
N	71 (50.4)	73 (52.5)	144 (51.4)	
N/A	8 (5.7)	6 (4.3)	14 (5.0)	
U	27 (19.1)	27 (19.4)	54 (19.3)	
Y	35 (24.8)	33 (23.7)	68 (24.3)	
Family History of ADHD-Children				
No. Patients	141	139	280	.917*
N	33 (23.4)	37 (26.6)	70 (25.0)	
N/A	54 (38.3)	53 (38.1)	107 (38.2)	
U	9 (6.4)	9 (6.5)	18 (6.4)	
Y	45 (31.9)	40 (28.8)	85 (30.4)	
Prior Stimulant Exposure				
No. Patients	141	139	280	.472*
N	79 (56.0)	71 (51.1)	150 (53.6)	
Y	62 (44.0)	68 (48.9)	130 (46.4)	

Population: All Randomized Patients.

Initial Visit ONLY

Input data from RMP.SAS.B4ZM.MCLYAASW

Output stored as RMP.B4ZO.LYAACTRM.FINAL(DE111004)

* Frequencies are analyzed using a Fishers-Exact test.

** Means are analyzed using a Type III Sum of Squares analysis of variance

(ANOVA): PROC GLM model=treatment.

XDES0001

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**Table LYAA.2. CAARS-Inv:SV Total ADHD Symptom Score
 Repeated Measures, Least Squares Mean
 Study Period II
 B4Z-MC-LYAA**

Visit	Atomoxetine			Placebo			Treatment Difference		
	LS Mean	SE	p-val a	LS Mean	SE	p-val a	LS Mean	SE	p-val b
4	28.82	0.90	<.001	30.76	0.93	<.001	-1.94	0.82	.020
5	27.67	0.99	<.001	28.62	1.02	<.001	-0.95	1.00	.342
6	25.23	1.00	<.001	28.18	1.03	<.001	-2.94	1.02	.004
7	23.90	1.10	<.001	27.44	1.12	<.001	-3.54	1.21	.004
8	23.88	1.13	<.001	27.60	1.15	<.001	-3.72	1.26	.004
95% Confidence Interval on Change from Baseline to Visit 8 (-12.04 , -7.57) (-8.35 , -3.81)									
Summary of Model Parameters				F-Value	P-Value c				
Baseline				210.55	<.001				
Treatment				8.33	.004				
Visit				15.06	<.001				
Investigator				1.25	.230				
Treatment*Visit				2.27	.063				
CYP2D6 Status				0.12	.730				

Results based on a mixed model with a term for visit, (treated as a class variable) baseline, treatment and treatment by visit interaction using an unstructured covariance matrix to model correlations within patient across visits.

- a P-values are from tests for a nonzero least squares mean at the given visit.
- b P-values are from tests for a treatment difference in least squares means at the given visit.
- c P-values are from F-tests for a nonzero coefficient estimate.

Program: RMP.B4ZSLYAA.SASPGM(EFF1A)

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Table LYAA.3. CAARS-Inv:SV Total ADHD Symptom Scores
Change from Baseline to Endpoint
Study Period II
B4Z-MC-LYAA

Treatment Group	n	Baseline		Endpoint		Change		p-Value (A)	p-value (B)
		Mean	SD	Mean	SD	Mean	SD		
All Patients									
Atomox.	133	33.6	7.2	24.1	11.2	-9.5	10.1	<.001	.006
PL	134	33.2	7.8	27.2	10.6	-6.0	9.3	<.001	----
95% C.I.: (-5.60 , -0.97)									
Extensive Metabolizers									
Atomox.	123	33.7	7.3	24.4	11.2	-9.3	9.9	<.001	.008
PL	126	33.4	7.8	27.4	10.6	-6.0	9.3	<.001	----
95% C.I.: (-5.61 , -0.86)									
Slow Metabolizers									
Atomox.	10	32.3	6.6	20.6	11.1	-11.7	12.3	.012	.974
PL	8	29.8	6.9	24.8	10.5	-5.0	9.5	.211	----
95% C.I.: (-21.1 , 21.71)									

(A) p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator, treatment, and CYP2D6 status for all patients and using least squares means from an ANOVA model with terms for investigator and treatment for the EM and PM subgroups. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAA.SASPGM(EFF2A)

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Table LYAA.4. CAARS-Inv:SV Inattentive, Hyperactive/Impulsive, and ADHD Index Subscales
Change from Baseline to Endpoint
Study Period II
B4Z-MC-LYAA

Treatment Group	n	Baseline		Endpoint		Change		p-Value (A)	p-value (B)
		Mean	SD	Mean	SD	Mean	SD		
ADHD Index Subscale									
Atomox.	133	18.8	5.1	14.3	6.7	-4.5	6.7	<.001	.010
PL	134	18.9	5.7	16.5	6.8	-2.4	5.6	<.001	----
95% C.I.: (-3.39 , -0.46)									
Hyperactive/Impulsive Subscale									
Atomox.	133	15.2	5.0	10.7	6.0	-4.5	5.1	<.001	.017
PL	134	14.5	5.4	11.6	5.9	-2.9	4.9	<.001	----
95% C.I.: (-2.67 , -0.27)									
Inattentive Subscale									
Atomox.	133	18.4	4.2	13.4	6.3	-5.0	5.7	<.001	.010
PL	134	18.6	4.4	15.6	6.1	-3.1	5.8	<.001	----
95% C.I.: (-3.20 , -0.43)									

(A) p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator, treatment, and CYP2D6 status. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAA.SASPGM(EFF2B)

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Table LYAA.5. CAARS-Self Total ADHD Symptom Score and Inattentive, Hyperactive/Impulsive, ADHD Index Subscales Change from Baseline to Endpoint Study Period II B4Z-MC-LYAA

Treatment Group	n	Baseline		Endpoint		Change		p-Value (A)	p-value (B)
		Mean	SD	Mean	SD	Mean	SD		
Total ADHD Symptom Score									
Atomox.	111	35.7	7.8	25.0	11.0	-10.6	10.7	<.001	.003
PL	114	34.7	8.0	28.5	9.8	-6.2	9.6	<.001	----
95% C.I.: (-6.85 , -1.43)									
Hyperactive/Impulsive Subscale									
Atomox.	111	15.8	5.6	10.9	6.0	-4.9	5.5	<.001	.016
PL	115	15.4	5.4	12.3	5.8	-3.1	5.1	<.001	----
95% C.I.: (-3.15 , -0.33)									
Inattentive Subscale									
Atomox.	111	19.8	3.9	14.1	6.1	-5.7	5.8	<.001	.001
PL	115	19.4	4.3	16.3	5.3	-3.1	5.1	<.001	----
95% C.I.: (-3.88 , -0.95)									

(continued)

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Table LYAA.5. CAARS-Self Total ADHD Symptom Score and Inattentive, Hyperactive/Impulsive, ADHD Index Subscales Change from Baseline to Endpoint Study Period II B4Z-MC-LYAA (concluded)

Treatment Group	n	Baseline		Endpoint		Change		p-Value(A)	p-value(B)
		Mean	SD	Mean	SD	Mean	SD		
ADHD Index Subscale Atomox.	113	23.1	5.4	16.5	7.3	-6.6	6.9	<.001	.002
PL	115	21.7	5.4	17.9	6.6	-3.7	6.2	<.001	----
95% C.I.: (-4.43 , -0.97)									

(A) p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator, treatment, and CYP2D6 status. All enrolled patients with a baseline and at least one postbaseline measurement included.
 Program: RMP.B4ZSLYAA.SASPGM(EFF2C)

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Table LYAA.6. CGI-ADHD-S
Change from Baseline to Endpoint
Study Period II
B4Z-MC-LYAA

Treatment Group	n	Baseline		Endpoint		Change		p-Value(A)	p-value(B)
		-----		-----		-----		-----	-----
		Mean	SD	Mean	SD	Mean	SD		
CGI-ADHD-S									
Atomox.	133	4.7	0.8	3.9	1.1	-0.8	1.2	<.001	.011
PL	134	4.7	0.7	4.3	1.1	-0.4	1.0	<.001	----
95% C.I.: (-0.61 , -0.08)									

(A) p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator, treatment, and CYP2D6 status. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAA.SASPGM(EFF4A)

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Table LYAA.7. WRAADDS
Change from Baseline to Endpoint
Study Period II
B4Z-MC-LYAA

Treatment Group	n	Baseline		Endpoint		Change		p-Value (A)	p-value (B)
		-----		-----		-----		-----	-----
		Mean	SD	Mean	SD	Mean	SD		
WRAADDS Total									
Atomox.	121	18.3	4.7	13.0	5.7	-5.3	6.6	<.001	.001
PL	120	17.6	4.2	14.7	5.7	-2.9	4.8	<.001	----
95% C.I.: (-3.82 , -0.92)									

(A) p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator, treatment, and CYP2D6 status. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAA.SASPGM(EFF4B)

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Table LYAA.8. HAMD-17 and HAMA
Change from Baseline to Endpoint
Study Period II
B4Z-MC-LYAA

Treatment Group	n	Baseline		Endpoint		Change		p-Value(A)	p-value(B)
		Mean	SD	Mean	SD	Mean	SD		
HAMA Total									
Atomox.	121	7.4	5.2	6.4	3.8	-1.0	5.3	.030	.913
PL	123	8.2	4.8	7.1	4.8	-1.2	4.8	.009	----
95% C.I.: (-1.20 , 1.34)									
HAMD Total									
Atomox.	121	5.1	3.6	4.9	3.0	-0.3	3.8	.594	.579
PL	123	5.9	3.9	5.3	4.1	-0.6	4.2	.044	----
95% C.I.: (-0.74 , 1.32)									

(A) p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator, treatment, and CYP2D6 status. All enrolled patients with a baseline and at least one postbaseline measurement included.
 Program: RMP.B4ZSLYAA.SASPGM(EFF2D)

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**Table LYAA.9. CAARS-Inv:SV Total ADHD Symptom Score and
 Subscale Scores
 Change from Baseline to Endpoint
 Study Period III
 B4Z-MC-LYAA**

Treatment Group	n	Baseline		Endpoint		Change		p-Value (A)	p-value (B)
		Mean	SD	Mean	SD	Mean	SD		
Total ADHD Symptoms Score									
ATX_NOTP	50	22.1	11.6	26.6	10.6	4.5	10.2	.002	.297
ATX_TAP	51	24.4	10.6	26.9	11.3	2.5	9.3	.079	----
95% C.I.: (-1.81 , 5.87)									
Hyperactive/Impulsive Subscale									
ATX_NOTP	50	9.4	6.0	11.6	6.3	2.2	4.8	.001	.154
ATX_TAP	51	11.0	5.6	11.9	6.1	0.9	4.5	.156	----
95% C.I.: (-0.51 , 3.19)									
Inattentive Subscale									
ATX_NOTP	50	12.7	6.8	15.0	5.8	2.3	6.2	.030	.547
ATX_TAP	51	13.4	6.3	15.0	6.1	1.6	5.3	.047	----
95% C.I.: (-1.58 , 2.96)									

(continued)

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**Table LYAA.9. CAARS-Inv:SV Total ADHD Symptom Score and
 Subscale Scores
 Change from Baseline to Endpoint
 Study Period III
 B4Z-MC-LYAA (concluded)**

Treatment Group	n	Baseline		Endpoint		Change		p-Value (A)	p-value (B)
		Mean	SD	Mean	SD	Mean	SD		
ADHD Index Subscale									
ATX_NOTP	50	13.1	6.5	15.5	6.3	2.5	5.9	<.001	.361
ATX_TAP	51	14.4	6.8	15.8	6.9	1.5	4.9	.067	----
95% C.I.: (-1.15 , 3.13)									

ATX_NOTP = Atomoxetine No Taper, ATX_TAP = Atomoxetine Taper

(A) p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with term for treatment.

All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAA.SASPGM(EFF3A)

**Table LYAA.10. Summary of Treatment-Emergent Adverse Events
with ≥ 5% Incidence
Study Period II
B4Z-MC-LYAA**

Event Classification	ATOMOX (N=141) n (%)	PLACEBO (N=138) n (%)	Total (N=279) n (%)	p-Value*
PATIENTS WITH ≥ 1 TESS	117 (83.0)	110 (79.7)	227 (81.4)	.540
PATIENTS WITH NO TESS	24 (17.0)	28 (20.3)	52 (18.6)	.540
RHINITIS	26 (18.4)	26 (18.8)	52 (18.6)	1.00
HEADACHE	27 (19.1)	21 (15.2)	48 (17.2)	.429
DRY MOUTH	33 (23.4)	10 (7.2)	43 (15.4)	<.001
INSOMNIA	24 (17.0)	9 (6.5)	33 (11.8)	.009
NAUSEA	19 (13.5)	8 (5.8)	27 (9.7)	.042
PHARYNGITIS	9 (6.4)	18 (13.0)	27 (9.7)	.070
CONSTIPATION	16 (11.3)	6 (4.3)	22 (7.9)	.044
ANOREXIA	13 (9.2)	5 (3.6)	18 (6.5)	.086
FLU SYNDROME	7 (5.0)	10 (7.2)	17 (6.1)	.463
BACK PAIN	4 (2.8)	10 (7.2)	14 (5.0)	.106
DIARRHEA	4 (2.8)	10 (7.2)	14 (5.0)	.106
FEVER	5 (3.5)	8 (5.8)	13 (4.7)	.409
LIBIDO DECREASED	10 (7.1)	3 (2.2)	13 (4.7)	.085
ABNORMAL DREAMS	8 (5.7)	3 (2.2)	11 (3.9)	.217
ASTHENIA	8 (5.7)	3 (2.2)	11 (3.9)	.217
SINUSITIS	7 (5.0)	4 (2.9)	11 (3.9)	.541
SWEATING	11 (7.8)	0	11 (3.9)	.001
VASODILATATION	8 (5.7)	3 (2.2)	11 (3.9)	.217
COUGH INCREASED	3 (2.1)	7 (5.1)	10 (3.6)	.214
DIZZINESS	7 (5.0)	2 (1.4)	9 (3.2)	.173
DYSURIA	9 (6.4)	0	9 (3.2)	.003
PALPITATION	7 (5.0)	1 (0.7)	8 (2.9)	.067

Population: Randomized patients who took at least 1 dose of study drug.

Baseline: Visits 1-3, Endpoint: Visits 4 - 8

Input data from RMP.SAS.B4ZM.MCLYAASW

Output stored as RMP.B4Z0.LYAACTRM.FINAL(AE2C1002)

* Frequencies are analyzed using a Fisher's Exact test.

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Table LYAA.11. Vital Signs
Mean Change from Baseline to Endpoint
Study Period II
B4Z-MC-LYAA

	PBO (all) N=134	p-value	ATX (all) N=134	ATX (EMs) N=124	ATX (PMs) N=10
diastolic BP (mm Hg)	+.0493	.063	+2.313	+2.343	+1.950
systolic BP (mm Hg)	-0.791	.015	+2.321	+2.710	-2.500
pulse (bpm)	-0.545	<.001	+6.657	+6.339	+10.600
weight (kg)	+0.246	<.001	-1.290	-1.295	-1.220
temperature (°C)	+0.057	.043	-0.071	-0.071	-0.078

Source data: RMP.B4ZO.LYAACTRM.FINAL (VI6L1002),
 RMP.B4ZO.LYAACTRM.FINAL (VI6L1005), RMP.B4ZO.LYAACTRM.FINAL (VI6L1006)

Summary ID#2561

Clinical Study Summary: Study B4Z-MC-LYAB

Title of Study: A Phase III Open-Label Safety and Efficacy Study of Atomoxetine Hydrochloride in Outpatients with ADHD, Ages 6 to 18 Years	
Investigators: This multicenter study included 62 principal investigators (PIs).	
Study Centers: This study was conducted at 58 study centers in the United States. (Four sites had two PIs each; hence the seeming discrepancy of 62 PIs at 58 study centers.)	
Length of Study: Approximately 2 years Date first patient enrolled: 06 March 2000 Date last patient completed: 05 December 2002	Phase of Development: 3
Objectives: The primary objective of this study was to demonstrate that atomoxetine (formerly called tomoxetine) up to a dose of 1.8 mg/kg/day is safe and well-tolerated when administered acutely (approximately 10 weeks), and for a longer term (approximately 2 years). The secondary objective of this study was to assess the efficacy of atomoxetine in child and adolescent patients with Attention-Deficit/Hyperactivity Disorder (ADHD) using the primary efficacy outcome instrument, the Attention-Deficit/Hyperactivity Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv).	
Study Design: Study LYAB was a Phase 3, multicenter, open-label investigation of the long-term safety and efficacy of atomoxetine in approximately 1000 outpatients who were at least 6 years of age but less than 18 years of age when informed consent was obtained, and who met <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</i> (DSM-IV) criteria for ADHD. Patients who responded to acute treatment with atomoxetine (Study Period II, approximately 10 weeks) were eligible to enter a long-term treatment phase (Study Period III, approximately 2 years).	
Number of Patients: Planned: 1000 Enrolled: 914 Completed: 294	
Diagnosis and Main Criteria for Inclusion: Patients at least 6 years of age but less than 18 years of age and who met DSM-IV criteria for ADHD at time of study entry.	
Test Product, Dose, and Mode of Administration: Atomoxetine 2.5 mg, 5 mg, 10 mg, and 20 mg capsules; dose individually titrated based on body weight starting at a total daily dose that is closest to, but does not exceed, 0.5 mg/kg/day and ending with a maximum dose of 1.8 mg/kg/day (or 120 mg/day); given in divided doses twice daily. Capsules supplied in bottles.	
Duration of Treatment: Approximately 2 years.	
Reference Therapy, Dose, and Mode of Administration: None.	
Variables: Efficacy: Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv), Total score, and subscale scores. Safety: Adverse events, vital signs, clinical laboratory measures, and electrocardiograms (ECGs). Health Outcomes: ADHD Impact Module (AIM) and Child Health Questionnaire (CHQ).	
Evaluation Methods: Statistical: Primary analyses performed include descriptive summary statistics such as mean, standard deviation, mean change from baseline to endpoint, 2-sided 95% confidence intervals, and Wilcoxon signed-rank test. Missing data were handled using a last-observation-carried-forward (LOCF) approach. Analysis	

of variance (ANOVA) models were used to assess subgroup differences, a repeated measures model was used to test for changes in the primary outcome over time in Study Period II, and survival analysis based on Kaplan-Meier product limit estimator was used to examine the number of days to relapse.

Summary:

Patient Disposition: There were 1046 patients who entered the study. Of these, 914 patients were enrolled into Study Period II (acute treatment). A total of 683 patients completed acute treatment and continued into Study Period III (long-term treatment), with 301 patients completing long-term atomoxetine treatment. There were 294 patients that completed the taper-off period (Study Period IV). Over the duration of the trial, a total of 26.1% discontinued due to lack of efficacy, 5.6% for adverse events, and 5.3% for protocol-defined clinical relapse.

Patient Demographics: Table LYAB.1 shows a summary of demographics and other patient characteristics for all entered patients. The population of patients treated with atomoxetine in this study was similar to those in other studies in that most were males (76.1%) and Caucasian (82.9%), with a mean age of 11.04 years. Prior stimulant use was reported by 76.6% of atomoxetine patients. Most atomoxetine patients were diagnosed with either the combined subtype (62.7%) or the inattention subtype (34.0%) of ADHD.

Efficacy: As Table LYAB.2 illustrates, there was a statistically significant reduction in mean change from baseline to LOCF endpoint in ADHDRS-IV-Parent:Inv Total score, T-scores, and the Inattention and Hyperactivity-Impulsivity subscale scores (all $p < .001$) during the acute treatment phase (Study Period II). For the primary efficacy variable (ADHDRS-IV-Parent:Inv Total score) during Study Period II, the mean change from baseline was -20.1 ($p < .001$). Outcomes on the ADHDRS-IV-Parent:Inv were similar for cytochrome P450 2D6 (CYP2D6) extensive metabolizer (EM) and poor metabolizer (PM) patients (subgroup effect p -value = .481).

During the long-term treatment phase (Study Period III), responses achieved during acute therapy appear to have been mostly maintained (Table LYAB.3).

Safety: 5.6% of patients discontinued due to an adverse event. The adverse event profile in this study is similar to that observed in other trials. Events did not increase over time. The adverse event profile reported for PM patients was similar to that for EM patients. Table LYAB.4 presents a summary of treatment-emergent adverse events occurring in $\geq 5\%$ of patients during Study Periods II and III combined. The three most common reported adverse events were headache (39.3%), abdominal pain upper (21.3%), and pharyngitis (20.7%). Headache was reported with a 10.7% frequency in the beginning of treatment and stabilized to a 23.6% frequency by the end of the study. There was no relationship between days of therapy and frequency of abdominal pain upper or pharyngitis.

Table LYAB.5 shows the observed mean changes in laboratory values from baseline to endpoint. Statistically significant non-zero changes do not suggest a drug effect, but are likely the result of the large sample size. Summaries of mean change from baseline to endpoint for laboratory values were computed for CYP2D6 EM and PM patients separately, as well.

Table LYAB.6 summarizes the mean change from baseline to endpoint for the entire treatment period (Study Periods II and III) in vital sign measures for all patients treated with atomoxetine who had at least one postbaseline measurement. A statistically significant increase in mean baseline to endpoint diastolic blood pressure (3.2 mm Hg, $p < .001$), systolic blood pressure (3.5 mm Hg, $p < .001$), and pulse (4.9 bpm, $p < .001$) were detected in this trial. Although there were incidents of weight loss postbaseline, an overall statistically significant mean weight increase from baseline to endpoint (4.0 kg, $p < .001$) was observed in this long-term trial. Over the duration of this trial, there was a statistically significant increase in mean change from baseline to endpoint height (6.0 cm, $p < .001$). During the course of therapy, the height and weight showed a decrease of 2 to 3 percentiles. Although changes in PM patients' vital signs were slightly more pronounced than those seen in EM patients, with the exception of heart rate, these changes do not appear excessive (heart rate change: 9.8 bpm [PM] versus 4.6 bpm [EM]), and do not suggest intolerability related to atomoxetine.

Effects on ECG parameters were consistent with an increased heart rate (Table LYAB.7). No evidence for a drug-related QTc prolongation was observed. There was no particular association between the patients' QTc interval prolongations and any particular adverse events or concomitant medication use. ECG results for PM patients were similar to the results in the total population.

Health Outcomes: There was a statistically significant improvement from baseline to endpoint for both the child and parent scales of the AIM (mean change of 17.0 for the child scale, mean change of 14.8 for the parent scale, $p < .001$ for both), suggesting a benefit of atomoxetine for both the child and family.

Statistically significant ($p < .001$) increases from baseline to endpoint were shown in the Psychosocial Summary Score (mean change of 7.1) and six of the CHQ Concepts (General Behavior [mean change of 13.5], Family Activities [mean change of 15.1], Mental Health [mean change of 4.7], Parental Impact-Emotional [mean change of 11.6], Parental Impact-Time [mean change of 8.7], Role/Social Emotional/Behavioral [mean change of 12.4], and Self-Esteem [mean change of 5.7]). The only measure that statistically significantly declined from baseline to endpoint was the Physical Summary Score (mean change of -0.9, $p < .001$).

Table LYAB.1. Summary of Demographics and Other Patient Characteristics
All Entered Patients
B4Z-MC-LYAB

Variable	ATOMOX (N=914)	NO DRUG (N=132)	Total (N=1046)
Sex: No. (%)			
No. Patients	914	132	1046
Female	218 (23.9)	31 (23.5)	249 (23.8)
Male	696 (76.1)	101 (76.5)	797 (76.2)
Origin: No. (%)			
No. Patients	914	132	1046
African Descent	49 (5.4)	13 (9.9)	62 (5.9)
Western Asian	2 (0.2)	0	2 (0.2)
Caucasian	758 (82.9)	105 (80.2)	863 (82.6)
East/Southeast A	8 (0.9)	0	8 (0.8)
Hispanic	67 (7.3)	10 (7.6)	77 (7.4)
Other	30 (3.3)	3 (2.3)	33 (3.2)
Unspecified	0	1	1
Age: yrs.			
No. Patients	914	132	1046
Mean	11.04	11.09	11.04
Median	10.85	10.58	10.82
Standard Dev.	2.79	3.18	2.84
Minimum	6.00	6.05	6.00
Maximum	17.97	20.09	20.09
Height: cm			
No. Patients	905	95	1000
Mean	144.19	144.96	144.26
Median	142.00	143.50	142.00
Standard Dev.	16.76	19.70	17.05
Minimum	101.50	79.50	79.50
Maximum	190.50	180.50	190.50
Unspecified	9	37	46
Weight: kg			
No. Patients	904	97	1001
Mean	41.01	43.26	41.22
Median	36.25	37.20	36.50
Standard Dev.	17.03	19.14	17.24
Minimum	18.20	18.50	18.20
Maximum	119.10	110.70	119.10
Unspecified	10	35	45
DSM-IV ADHD SUBTYPE			
No. Patients	914	132	1046
HYP/IMP	30 (3.3)	3 (2.8)	33 (3.2)
INATTV	311 (34.0)	34 (31.2)	345 (33.7)
MIXED	573 (62.7)	72 (66.1)	645 (63.0)
Unspecified	0	23	23
Family History of ADHD-Mother			
No. Patients	914	132	1046
N	636 (70.0)	89 (83.2)	725 (71.4)
U	121 (13.3)	13 (12.1)	134 (13.2)
Y	152 (16.7)	5 (4.7)	157 (15.5)
Unspecified	5	25	30

(continued)

Table LYAB.1. Summary of Demographics and Other Patient Characteristics
All Entered Patients
B4Z-MC-LYAB (Continued)

Variable	ATOMOX (N=914)	NO DRUG (N=132)	Total (N=1046)
Family History of ADHD-Father			
No. Patients	914	132	1046
N	535 (58.9)	59 (55.1)	594 (58.5)
U	159 (17.5)	18 (16.8)	177 (17.4)
Y	215 (23.7)	30 (28.0)	245 (24.1)
Unspecified	5	25	30
Family History of ADHD-Grandparents			
No. Patients	914	132	1046
N	635 (69.9)	79 (73.8)	714 (70.3)
U	204 (22.4)	18 (16.8)	222 (21.9)
Y	70 (7.7)	10 (9.3)	80 (7.9)
Unspecified	5	25	30
Family History of ADHD-Siblings			
No. Patients	914	132	1046
N	466 (51.3)	61 (57.0)	527 (51.9)
N/A	58 (6.4)	8 (7.5)	66 (6.5)
U	103 (11.3)	11 (10.3)	114 (11.2)
Y	282 (31.0)	27 (25.2)	309 (30.4)
Unspecified	5	25	30
Prior Stimulant Exposure			
No. Patients	914	132	1046
N	213 (23.4)	46 (38.3)	259 (25.1)
Y	698 (76.6)	74 (61.7)	772 (74.9)
Unspecified	3	12	15
DRD4 Allele			
No. Patients	914	132	1046
Unspecified	914	132	1046
Grade in School			
No. Patients	914	132	1046
1	68 (7.4)	13 (10.5)	81 (7.8)
2	86 (9.4)	17 (13.7)	103 (9.9)
3	110 (12.0)	13 (10.5)	123 (11.8)
4	106 (11.6)	12 (9.7)	118 (11.4)
5	125 (13.7)	12 (9.7)	137 (13.2)
6	107 (11.7)	18 (14.5)	125 (12.0)
7	93 (10.2)	12 (9.7)	105 (10.1)
8	74 (8.1)	4 (3.2)	78 (7.5)
9	54 (5.9)	9 (7.3)	63 (6.1)
0	14 (1.5)	2 (1.6)	16 (1.5)
10	41 (4.5)	6 (4.8)	47 (4.5)
11	24 (2.6)	5 (4.0)	29 (2.8)
12	11 (1.2)	0	11 (1.1)
13	1 (0.1)	1 (0.8)	2 (0.2)
Unspecified	0	8	8

(continued)

Table LYAB.1. Summary of Demographics and Other Patient Characteristics
All Entered Patients
B4Z-MC-LYAB (Continued)

Variable	ATOMOX (N=914)	NO DRUG (N=132)	Total (N=1046)
WISC full scale IQ			
No. Patients	878	77	955
Mean	106.21	90.69	104.95
Median	105.00	90.00	105.00
Standard Dev.	16.12	22.27	17.22
Minimum	55.00	17.00	17.00
Maximum	149.00	133.00	149.00
Unspecified	33	11	44
WRAT Reading Raw Score			
No. Patients	884	82	966
Mean	34.63	30.74	34.30
Median	35.00	30.00	34.50
Standard Dev.	8.92	10.71	9.14
Minimum	0.00	0.00	0.00
Maximum	54.00	54.00	54.00
Unspecified	27	6	33
WRAT Reading Standard Score			
No. Patients	886	82	968
Mean	99.77	90.13	98.95
Median	101.00	90.00	100.00
Standard Dev.	15.58	17.62	15.98
Minimum	44.00	45.00	44.00
Maximum	147.00	127.00	147.00
Unspecified	25	6	31
WRAT Spelling Raw Score			
No. Patients	884	81	965
Mean	29.55	27.09	29.34
Median	29.00	26.00	29.00
Standard Dev.	7.96	9.33	8.11
Minimum	0.00	0.00	0.00
Maximum	54.00	51.00	54.00
Unspecified	27	7	34
WRAT Spelling Standard Score			
No. Patients	885	81	966
Mean	97.68	90.77	97.10
Median	97.00	89.00	97.00
Standard Dev.	15.02	16.32	15.24
Minimum	51.00	48.00	48.00
Maximum	140.00	133.00	140.00
Unspecified	26	7	33
WRAT Arithmetic Raw Score			
No. Patients	884	82	966
Mean	29.91	27.49	29.71
Median	30.00	28.00	30.00
Standard Dev.	8.34	9.35	8.45
Minimum	8.00	8.00	8.00
Maximum	51.00	45.00	51.00
Unspecified	27	6	33

(continued)

Table LYAB.1. **Summary of Demographics and Other Patient Characteristics**
All Entered Patients
B4Z-MC-LYAB (Concluded)

Variable	ATOMOX (N=914)	NO DRUG (N=132)	Total (N=1046)

WRAT Arithmetic Standard Score			
No. Patients	886	82	968
Mean	96.93	89.24	96.28
Median	97.00	91.00	97.00
Standard Dev.	15.44	17.01	15.72
Minimum	44.00	45.00	44.00
Maximum	152.00	126.00	152.00
Unspecified	25	6	31

Population: All Entered Patients.
 Study Period XX: Specialized Reporting All Visits 1-38
 Input data from RMP.SAS.B4ZM.MCLYABSW.FINAL
 Output stored as RMP.B4ZO.LYABCTRM.FINAL(DE1C3001)
 XDES0001

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**Table LYAB.2. ADHDRS-IV-Parent:Inv Total Score, T-score, and Subscales
 Change From Baseline to Endpoint
 Study Period II
 B4Z-MC-LYAB**

Treatment	n	Baseline		Endpoint		Change				p-Value*
		Mean	SD	Mean	SD	Mean	SD	LCI	UCI	
Total Score	909	37.9	9.8	17.8	12.3	-20.1	12.8	-21.0	-19.3	<.001
T-Score	909	79.0	11.3	57.7	13.2	-21.3	13.9	-22.2	-20.4	<.001
Inattentive Subscale Score	909	21.6	4.5	10.7	6.8	-10.9	7.3	-11.4	-10.4	<.001
Hyperactive Subscale Score	909	16.3	7.5	7.1	6.7	-9.2	7.0	-9.7	-8.8	<.001

Abbreviations: ATMX: atomoxetine; n = number of patients with a baseline and at least one postbaseline measurement;

SD = standard deviation; Change = endpoint-baseline; C.I. = 95% 2-sided Confidence Interval of Change;

LCI = Lower bound of 95% C.I.; UCI = Upper bound of 95% C.I.; Baseline: Visit 1-3; Endpoint: Visit 4-13.

*p-Value is from Wilcoxon signed-rank test

Source data: RMP.B4ZSLYAB.SASPGM(EFF1)

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**Table LYAB.3. ADHDRS-IV-Parent:Inv Total Score
 Change from Baseline to Endpoint
 Study Period III**

Treatment		Baseline		Endpoint		Change				p-Value*
Atomoxetine	n	Mean	SD	Mean	SD	Mean	SD	LCI	UCI	
Total ADHD Score	677	13.7	9.0	16.0	11.7	2.3	10.0	1.6	3.1	<.001
Hyperactive/Impulsive Subscale	677	5.2	5.1	5.9	6.0	0.7	4.9	0.3	1.1	.004
Inattention Subscale	677	8.5	5.2	10.0	6.9	1.6	6.1	1.1	2.0	<.001

*p-Value is from Wilcoxon signed-rank test

Abbreviations: n = number of patients with a baseline and at least one postbaseline measurement;

SD = standard deviation; Change = endpoint-baseline; C.I. = 95% 2-sided Confidence Interval of Change;

LCI = Lower bound of 95% C.I.; UCI = Upper bound of 95% C.I.; Baseline: Visit 1-13; Endpoint: Visit 14-36.

Source data: RMP.B4ZSLYAB.SASPGM(LOAD4K1)

**Table LYAB.4. Summary of Treatment-Emergent Adverse Events
Incidence $\geq 5\%$ in Study Periods II and III**

Preferred Term	ATOMOX (N=912)	
	n	(%)
PATIENTS WITH ≥ 1 TESS	822	(90.1)
PATIENTS WITH NO TESS	90	(9.9)
Headache	358	(39.3)
Abdominal pain upper	194	(21.3)
Pharyngitis	189	(20.7)
Nasopharyngitis	187	(20.5)
Vomiting NOS	177	(19.4)
Cough	176	(19.3)
Upper respiratory tract infection NOS	169	(18.5)
Nausea	148	(16.2)
Pyrexia	135	(14.8)
Appetite decreased NOS	120	(13.2)
Nasal congestion	115	(12.6)
Fatigue	103	(11.3)
Influenza	84	(9.2)
Insomnia	83	(9.1)
Diarrhoea NOS	80	(8.8)
Sinusitis NOS	80	(8.8)
Dizziness	79	(8.7)
Irritability	79	(8.7)
Gastroenteritis viral NOS	77	(8.4)
Somnolence	76	(8.3)
Pharyngitis streptococcal	68	(7.5)
Dyspepsia	64	(7.0)
Constipation	60	(6.6)
Unexpected therapeutic drug effect	52	(5.7)
Rash NOS	50	(5.5)
Viral infection NOS	50	(5.5)
Otitis media NOS	49	(5.4)
Abdominal pain NOS	48	(5.3)

Population: Randomized patients who took at least 1 dose of study drug.

Baseline: Visits 1-3, Endpoint: Visits 4 - 36

Input data from RMP.SAS.B4ZM.MCLYABSW.FINAL

Output stored as RMP.B4Z0.LYABCTRM.FINAL(AE21201A)

XAES0002 MEDDRA VERSION: 5.1

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**Table LYAB.5. Summary of Laboratory Data
 Change From Baseline to Endpoint
 Study Periods II and III**

Lab Test	Lab Unit	N	Baseline		Change		p-value	
			Mean	SD	Mean	SD	increased	decreased
HEMATOCRIT	1	868	0.389	0.030	0.010	0.031	<0.001	----
HEMOGLOBIN	mmL/L-Fe	874	8.385	0.619	0.128	0.515	<0.001	----
ERYTHROCYTE COUNT	TI/L	874	4.727	0.333	0.050	0.267	<0.001	----
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)	mmL/L-Fe	868	21.638	0.874	-0.225	1.141	----	<0.001
MEAN CELL HEMOGLOBIN (MCH)	fmoL(Fe)	874	1.780	0.095	0.008	0.062	<0.001	----
LEUKOCYTE COUNT	GI/L	874	6.823	1.814	0.120	2.022	0.208	----
BANDS	GI/L	873	0.000	0.000	0.000	0.007	0.125	----
NEUTROPHILS, SEGMENTED	GI/L	873	3.541	1.395	0.215	1.712	<0.001	----
LYMPHOCYTES	GI/L	873	2.610	0.736	-0.075	0.659	----	<0.001
MONOCYTES	GI/L	873	0.400	0.145	-0.003	0.153	----	0.273
EOSINOPHILS	GI/L	873	0.221	0.203	-0.022	0.185	----	<0.001
BASOPHILS	GI/L	873	0.047	0.028	0.003	0.034	<0.001	----
MEAN CELL VOLUME (MCV)	fL	868	82.365	4.350	1.301	4.235	<0.001	----
PLATELET COUNT	GI/L	868	282.181	61.764	9.173	51.852	<0.001	----
LYMPHOCYTES, ATYPICAL	GI/L	3	0.450	0.246	-0.143	0.278	----	0.750
UA-SPECIFIC GRAVITY	NO UNITS	830	1.025	0.007	0.001	0.009	0.001	----
AST/SGOT	U/L	878	27.167	6.777	-0.838	6.581	----	<0.001
ALT/SGPT	U/L	878	18.527	8.157	-0.800	8.252	----	0.004
CREATINE PHOSPHOKINASE	U/L	878	135.944	76.741	6.880	167.542	0.016	----
ALKALINE PHOSPHATASE	U/L	876	238.228	75.803	-11.618	66.599	----	<0.001
GGT (GGPT/SGGT/YGGT)	U/L	878	12.995	4.594	0.362	3.843	0.004	----
UREA NITROGEN	mmol/L	878	4.749	1.129	-0.040	1.309	----	0.305
CALCIUM	mmol/L	878	2.437	0.113	0.031	0.129	<0.001	----
INORGANIC PHOSPHORUS	mmol/L	874	1.594	0.197	-0.024	0.235	----	0.004
SODIUM	mmol/L	875	140.966	2.258	0.753	2.925	<0.001	----
POTASSIUM	mmol/L	872	4.245	0.378	0.020	0.491	0.207	----
CHLORIDE	mmol/L	876	104.452	2.405	0.163	3.014	0.275	----
TOTAL PROTEIN	g/L	878	73.243	4.550	-0.207	4.680	----	0.222
ALBUMIN	g/L	878	43.274	3.004	0.757	3.452	<0.001	----
GLUCOSE, NON-FASTING	mmol/L	875	5.008	0.852	0.113	1.118	0.001	----
URIC ACID	umol/L	878	247.818	72.630	12.404	53.332	<0.001	----
CHOLESTEROL	mmol/L	878	4.252	0.694	-0.061	0.545	----	<0.001

(continued)

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**Table LYAB.5. Summary of Laboratory Data
 Change From Baseline to Endpoint
 Study Periods II and III (Concluded)**

Lab Test	Lab Unit	N	Baseline		Change		p-value	
			Mean	SD	Mean	SD	increased	decreased
BICARBONATE, HCO3	mmol/L	876	24.609	2.324	-0.952	2.913	----	<0.001
CREATININE	umol/L	878	47.563	12.548	5.215	11.091	<0.001	----
BILIRUBIN, TOTAL	umol/L	673	6.888	4.340	0.569	3.350	0.054	----

Abbreviations: N = number of patients with a baseline and at least one postbaseline measurement.
 SD = standard deviation, p Value is from Wilcoxon signed rank test
 Change = endpoint - baseline, Baseline: Visit 1-3, Endpoint: Visit 4-36
 Program: RMP.B4ZSLYAB.SASPGM(LOLABL1)
 Data: RMP.SAS.B4ZM.MCLYABSW.FINAL

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**Table LYAB.6. Summary of Vital Signs
 Change from Baseline to Endpoint
 Study Periods II and III**

Treatment	n	Baseline		Endpoint		Change				p-Value*
		Mean	SD	Mean	SD	Mean	SD	LCI	UCI	
ATMX										
Height	834	144.5	16.7	150.5	17.0	6.0	5.8	5.6	6.4	<0.001
Weight	910	41.6	17.3	45.7	18.7	4.0	6.1	3.6	4.4	<0.001
Pulse	910	81.0	11.2	85.9	12.3	4.9	12.9	4.0	5.7	<0.001
Temperature	910	36.6	0.5	36.5	0.5	-0.0	0.6	-0.1	0.0	0.016
Systolic Blood Pressure	910	103.6	10.5	107.1	10.7	3.5	10.9	2.8	4.2	<0.001
Diastolic Blood Pressure	910	64.8	8.5	68.1	8.3	3.2	9.4	2.6	3.9	<0.001

*p-Value is from Wilcoxon signed-rank test

Abbreviations: ATMX: atomoxetine; n = number of patients with a baseline and at least one postbaseline measurement;

SD = standard deviation; Change = endpoint-baseline; C.I. = 95% 2-sided Confidence Interval of Change;

LCI = Lower bound of 95% C.I.; UCI = Upper bound of 95% C.I.; Baseline: Visit 1-3; Endpoint: Visit 4-36.

Source data: RMP.B4ZSLYAB.SASPGM(LOVITK1)

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Table LYAB.7. Summary of ECG Changes
Change from Baseline to Endpoint
Study Periods II and III

Treatment	n	Baseline		Endpoint		Change				p-Value*
		Mean	SD	Mean	SD	Mean	SD	LCI	UCI	
ATMX										
Heart Rate	909	77.3	11.9	84.3	13.6	7.0	12.5	6.2	7.8	<0.001
RR Interval	909	795.2	127.9	731.1	123.9	-64.1	119.9	-71.9	-56.3	<0.001
QRS Interval	909	84.3	8.8	85.3	9.4	1.0	6.5	0.5	1.4	<0.001
QT Bazett Correction	909	416.1	16.1	420.1	17.5	4.0	17.2	2.9	5.2	<0.001
QT Data Correction	909	405.6	13.9	405.7	14.9	0.1	14.3	-0.8	1.0	0.736
QT Fridericia Correction	909	400.1	14.1	398.2	15.0	-1.8	14.1	-2.8	-0.9	<0.001

*p-Value is from Wilcoxon signed-rank test

Abbreviations: ATMX: atomoxetine; n = number of patients with a baseline and at least one postbaseline measurement;

SD = standard deviation; Change = endpoint-baseline; C.I. = 95% 2-sided Confidence Interval of Change;

LCI = Lower bound of 95% C.I.; UCI = Upper bound of 95% C.I.; Baseline: Visit 1-3; Endpoint: Visit 4-36.

Source data: RMP.B4ZSLYAB.SASPGM(LOECGK1)

Summary ID#2746

Clinical Study Summary: Study B4Z-MC-LYAT

Date summary approved by Lilly: 11 November 2004

Amended summary approved by Lilly: 25 April 2007

The summary was amended to correct the information on page 1. Phase of Development is Phase 3, rather than Phase 4 as previously posted on 08 December 2004.

Title of Study: Efficacy, Tolerability, and Safety of Once-Daily Atomoxetine Hydrochloride versus Placebo in Children with Attention-Deficit/Hyperactivity Disorder	
Investigators: This multicenter study included 9 principal investigators.	
Study Centers: This study was conducted at 9 study centers in the United States.	
Length of Study: 3 months Date first patient enrolled: 06 February 2001 Date last patient completed: 18 May 2001	Phase of Development: 3
Objectives: The primary objective of this study was to test the hypothesis that atomoxetine (formerly called tomoxetine) administered as a single daily dose provided superior efficacy compared with placebo in children with Attention-Deficit/Hyperactivity Disorder (ADHD). The secondary objectives of the study were as follows: • To compare the improvement in symptoms associated with ADHD in children achieved by once-daily dosing of atomoxetine or placebo as defined by a >25% reduction in the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) score and by mean reductions in the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) and ADHDRS-IV-Parent:Inv subscale scores. • To compare the reduction in non-school-related symptoms between atomoxetine and placebo as assessed by the Daily Parent Ratings of Evening and Morning Behavior (DPREMB) and the Social Skills Rating System-Parent Form (SSRS-P). • To compare the reduction in school-related symptoms between atomoxetine and placebo as assessed by the Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R:S). • To assess the safety and tolerability of once-daily dosing of atomoxetine.	

Study Design: Study B4Z-MC-LYAT (LYAT) was a child and adolescent placebo-controlled study conducted with 171 enrolled patients aged 6 to 16 years who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for ADHD.

Patients were randomized to either placebo or once-daily dosing of atomoxetine. Atomoxetine was administered as a single dose in the early morning and titrated on a weight-adjusted basis according to clinical response. The maximum atomoxetine dose was 1.5 mg/kg/day.

The study included three treatment periods. Patients who met entry criteria completed an initial evaluation period of 3 to 20 days (Study Period I; Visit 1 and Visit 2), that included full clinical assessment, diagnostic assessment, and a washout phase. At the end of Visit 2, patients were randomized.

During the 6-week, double-blind, acute treatment phase (Study Period II; Visit 3 through Visit 6), dose was titrated according to prespecified response criteria. Following Visit 6, patients who wished to continue atomoxetine treatment and who met entry qualifications were eligible for participation in a long-term atomoxetine study, such as Study B4Z-MC-LYAI. No patients continued into Study Period III and entered the 7- to 18-day optional study drug discontinuation phase.

Number of Patients:

Planned: 80 atomoxetine, 80 placebo

Randomized: 85 atomoxetine, 86 placebo

Completed: 73 atomoxetine, 75 placebo

Diagnosis and Main Criteria for Inclusion: Patients were at least 6 years of age but not more than 16 years of age at the time informed consent was obtained (Visit 1). Patients met DSM-IV diagnostic and severity criteria for ADHD assessed by modules of the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version: Behavioral Disorders Supplement (K-SADS:PL-Behavioral). Each patient's score from the ADHDRS-IV-Parent:Inv was at least 1.5 standard deviations above the age/gender norm for their diagnostic subtype at Visit 1 and was maintained at Visit 2.

Test Product, Dose, and Mode of Administration: Atomoxetine capsules, given once daily.

Duration of Treatment: 6 weeks.

Reference Therapy, Dose, and Mode of Administration: Placebo capsules, given once daily.

Variables:

Efficacy: Reduction in the severity of symptoms was measured using the Total score for ADHDRS-IV-Parent:Inv.

Safety: Analysis of adverse events included the 170 enrolled patients who took at least one dose of study drug. One patient was randomized but never took study drug. The analysis for clinical laboratory studies, vital signs, and electrocardiogram (ECG) data included patients who received at least one dose of study drug and had a baseline and a postbaseline measurement.

Evaluation Methods:

Statistical: The primary analysis was a comparison of atomoxetine with placebo at Visit 6 using a contrast from a repeated measures mixed effects model. The dependent variable in the model was the ADHDRS-IV-Parent:Inv Total scores (from Visit 3 through Visit 6; all Study Period II postbaseline data). The model contained fixed class effect terms for treatment, investigator, visit, and an interaction term between treatment and visit. The model also included a random subject effect and baseline (Visit 2) ADHDRS-IV-Parent:Inv Total score as a covariate. Secondary analyses using the primary efficacy variable included an analysis of change from baseline to endpoint using an analysis of variance (ANOVA) model containing terms for treatment and investigational site, an analysis of T-scores, analysis of percentage of responders, and subgroup analyses by investigational site. All tests were performed using a 2-sided, 0.05 significance level.

Secondary efficacy variables were analyzed using similar methods.

Summary:

Patient Disposition: Of the 197 patients who entered Study LYAT, 26 were not randomized (that is, were discontinued prior to randomization at Visit 2). Patients were not randomized for the following

reasons: lost to follow-up (1); personal conflict (9); and entry criteria not met (16).

At the end of Visit 2, 86 patients were randomized to placebo (60 male, 26 female); 85 were randomized to atomoxetine (59 male, 26 female). Of the 171 patients randomized, 148 completed Study Period II. No patients chose to enter Study Period III, the optional study discontinuation phase.

Patient Demographics: Table LYAT.1 shows demographic characteristics for randomized patients who took at least 1 dose of study drug. Of the 170 randomized patients who took at least one dose of study drug, 70.6% were male; 78.8% were Caucasian; 44.7% had no prior stimulant exposure, and 2.9% were determined to be poor cytochrome P450 2D6 (CYP2D6) metabolizer patients. The mean age was 10.28 years (range of 6.1 years to 16.2 years) and 60.6% of the patients were in the first through fifth grades in school.

Patients were required to meet DSM-IV criteria for ADHD following clinical examination and with the ADHD module of the K-SADS-PL:Behavioral. Of the randomized patients, 57.6% met criteria for the combined ADHD subtype, with 40.6% classified as predominantly inattentive and 1.8% as hyperactive-impulsive.

Efficacy: As Table LYAT.2 illustrates, the primary analysis (the analysis at Visit 6) of the primary efficacy variable (the ADHDRS-IV-Parent:Inv Total score) produced a mean score for atomoxetine-treated patients of 23.81 and a mean score for placebo-treated patients of 31.75, giving a mean treatment difference of -7.94 ($p < .001$). Secondary efficacy variables included the ADHDRS-IV-Parent:Inv subscale scores (Table LYAT.3), the DPREMB (Table LYAT.4 and Table LYAT.5), the Clinical Global Impressions – ADHD Severity (CGI-ADHD-Severity) scale (Table LYAT.6), the CPRS-R:S (Table LYAT.7), the CTRS-R:S (Table LYAT.8), and the SSRS-P (Table LYAT.9). The proportion of patients achieving a 25% reduction in their ADHDRS-IV score was statistically significantly greater in the atomoxetine group versus the placebo group (59.5% versus 31.3%, $p < .001$). The mean reductions and treatment difference from placebo on the ADHDRS-IV-Parent:Inv were similar with once-daily dosing (effect size = 0.71) compared with 3 placebo-controlled twice-daily-dosed trials (effect sizes of 0.77, 0.67, and 0.63) that used a similar total daily dose of atomoxetine.

A question relative to once-daily dosing was whether symptom control was maintained late in the day. That was an important issue for many patients because patients with ADHD had, by DSM-IV definition, impairment in more than one setting, and situations outside of school, such as homework and bedtime, were often difficult for patients. This study specifically queried parents of patients about behavior late in the day and in the morning prior to school using a daily diary (DPREMB) at baseline and during the final visit interval. Because that was the first use of that instrument and its psychometric properties were not known, conclusions based on its results must have been considered tentative. Nonetheless, as Table LYAT.4 and Table LYAT.5 show, the data did provide preliminary evidence of improvement in atomoxetine-treated patients compared with placebo for inattention behaviors late in the day (Item 8) and settling down at bedtime (Item 12). The preliminary evidence did not appear to be an artifact of sedative properties of the drug, since sedation did not appear to be a drug-specific adverse event. No drug-specific effects were noted relative to early morning behavior.

Because this study used dose-titration based on clinical response, we could not determine a dose-response relationship. However, the final mean dose of 1.35 mg/kg/day was consistent with the final total daily dose observed in other atomoxetine studies that had employed dose-titration based on clinical response. It was also consistent with the results of the dose-finding study (Study LYAC), which demonstrated that a dose of approximately 1.2 mg/kg/day was associated with maximal response for most patients.

Safety: The safety of once-daily administration of atomoxetine in children and adolescents with ADHD was evaluated by comparing safety parameters between a group of 85 patients randomized to atomoxetine and 86 patients randomized to placebo treatment for an acute phase of approximately 6 weeks. The mean final atomoxetine dose was 1.3 mg/kg/day.

Greater than 85% of patients in both treatment groups completed the acute study. No statistically significant treatment differences were noted in any specific reason for study discontinuation.

No patients died during the study. No serious adverse events associated with atomoxetine treatment were reported.

Two of 85 (2.4%) patients randomized to atomoxetine discontinued from the study because of an adverse event (somnolence, vomiting) and 1 of 86 placebo-treated patients (1.2%) discontinued from the study because of an adverse event (emotional lability). That treatment difference was not statistically significant.

Among treatment-emergent adverse events, anorexia (typically captured as “decreased appetite”), vomiting, nausea, asthenia, and dyspepsia were reported statistically significantly more frequently in atomoxetine-treated patients than in placebo-treated patients.

Table LYAT.10 presents a summary of the treatment-emergent adverse events for events that occurred in at least 5% of the patients. The most commonly reported treatment-emergent adverse events ($\geq 5\%$ incidence) among atomoxetine-treated patients were anorexia (typically captured as “decreased appetite”), headache, abdominal pain, somnolence, rhinitis, vomiting, nausea, asthenia, emotional lability, rash, accidental injury, fever, dyspepsia, and dizziness. Among placebo-treated patients, the most common events were rhinitis, headache, pharyngitis, and cough increased.

A statistically significantly greater percentage of atomoxetine-treated patients had treatment-emergent high levels of calcium than did placebo-treated patients. In contrast, a statistically significantly greater percentage of placebo-treated patients had treatment-emergent low levels of hematocrit and treatment-emergent high levels of inorganic phosphorus than did atomoxetine-treated patients. Statistically significant differences between atomoxetine and placebo were found for systolic blood pressure, pulse, and weight (Table LYAT.11). There was an increase in systolic blood pressure (2.00 mm Hg, $p=.030$) and pulse (6.8 bpm, $p<.001$) in the atomoxetine treatment group. The data also showed a decrease in mean weight in atomoxetine-treated patients, with atomoxetine treatment resulting in a mean weight loss of 0.9 kg, and 36.9% of patients losing at least 3.5% body weight (compared to a slight increase in weight in the placebo-treatment group [about 0.8 kg]).

Atomoxetine-treated patients had statistically significantly greater mean reductions in RR interval (-71.646, $p<.001$), PR interval (-3.659, $p=.023$), and QT interval (-11.317, $p<.001$) compared with placebo-treated patients. Atomoxetine-treated patients also had statistically significantly greater mean increases in heart rate (7.646, $p<.001$) and Bazett’s corrected QT interval (6.683, $p=.001$) than did placebo-treated patients. Treatment differences in the RR, PR, QT, and Bazett’s QT interval were related to the increase in heart rate for the atomoxetine treatment group. Treatment differences in the Fridericia corrected QT interval were not statistically significant.

Analysis of baseline and endpoint ECGs showed an increase in heart rate consistent with that noted by clinician assessment of pulse and consistent with other atomoxetine studies. Assessment of QT interval corrected by the Fridericia method did not demonstrate any effects on cardiac repolarization.

Table LYAT.1. Summary of Demographics and Other Patient Characteristics Randomized Patients B4Z-MC-LYAT

Variable	ATOMOX (N=85)	PLACEBO (N=85)	Total (N=170)	p-Value
Sex: No. (%)				
No. Patients	85	85	170	1.00*
Female	25 (29.4)	25 (29.4)	50 (29.4)	
Male	60 (70.6)	60 (70.6)	120 (70.6)	
Origin: No. (%)				
No. Patients	85	85	170	.373*
African Descent	8 (9.4)	13 (15.3)	21 (12.4)	
Caucasian	68 (80.0)	66 (77.6)	134 (78.8)	
East/Southeast A	1 (1.2)	1 (1.2)	2 (1.2)	
Hispanic	3 (3.5)	4 (4.7)	7 (4.1)	
Other	5 (5.9)	1 (1.2)	6 (3.5)	
Age: yrs.				
No. Patients	85	85	170	.205**
Mean	10.05	10.52	10.28	
Median	9.85	9.83	9.84	
Standard Dev.	2.28	2.53	2.41	
Minimum	6.06	6.32	6.06	
Maximum	15.08	16.19	16.19	
CYP2D6				
No. Patients	85	85	170	.368*
EXTN	84 (98.8)	81 (95.3)	165 (97.1)	
SLOW	1 (1.2)	4 (4.7)	5 (2.9)	
Height: cm				
No. Patients	83	82	165	.367**
Mean	140.30	142.39	141.34	
Median	138.50	142.00	140.00	
Standard Dev.	14.78	14.95	14.86	
Minimum	111.50	115.00	111.50	
Maximum	173.50	179.00	179.00	
Unspecified	2	3	5	
Weight: kg				
No. Patients	85	85	170	.450**
Mean	38.92	40.45	39.68	
Median	36.50	38.00	36.95	
Standard Dev.	12.76	13.60	13.17	
Minimum	20.00	20.10	20.00	
Maximum	67.70	68.80	68.80	
DSM-IV ADHD Subtype				
No. Patients	85	85	170	.273*
HYP/IMP	3 (3.5)	0	3 (1.8)	
INATTV	35 (41.2)	34 (40.0)	69 (40.6)	
MIXED	47 (55.3)	51 (60.0)	98 (57.6)	
Family History of ADHD-Mother				
No. Patients	85	85	170	1.00*
N	62 (72.9)	63 (74.1)	125 (73.5)	
U	8 (9.4)	7 (8.2)	15 (8.8)	
Y	15 (17.6)	15 (17.6)	30 (17.6)	

(continued)

Table LYAT.1. Summary of Demographics and Other Patient Characteristics Randomized Patients B4Z-MC-LYAT (concluded)

Variable	ATOMOX (N=85)	PLACEBO (N=85)	Total (N=170)	p-Value
Family History of ADHD-Father				
No. Patients	85	85	170	.357*
N	55 (64.7)	62 (72.9)	117 (68.8)	
U	12 (14.1)	12 (14.1)	24 (14.1)	
Y	18 (21.2)	11 (12.9)	29 (17.1)	
Family History of ADHD-Grandparents				
No. Patients	85	85	170	.492*
N	64 (75.3)	70 (82.4)	134 (78.8)	
U	16 (18.8)	11 (12.9)	27 (15.9)	
Y	5 (5.9)	4 (4.7)	9 (5.3)	
Family History of ADHD-Siblings				
No. Patients	85	85	170	.476*
N	50 (58.8)	54 (63.5)	104 (61.2)	
N/A	9 (10.6)	4 (4.7)	13 (7.6)	
U	8 (9.4)	6 (7.1)	14 (8.2)	
Y	18 (21.2)	21 (24.7)	39 (22.9)	
Prior Stimulant Exposure				
No. Patients	85	85	170	.877*
N	37 (43.5)	39 (45.9)	76 (44.7)	
Y	48 (56.5)	46 (54.1)	94 (55.3)	
Grade in School				
No. Patients	85	85	170	.575*
1	12 (14.1)	6 (7.1)	18 (10.6)	
2	13 (15.3)	15 (17.6)	28 (16.5)	
3	15 (17.6)	17 (20.0)	32 (18.8)	
4	9 (10.6)	5 (5.9)	14 (8.2)	
5	7 (8.2)	4 (4.7)	11 (6.5)	
6	15 (17.6)	14 (16.5)	29 (17.1)	
7	9 (10.6)	9 (10.6)	18 (10.6)	
8	2 (2.4)	5 (5.9)	7 (4.1)	
9	2 (2.4)	4 (4.7)	6 (3.5)	
0	1 (1.2)	3 (3.5)	4 (2.4)	
10	0	2 (2.4)	2 (1.2)	
11	0	1 (1.2)	1 (0.6)	

Population: Randomized patients who took at least 1 dose of study drug.
Visits 1-7

Input data from RMP.SAS.B4ZM.MCLYATSW

Output stored as RMP.B4ZO.LYATCTRM.SUBMISSN(DE120004)

* Frequencies are analyzed using a Fishers-Exact test.

** Means are analyzed using a Type III Sum of Squares analysis of variance
(ANOVA): PROC GLM model=treatment.

XDES0001

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Approved: 25 April 2007

Table LYAT.2. ADHRS-IV-Parent:Inv Total Score
Repeated Measures Least Squares Means
Study Period II - B4Z-MC-LYAT

Atomoxetine	Placebo			Treatment Difference					
Visit	LS Mean	SE	p-val ^a	LS Mean	SE	p-val ^a	LS Mean	SE	p-val ^b
3	28.91	0.94	<.001	33.09	0.95	<.001	-4.18	1.27	.001
4	25.52	1.14	<.001	32.00	1.15	<.001	-6.48	1.56	<.001
5	24.45	1.22	<.001	31.29	1.23	<.001	-6.84	1.69	<.001
6	23.81	1.31	<.001	31.75	1.32	<.001	-7.94	1.82	<.001
95% Confidence Interval on Change from Baseline to Visit 6									
(-15.93 , -10.74) (-8.00 , -2.78)									
Summary of Model Parameters			F-Value	P-Value ^c					
Baseline			103.20	<.001					
Treatment			21.01	<.001					
Visit			7.73	<.001					
Investigator			1.50	.161					
Treatment*Visit			2.17	.094					

Results based on a mixed model with a term for visit, (treated as a class variable) baseline, treatment and treatment by visit interaction using an unstructured covariance matrix to model correlations within patient across visits.

^a P-values are from tests for a nonzero least squares mean at the given visit.

^b P-values are from tests for a treatment difference in least squares means at the given visit.

^c P-values are from F-tests for a nonzero coefficient estimate.

Source-PROGRAM: RMP.B4ZSLYAT.SASPGM(EFF1A)

**Table LYAT.3. ADHRS-IV-Parent:Inv Subscale Scores - Imputed
Change from Baseline to Endpoint – Study Period II
B4Z-MC-LYAT**

		-----Baseline-----		Change to -----Endpoint-----		p-Values	
Variables Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy (Int*1)
AD4PIHII	ATOMOX	84	15.702	7.992	-5.702	6.824	<.001
	PLACEBO	83	15.289	7.125	-2.060	5.747	(.410)
AD4PIINI	ATOMOX	84	21.869	3.453	-7.083	6.852	<.001
	PLACEBO	83	21.434	3.967	-2.892	5.704	(.462)

Population: Randomized patients who took at least 1 dose of study drug.

Baseline: Visits 1-2, Endpoint: Visits 3 - 6

Input data from RMP.SAS.B4ZM.MCLYATSW

Output stored as RMP.B4ZO.LYATCTRM.SUBMISSN(EF6LF001)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDUC1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for
error.

Note: Each investigator has at least one patient in each treatment group.

XLAS0006

Legend of Variable Abbreviations:

Abbrev.	Description
-----	-----
AD4PIHII	ADHRS-IV Par/Inv Hyp/Imp Impute Score
AD4PIINI	ADHRS-IV Par/Inv Inatt. Impute Score

Table LYAT.4. DPREMB Item Scores (1 through 9)
Change from Baseline to Endpoint – Study
Period II B4Z-MC-LYAT

		-----Baseline-----		Change to -----Endpoint-----		p-Values	
Variables Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy (Int*1)
DPRMA01	ATOMOX	58	1.054	0.908	-0.252	0.720	.521
	PLACEBO	58	1.097	0.756	-0.171	0.690	(.624)
DPRMA02	ATOMOX	58	1.511	0.764	-0.469	0.727	.212
	PLACEBO	58	1.421	0.770	-0.277	0.749	(.296)
DPRMA03	ATOMOX	58	1.033	0.660	-0.214	0.570	.624
	PLACEBO	58	1.000	0.799	-0.168	0.620	(.542)
DPRMA04	ATOMOX	58	0.788	0.681	-0.064	0.608	.732
	PLACEBO	58	0.817	0.761	-0.123	0.663	(.694)
DPRMA05	ATOMOX	58	1.848	0.878	-0.501	0.837	.485
	PLACEBO	58	1.821	0.904	-0.289	0.840	(.933)
DPRMA06	ATOMOX	58	1.306	0.949	-0.392	0.835	.176
	PLACEBO	58	1.029	0.882	-0.137	0.715	(.911)
DPRMA07	ATOMOX	58	1.519	0.946	-0.525	0.746	.147
	PLACEBO	58	1.446	0.930	-0.266	0.875	(.212)
DPRMA08	ATOMOX	58	1.945	0.748	-0.731	0.874	.003
	PLACEBO	58	1.761	0.733	-0.253	0.624	(.656)
DPRMA09	ATOMOX	58	1.491	0.741	-0.365	0.775	.886
	PLACEBO	58	1.445	0.864	-0.333	0.617	(.335)

Population: Randomized patients who took at least 1 dose of study drug.

Baseline: Visits 1-2, Endpoint: Visits 3 - 6

Input data from RMP.SAS.B4ZM.MCLYATSW

Output stored as RMP.B4ZO.LYATCTRM.SUBMISSN(EF6LG001)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

XLAS0006

Note: Models:

RDUC1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for
error.

Note: Each investigator has at least one patient in each treatment group.

XLAS0006

Legend of Variable Abbreviations:

Abbrev.	Description
DPRMA01	DPREMB Average Question 1
DPRMA02	DPREMB Average Question 2
DPRMA03	DPREMB Average Question 3
DPRMA04	DPREMB Average Question 4
DPRMA05	DPREMB Average Question 5
DPRMA06	DPREMB Average Question 6
DPRMA07	DPREMB Average Question 7
DPRMA08	DPREMB Average Question 8
DPRMA09	DPREMB Average Question 9

Table LYAT.5. DPREMB Item Scores (10 through 13)
Change from Baseline to Endpoint – Study
Period II B4Z-MC-LYAT

Variables Analyzed	Therapy	n	-----Baseline-----		Change to -----Endpoint-----		p-Values
			Mean	SD	Mean	SD	
DPRMA10	ATOMOX	58	1.072	0.821	-0.149	0.690	.424
	PLACEBO	58	1.263	0.913	-0.255	0.658	(.264)
DPRMA11	ATOMOX	58	1.589	0.794	-0.568	0.843	.130
	PLACEBO	58	1.545	0.773	-0.310	0.642	(.858)
DPRMA12	ATOMOX	58	1.822	1.056	-0.744	0.943	.023
	PLACEBO	58	1.673	0.933	-0.298	0.817	(.444)
DPRMA13	ATOMOX	58	1.769	1.197	-0.607	0.982	.292
	PLACEBO	58	1.592	1.000	-0.361	0.989	(.882)

Population: Randomized patients who took at least 1 dose of study drug.

Baseline: Visits 1-2, Endpoint: Visits 3 - 6

Input data from RMP.SAS.B4ZM.MCLYATSW

Output stored as RMP.B4ZO.LYATCTRM.SUBMISSN(EF6LL001)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDCU1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
 model=investigator and treatment for the overall p-Value and
 model=investigator, treatment, and interaction for the interaction p-Value.
 Least-squares mean option in PROC GLM from the ANOVA using the mean square for
 error.

Note: Each investigator has at least one patient in each treatment group.

XLAS0006

Legend of Variable Abbreviations:

Abbrev.	Description
DPRMA10	DPREMB Average Question 10
DPRMA11	DPREMB Average Question 11
DPRMA12	DPREMB Average Question 12
DPRMA13	DPREMB Average Question 13

Table LYAT.6. CGI-ADHD-Severity Score
Change from Baseline to Endpoint – Study
Period II B4Z-MC-LYAT

			-----Baseline-----		Change to -----Endpoint-----		p-Values
Variables	Therapy	n	Mean	SD	Mean	SD	Therapy (Int*1)
CGIADS	ATOMOX	84	4.655	0.591	-1.238	1.267	<.001
	PLACEBO	83	4.578	0.607	-0.542	1.028	(.784)

Population: Randomized patients who took at least 1 dose of study drug.

Baseline: Visits 1-2, Endpoint: Visits 3 - 6

Input data from RMP.SAS.B4ZM.MCLYATSW

Output stored as RMP.B4Z0.LYATCTRM.SUBMISSN(EF6LH001)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDUC1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for
error.

Note: Each investigator has at least one patient in each treatment group.

XLAS0006

Legend of Variable Abbreviations:

Abbrev.	Description
CGIADS	CGI ADHD Severity

Table LYAT.7. CPRS-R:S Subscale Scores
Change from Baseline to Endpoint – Study
Period II B4Z-MC-LYAT

		-----Baseline-----			Change to -----Endpoint-----		p-Values
Variables Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy (Int*1)
CPRSOPP	ATOMOX	80	7.988	4.350	-1.125	4.165	.211
	PLACEBO	77	8.455	4.260	-0.387	3.595	(.309)
CPRSCOG	ATOMOX	80	13.933	3.637	-3.930	5.032	<.001
	PLACEBO	77	13.595	3.592	-1.094	3.913	(.978)
CPRSHYP	ATOMOX	80	9.438	5.329	-3.298	4.264	<.001
	PLACEBO	77	9.390	4.481	-0.842	3.499	(.279)
CPRSADI	ATOMOX	80	26.972	5.482	-7.618	8.215	<.001
	PLACEBO	77	26.505	5.750	-2.351	7.026	(.830)

Population: Randomized patients who took at least 1 dose of study drug.

Baseline: Visits 1-2, Endpoint: Visits 3 - 6

Input data from RMP.SAS.B4ZM.MCLYATSW

Output stored as RMP.B4ZO.LYATCTRM.SUBMISSN(EF6LI001)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDU1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for
error.

Note: Each investigator has at least one patient in each treatment group.

XLAS0006

Legend of Variable Abbreviations:

Abbrev.	Description
-----	-----
CPRSADI	CPRS ADHD Index Subscale Score
CPRSCOG	CPRS Cognitive Problems Subscale Score
CPRSHYP	CPRS Hyperactivity Subscale Score
CPRSOPP	CPRS Oppositional Subscale Score

Table LYAT.8. **CTRS-R:S Subscale Scores**
Change from Baseline to Endpoint – Study
Period II B4Z-MC-LYAT

		-----Baseline-----			Change to -----Endpoint-----		p-Values
Variables	Therapy	n	Mean	SD	Mean	SD	Therapy (Int*1)
CTRSOPP	ATOMOX	67	3.840	4.376	-1.250	3.152	.039
	PLACEBO	70	3.271	3.595	-0.079	3.043	(.114)
CTRSCOG	ATOMOX	67	6.728	3.917	-1.205	2.368	.742
	PLACEBO	70	6.832	3.723	-0.900	3.047	(.448)
CTRSHYP	ATOMOX	67	8.831	6.002	-2.473	4.858	.072
	PLACEBO	70	9.736	6.547	-0.995	4.806	(.385)
CTRSADI	ATOMOX	67	21.486	8.701	-5.142	7.970	.016
	PLACEBO	70	21.577	8.978	-1.562	8.319	(.284)

Population: Randomized patients who took at least 1 dose of study drug.

Baseline: Visits 1-2, Endpoint: Visits 3 - 6

Input data from RMP.SAS.B4ZM.MCLYATSW

Output stored as RMP.B4ZO.LYATCTRM.SUBMISSN(EF6LJ001)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDUC1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
 model=investigator and treatment for the overall p-Value and
 model=investigator, treatment, and interaction for the interaction p-Value.
 Least-squares mean option in PROC GLM from the ANOVA using the mean square for
 error.

Note: Each investigator has at least one patient in each treatment group.

XLAS0006

Legend of Variable Abbreviations:

Abbrev.	Description
-----	-----
CTRSADI	CTRS ADHD Index Subscale Score
CTRSCOG	CTRS Cognitive Problems Subscale Score
CTRSHYP	CTRS Hyperactivity Subscale Score
CTRSOPP	CTRS Oppositional Subscale Score

**Table LYAT.9. SSRS-P Social Skills and Problem Behavior Scores
Change from Baseline to Endpoint – Study Period II
B4Z-MC-LYAT**

		-----Baseline-----			Change to -----Endpoint-----		p-Values
Variables Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy (Int*1)
SSRSPSS	ATOMOX	78	41.333	10.344	3.897	10.520	.096
	PLACEBO	78	42.397	10.316	1.718	7.454	(.204)
SSRSPSSS	ATOMOX	78	82.423	14.864	5.808	15.300	.111
	PLACEBO	78	83.551	15.042	2.769	10.796	(.146)
SSRSPPB	ATOMOX	78	18.256	6.502	-2.359	5.279	.090
	PLACEBO	78	19.436	6.701	-1.051	4.190	(.613)
SSRSPPBS	ATOMOX	78	115.782	13.825	-5.756	12.759	.058
	PLACEBO	78	119.846	13.355	-2.244	10.459	(.576)

Population: Randomized patients who took at least 1 dose of study drug.

Baseline: Visits 1-2, Endpoint: Visits 3 - 6

Input data from RMP.SAS.B4ZM.MCLYATSW

Output stored as RMP.B4ZO.LYATCTRM.SUBMISSN(EF6LK001)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDU1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for
error.

Note: Each investigator has at least one patient in each treatment group.

XLAS0006

Legend of Variable Abbreviations:

Abbrev.	Description
-----	-----
SSRSPPB	SSRSP Problem Behavior Raw Score
SSRSPPBS	SSRSP Problem Behavior Standard Score
SSRSPSS	SSRSP Social Skill Raw Score
SSRSPSSS	SSRSP Social Skill Standard Score

Table LYAT.10. Summary of Treatment-Emergent Adverse Events Experienced by at Least 5% of Patients B4Z-MC-LYAT

Event Classification	ATOMOX (N=85) n (%)	PLACEBO (N=85) n (%)	Total (N=170) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	69 (81.2)	60 (70.6)	129 (75.9)	.151
PATIENTS WITH NO TESS	16 (18.8)	25 (29.4)	41 (24.1)	.151
HEADACHE	17 (20.0)	15 (17.6)	32 (18.8)	.845
RHINITIS	14 (16.5)	18 (21.2)	32 (18.8)	.557
ANOREXIA	17 (20.0)	5 (5.9)	22 (12.9)	.011
ABDOMINAL PAIN	14 (16.5)	7 (8.2)	21 (12.4)	.161
PHARYNGITIS	6 (7.1)	13 (15.3)	19 (11.2)	.143
COUGH INCREASED	6 (7.1)	11 (12.9)	17 (10.0)	.307
SOMNOLENCE	9 (10.6)	6 (7.1)	15 (8.8)	.590
VOMITING	13 (15.3)	1 (1.2)	14 (8.2)	.001
NAUSEA	10 (11.8)	2 (2.4)	12 (7.1)	.032
ASTHENIA	9 (10.6)	1 (1.2)	10 (5.9)	.018
EMOTIONAL LABILITY	6 (7.1)	4 (4.7)	10 (5.9)	.746
RASH	6 (7.1)	4 (4.7)	10 (5.9)	.746
ACCIDENTAL INJURY	5 (5.9)	4 (4.7)	9 (5.3)	1.00
FEVER	6 (7.1)	3 (3.5)	9 (5.3)	.496
DYSPEPSIA	8 (9.4)	0	8 (4.7)	.007
DIZZINESS	5 (5.9)	0	5 (2.9)	.059

Population: Randomized patients who took at least 1 dose of study drug.

Baseline: Visits 1-2, Endpoint: Visits 3 - 6

Input data from RMP.SAS.B4ZM.MCLYATSW

Output stored as RMP.B4ZO.LYATCTRM.SUBMISSN(AE2C1001)

* Frequencies are analyzed using a Fisher's Exact test.

XAES0002

**Table LYAT.11. Summary of Vital Signs
Change from Baseline to Endpoint
B4Z-MC-LYAT**

		-----Baseline-----		Change to -----Endpoint-----		p-Values	
Variables Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy
DIASAVG	ATOMOX	84	64.589	7.381	2.304	8.704	.632
	PLACEBO	83	62.976	8.186	1.699	7.555	
SYSAVG	ATOMOX	84	102.417	8.988	2.006	8.681	.030
	PLACEBO	83	103.259	8.237	-0.711	7.339	
PULSAVG	ATOMOX	84	85.232	8.483	6.804	11.962	<.001
	PLACEBO	83	83.753	11.615	-1.223	10.269	
WEIGHT	ATOMOX	84	39.158	12.793	-0.933	0.947	<.001
	PLACEBO	83	40.953	13.691	0.828	1.137	
HEIGHT	ATOMOX	78	140.260	14.962	0.864	1.315	.646
	PLACEBO	74	142.584	15.073	0.776	1.026	
TEMP	ATOMOX	84	36.699	0.536	0.020	0.583	.713
	PLACEBO	83	36.630	0.480	0.054	0.629	

Population: Randomized patients who took at least 1 dose of study drug.

Baseline: Visits 1-2, Endpoint: Visits 3 - 6

Input data from RMP.SAS.B4ZM.MCLYATSW

Output stored as RMP.B4Z0.LYATCTRM.SUBMISSN(VI6L1001)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=treatment.

Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

XLAS0006

Legend of Variable Abbreviations:

Abbrev.	Description
DIASAVG	Diastolic BP Average
HEIGHT	Height in CM
PULSAVG	Heart Rate Average
SYSAVG	Systolic BP Average
TEMP	Temperature in Centigrade
WEIGHT	Weight in KG

Summary ID#3468

Clinical Study Summary: Study B4Z-MC-LYAC

Title of Study: A Phase 3 Randomized, Double-blind, Placebo-Controlled Efficacy and Safety Comparison of Fixed-Dose Ranges (mg/kg/day) of Atomoxetine with Placebo in Child and Adolescent Outpatients with ADHD, Aged 8 to 18 Years	
Investigators: This multicenter study included 13 principal investigators.	
Study Centers: This study was conducted at 13 study centers in the United States.	
Length of Study: 56 weeks. Date first patient enrolled: 10 April 2000 Date last patient completed: 19 February 2002	Phase of Development: 3
Objectives: The primary objective of this study was to test the hypothesis that acute treatment for approximately 8 weeks with atomoxetine (formerly called tomoxetine), either 1.2 mg/kg/day or 1.8 mg/kg/day, would be statistically significantly more effective in reducing the severity of Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms than placebo. The secondary objectives of the study were: • To compare the safety of three fixed-dose ranges of atomoxetine with placebo in a population of pediatric and adolescent patients who meet <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</i> (DSM-IV) criteria for ADHD. • To assess whether patients who failed to respond to their initial dose of atomoxetine within 8 weeks benefited from a dose adjustment. • To assess the relationship between atomoxetine dose and both efficacy and safety variables in a population of pediatric and adolescent patients who met DSM-IV criteria for ADHD. • To compare the efficacy of each of 3 fixed-doses of atomoxetine with one another and with placebo in children and adolescents who had not had prior treatment with psychostimulants. • To assess the relationship between efficacy and systemic exposure of atomoxetine. • To assess the long-term (approximately 1 year) clinical course and safety in patients who respond to acute treatment with one of three doses of atomoxetine or placebo. • To compare discontinuation adverse events in a population of patients who had atomoxetine abruptly discontinued versus those patients who had their atomoxetine tapered prior to discontinuation.	

Study Design: Study B4Z-MC-LYAC (LYAC) was a Phase 3, randomized, double-blind, placebo-controlled study of 297 pediatric outpatients who met DSM-IV and Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version:Behavioral Disorders Supplement (K-SADS-PL:Behavioral) criteria for ADHD. Patients were at least 8 years of age and less than 18 years of age at the time informed consent and assent were signed (entry) for this study.

Patients were randomized to one of four treatment groups: low-dose atomoxetine (target dose 0.5 mg/kg/day); intermediate-dose atomoxetine (target dose 1.2 mg/kg/day); high-dose atomoxetine (target dose 1.8 mg/kg/day); and placebo. The total daily dose for each patient was administered as a divided dose on a twice-daily dosing schedule. To ensure balance across treatment groups, randomization was stratified by cytochrome P450 2D6 (CYP2D6) status and (for extensive metabolizer [EM] patients) by whether or not patients had a prior history of stimulant treatment. Poor metabolizer (PM) patients were not stratified by prior use of psychostimulants because of the low numbers of PM patients in this population.

Patients who met entry criteria completed an initial washout, screening, and assessment period of 10 to 28 days (Study Period I) and were then randomized. After 8 weeks of acute treatment (Study Period II), patients who did not meet prespecified response criteria at the end of Study Period II were allowed a dose adjustment and were reevaluated for response at the end of a 4-week period (Study Period III). Patients who were responding to treatment at the end of Study Period II continued into a long-term extension phase lasting approximately 56 weeks (Study Period IV). If patients who did not show response at Visit 9 (end of Study Period II) showed response at Visit 13 (end of Study Period III), they also continued into the long-term extension phase (Study Period IV). Patients who continued to be nonresponders at Visit 13 proceeded to Study Period V in order to be discontinued from the study. After approximately 56 weeks, patients' dosages were either abruptly discontinued or were tapered and discontinued under double-blind conditions (Study Period V).

Number of Patients:

Planned: 185 atomoxetine, 74 placebo

Randomized: 213 atomoxetine, 84 placebo

Completed Study Periods I and II: 176 atomoxetine, 72 placebo

Completed Study Periods III-V: 140 atomoxetine, 4 placebo

Diagnosis and Main Criteria for Inclusion: Patients were at least 8 years of age but less than 18 years of age at the time informed consent was obtained (Visit 1) and met DSM-IV diagnostic criteria for ADHD. At both Visit 2 and Visit 3, each patient's score from the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) was at least 1.5 standard deviations above the age/gender norm for their diagnostic subtype (predominantly inattentive or predominantly hyperactive-impulsive) or the total score for the combined subtype (if the child met DSM-IV criteria for the combined subtype) using published norms for the ADHDRS-IV-Parent:Inv. In addition, at both Visit 2 and Visit 3, each patient's score from the Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) scale was at least 3.

Test Product, Dose, and Mode of Administration: Atomoxetine hydrochloride; 5-mg, 7.5-mg, 10-mg, 12.5-mg, 15-mg, 17.5-mg, 20-mg, 22.5-mg, 25-mg, 27.5-mg, 30-mg, 40-mg, 45-mg, 50-mg, and 60-mg capsules; fixed doses of 0.5 mg/day, 1.2 mg/kg/day, or 1.8 mg/kg/day, given twice daily.

Duration of Treatment: 52 weeks (8 weeks for Study Periods I-II and 44 weeks for Study Periods III-V).

Reference Therapy, Dose, and Mode of Administration: Placebo capsules, given twice daily.

Variables:

Efficacy: Reduction in the severity of symptoms was measured using the total score for ADHDRS-IV-Parent:Inv.

Safety: Analysis of adverse events included the 294 enrolled patients who took at least one dose of study drug. Three patients were randomized but never took study drug. The analysis for clinical laboratory studies, vital signs, and electrocardiogram (ECG) data included patients who received at least one dose of study drug and had a baseline and a postbaseline measurement.

Pharmacokinetic: All patients provided blood samples for assessment of plasma concentrations and pharmacokinetics of atomoxetine, 4-hydroxyatomoxetine, and *N*-desmethyatomoxetine.

Evaluation Methods:

Statistical: The primary efficacy analyses were pairwise treatment comparisons between atomoxetine 1.2 mg/kg/day and placebo, and between atomoxetine 1.8 mg/kg/day and placebo from an analysis of covariance (ANCOVA) model on change from baseline to endpoint ADHDRS-IV-Parent:Inv total scores. This primary efficacy analysis was an intent-to-treat analysis with change from baseline-to-endpoint scores during Study Period II computed on a last visit carried forward basis. For secondary efficacy and safety variables, treatment differences in mean change scores from continuous measures were assessed using analysis of variance (ANOVA), while Fisher's exact test was used to assess treatment differences in binary data. All tests were performed using a 2-sided, 0.05 significance level.

For each of Study Periods II, III, IV, and V, changes from baseline to endpoint in ADHDRS-IV-Parent:Inv Total score were compared within patient groups using the Wilcoxon signed-rank test separately for each treatment group. For the primary analyses, baseline for a given study period was the last observation taken prior to dosing within that study period. Safety measures collected while assigned to atomoxetine dosing were summarized across all of Study Period II through Study Period V with changes from baseline to endpoint evaluated using the Wilcoxon signed-rank test.

Pharmacokinetic: A population pharmacokinetic analysis using Nonlinear Mixed Effect Modeling (NONMEM) computer program was performed to analyze the atomoxetine concentration data and obtain an individual atomoxetine clearance estimate for each patient. The clearance estimates were then used to estimate area under the plasma drug concentration versus time curve over the dosing interval (from time 0 to tau) ($AUC_{0-\tau}$) for each patient. The relationship between $AUC_{0-\tau}$ and the primary efficacy measure was evaluated.

Summary:

Patient Disposition: Of the 383 patients who entered Study B4Z-MC-LYAC (LYAC), 86 were not randomized (that is, were discontinued prior to randomization at Visit 3). Patients were not randomized for the following reasons: lost to follow-up (6); personal conflict (17); entry criteria not met (59); sponsor's decision (1); physician's decision (1); and protocol violation (2).

At Visit 3, 84 patients were randomized to placebo (60 male, 24 female); 44 were randomized to atomoxetine 0.5 mg/kg/day (31 male, 13 female); 84 to atomoxetine 1.2 mg/kg/day (60 male, 24 female); and 85 to atomoxetine 1.8 mg/kg/day (61 male, 24 female). Of the 297 patients randomized, 248 (83.5%) completed Study Period II.

At the end of the acute double-blind portion of this study (Study Periods I-II), 248 patients elected to continue into other periods of this study. Fifty one (51) of those patients were classified as a responder because their last acute-period Clinical Global Impressions-Severity (CGI-S) score was ≤ 2 . Those patients were allowed to skip Study Period III and enter Study Period IV. The remaining 197 patients entered Study Period III. During Study Period III, the response to study drug was reassessed. During that study period, 28 patients discontinued. At the end of Study Period III, 69 patients met response criteria and were allowed to continue to Study Period IV(long term extension). The remaining 100 patients went directly to Study Period V (discontinuation phase).

One hundred twenty (120) patients entered Study Period IV. Of those, 58 completed Study Period IV and entered Study Period V. The remaining 62 patients discontinued. One hundred fifty eight (158) patients entered Study Period V. Fourteen (14) patients discontinued before the end of the study. The remaining 144 patients completed the study.

Patient Demographics: Table LYAC.1 shows demographic and other patient characteristics for all randomized patients. Of the 297 enrolled patients, 71.4% were male, 75.8% were Caucasian, 28.6% had no prior stimulant exposure, 5.7% were determined to be poor cytochrome P450 2D6 (CYP2D6) metabolizer patients, and 71.7% were in the 2nd to 6th elementary school grades (United States). The mean age was 11.2 years (range of 8.0 to 17.5), and the mean intelligence quotient (IQ) was 100.5 (range 69 to 148).

Patients were required to meet the DSM-IV criteria for ADHD following clinical examination and with the ADHD module of the K-SADS-PL:Behavioral (lifetime). Of those patients, 67.2% met criteria for the mixed ADHD subtype, with 31.1% classified as predominantly inattentive, and 1.7% as hyperactive-impulsive. Comorbid DSM-IV diagnoses were assessed using the ADHD, Affective Disorder, and Anxiety Disorder modules of the K-SADS-PL. The most common present comorbid diagnosis was oppositional defiant disorder (ODD), which was found in 38% of randomized patients. All other diagnoses were seen in less than 2% of the randomized population.

Efficacy: Change in the primary outcome measure (symptom reduction in both the 1.2 mg/kg/day and 1.8 mg/kg/day groups compared with placebo as assessed by mean change on the total ADHDRS-IV) was statistically superior in favor of atomoxetine. As shown in Table LYAC.2, observed mean reductions from baseline for the four dosing groups were -5.8 for placebo, -9.9 for atomoxetine 0.5 mg/kg/day, -13.6 for atomoxetine 1.2 mg/kg/day, and -13.5 for atomoxetine 1.8 mg/kg/day. Those improvements were statistically significantly larger for the atomoxetine 1.2 mg/kg/day and for the atomoxetine 1.8 mg/kg/day groups than for placebo (adjusted p-values <.001). The mean improvements seen for the atomoxetine 0.5-mg/kg/day group on the primary outcome measure were not statistically significant. The atomoxetine 0.5-mg/kg/day group did show evidence of statistical superiority to placebo on a number of secondary measures, however, including parent reports (for example, Conners' Parent Rating Scale), despite the fact that fewer patients were randomized to 0.5 mg/kg/day (by design). In general, outcomes in the 0.5-mg/kg/day group were intermediate between placebo and 1.2 mg/kg/day. This was consistent with the finding of statistically significant evidence for a dose-response (greater decrease in symptoms with increased dose) on most measures. Similarly, as Figure LYAC.1 illustrates, there appeared to be a relationship between systemic exposure (AUC) and efficacy, which was comparable to the relationship between dose and efficacy. Taken together, those data suggested a graded dose response, with maximal symptom reduction at 1.2 mg/kg/day and little additional benefit related to the higher 1.8-mg/kg/day dose.

In addition to its fixed dose design, this study differed from the two previous placebo-controlled studies in children by including CYP2D6 PM patients and by including adolescents. With respect to PM patients, the number of patients overall was small, which limited the conclusions that could be drawn. Nonetheless, the data suggested that the dose-response pattern observed in the overall group was also present in the PM patients, with maximal responses at the two higher atomoxetine doses. Further, the magnitude of symptom reduction in the PM patients at the two highest doses was much more marked than that in the overall group, with mean endpoint scores in a range that would be consistent with complete symptom remission.

The results of this study also extended those of the previous placebo-controlled studies in having included adolescents in the sample. In that regard, outcomes in adolescents were similar to those in children on the primary outcome measure as assessed by examining outcomes based above and below the mean age.

As with previous studies, both patients with prior stimulant exposure and stimulant naïve patients were enrolled. No statistically significant differences were noted between the responses to atomoxetine treatment for stimulant naïve patients versus those with prior exposure ($p=.27$). At baseline, few children exhibited marked comorbid symptoms or syndromes other than the expected finding of a substantial number of children with oppositional behavior (oppositional defiant disorder). In particular there was little evidence of depression or anxiety disorders or of marked depressive symptomatology, as assessed by baseline Children's Depression Rating Scale-Revised (CDRS-R) scores. Despite this, results on a number of measures (including the CDRS-R and Child Health Questionnaire [CHQ]) suggested improved outcomes with respect to affect, self-esteem, and overall functioning specific to atomoxetine. Data on the CDRS-R scores are provided in Table LYAC.3 and data on the scores for the various mental health subscales of the CHQ are provided in Table LYAC.4 through Table LYAC.7.

In Study Period III through Study Period V, patients who did not meet response criteria while on placebo or atomoxetine 0.5 mg/kg/day showed a significant reduction in their ADHD symptoms (as measured by ADHDRS-IV-Parent:Inv Total score) by increasing their atomoxetine dosage to 1.2 mg/kg/day (Table LYAC.8). Smaller improvements in symptoms were seen for patients who did not respond to 1.2

mg/kg/day and increased their dosage to 1.8 mg/kg/day and for patients who did not respond to 1.8 mg/kg/day and decreased their dosage to 1.2 mg/kg/day. Patients who met response criteria while on atomoxetine (both early responders and later responders) were able to keep most of that response during long-term dosing (Table LYAC.9 and Table LYAC.10). As Table LYAC.11 shows, Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms returned upon either tapered or abrupt discontinuation of atomoxetine, but there was no rebound of symptoms above baseline levels for the entire study (prior to initiation of atomoxetine treatment).

Safety: Four adverse events were reported as being serious during Study Periods I and II. Two of these met the regulatory definition of serious, and two did not. None of these (burn, overdose, surgery, and urinary tract infection/nephritis) was reported by investigators to be related to atomoxetine.

Nonserious clinically significant adverse events were considered those which led to discontinuation of study drug. Seven patients discontinued their participation in this study due to adverse events. Six of those were either unrelated to atomoxetine or were expected with a noradrenergic agent. A case of an allergic reaction was clinically significant since it involved edema (swelling), pruritus, and rash, all of which were rated as severe by the investigator. Onset of edema 2 days after starting atomoxetine suggested a drug reaction, especially with no other explanation.

Table LYAC.12 summarizes unsolicited (spontaneous) adverse events occurring in at least 5% of patients during the acute treatment period (Study Period II); only dizziness was reported statistically significantly more often by patients taking any dose of atomoxetine than by those taking placebo, and that was only true for the lowest atomoxetine dose. Dizziness was reported statistically significantly more often in the atomoxetine 0.5-mg group than by those taking placebo. At the higher atomoxetine doses, frequency of dizziness was not statistically significant from placebo. In the atomoxetine 1.2-mg group, the adverse event of depression occurred statistically significantly less than with placebo. No statistical difference versus placebo was noted for this adverse event in the 0.5-mg and 1.8-mg groups.

A relationship to dose was detected for anorexia (typically captured as “decreased appetite”) and somnolence, although those trends did not reach statistical significance. At the highest dose of atomoxetine, anorexia, which in most cases was actually reported as “decreased appetite,” was reported by 12.0% of patients, and somnolence was reported by 10.8% of patients. Statistically significant dose trends were detected for pruritus, tachycardia, and infection. Pruritus and tachycardia, but not infection, appeared to be related to atomoxetine use. Adverse event reports did not increase in frequency over the duration of the trial, but decreased or remained stable. Anorexia (typically captured as “decreased appetite”) and somnolence were reported more frequently at the higher atomoxetine doses, but severity was not dose-related. Rash and pruritus were reported infrequently, but their incidence and severity did increase with dose.

No difference in the adverse event profile was detected when patients were categorized by gender, age, and CYP2D6 genotype.

Analysis of a solicited adverse event questionnaire confirmed decreased appetite as associated with atomoxetine in a dose-related manner. Dizziness was also reported more frequently than in the placebo group, but reached statistical significance only with the two lower doses of atomoxetine.

Table LYAC.13 summarizes changes in vital signs from baseline to endpoint for Study Period II, the acute treatment period. A slight increase in diastolic blood pressure was observed at all doses of atomoxetine, but only at the two higher doses (1.2 mg/kg/day and 1.8 mg/kg/day) was the mean change statistically significant when compared to placebo ($p=.006$ and $p=.043$, respectively). The dose-response relationship was statistically significant ($p=.025$). Increase in mean heart rate was statistically significant at all doses of atomoxetine (0.5 mg/kg/day, 1.2 mg/kg/day, and 1.8 mg/kg/day) when compared with placebo ($p=.044$, $p=.007$, and $p<.001$, respectively). The dose-response relationship was highly significant ($p<.001$). Mean increases in height were observed for all groups, but for the atomoxetine 1.2 mg/kg/day group, the increase (0.7 cm) was statistically significantly less than observed in the placebo group (1.3 cm, $p=.028$). Mean height increases were less for the two higher doses of atomoxetine than for placebo, but

there was no statistical evidence of a dose relationship. Weight changes were clearly dose-related ($p < .001$) for all doses versus placebo. At the two higher atomoxetine doses (1.2 mg/kg/day and 1.8 mg/kg/day), a mean weight loss (-0.4 kg and -0.5 kg, respectively) was observed, and these were significantly different from the weight gain observed on placebo (1.7 kg, $p < .001$). With the 0.5-mg/kg/day dose of atomoxetine, a mean weight increase (0.3 kg) was seen, but that was statistically less than the weight gain on placebo ($p < .001$).

Analysis of electrocardiogram (ECG) data confirmed the dose-related increase in heart rate. There was no evidence of an effect on cardiac repolarization, as measured by QTc interval.

Treatment-emergent adverse events for the study as a whole (Study Period I through Study Period V) were similar to those observed in other studies, but with a somewhat lower frequency. Patients taking atomoxetine at a dose of ≥ 1.2 mg/kg/day reported an adverse event profile similar to the overall population, but at slightly higher frequencies. Of the more common events reported, decreased appetite was the only one likely related to atomoxetine use. Serious adverse events were reported by 3 patients (appendicitis, constipation and abdominal pain lower, and psychotic disorder) in Study Period III through Study Period V. One of those (constipation and abdominal pain lower) was taking placebo at the time; the others were taking atomoxetine. One of those (psychotic disorder) also discontinued due to the adverse event. Five other patients discontinued due to adverse events (aggression, negativism, abdominal pain, anxiety, and somnolence); all were taking atomoxetine at the time. Upon medical review, these adverse events were determined to not be related to atomoxetine. Changes in vital signs, weight, and height are summarized in Table LYAC.13. Because there were no discontinuations due to adverse events in Study Period V, there is no comparison of discontinuation adverse events between those patients who had atomoxetine abruptly discontinued versus those patients who had their atomoxetine tapered prior to discontinuation.

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**Table LYAC.1. Summary of Demographics and Other Patient Characteristics
 All Randomized Patients B4Z-MC-LYAC**

Variable	PLACEBO (N=84)	TMX 0.5 (N=44)	TMX 1.2 (N=84)	TMX 1.8 (N=85)	Total (N=297)	p-Value
Sex: No. (%)						
No. Patients	84	44	84	85	297	.999*
Female	24 (28.6)	13 (29.5)	24 (28.6)	24 (28.2)	85 (28.6)	
Male	60 (71.4)	31 (70.5)	60 (71.4)	61 (71.8)	212 (71.4)	
Origin: No. (%)						
No. Patients	84	44	84	85	297	.709*
African Descent	17 (20.2)	7 (15.9)	12 (14.3)	17 (20.0)	53 (17.8)	
Caucasian	59 (70.2)	35 (79.5)	66 (78.6)	65 (76.5)	225 (75.8)	
East/Southeast A	1 (1.2)	0	2 (2.4)	0	3 (1.0)	
Hispanic	2 (2.4)	0	2 (2.4)	2 (2.4)	6 (2.0)	
Other	5 (6.0)	2 (4.5)	2 (2.4)	1 (1.2)	10 (3.4)	
Age: yrs.						
No. Patients	84	44	84	85	297	.428**
Mean	10.89	11.25	11.45	11.08	11.16	
Median	10.71	10.70	11.20	10.80	10.76	
Standard Dev.	2.12	2.53	2.38	2.13	2.26	
Minimum	8.09	8.05	8.12	8.02	8.02	
Maximum	17.42	17.41	17.52	17.41	17.52	
CYP2D6						
No. Patients	84	44	84	85	297	.869*
EXTN	78 (92.9)	41 (93.2)	80 (95.2)	81 (95.3)	280 (94.3)	
SLOW	6 (7.1)	3 (6.8)	4 (4.8)	4 (4.7)	17 (5.7)	
Height: cm						
No. Patients	83	44	82	85	294	.400**
Mean	142.51	144.60	146.12	144.10	144.29	
Median	139.50	142.75	142.50	141.50	142.00	
Standard Dev.	11.96	14.06	14.48	13.91	13.58	
Minimum	123.00	114.50	122.00	118.50	114.50	
Maximum	178.50	177.50	188.00	184.50	188.00	
Unspecified	1	0	2	0	3	

(continued)

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Table LYAC.1. Summary of Demographics and Other Patient Characteristics
All Randomized Patients B4Z-MC-LYAC (continued)

Variable	PLACEBO (N=84)	TMX 0.5 (N=44)	TMX 1.2 (N=84)	TMX 1.8 (N=85)	Total (N=297)	p-Value
Weight: kg						
No. Patients	81	44	83	83	291	.634**
Mean	39.07	40.07	41.71	40.69	40.44	
Median	36.40	36.05	36.30	37.00	36.40	
Standard Dev.	11.90	13.99	13.26	13.80	13.14	
Minimum	24.40	20.00	23.30	20.00	20.00	
Maximum	65.00	74.50	75.00	77.40	77.40	
Unspecified	3	0	1	2	6	
DSM-IV ADHD Subtype						
No. Patients	84	44	84	85	297	.947*
HYP/IMP	2 (2.4)	1 (2.3)	1 (1.2)	1 (1.2)	5 (1.7)	
INATTV	28 (33.7)	13 (29.5)	23 (27.4)	28 (32.9)	92 (31.1)	
MIXED	53 (63.9)	30 (68.2)	60 (71.4)	56 (65.9)	199 (67.2)	
Unspecified	1	0	0	0	1	
Family History of ADHD-Mother						
No. Patients	84	44	84	85	297	.859*
N	60 (71.4)	34 (77.3)	65 (77.4)	65 (76.5)	224 (75.4)	
U	14 (16.7)	5 (11.4)	10 (11.9)	8 (9.4)	37 (12.5)	
Y	10 (11.9)	5 (11.4)	9 (10.7)	12 (14.1)	36 (12.1)	
Family History of ADHD-Father						
No. Patients	84	44	84	85	297	.489*
N	40 (47.6)	26 (59.1)	53 (63.1)	51 (60.0)	170 (57.2)	
U	22 (26.2)	7 (15.9)	14 (16.7)	15 (17.6)	58 (19.5)	
Y	22 (26.2)	11 (25.0)	17 (20.2)	19 (22.4)	69 (23.2)	
Family History of ADHD-Grandparents						
No. Patients	84	44	84	85	297	.843*
N	57 (67.9)	34 (77.3)	62 (73.8)	66 (77.6)	219 (73.7)	
U	20 (23.8)	7 (15.9)	15 (17.9)	14 (16.5)	56 (18.9)	
Y	7 (8.3)	3 (6.8)	7 (8.3)	5 (5.9)	22 (7.4)	

(continued)

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Table LYAC.1. Summary of Demographics and Other Patient Characteristics
All Randomized Patients B4Z-MC-LYAC (continued)

Variable	PLACEBO (N=84)	TMX 0.5 (N=44)	TMX 1.2 (N=84)	TMX 1.8 (N=85)	Total (N=297)	p-Value
Family History of ADHD-Siblings						
No. Patients	84	44	84	85	297	.384*
N	52 (61.9)	25 (56.8)	50 (59.5)	57 (67.1)	184 (62.0)	
N/A	6 (7.1)	1 (2.3)	8 (9.5)	1 (1.2)	16 (5.4)	
U	8 (9.5)	6 (13.6)	6 (7.1)	6 (7.1)	26 (8.8)	
Y	18 (21.4)	12 (27.3)	20 (23.8)	21 (24.7)	71 (23.9)	
Prior Stimulant Exposure						
No. Patients	84	44	84	85	297	.875*
N	22 (26.2)	12 (27.3)	24 (28.6)	27 (31.8)	85 (28.6)	
Y	62 (73.8)	32 (72.7)	60 (71.4)	58 (68.2)	212 (71.4)	
DRD4 Allele						
No. Patients	84	44	84	85	297	
Unspecified	84	44	84	85	297	
Grade in School						
No. Patients	84	44	84	85	297	.974*
2	8 (9.5)	3 (6.8)	3 (3.6)	5 (5.9)	19 (6.4)	
3	12 (14.3)	8 (18.2)	11 (13.1)	13 (15.3)	44 (14.8)	
4	15 (17.9)	10 (22.7)	17 (20.2)	17 (20.0)	59 (19.9)	
5	13 (15.5)	4 (9.1)	12 (14.3)	14 (16.5)	43 (14.5)	
6	16 (19.0)	6 (13.6)	14 (16.7)	12 (14.1)	48 (16.2)	
7	9 (10.7)	5 (11.4)	9 (10.7)	9 (10.6)	32 (10.8)	
8	4 (4.8)	3 (6.8)	6 (7.1)	4 (4.7)	17 (5.7)	
9	3 (3.6)	0	5 (6.0)	7 (8.2)	15 (5.1)	
10	2 (2.4)	3 (6.8)	3 (3.6)	2 (2.4)	10 (3.4)	
11	1 (1.2)	1 (2.3)	3 (3.6)	2 (2.4)	7 (2.4)	
12	1 (1.2)	1 (2.3)	0	0	2 (0.7)	
13	0	0	1 (1.2)	0	1 (0.3)	

(continued)

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Table LYAC.1. Summary of Demographics and Other Patient Characteristics
All Randomized Patients B4Z-MC-LYAC (concluded)

Variable	PLACEBO (N=84)	TMX 0.5 (N=44)	TMX 1.2 (N=84)	TMX 1.8 (N=85)	Total (N=297)	p-Value

WISC full scale IQ						
No. Patients	83	43	82	84	292	.759**
Mean	101.27	98.26	100.41	100.98	100.50	
Median	100.00	98.00	97.00	100.00	98.00	
Standard Dev.	16.41	12.10	16.31	15.55	15.53	
Minimum	69.00	81.00	77.00	70.00	69.00	
Maximum	146.00	124.00	148.00	134.00	148.00	

Population: All Randomized Patients.

Initial Visit ONLY

Input data from RMP.SAS.B4ZR.MCLYACSW

Output stored as RMP.B4ZO.LYACCTRM.INTERIM1(DE103009)

* Frequencies are analyzed using a Chi-Square test.

** Means are analyzed using a Type III Sum of Squares analysis of variance
 (ANOVA): PROC GLM model=treatment.

Table LYAC.2. ADHD Rating Scale IV-Parent Version: Investigator Scored (ADHDRS-IV-Parent:Inv) Total Score Change from Baseline to Endpoint – Study Period II B4Z-MC-LYAC

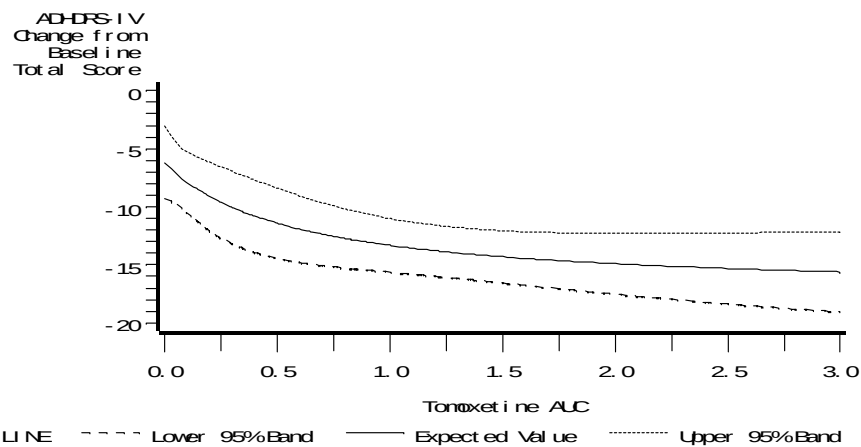
Treatment	n	Baseline		Endpoint		Change		p-val* vs Pla	
		Mean	SD	Mean	SD	Mean	SD	Adj. (UnAdj.)	
Placebo	83	38.3	8.9	32.5	13.8	-5.8	10.9		
TMX0.5	43	40.2	9.6	30.3	15.2	-9.9	14.6		(.155)
TMX1.2	84	39.2	9.2	25.5	13.8	-13.6	14.0	<.001	(<.001)
TMX1.8	82	39.7	8.7	26.2	14.8	-13.5	14.5	<.001	(<.001)
Dose Response**:									
Linear p_value=<.001				Unadjusted Pairwise treatment p-values***					
Quadratic p_value= .113				PLA	T0.5	T1.2	T1.8		
				PLA	----	.155	<.001	<.001	
				T0.5	----	----	.072	.107	
				T1.2	----	----	----	.829	

*Between treatment group unadjusted p-values are from pairwise tests of treatment differences vs. placebo in mean change from baseline to endpoint(last visit carried forward) scores using least squares means from an ANOVA model with terms for baseline, investigator, treatment and CYP2D6 status. Adjusted p-values are computed using Dunnett's procedure.

**Dose response p-values are from an ANOVA model with terms for investigator, CYP2D6, dose, dose squared and dose cubed.

***Pairwise treatment p-values are computed using least squares means from the above ANOVA model.

All enrolled patients with a baseline and at least one postbaseline measurement included.
Source data: eagle:\programs._g\rmp\b4zs\lyac\interim analysis\efficacy1.sas



Source Data: eagle:\programs._g\rmf\b4zs\lyac\interim analysis\LYAC auc vs efficacy nlin plots.sas

Figure LYAC.1. Model predicted mean change from baseline to endpoint in ADHDRS-IV-Parent:Inv total score and atomoxetine AUC for EM patients with confidence bounds, B4Z-MC-LYAC.

**Table LYAC.3. Children's Depression Rating Scale
Change from Baseline to Endpoint
Total Score – Study Period II
B4Z-MC-LYAC**

Treatment	n	Baseline		Endpoint		Change		p-values*	
		Mean	SD	Mean	SD	Mean	SD	within	vs.PLA
Placebo	78	24.8	8.0	25.9	8.1	1.1	6.4	.092	
TMX0.5	37	26.3	7.3	26.0	8.0	-0.3	8.8	.357	.415
TMX1.2	73	25.3	7.3	23.8	8.3	-1.5	6.0	.008	.018
TMX1.8	79	27.1	8.0	25.1	8.3	-2.0	7.7	.014	.011

Dose Response:**

Linear p_value= .005
Quadratic p_value= .452

Unadjusted Pairwise treatment p-values*

	PLA	T0.5	T1.2	T1.8
PLA	----	.415	.018	.011
T0.5	----	----	.266	.214
T1.2	----	----	----	.889

* Within treatment group p-values are from Wilcoxon's signed rank test.
Between treatment group p-values are from pairwise tests of treatment differences vs. placebo in mean change from baseline to endpoint(last visit carried forward) scores using least squares means from an ANOVA model with terms for treatment, investigator and CYP2D6. Pairwise treatment p-values are computed using least squares means from the above ANOVA model.

** Dose response p-values are from an ANOVA model with terms for investigator and CYP2D6 dose, dose squared and dose cubed.

All enrolled patients with a baseline and at least one postbaseline measurement included.
Source data: eagle:/programs_.g/rmp/b4zs/lyac/interim analysis/efficacy2[new200103a].sas.

**Table LYAC.4. Child Health Questionnaire (CHQ)
Mental Health Subscale and Psychosocial Summary Scores
Change from Baseline to Endpoint – Study Period II
B4Z-MC-LYAC**

Measure/ Treatment	n	Baseline		Endpoint		Change		p-values*	
		Mean	SD	Mean	SD	Mean	SD	within	vs.PLA
Mental Health Subscale									
Placebo	78	72.5	17.7	70.6	15.6	-1.9	16.0	.355	
TMX0.5	39	68.1	17.1	75.8	17.0	7.7	17.7	.024	.001
TMX1.2	75	72.9	13.9	77.4	13.0	4.5	12.5	.004	.009
TMX1.8	80	66.6	16.0	75.5	12.4	8.9	14.1	<.001	<.001
Dose Response**:					Unadjusted Pairwise treatment p-values*				
Linear p_value=<.001					PLA	T0.5	T1.2	T1.8	
Quadratic p_value= .348					PLA	----	.001	.009	<.001
					T0.5	----	----	.296	.764
					T1.2	----	----	----	.101
Psychosocial Score									
Placebo	76	35.2	11.4	34.3	13.3	-0.9	11.8	.727	
TMX0.5	38	32.9	9.6	37.3	11.8	4.4	10.3	.026	.014
TMX1.2	74	35.4	10.4	41.3	11.1	6.0	9.0	<.001	<.001
TMX1.8	79	31.3	10.6	40.4	11.1	9.1	11.1	<.001	<.001
Dose Response**:					Unadjusted Pairwise treatment p-values*				
Linear p_value=<.001					PLA	T0.5	T1.2	T1.8	
Quadratic p_value= .530					PLA	----	.014	<.001	<.001
					T0.5	----	----	.529	.033
					T1.2	----	----	----	.068

* Within treatment group p-values are from Wilcoxon's signed rank test.
Between treatment group p-values are from pairwise tests of treatment differences vs. placebo in mean change from baseline to endpoint(last visit carried forward) scores using least squares means from an ANOVA model with terms for treatment, investigator and CYP2D6. Pairwise treatment p-values are computed using least squares means from the above ANOVA model.

** Dose response p-values are from an ANOVA model with terms for investigator and CYP2D6 dose, dose squared and dose cubed.

All enrolled patients with a baseline and at least one postbaseline measurement included.
Source data: eagle:\programs._g\rmp\b4zs\lyac\interim analysis\efficacy6[new200103a].sas.

**Table LYAC.5. Child Health Questionnaire (CHQ)
Behavior and Family Activities Subscale Scores
Change from Baseline to Endpoint – Study Period II
B4Z-MC-LYAC**

Measure/ Treatment	n	Baseline		Endpoint		Change		p-values*	
		Mean	SD	Mean	SD	Mean	SD	within	vs.PLA
Behavior Subscale									
Placebo	77	47.2	19.7	46.7	22.6	-0.4	16.6	.929	
TMX0.5	39	43.2	17.2	51.4	20.8	8.2	18.1	.011	.015
TMX1.2	75	44.8	19.1	57.8	20.4	13.0	18.8	<.001	<.001
TMX1.8	80	41.0	16.2	57.3	20.9	16.3	19.3	<.001	<.001
Dose Response**:					Unadjusted Pairwise treatment p-values*				
Linear p_value=<.001					PLA	T0.5	T1.2	T1.8	
Quadratic p_value= .176					PLA	----	.015	<.001	<.001
					T0.5	----	----	.166	.025
					T1.2	----	----	----	.308
Family Activities Subscale									
Placebo	78	58.3	23.9	59.0	26.0	0.7	22.6	.612	
TMX0.5	38	44.5	22.1	53.2	26.4	8.7	27.5	.078	.066
TMX1.2	74	52.1	24.9	66.7	25.3	14.6	22.4	<.001	<.001
TMX1.8	80	48.9	26.0	64.1	27.6	15.2	24.6	<.001	<.001
Dose Response**:					Unadjusted Pairwise treatment p-values*				
Linear p_value=<.001					PLA	T0.5	T1.2	T1.8	
Quadratic p_value= .151					PLA	----	.066	<.001	<.001
					T0.5	----	----	.271	.196
					T1.2	----	----	----	.829

* Within treatment group p-values are from Wilcoxon's signed rank test.
Between treatment group p-values are from pairwise tests of treatment differences vs. placebo in mean change from baseline to endpoint(last visit carried forward) scores using least squares means from an ANOVA model with terms for treatment, investigator and CYP2D6. Pairwise treatment p-values are computed using least squares means from the above ANOVA model.
** Dose response p-values are from an ANOVA model with terms for investigator and CYP2D6 dose, dose squared and dose cubed.
All enrolled patients with a baseline and at least one postbaseline measurement included.
Source data: eagle:\programs._g\rmp\b4zs\lyac\interim analysis\efficacy6[new200103a].sas.

**Table LYAC.6. Child Health Questionnaire (CHQ)
Role-Emotion/Behavior and Self-Esteem Subscale Scores
Change from Baseline to Endpoint – Study Period II
B4Z-MC-LYAC**

Measure/ Treatment	n	Baseline		Endpoint		Change		p-values*	
		Mean	SD	Mean	SD	Mean	SD	within	vs.PLA
Role-Emotion/Behave Subscale									
Placebo	78	67.6	33.2	63.2	35.2	-4.4	40.2	.324	
TMX0.5	39	60.8	39.6	68.4	33.7	7.6	35.8	.207	.126
TMX1.2	75	67.6	35.3	75.4	30.6	7.9	33.8	.025	.059
TMX1.8	80	61.0	34.2	76.9	32.6	15.9	40.0	<.001	.001
Dose Response**:					Unadjusted Pairwise treatment p-values*				
Linear p_value= .002					PLA	T0.5	T1.2	T1.8	
Quadratic p_value= .844					PLA	----	.126	.059	.001
					T0.5	----	----	.971	.269
					T1.2	----	----	----	.195
Self-Esteem Subscale									
Placebo	78	65.4	20.1	64.1	22.0	-1.4	18.7	.612	
TMX0.5	39	64.9	16.4	66.3	19.5	1.4	18.6	.486	.518
TMX1.2	75	66.5	18.3	71.9	17.9	5.4	16.8	.007	.039
TMX1.8	80	60.6	21.5	68.9	18.1	8.4	19.5	<.001	<.001
Dose Response**:					Unadjusted Pairwise treatment p-values*				
Linear p_value=<.001					PLA	T0.5	T1.2	T1.8	
Quadratic p_value= .831					PLA	----	.518	.039	<.001
					T0.5	----	----	.289	.033
					T1.2	----	----	----	.195

* Within treatment group p-values are from Wilcoxon's signed rank test.
Between treatment group p-values are from pairwise tests of treatment differences vs. placebo in mean change from baseline to endpoint(last visit carried forward) scores using least squares means from an ANOVA model with terms for treatment, investigator and CYP2D6. Pairwise treatment p-values are computed using least squares means from the above ANOVA model.
** Dose response p-values are from an ANOVA model with terms for investigator and CYP2D6 dose, dose squared and dose cubed.
All enrolled patients with a baseline and at least one postbaseline measurement included.
Source data: eagle:\programs._g\rmp\b4zs\lyac\interim analysis\efficacy6[new200103a].sas.

**Table LYAC.7. Child Health Questionnaire (CHQ)
Parent Impact-Emotional and Parent Impact
Time Subscale Scores
Change from Baseline to Endpoint – Study Period II
B4Z-MC-LYAC**

Measure/ Treatment	n	Baseline		Endpoint		Change		p-values*		
		Mean	SD	Mean	SD	Mean	SD	within	vs.PLA	
Parent Impact-Emotional subscale										
Placebo	77	48.1	22.6	51.1	21.8	3.0	22.4	.186		
TMX0.5	39	46.5	17.6	52.2	18.8	5.7	21.3	.082	.564	
TMX1.2	74	48.4	17.0	58.6	21.9	10.1	19.4	<.001	.060	
TMX1.8	80	44.4	19.3	55.3	23.2	11.0	24.3	<.001	.022	
Dose Response**:				Unadjusted Pairwise treatment p-values*						
Linear p_value= .013				PLA		T0.5		T1.2		T1.8
Quadratic p_value= .710				PLA		.564		.060		.022
				T0.5		.324		.191		
				T1.2		.707				
Parent Impact-Time Subscale										
Placebo	78	67.2	23.2	67.3	23.8	0.2	26.1	.784		
TMX0.5	38	64.4	23.5	66.2	27.2	1.8	26.0	.814	.767	
TMX1.2	74	69.3	22.2	75.6	23.2	6.3	21.8	.019	.163	
TMX1.8	79	64.0	23.5	72.8	25.1	8.8	25.2	.001	.035	
Dose Response**:				Unadjusted Pairwise treatment p-values*						
Linear p_value= .024				PLA		T0.5		T1.2		T1.8
Quadratic p_value= .933				PLA		.767		.163		.035
				T0.5		.396		.154		
				T1.2		.488				

* Within treatment group p-values are from Wilcoxon's signed rank test.
Between treatment group p-values are from pairwise tests of treatment differences vs. placebo in mean change from baseline to endpoint(last visit carried forward) scores using least squares means from an ANOVA model with terms for treatment, investigator and CYP2D6. Pairwise treatment p-values are computed using least squares means from the above ANOVA model.

** Dose response p-values are from an ANOVA model with terms for investigator and CYP2D6 dose, dose squared and dose cubed.

All enrolled patients with a baseline and at least one postbaseline measurement included.
Source data: eagle:\programs._g\rmp\b4zs\lyac\interim analysis\efficacy6[new200103a].sas.

**Table LYAC.8. ADHDRS-IV-Parent:Inv Total Score
Change from Baseline to Endpoint
Study Period III**

Period II Treatment Group	n	Baseline		Endpoint		Change		p-Value(A)
		Mean	SD	Mean	SD	Mean	SD	
PLACEBO	61	34.6	11.0	21.7	13.5	-12.9	12.5	<.001
TOMOX0.5	28	35.0	12.2	23.0	13.8	-12.0	11.6	<.001
TOMOX1.2	49	29.0	11.4	20.8	14.0	-8.2	12.5	<.001
TOMOX1.8	56	31.1	12.5	21.5	12.6	-9.7	11.2	<.001

(A) p-Value is from Wilcoxon signed-rank test.
All enrolled patients with a baseline and at least one postbaseline measurement included.
Baseline: Visits 3-9 (last observation prior to Study Period III);
Endpoint: Visits 10-13
Source data: RMP.B4ZSLYAC.SASPGM(EFF4A)

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Table LYAC.9 **ADHDRS-IV-Parent:Inv Total Score**
Change from Baseline to Endpoint
Early Responders
Study Period IV

Treatment Group	n	Baseline		Endpoint		Change		p-Value(A)
		Mean	SD	Mean	SD	Mean	SD	
PLACEBO	10	8.2	4.4	16.0	11.0	7.8	9.2	.027
TOMOX0.5	6	7.3	5.2	11.8	8.4	4.5	6.7	.063
TOMOX1.2	19	8.7	6.1	10.0	5.7	1.3	5.2	.210
TOMOX1.8	15	8.0	4.0	8.7	6.6	0.7	6.3	.965

(A) p-Value is from Wilcoxon signed-rank test.

All enrolled patients with a baseline and at least one postbaseline measurement included.

Baseline: Visits 3-9 (last observation prior to Study Period IV); Endpoint: Visits 14-24

Source data: RMP.B4ZSLYAC.SASPGM(EFF4D)

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**Table LYAC.10. ADHDRS-IV-Parent:Inv Total Score
 Change from Baseline to Endpoint
 Later Responders
 Study Period IV**

Treatment Group	n	Baseline		Endpoint		Change		p-Value(A)
		Mean	SD	Mean	SD	Mean	SD	
TOMOX1.2	49	10.0	5.0	16.4	10.9	6.5	9.4	<.001
TOMOX1.8	17	7.3	5.8	12.9	10.5	5.6	9.1	.022

(A) p-Value is from Wilcoxon signed-rank test.

All enrolled patients with a baseline and at least one postbaseline measurement included.

Baseline: Visits 3-13 (last observation prior to Study Period IV) Endpoint: Visits 14-24

Source data: RMP.B4ZSLYAC.SASPGM(EFF4E)

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**Table LYAC.11. ADHDRS-IV-Parent:Inv Total Score
 Change from Baseline to Endpoint
 Study Period V**

Treatment Group	n	Baseline		Endpoint		Change		p-Value(A)	p-value(B)
		Mean	SD	Mean	SD	Mean	SD		
ADHDRS - Total Score									
NO TAPER	28	12.4	10.3	18.3	12.8	5.9	10.2	.004	.819
TAPER	25	8.8	5.4	14.2	10.9	5.4	7.4	<.001	----

(A) p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for treatment. All enrolled patients who completed Study Period IV with a baseline and at least one postbaseline measurement included.

Baseline: Visit 24 (last visit prior to Study Period V) Endpoint: Visit 26

Source data: RMP.B4ZSLYAC.SASPGM(EFF5A)

Table LYAC.12. Treatment-Emergent Adverse Events Experienced by at Least 5% of Patients—Study Period II B4Z-MC-LYAC

Event	Placebo	TMX0.5	TMX1.2	TMX1.8	-----p-values*-----			
	N=83 n (%)	N=44 n (%)	N=84 n (%)	N=83 n (%)	PBO vs. TMX0.5	PBO vs. TMX1.2	PBO vs. TMX1.8	CA trend
HEADACHE	19(22.9)	11(25.0)	20(23.8)	20(24.1)	.828	1.000	1.000	.894
RHINITIS	18(21.7)	7(15.9)	10(11.9)	12(14.5)	.490	.101	.313	.151
ABDOMINAL PAIN	9(10.8)	5(11.4)	12(14.3)	12(14.5)	1.000	.642	.641	.418
PHARYNGITIS	12(14.5)	4(9.1)	9(10.7)	9(10.8)	.575	.493	.641	.525
ANOREXIA	4(4.8)	3(6.8)	10(11.9)	10(12.0)	.693	.161	.161	.065
COUGH INCREASED	4(4.8)	6(13.6)	6(7.1)	7(8.4)	.094	.746	.535	.646
VOMITING	5(6.0)	3(6.8)	6(7.1)	9(10.8)	1.000	1.000	.403	.271
SOMNOLENCE	3(3.6)	2(4.5)	6(7.1)	9(10.8)	1.000	.496	.131	.055
INSOMNIA	5(6.0)	4(9.1)	5(6.0)	4(4.8)	.718	1.000	1.000	.616
RASH	3(3.6)	3(6.8)	5(6.0)	7(8.4)	.417	.720	.328	.240
NAUSEA	5(6.0)	2(4.5)	6(7.1)	4(4.8)	1.000	1.000	1.000	.905
NERVOUSNESS	4(4.8)	3(6.8)	5(6.0)	5(6.0)	.693	1.000	1.000	.789
FEVER	5(6.0)	1(2.3)	7(8.3)	3(3.6)	.664	.766	.720	.853
PAIN	5(6.0)	4(9.1)	2(2.4)	5(6.0)	.718	.277	1.000	.610
ACCIDENTAL INJURY	7(8.4)	1(2.3)	3(3.6)	3(3.6)	.261	.211	.328	.183
ASTHENIA	4(4.8)	3(6.8)	2(2.4)	4(4.8)	.693	.443	1.000	.709
INFECTION	1(1.2)	0(0.0)	5(6.0)	6(7.2)	1.000	.210	.117	.018
DIZZINESS	1(1.2)	4(9.1)	2(2.4)	4(4.8)	.049	1.000	.367	.541
DIARRHEA	5(6.0)	0(0.0)	4(4.8)	0(0.0)	.163	.746	.059	.093
DEPRESSION	5(6.0)	1(2.3)	0(0.0)	2(2.4)	.664	.028	.443	.096
PRURITUS	0(0.0)	0(0.0)	1(1.2)	5(6.0)	----	1.000	.059	.007

*p-values are from Fisher exact test and Cochran-Armitage(CA) test for trend.

Source data: eagle:/programs_.g/rmp/b4zs/lyac/interim analysis/
safety1 with 5% cutoff.sas.

**Table LYAC.13. Vital Signs Change from Baseline to Endpoint
Study Period II B4Z-MC-LYAC**

Measure/ Treatment	n	Baseline		Endpoint		Change		p-values*	
		Mean	SD	Mean	SD	Mean	SD	within	vs.PLA
Systolic Blood Pressure									
Placebo	83	102.7	8.7	104.7	10.5	2.1	9.5	.083	
TMX0.5	43	104.2	9.6	107.5	10.6	3.3	10.4	.033	.492
TMX1.2	84	103.8	8.4	108.1	9.1	4.3	10.4	<.001	.143
TMX1.8	81	103.9	8.5	106.3	9.0	2.5	8.8	.008	.801
Dose Response**:		Linear p_value=		.634		Quadratic p_value=		.141	
Diastolic Blood Pressure									
Placebo	83	64.9	8.1	63.5	7.2	-1.4	9.8	.275	
TMX0.5	43	65.4	7.6	66.9	9.6	1.5	9.5	.314	.118
TMX1.2	84	64.7	7.4	67.5	8.3	2.8	9.1	.002	.006
TMX1.8	81	65.7	8.4	67.4	7.8	1.7	10.5	.165	.043
Dose Response**:		Linear p_value=		.025		Quadratic p_value=		.072	
Heart Rate (pulse)									
Placebo	83	81.9	10.7	83.5	10.6	1.6	10.5	.267	
TMX0.5	43	83.5	7.9	89.3	10.6	5.8	9.6	<.001	.044
TMX1.2	84	80.3	8.7	86.6	12.8	6.3	11.9	<.001	.007
TMX1.8	81	81.7	11.3	90.0	14.1	8.3	11.6	<.001	<.001
Dose Response**:		Linear p_value=<.001				Quadratic p_value=		.496	
Temperature									
Placebo	83	36.7	0.4	36.6	0.5	-0.1	0.6	.054	
TMX0.5	43	36.8	0.5	36.6	0.5	-0.1	0.6	.149	.899
TMX1.2	84	36.8	0.5	36.7	0.4	-0.1	0.5	.017	.819
TMX1.8	81	36.6	0.4	36.6	0.5	-0.1	0.5	.374	.390
Dose Response**:		Linear p_value=		.373		Quadratic p_value=		.634	
Height									
Placebo	72	143.4	12.2	144.7	12.5	1.3	1.8	<.001	
TMX0.5	38	144.3	14.0	145.6	14.2	1.3	1.1	<.001	.853
TMX1.2	70	146.2	14.6	146.8	14.6	0.7	2.0	<.001	.028
TMX1.8	69	144.0	14.3	145.0	14.5	1.0	1.0	<.001	.335
Dose Response**:		Linear p_value=		.111		Quadratic p_value=		.243	
Weight									
Placebo	82	39.6	12.0	41.3	12.6	1.7	1.6	<.001	
TMX0.5	43	40.0	13.9	40.3	13.7	0.3	1.1	.235	<.001
TMX1.2	84	42.1	13.3	41.7	13.3	-0.4	1.4	.004	<.001
TMX1.8	80	40.5	13.3	40.0	13.3	-0.5	1.7	.007	<.001
Dose Response**:		Linear p_value=<.001				Quadratic p_value=<.001			

* Within treatment group p-values are from Wilcoxon's signed rank test.
Between treatment group p-values are from pairwise tests of treatment differences vs. placebo in mean change from baseline to endpoint (last visit carried forward) scores using least squares means from an ANOVA model with terms for treatment,
** Dose response p-values are from an ANOVA model with terms for dose, dose squared and dose cubed.

All enrolled patients taking at least one dose of study drug with a baseline and at least one postbaseline measurement included.

Source data: eagle:\programs._g\rmp\b4zs\lyac\interim analysis\efficacy6[new200103a].sas.

Summary ID#4642

Clinical Study Summary: Study B4Z-MC-LYAO

Title of Study: A Phase III Randomized, Double-Blind Comparison of Placebo and Atomoxetine Hydrochloride in Adult Outpatients with DSM-IV Attention-Deficit/Hyperactivity Disorder	
Investigators: This multicenter study included 14 principal investigators.	
Study Centers: This study was conducted at 14 study centers in the United States.	
Length of Study: 8.5 months Date first patient enrolled: 12 August 2000 Date last patient completed: 24 April 2001	Phase of Development: 3
Objectives: The primary objective of this study was to test the hypothesis that, compared with placebo, administration of atomoxetine (formerly called tomoxetine) at total daily doses of 60 mg to 120 mg for up to 10 weeks would result in a statistically significantly greater reduction in mean Total Attention-Deficit/Hyperactivity Disorder (ADHD) Symptom Score on the investigator-administered and scored Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV). The secondary objectives of the study were as follows: • To compare percentages of responders among atomoxetine-treated and placebo-treated patients who had completed a minimum of three visits following randomization. Determination of clinical response was based on the CAARS-Inv:SV and the Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) scores. • To compare improvement of neurocognitive function during treatment with atomoxetine to improvement during treatment with placebo using the Stroop Color Word Test (Stroop). • To compare the safety of atomoxetine with placebo in a population of adult patients who met <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</i> (DSM-IV) criteria for ADHD. • To assess changes in health outcomes.	
Study Design: Study B4Z-MC-LYAO (LYAO) was a Phase 3, randomized, double-blind, placebo-controlled study, in which 256 adult outpatients were enrolled. Patients were at least 18 years old at the time of entry into this study and met DSM-IV and CAARS-Inv:SV criteria for ADHD, in addition to all enrollment criteria. After an initial washout, screening, and entry period, patients completed a 2-week placebo lead-in period, followed by randomization to study drug or placebo at Visit 3. During the 10-week acute treatment phase of Study LYAO, patients were titrated to a maximum tolerated dose, not to exceed 120 mg/day. After completing the acute treatment phase, patients proceeded to Study Period III, and were randomized to one of two groups. One group had study drug abruptly discontinued; the other group had study drug tapered and discontinued over a 4-week period.	
Number of Patients: Planned: 95 atomoxetine hydrochloride, 95 placebo Randomized: 129 atomoxetine hydrochloride, 127 placebo Completed: 67 atomoxetine hydrochloride, 74 placebo	
Diagnosis and Main Criteria for Inclusion: Patients had to meet DSM-IV diagnostic criteria for ADHD on the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAAR-D) at Visit 1 for both childhood and current symptoms, as well as meeting criteria based on the investigator's clinical assessment. In addition, the patient's score on either the inattentive or hyperactive subscales of the CAARS-Inv:SV screening instrument had to have at least 6 of the symptoms in either subscale rated 2 ('pretty much/often') or greater and a Total ADHD Symptom Score ≥ 20. At Visit 1 and Visit 2 patients also had to have a Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) score of 4 (moderate symptoms) or greater.	
Test Product, Dose, and Mode of Administration: Atomoxetine hydrochloride; 2.5-mg, 5-mg, 10-mg, 20-mg, 25-mg, and 40-mg capsules; 60 mg/day to 120 mg/day, given twice daily	

Duration of Treatment: Approximately 10 weeks.
Reference Therapy, Dose, and Mode of Administration: Placebo capsules.
Variables: Efficacy: The primary efficacy analysis was a comparison of the CAARS-Inv:SV Total ADHD Symptom Scores between atomoxetine and placebo during Study Period II. Safety: Adverse events were collected by open-ended discussion and by the Association for Methodology and Documentation in Psychiatry-5: Somatic Signs (AMDP-5) questionnaire. Electrocardiograms (ECGs) and vital signs, cytochrome P450 2D6 (CYP2D6) genotype characterization and clinical laboratory tests were also performed. Safety analyses included all patients who took at least one dose of study drug. Pharmacokinetic: Patients provided blood samples for assessment of plasma concentrations of atomoxetine, 4-hydroxyatomoxetine, and N-desmethyatomoxetine to evaluate the relationship, if any, between QTc and atomoxetine plasma concentration.
Evaluation Methods: Statistical: The primary efficacy analysis was an F-test for a treatment difference between atomoxetine and placebo at Visit 8 (the last Study Period II visit) from a repeated measures mixed model analysis of the CAARS-Inv:SV Total ADHD Symptom Score. The repeated measures mixed model included terms for treatment, investigational site, visit, CYP2D6 metabolism status, and an interaction between treatment and visit. The model also included baseline CAARS-Inv:SV Total ADHD Symptom score as a covariate and patient as a random effect. For secondary efficacy and safety assessments, treatment differences in mean change scores from continuous measures were assessed using analysis of variance (ANOVA), while the Fisher's exact test was used to assess treatment differences in binary data.
Summary: Patient Disposition: Three hundred eighty-eight (388) patients entered Study B4Z-MC-LYAO (LYAO). Of those, 132 were not randomized (that is, were discontinued prior to randomization at Visit 3). Patients were not randomized for the following reasons: adverse event (N=2); lack of efficacy, patient perception (N=2); lost to follow-up (N=16); personal conflict (N=32); patient moved (N=1); entry criteria not met (N = 63); sponsor's decision (N=6); physician's decision (N=7); and protocol violation (N=3). Of the 388 patients entered, 256 were screened in Study Period I (Medication Washout, Screening, and Assessment) and were subsequently randomized to Study Period II (Randomized, Double-Blind, Acute Treatment) at Visit 3. At Visit 3, 129 patients were randomized to atomoxetine and 127 to placebo. Of the 256 randomized patients, 171 (66.8%) completed Study Period II, and proceeded to Study Period III (Double-Blind Discontinuation). Of the 171 patients continuing to Study Period III, 141 (82.5%) completed the protocol. Patient Demographics: Table LYAO.1 shows demographic characteristics for all randomized patients. Of the 256 enrolled patients, 66.4% were male, 94.5% were Caucasian, and 53.1% had no prior stimulant exposure. The mean age for these patients was 42.1 years (range of 18.6 years to 76.7 years). Patients were required to meet DSM-IV diagnostic criteria for current ADHD as well as meeting criteria for a historical diagnosis of ADHD during childhood, both assessed by the CAAR-D. The most common diagnosis was the combined ADHD subtype (60.5%), followed by the predominantly inattentive subtype (35.2%), and hyperactive/impulsive subtype (4.3%). Comorbid DSM-IV diagnoses were assessed using the Structured Clinical Interview for DSM-IV Axis Disorders – Modified (SCID). Because the protocol excluded most comorbid diagnoses, depressive disorder NOS was the only comorbid DSM-IV diagnosis reported as present by any patient in the study. Of the 256 enrolled patients, 2 (0.8%) reported depressive disorder NOS, 1 patient in each treatment group. Efficacy: There was a statistically significant difference between treatment groups on the primary outcome measure, the CAARS-Inv:SV Total ADHD Symptom Score. As Table LYAO.2 shows, the mean score for atomoxetine-treated patients for the repeated measures analysis at Visit 8 was 22.63 and the mean score for placebo-treated patients was 27.23, giving a mean treatment difference of -4.60 (p<.001). As

Table LYAO.3 shows, the mean change from baseline to endpoint for atomoxetine-treated patients was -10.5 compared to a mean change of -6.7 for placebo-treated patients ($p < .002$).

The significance of the outcomes on the primary efficacy measure were supported by the outcomes on the secondary measures, including the CAARS-Inv:SV subscale scores (Table LYAO.4), Conners' Adult ADHD Rating Scale-Self-Administered (CAARS-Self) Total ADHD Symptom Score and subscale scores (Table LYAO.5), CGI-ADHD-S (Table LYAO.6), and Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS; Table LYAO.7), which was intended to measure the severity of the target symptoms (from the Utah Criteria) of adults with ADHD. Results on the Hamilton Depression Rating Scale (HAMD-17) and the Hamilton Anxiety Rating Scale (HAMA) show that these efficacy results were specific for ADHD symptoms, as opposed to affective or anxiety symptoms (Table LYAO.8). The absence of significant differences between groups experiencing abrupt versus tapered discontinuation of atomoxetine indicated that treatment with atomoxetine did not result in either dependence or a withdrawal syndrome. No symptom rebound was observed when atomoxetine was discontinued with or without a taper (Table LYAO.9).

The percentage of patients meeting responder criteria in the atomoxetine treatment group was not statistically significantly different from the placebo treatment group using all three prespecified definitions. For the CAARS-Inv:SV Total ADHD Symptom Score response criterion, 50.0% of the atomoxetine-treated and 39.5% of the placebo-treated patients met response criterion ($p = .125$). Lower percentages of patients in both treatment groups met response criteria for the CGI-ADHD-S (atomoxetine 34.7%, placebo 26.8%, $p = .215$) and the CGI-Efficacy Index (atomoxetine 31.5%, placebo 21.3%, $p = .083$).

There were no statistically significant differences between the atomoxetine-treated patients compared to placebo-treated patients for any of the Stroop T-scores.

The Arizona Sexual Experiences Scale (ASEX), the Psychological General Well-Being (PGWB), and the Sheehan Disability Scale and Habits Questionnaire were administered to assess changes in health outcomes. Atomoxetine treatment resulted in no significant statistical difference on the score for the female version of the ASEX. In contrast, atomoxetine treatment resulted in a statistically significant increase on the score for the male version of the ASEX as compared to placebo (mean change for atomoxetine = 2.8, mean change for placebo = 0.2, $p < .001$). There were no statistically significant differences between atomoxetine and placebo on the PGWB or the three subscales of the Sheehan Disability Scale. Atomoxetine treatment resulted in a significant decrease ($p = .029$) versus placebo treatment in caffeine consumption on the Habits Questionnaire. There were no significant differences between atomoxetine and placebo treatment groups in alcohol consumption or nonprescribed psychotropic medications on the Habits Questionnaire.

Safety: There were no deaths in this study. Adverse events resulted in discontinuation for 12 patients treated with atomoxetine, and were most commonly related to the urogenital system (urinary retention, abnormal ejaculation, and libido decreased). Table LYAO.10 summarizes the treatment-emergent adverse events with an incidence of at least 5% during Study Period II. Unsolicited (spontaneous) adverse events reported statistically significantly more often by patients taking atomoxetine than by those taking placebo were insomnia, dry mouth, anorexia (typically captured as "decreased appetite"), constipation, impotence, chills, urinary retention, and urination impaired. Differences that approached statistical significance were detected for nausea ($p = .054$), dizziness ($p = .084$), libido decreased ($p = .060$), and myalgia ($p = .060$). The events described would be expected with a noradrenergic drug. For some adverse events (insomnia, dry mouth, anorexia [typically captured as "decreased appetite"], constipation, impotence, libido decreased, and myalgia) reporting rates appeared to persist throughout the course of this 10-week study. Reports of nausea and dizziness peaked early, and then subsided.

Analysis of laboratory data showed that the mean change from baseline to endpoint for alkaline phosphatase was +2.147 U/L in atomoxetine-treated patients versus -2.130 U/L in placebo-treated patients ($p < .001$); no abnormally high or low values were recorded in either group.

Table LYAO.11 summarizes the mean change from baseline to endpoint in vital sign measures for Study

Period II, the acute treatment period. A statistical comparison for the mean change in the atomoxetine (all patients) group compared to the mean change for patients taking placebo is shown. Mean changes for EMs and PMs taking atomoxetine are provided, but no statistical comparison is given because the number of PMs is so small. As in other studies, use of atomoxetine was found to be associated with an elevation of heart rate (a mean change of 3.754 beats per minute [bpm] for atomoxetine-treated patients versus -0.093 bpm for placebo-treated patients; $p=.002$). Systolic blood pressure was slightly elevated (a mean change of 3.460 mm Hg in atomoxetine-treated patients versus a mean change of 0.851 mm Hg in placebo-treated patients; $p=.059$). Mean weight was statistically significantly decreased in the atomoxetine group (-1.119 kg) versus the placebo group (0.473 kg, $p<.001$). Effects on the ECG were consistent with an increase in heart rate. The QT interval was not prolonged.

Pharmacokinetic: There was no relationship between baseline to endpoint changes in the QTc interval relative to plasma atomoxetine concentrations. This was true for EMs ($p=.478$) and PMs ($p=.250$).

Table LYAO.1. Summary of Demographics and Other Patient Characteristics
All Randomized Patients
B4Z-MC-LYAO

Variable	ATOMOX (N=129)	PLACEBO (N=127)	Total (N=256)	p-Value
Sex: No. (%)				
No. Patients	129	127	256	.510*
Female	46 (35.7)	40 (31.5)	86 (33.6)	
Male	83 (64.3)	87 (68.5)	170 (66.4)	
Origin: No. (%)				
No. Patients	129	127	256	.649*
African Descent	1 (0.8)	2 (1.6)	3 (1.2)	
Caucasian	124 (96.1)	118 (92.9)	242 (94.5)	
East/Southeast A	1 (0.8)	1 (0.8)	2 (0.8)	
Hispanic	3 (2.3)	4 (3.1)	7 (2.7)	
Other	0	2 (1.6)	2 (0.8)	
Age: yrs.				
No. Patients	129	127	256	.186**
Mean	42.97	41.18	42.08	
Median	43.10	41.51	42.76	
Standard Dev.	10.32	11.24	10.80	
Minimum	18.79	18.62	18.62	
Maximum	76.71	65.31	76.71	
Height: cm				
No. Patients	128	126	254	.536**
Mean	174.26	173.45	173.86	
Median	175.50	173.00	175.00	
Standard Dev.	10.84	9.83	10.34	
Minimum	133.00	149.00	133.00	
Maximum	205.50	193.00	205.50	
Unspecified	1	1	2	
Weight: kg				
No. Patients	128	126	254	.576**
Mean	84.02	82.71	83.37	
Median	82.70	82.65	82.70	
Standard Dev.	18.83	18.34	18.56	
Minimum	49.80	44.00	44.00	
Maximum	151.60	135.60	151.60	
Unspecified	1	1	2	
Family History of ADHD-Mother				
No. Patients	129	127	256	.198*
N	84 (65.1)	90 (71.4)	174 (68.2)	
U	32 (24.8)	20 (15.9)	52 (20.4)	
Y	13 (10.1)	16 (12.7)	29 (11.4)	
Unspecified	0	1	1	
Family History of ADHD-Father				
No. Patients	129	127	256	.146*
N	80 (62.0)	86 (68.3)	166 (65.1)	
U	33 (25.6)	20 (15.9)	53 (20.8)	
Y	16 (12.4)	20 (15.9)	36 (14.1)	
Unspecified	0	1	1	
Family History of ADHD-Grandparents				
No. Patients	129	127	256	.281*
N	65 (50.4)	74 (58.7)	139 (54.5)	
U	59 (45.7)	50 (39.7)	109 (42.7)	
Y	5 (3.9)	2 (1.6)	7 (2.7)	
Unspecified	0	1	1	

(continued)

Table LYAO.1. Summary of Demographics and Other Patient Characteristics
All Randomized Patients
B4Z-MC-LYAO (concluded)

Variable	ATOMOX (N=129)	PLACEBO (N=127)	Total (N=256)	p-Value
Family History of ADHD-Siblings				
No. Patients	129	127	256	.459*
N	78 (60.5)	76 (59.8)	154 (60.2)	
N/A	5 (3.9)	3 (2.4)	8 (3.1)	
U	20 (15.5)	14 (11.0)	34 (13.3)	
Y	26 (20.2)	34 (26.8)	60 (23.4)	
Family History of ADHD-Children				
No. Patients	129	127	256	.553*
N	38 (29.5)	29 (23.0)	67 (26.3)	
N/A	30 (23.3)	37 (29.4)	67 (26.3)	
U	11 (8.5)	9 (7.1)	20 (7.8)	
Y	50 (38.8)	51 (40.5)	101 (39.6)	
Unspecified	0	1	1	
Prior Stimulant Exposure				
No. Patients	129	127	256	.263*
N	64 (49.6)	72 (56.7)	136 (53.1)	
Y	65 (50.4)	55 (43.3)	120 (46.9)	

Population: All Randomized Patients.

Initial Visit ONLY

Input data from RMP.SAS.B4ZM.MCLYAOSW

Output stored as RMP.B4ZO.LYAOCTRM.FINAL(DE111003)

* Frequencies are analyzed using a Fishers-Exact test.

** Means are analyzed using a Type III Sum of Squares analysis of variance

(ANOVA): PROC GLM model=treatment.

XDES0001

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**Table LYAO.2. CAARS-Inv:SV Total ADHD Symptom Score
 Repeated Measures, Least Squares Means
 Study Period II
 B4Z-MC-LYAO**

Visit	Atomoxetine			Placebo			Treatment Difference		
	LS Mean	SE	p-val a	LS Mean	SE	p-val a	LS Mean	SE	p-val b
4	28.81	1.17	<.001	31.43	1.14	<.001	-2.62	0.95	.006
5	26.61	1.24	<.001	28.80	1.22	<.001	-2.19	1.12	.052
6	24.87	1.29	<.001	28.74	1.27	<.001	-3.87	1.23	.002
7	23.88	1.34	<.001	27.89	1.31	<.001	-4.01	1.32	.003
8	22.63	1.37	<.001	27.23	1.33	<.001	-4.60	1.37	<.001
95% Confidence Interval on Change from Baseline to Visit 8 (-14.57 , -9.18) (-9.90 , -4.65)									
Summary of Model Parameters				F-Value	P-Value c				
Baseline				151.23	<.001				
Treatment				12.15	<.001				
Visit				17.71	<.001				
Investigator				1.91	.030				
Treatment*Visit				1.05	.382				
CYP2D6 Status				0.20	.653				

Results based on a mixed model with a term for visit, (treated as a class variable) baseline, treatment and treatment by visit interaction using an unstructured covariance matrix to model correlations within patient across visits.

- a P-values are from tests for a nonzero least squares mean at the given visit.
- b P-values are from tests for a treatment difference in least squares means at the given visit.
- c P-values are from F-tests for a nonzero coefficient estimate.

Program: RMP.B4ZSLYAO.SASPGM(EFF1A)

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Table LYAO.3. CAARS-Inv:SV Total ADHD Symptom Scores
Change from Baseline to Endpoint
Study Period II
B4Z-MC-LYAO

Treatment Group	n	Baseline		Endpoint		Change		p-Value (A)	p-value (B)
		Mean	SD	Mean	SD	Mean	SD		
All Patients									
Atomox.	124	34.9	6.9	24.4	11.1	-10.5	10.9	<.001	.002
PL	124	34.2	7.5	27.5	11.4	-6.7	9.3	<.001	----
95% C.I.: (-6.42 , -1.50)									
Extensive Metabolizers									
Atomox.	118	34.8	6.8	24.5	11.2	-10.3	11.0	<.001	.005
PL	117	34.1	7.5	27.3	11.5	-6.8	9.5	<.001	----
95% C.I.: (-6.23 , -1.13)									
Slow Metabolizers									
Atomox.	6	36.2	9.6	21.8	9.6	-14.3	6.5	.031	.167
PL	7	34.9	7.3	30.0	10.0	-4.9	6.0	.125	----
95% C.I.: (-22.6 , 7.64)									

(A) p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator, treatment, and CYP2D6 status for all patients and using least squares means from an ANOVA model with terms for investigator and treatment for the EM and PM subgroups. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAO.SASPGM(EFF2A)

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Table LYAO.4. CAARS-Inv:SV Inattentive, Hyperactive/Impulsive, and ADHD Index Subscales
Change from Baseline to Endpoint
Study Period II
B4Z-MC-LYAO

Treatment Group	n	Baseline		Endpoint		Change		p-Value (A)	p-value (B)
		Mean	SD	Mean	SD	Mean	SD		
ADHD Index Subscale									
Atomox.	124	21.0	5.2	15.0	7.8	-6.0	7.0	<.001	.002
PL	124	20.0	5.6	16.3	7.2	-3.7	6.0	<.001	----
95% C.I.: (-4.01 , -0.88)									
Hyperactive/Impulsive Subscale									
Atomox.	124	14.8	4.8	10.1	5.7	-4.7	5.3	<.001	.012
PL	124	14.9	5.2	11.7	6.5	-3.2	4.7	<.001	----
95% C.I.: (-2.80 , -0.35)									
Inattentive Subscale									
Atomox.	124	20.0	4.1	14.2	6.6	-5.8	6.5	<.001	.001
PL	124	19.3	4.3	15.7	6.5	-3.5	5.3	<.001	----
95% C.I.: (-3.84 , -0.93)									

(A) p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator, treatment, and CYP2D6 status. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAO.SASPGM(EFF2B)

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Table LYAO.5. CAARS-Self Total ADHD Symptom Score and Inattentive, Hyperactive/Impulsive, and ADHD Index Subscales
Change from Baseline to Endpoint
Study Period II
B4Z-MC-LYAO

Treatment Group	n	Baseline		Endpoint		Change		p-Value (A)	p-value (B)
		Mean	SD	Mean	SD	Mean	SD		
Total ADHD Symptom Score Atomox.	102	35.5	7.4	24.3	10.2	-11.2	11.3	<.001	.008
PL	105	34.1	8.9	26.6	11.2	-7.5	10.1	<.001	----
95% C.I.: (-6.94 , -1.07)									
Hyperactive/Impulsive Subscale Atomox.	103	15.8	4.7	10.7	5.3	-5.1	5.7	<.001	.026
PL	105	15.3	5.8	11.7	6.4	-3.6	5.4	<.001	----
95% C.I.: (-3.24 , -0.21)									
Inattentive Subscale Atomox.	103	19.6	4.1	13.6	6.0	-6.0	6.3	<.001	.012
PL	105	18.8	5.0	14.8	6.5	-4.0	5.7	<.001	----
95% C.I.: (-3.78 , -0.47)									
ADHD Index Subscale Atomox.	103	22.6	5.0	16.4	7.2	-6.3	6.8	<.001	.065
PL	105	20.9	5.7	16.2	7.2	-4.7	6.6	<.001	----
95% C.I.: (-3.57 , 0.11)									

(Footnotes on next page)

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Footnotes for Table LYA0.4

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(A) p-Value is from Wilcoxon signed-rank test.
(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator, treatment, and CYP2D6 status. All enrolled patients with a baseline and at least one postbaseline measurement included.
Program: RMP.B4ZSLYA0.SASPGM(EFF2C)

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Table LYAO.6. CGI-ADHD-S
Change from Baseline to Endpoint
Study Period II
B4Z-MC-LYAO

Treatment Group	n	Baseline		Endpoint		Change		p-Value (A)	p-value (B)
		-----		-----		-----		-----	-----
		Mean	SD	Mean	SD	Mean	SD		
CGI-ADHD-S									
Atomox.	124	4.6	0.6	3.7	1.2	-0.9	1.2	<.001	.002
PL	123	4.6	0.7	4.1	1.1	-0.5	1.0	<.001	----
95% C.I.: (-0.67 , -0.15)									

(A) p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator, treatment, and CYP2D6 status. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAO.SASPGM(EFF4A)

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Table LYAO.7. WRAADDS
Change from Baseline to Endpoint
Study Period II
B4Z-MC-LYAO

Treatment Group	n	Baseline		Endpoint		Change		p-Value (A)	p-value (B)
		-----		-----		-----		-----	-----
		Mean	SD	Mean	SD	Mean	SD		
WRAADDS Total									
Atomox.	101	16.5	5.0	12.0	6.7	-4.5	5.9	<.001	.041
PL	104	15.5	5.7	12.8	6.4	-2.8	5.7	<.001	----
95% C.I.: (-3.28 , -0.07)									

(A) p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator, treatment, and CYP2D6 status. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAO.SASPGM(EFF4B)

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Table LYAO.8. HAMD-17 and HAMA
Change from Baseline to Endpoint
Study Period II
B4Z-MC-LYAO

Treatment Group	n	Baseline		Endpoint		Change		p-Value (A)	p-value (B)
		Mean	SD	Mean	SD	Mean	SD		
HAMA Total									
Atomox.	102	6.5	5.1	5.8	4.7	-0.7	4.3	.069	.747
PL	107	5.9	4.5	4.9	5.1	-1.0	5.4	.003	----
95% C.I.: (-1.12 , 1.56)									
HAMD Total									
Atomox.	103	4.7	3.7	4.9	4.1	0.2	3.6	.655	.014
PL	107	4.6	3.2	3.6	3.6	-1.0	3.5	<.001	----
95% C.I.: (0.26 , 2.20)									

(A) p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator, treatment, and CYP2D6 status. All enrolled patients with a baseline and at least one postbaseline measurement included.
 Program: RMP.B4ZSLYAO.SASPGM(EFF2D)

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**Table LYAO.9. CAARS-Inv:SV Total ADHD Symptom Score and
 Subscale Scores
 Change from Baseline to Endpoint
 Study Period III
 B4Z-MC-LYAO**

Treatment Group	n	Baseline		Endpoint		Change		p-Value (A)	p-value (B)
		Mean	SD	Mean	SD	Mean	SD		
Total ADHD Symptoms Score									
ATX_NOTP	39	22.3	10.9	28.2	11.9	5.8	10.4	<.001	.740
ATX_TAP	42	23.9	10.9	28.9	12.9	5.0	10.5	<.001	----
95% C.I.: (-3.85 , 5.40)									
Hyperactive/Impulsive Subscale									
ATX_NOTP	39	9.2	5.2	12.1	6.6	2.8	5.9	.004	.461
ATX_TAP	42	10.2	5.8	12.1	7.1	1.9	5.5	.032	----
95% C.I.: (-1.59 , 3.47)									
Inattentive Subscale									
ATX_NOTP	39	13.1	6.6	16.1	6.1	3.0	5.3	<.001	.895
ATX_TAP	42	13.6	6.4	16.8	7.2	3.2	6.0	.001	----
95% C.I.: (-2.68 , 2.34)									

(continued)

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**Table LYAO.9. CAARS-Inv:SV Total ADHD Symptom Score and
 Subscale Scores
 Change from Baseline to Endpoint
 Study Period III
 B4Z-MC-LYAO (concluded)**

Treatment Group	n	Baseline		Endpoint		Change		p-Value (A)	p-value (B)
		Mean	SD	Mean	SD	Mean	SD		
ADHD Index Subscale									
ATX_NOTP	39	13.4	7.7	16.6	7.9	3.3	7.1	.002	.786
ATX_TAP	42	14.4	7.4	17.2	8.1	2.9	6.2	.007	----
95% C.I.: (-2.55 , 3.36)									

ATMX_TAP = Atomoxetine Taper, ATX_NOTP = Atomoxetine No Taper.

(A) p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with term for treatment.

All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAO.SASPGM(EFF3A)

**Table LYAO.10. Summary of Treatment-Emergent Adverse Events
with $\geq 5\%$ Incidence
Study Period II
B4Z-MC-LYAO**

Event Classification	ATOMOX (N=128) n (%)	PLACEBO (N=125) n (%)	Total (N=253) n (%)	p-Value*
PATIENTS WITH ≥ 1 TESS	114 (89.1)	104 (83.2)	218 (86.2)	.204
PATIENTS WITH NO TESS	14 (10.9)	21 (16.8)	35 (13.8)	.204
HEADACHE	27 (21.1)	25 (20.0)	52 (20.6)	.877
INSOMNIA	32 (25.0)	14 (11.2)	46 (18.2)	.005
RHINITIS	18 (14.1)	24 (19.2)	42 (16.6)	.312
PHARYNGITIS	19 (14.8)	19 (15.2)	38 (15.0)	1.00
DRY MOUTH	24 (18.8)	8 (6.4)	32 (12.6)	.004
ANOREXIA	18 (14.1)	4 (3.2)	22 (8.7)	.003
PAIN	14 (10.9)	7 (5.6)	21 (8.3)	.171
FLU SYNDROME	7 (5.5)	13 (10.4)	20 (7.9)	.167
NAUSEA	14 (10.9)	5 (4.0)	19 (7.5)	.054
DYSPEPSIA	10 (7.8)	8 (6.4)	18 (7.1)	.808
CONSTIPATION	13 (10.2)	4 (3.2)	17 (6.7)	.042
SINUSITIS	11 (8.6)	6 (4.8)	17 (6.7)	.316
ABDOMINAL PAIN	7 (5.5)	7 (5.6)	14 (5.5)	1.00
COUGH INCREASED	5 (3.9)	9 (7.2)	14 (5.5)	.283
SOMNOLENCE	9 (7.0)	5 (4.0)	14 (5.5)	.411
ASTHENIA	8 (6.3)	5 (4.0)	13 (5.1)	.571
DIZZINESS	10 (7.8)	3 (2.4)	13 (5.1)	.084
IMPOTENCE	11 (8.6)	0	11 (4.3)	.001
LIBIDO DECREASED	9 (7.0)	2 (1.6)	11 (4.3)	.060
MYALGIA	9 (7.0)	2 (1.6)	11 (4.3)	.060
RASH	7 (5.5)	3 (2.4)	10 (4.0)	.334

Population: Randomized patients who took at least 1 dose of study drug.

Baseline: Visits 1-3, Endpoint: Visits 4 - 8

Input data from RMP.SAS.B4ZM.MCLYA0SW

Output stored as RMP.B4Z0.LYAOCTRM.FINAL(AE2C1005)

* Frequencies are analyzed using a Fisher's Exact test.

XAES0002

Atomoxetine hydrochloride
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Approved: 11 November 2004

Table LYAO.11. Vital Signs
Mean Change from Baseline to Endpoint
Study Period II
B4Z-MC-LYAO

	PBO (all) N=124	p-value	ATX (all) N=124	ATX (EM) N=118	ATX (PM) N=6
diastolic BP (mm Hg)	+0.560	.556	+1.185	+1.216	+0.583
systolic BP (mm Hg)	+0.851	.059	+3.460	+3.614	+0.417
pulse (bpm)	-0.093	.002	+3.754	+3.335	+12.000
weight (kg)	+0.473	<.001	-1.119	-1.149	-0.517
temperature (°C)	0.0	.195	+0.079	+0.086	-0.067

Source data: RMP.B4ZO.LYAOCTRM.FINAL (VI6L1005), RMP.B4ZO.LYAOCTRM.FINAL (VI6L100U), RMP.B4ZO.LYAOCTRM.FINAL (VI6L100V)

Summary ID#4668

Clinical Study Summary: Study B4Z-MC-LYAQ

Date summary approved by Lilly: 09 August 2005

Title of Study: Safety and Efficacy of Atomoxetine or Atomoxetine Plus Fluoxetine in the Treatment of Mixed Attentional and Affective Disorders	
Investigators: This multicenter study included 21 principal investigators.	
Study Centers: There were 21 study centers in the US, although only 20 centers enrolled patients.	
Length of Study: 6 months Date first patient enrolled: 20 February 2001 Date last patient completed: 24 August 2001	Phase of Development: 3
Objectives: The primary objective of Study B4Z-MC-LYAQ (LYAQ) was to assess the tolerability and safety of atomoxetine (formerly called tomoxetine) in doses up to 1.8 mg/kg/day in patients who had a cytochrome P450 2D6 (CYP2D6) poor metabolizer (PM) phenotype. Three secondary objectives were identified for this study: • To test the hypothesis that atomoxetine 1.2 mg/kg/day alone is noninferior to atomoxetine 1.2 mg/kg/day plus fluoxetine 20 mg/day in the treatment of mixed attentional and affective symptoms. • To compare the safety of the combination of atomoxetine in doses up to 1.8 mg/kg/day and fluoxetine 20 mg/day with that of atomoxetine alone at doses up to 1.8 mg/kg/day. • To assess speed of onset of therapeutic effect in the setting of CYP2D6 rapid or poor metabolism as assessed by Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv).	
Study Design: This study comprised three active treatment groups and lasted approximately 12 weeks (approximately 6 weeks atomoxetine exposure). Patients entering the study who were already in treatment for an affective disorder or an anxiety disorder with a stable dose of fluoxetine between 10 mg/day and 40 mg/day entered an open-label combined fluoxetine/atomoxetine therapy. Patients who were not taking fluoxetine at the outset of the study were randomly assigned to a double-blind treatment arm and received either atomoxetine only or combined atomoxetine/fluoxetine therapy. After the treatment period (Study Period II), patients on double-blind therapy were randomly assigned to tapered or nontapered dosing in an approximate 2-week double-blind discontinuation period.	
Number of Patients: Planned: 80 already taking fluoxetine, 220 not already taking fluoxetine Randomized: 14 atomoxetine/fluoxetine open-label, 127 atomoxetine/fluoxetine double-blind, 46 atomoxetine/placebo double-blind Completed: 11 atomoxetine/fluoxetine open-label, 102 atomoxetine/fluoxetine double-blind, 36 atomoxetine/placebo double-blind	

Diagnosis and Main Criteria for Inclusion: Patients were at least 7 years but less than 18 years of age who met DSM-IV criteria for ADHD and had concurrent symptoms of depression or anxiety, or patients met DSM-IV criteria for an anxiety or depressive disorder and had concurrent symptoms of ADHD.
Test Product, Dose, and Mode of Administration: Atomoxetine capsules: Target dose of 1.2 mg/kg/day or 1.8 mg/kg/day given as a divided dose.
Duration of Treatment: Atomoxetine: Approximately 6 weeks Fluoxetine: Approximately 11 weeks
Reference Therapy, Dose, and Mode of Administration: Fluoxetine capsules 10 to 30 mg (for open-label group) and 20 mg (for double-blind group). Placebo capsules (for double-blind group).
Variables: Efficacy: The primary efficacy variable was the change from baseline to endpoint in the Clinical Global Impressions-Severity (CGI-S) rating score. Severity was rated on a 7-point scale with a higher score indicating greater severity of the ADHD, affective, and anxiety symptoms. The primary efficacy analysis was a test of the noninferiority of change in CGI-S in the atomoxetine plus placebo group compared with the atomoxetine plus fluoxetine group. Safety: Analysis of adverse events included the enrolled patients who received at least 1 dose of atomoxetine. Percentages of patients with treatment-emergent adverse events and treatment-emergent out-of-range laboratory analyte values were computed for each treatment group. Changes from baseline (last measurement on or before Visit 4) to endpoint in continuous laboratory values, electrocardiogram (ECG) intervals, and vital signs were computed by treatment group. Percentages of patients meeting categorical criteria for ECG intervals and vital signs were also computed. Pharmacokinetic: Blood samples for determination of plasma atomoxetine concentrations at trough and peak timepoints were obtained from each patient at Visit 8, at which time steady-state was achieved on either the 1.2 mg/kg/day or the 1.8 mg/kg/day atomoxetine treatment. To assess the relationship between atomoxetine plasma concentration and safety measures, the correlation between selected safety measures and plasma concentrations at Visit 8 were computed. In addition, a repeated measures model was utilized to assess any relationship between plasma concentration and safety variables.
Evaluation Methods: Statistical: Test for noninferiority: 1-sided 95% confidence interval from an analysis of variance (ANOVA) containing terms for treatment and investigational site. Fisher's exact test to compare the percentage of responders and other categorical variables, ANOVA to compare continuous data, and Wilcoxon signed-rank test to test for within-group changes. Other methods used included 2-sided 95% confidence intervals, Pearson correlation coefficient, and repeated-measures mixed model. Missing data were handled using a last-observation-carried-forward (LOCF) approach for change from baseline to endpoint analyses. Electrocardiogram QT Interval data were corrected using the following three methods: Bazett's correction method (QTcB; division of QT by RR 0.5), Fridericia's correction method (QTcF; division of QT by RR 0.33), and a data correction method proposed by Lilly (QTcD; division of QT by RR 0.39).
Summary: Patient Disposition: Four patients (2.1%) discontinued their participation in this study due to adverse events. These 4 patients were patients for whom no pharmacokinetic (PK) data were available, and they did not participate in the comparison of phenotypic poor metabolizer (PM) patients to phenotypic extensive metabolizer (EM) patients. One patient (0.5%) discontinued from the study due to adverse events (coded in the database as discontinued due to physician decision) prior to atomoxetine exposure.

A total of 148 patients were determined to be either phenotypic EM patients (N=97) or phenotypic PM patients (N=51). All patients for whom a phenotype was determined completed Study Period II. No serious adverse events occurred and no deaths were reported.

Patient Demographics: Table LYAQ.1 shows demographic and other patient characteristics for all randomized patients. Two hundred twenty (220) patients entered the study; of these, 187 were enrolled. Comorbid DSM-IV diagnoses were assessed using the Behavioral Disorder (including ADHD), Affective Disorder, Anxiety Disorder, and Post Traumatic Stress Disorder modules of the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL).

Efficacy: The primary efficacy variable was the change from baseline to endpoint in the CGI-S rating score. Baseline was defined as the last nonmissing measurement obtained on or prior to Visit 2. The primary efficacy analysis defined in the protocol was a test of the noninferiority of change in CGI-S in the atomoxetine plus placebo group compared with the atomoxetine plus fluoxetine group. As Table LYAQ.2 shows, both atomoxetine plus placebo and atomoxetine plus fluoxetine produced statistically significant reductions (improvements) from baseline to endpoint in the CGI-S rating score. Because the resulting lower limit of the confidence interval for the difference in change between the treatment groups was below an effect size of -0.45 (prospectively specified in the protocol), noninferiority between atomoxetine and atomoxetine plus fluoxetine was not supported.

Patients were considered responders if their endpoint CGI-S score was at most 2. Fourteen (14) patients (31.8%) in the atomoxetine plus placebo treatment group and 49 patients (43.4%) in the atomoxetine plus fluoxetine treatment group were responders. The treatment difference was not statistically significant ($p = 0.208$).

Comparisons of the results of the secondary measures between the atomoxetine plus placebo group and the atomoxetine plus fluoxetine group showed a similar pattern to the primary efficacy measure, with differences between the groups not reaching statistical significance (Table LYAQ.3).

Analysis of results comparing patients who did or did not meet plasma concentration criteria for PM status did not show any significant differences between EM and PM patients.

The results did not support the primary efficacy hypothesis of the study (that atomoxetine alone would be noninferior to atomoxetine plus fluoxetine in reducing overall symptoms).

Safety: The percentage of patients discontinuing the study due to an adverse event was 2.1%. Table LYAQ.4 summarizes treatment-emergent adverse events occurring in $\geq 5\%$ of all phenotypic PM versus phenotypic EM patients and Table LYAQ.5 summarizes treatment-emergent adverse events occurring with $\geq 5\%$ incidence in all enrolled patients who received at least 1 dose of atomoxetine by treatment group. No statistically significant differences between the double-blind groups were detected.

Table LYAQ.6 summarizes data for laboratory analytes for which statistically significant differences were detected in the comparison of phenotypic PM to phenotypic EM patients. Data for all comparisons are shown, with those for which a statistically significant difference was found being indicated in bold.

Table LYAQ.7 provides a summary for laboratory analytes for which a statistically significant by-treatment-group difference was detected in the double-blind portion of the study (indicated in table in bold text). P-values for comparisons between the double-blind atomoxetine plus placebo versus the double-blind atomoxetine plus fluoxetine group are shown. Values (mean change and percent low or high) for the open-label atomoxetine plus fluoxetine group are also shown, but without a statistical comparison. Neither comparison reveals a pattern of abnormalities suggestive of organ toxicity.

In the comparison of all phenotypic PM to all phenotypic EM patients (Table LYAQ.8), no statistically significant differences were noted regarding effects on vital signs. A comparison of the increase in mean systolic blood pressure between phenotypic PM patients (+4.65 mm Hg) and all phenotypic EM patients (+1.12 mm Hg) did not reach statistical significance ($p=.072$).

Table LYAQ.9 summarizes the mean change from baseline to endpoint in vital sign measures for Study Period II for phenotypic PM patients and phenotypic EM patients who received at least 1.2 mg/kg/day of atomoxetine and had both baseline and at least 1 postbaseline measurement. The difference in mean systolic blood pressure changes between phenotypic PM patients (+5.54 mm Hg) and phenotypic EM patients (+1.05 mm Hg) was statistically significant ($p=.037$).

Table LYAQ.10 provides a summary of vital sign changes for all enrolled patients by treatment groups along with p-values for within-group changes and p-values for the comparison between the treatment groups (double-blind atomoxetine versus double-blind atomoxetine plus fluoxetine, and double-blind atomoxetine plus fluoxetine versus open-label atomoxetine plus fluoxetine). The atomoxetine plus fluoxetine group experienced larger and statistically significant changes in diastolic blood pressure, pulse and weight compared to the atomoxetine plus placebo group.

Table LYAQ.11 provides a summary of the mean change from baseline to endpoint in ECG intervals and heart rate for Study Period II for all phenotypic PM and phenotypic EM patients who had both baseline and at least 1 postbaseline measurement. Table LYAQ.12 summarizes the mean change from baseline to endpoint in ECG intervals and heart rate for Study Period II for all phenotypic PM and phenotypic EM patients who received at least 1.2 mg/kg/day of atomoxetine and who had both baseline and at least 1 postbaseline measurement. Atomoxetine was associated with increased heart rate in all groups. Changes in the QTcD interval were not statistically significant for either EM or PM patients, nor were there statistically significant differences between treatment groups. As Table LYAQ.13 shows, however, there was an increase in QTcD for the combined group of all patients coadministered fluoxetine compared to the atomoxetine plus placebo group. Among the patients who were coadministered fluoxetine and atomoxetine, there was no difference in mean change in QTcD among those who were phenotypic EM patients and those who were phenotypic PM patients (+5.63 msec, +3.12 msec, respectively, $p=.24$), and there was no relationship between plasma atomoxetine concentrations and change in QTcD (slope = -0.0008 , $p=.699$; Figure LYAQ.1). No effect on QTcD was seen among patients who were administered atomoxetine only.

Pharmacokinetic: Forty-six (46) of 112 genotypic EM patients (41%) with plasma atomoxetine concentration data were considered phenotypic PMs when coadministered fluoxetine because their peak plasma atomoxetine concentration was within (or greater than) 2 standard deviations of the mean expected plasma atomoxetine concentration for PM patients. Of the patients who were considered phenotypic PMs, 36 patients achieved doses equal or greater than 1.2 mg/kg/day. Figure LYAQ.2 shows peak plasma concentration data for patients who received atomoxetine plus fluoxetine. Figure LYAQ.3 shows peak plasma concentration data for patients who received atomoxetine only. These 2 figures also show a line representing the mean minus 2 standard deviations for genotypic PM patients. These figures illustrate the increase in atomoxetine concentration observed with coadministration of fluoxetine. Also shown on these graphs are the 5 genotypic PM patients who participated in this study and their plasma concentration data.

Table LYAQ.14 and Table LYAQ.15 summarize the correlation between actual atomoxetine plasma concentration and ECG measurements at Visit 8 (or Visit 9) for patients who received atomoxetine plus fluoxetine and patients who received atomoxetine only. There was a statistically significant correlation between Bazett-corrected QT interval and atomoxetine trough plasma concentration for patients on atomoxetine plus fluoxetine. There were no statistically significant correlations between QTc values using data or Fridericia correction methods and atomoxetine plasma concentrations for patients on either treatment. Results from the repeated measures model indicated that there was no statistically significant relationship between the QTcD interval and plasma atomoxetine concentrations (slope= 0.0005 , $p=.716$).

**Table LYAQ.1. Summary of Demographics and Other Patient Characteristics
All Randomized Patients**

Variable	OL_ATXFL (N=14)	DB_ATXFL (N=127)	DB_ATXPL (N=46)	Total (N=187)
Sex: No. (%)				
No. Patients	14	127	46	187
Female	5 (35.7)	32 (25.2)	16 (34.8)	53 (28.3)
Male	9 (64.3)	95 (74.8)	30 (65.2)	134 (71.7)
Origin: No. (%)				
No. Patients	14	127	46	187
African Descent	1 (7.1)	6 (4.7)	6 (13.0)	13 (7.0)
Caucasian	12 (85.7)	106 (83.5)	39 (84.8)	157 (84.0)
East/Southeast A	0	1 (0.8)	0	1 (0.5)
Hispanic	0	6 (4.7)	1 (2.2)	7 (3.7)
Other	1 (7.1)	8 (6.3)	0	9 (4.8)
Age: yrs.				
No. Patients	14	127	46	187
Mean	12.18	11.20	11.59	11.37
Median	11.74	10.88	11.38	11.02
Standard Dev.	2.20	2.69	2.39	2.59
Minimum	9.29	7.01	7.26	7.01
Maximum	16.83	17.81	17.80	17.81
CYP2D6				
No. Patients	14	127	46	187
EXTN	13 (92.9)	125 (98.4)	42 (95.5)	180 (97.3)
SLOW	1 (7.1)	2 (1.6)	2 (4.5)	5 (2.7)
Unspecified	0	0	2	2
Height: cm				
No. Patients	14	127	46	187
Mean	154.95	145.55	145.91	146.34
Median	154.75	144.00	143.25	144.50
Standard Dev.	12.14	15.31	15.30	15.22
Minimum	133.50	116.30	123.00	116.30
Maximum	176.30	192.00	183.00	192.00
Weight: kg				
No. Patients	14	126	46	186
Mean	51.07	42.05	40.11	42.25
Median	51.30	39.60	37.70	39.60
Standard Dev.	13.20	14.14	11.85	13.74
Minimum	27.20	21.80	24.10	21.80
Maximum	69.00	82.20	69.00	82.20
Unspecified	0	1	0	1
DSM-IV ADHD Subtype				
No. Patients	14	127	46	187
HYP/IMP	0	5 (4.0)	0	5 (2.7)
INATTN	4 (28.6)	33 (26.2)	7 (15.2)	44 (23.7)
MIXED	10 (71.4)	88 (69.8)	39 (84.8)	137 (73.7)
Unspecified	0	1	0	1
Family History-ADHD-Mother				
No. Patients	14	127	46	187
N	8 (57.1)	93 (74.4)	25 (54.3)	126 (68.1)
U	2 (14.3)	8 (6.4)	11 (23.9)	21 (11.4)
Y	4 (28.6)	24 (19.2)	10 (21.7)	38 (20.5)
Unspecified	0	2	0	2

(continued)

Table LYAQ.1. Summary of Demographics and Other Patient Characteristics
All Randomized Patients (continued)

Variable	OL_ATXFL (N=14)	DB_ATXFL (N=127)	DB_ATXPL (N=46)	Total (N=187)
Family History-ADHD-Father				
No. Patients	14	127	46	187
N	8 (57.1)	73 (58.4)	20 (43.5)	101 (54.6)
U	3 (21.4)	15 (12.0)	13 (28.3)	31 (16.8)
Y	3 (21.4)	37 (29.6)	13 (28.3)	53 (28.6)
Unspecified	0	2	0	2
Family History-ADHD-Grandparents				
No. Patients	14	127	46	187
N	10 (71.4)	96 (76.8)	29 (63.0)	135 (73.0)
U	4 (28.6)	16 (12.8)	14 (30.4)	34 (18.4)
Y	0	13 (10.4)	3 (6.5)	16 (8.6)
Unspecified	0	2	0	2
Family History-ADHD-Siblings				
No. Patients	14	127	46	187
N	6 (42.9)	78 (62.4)	20 (43.5)	104 (56.2)
N/A	0	7 (5.6)	1 (2.2)	8 (4.3)
U	1 (7.1)	4 (3.2)	11 (23.9)	16 (8.6)
Y	7 (50.0)	36 (28.8)	14 (30.4)	57 (30.8)
Unspecified	0	2	0	2
Family History-Anxiety-Mother				
No. Patients	14	127	46	187
N	9 (64.3)	76 (60.8)	28 (60.9)	113 (61.1)
U	2 (14.3)	7 (5.6)	9 (19.6)	18 (9.7)
Y	3 (21.4)	42 (33.6)	9 (19.6)	54 (29.2)
Unspecified	0	2	0	2
Family History-Anxiety-Father				
No. Patients	14	127	46	187
N	12 (85.7)	90 (72.0)	30 (65.2)	132 (71.4)
U	2 (14.3)	15 (12.0)	10 (21.7)	27 (14.6)
Y	0	20 (16.0)	6 (13.0)	26 (14.1)
Unspecified	0	2	0	2
Family History-Anxiety-Grandparents				
No. Patients	14	127	46	187
N	8 (57.1)	87 (69.6)	26 (56.5)	121 (65.4)
U	2 (14.3)	10 (8.0)	10 (21.7)	22 (11.9)
Y	4 (28.6)	28 (22.4)	10 (21.7)	42 (22.7)
Unspecified	0	2	0	2
Family History-Anxiety-Siblings				
No. Patients	14	127	46	187
N	9 (64.3)	94 (75.2)	33 (71.7)	136 (73.5)
N/A	0	7 (5.6)	1 (2.2)	8 (4.3)
U	2 (14.3)	8 (6.4)	6 (13.0)	16 (8.6)
Y	3 (21.4)	16 (12.8)	6 (13.0)	25 (13.5)
Unspecified	0	2	0	2
Family History-Affective-Mother				
No. Patients	14	127	46	187
N	7 (50.0)	69 (55.2)	24 (52.2)	100 (54.1)
U	2 (14.3)	9 (7.2)	6 (13.0)	17 (9.2)
Y	5 (35.7)	47 (37.6)	16 (34.8)	68 (36.8)
Unspecified	0	2	0	2

(continued)

Table LYAQ.1. Summary of Demographics and Other Patient Characteristics
All Randomized Patients (concluded)

Variable	OL_ATXFL (N=14)	DB_ATXFL (N=127)	DB_ATXPL (N=46)	Total (N=187)
Family History-Affective-Father				
No. Patients	14	127	46	187
N	10 (71.4)	82 (65.6)	31 (67.4)	123 (66.5)
U	2 (14.3)	15 (12.0)	9 (19.6)	26 (14.1)
Y	2 (14.3)	28 (22.4)	6 (13.0)	36 (19.5)
Unspecified	0	2	0	2
Family History-Affective-Grandparents				
No. Patients	14	127	46	187
N	7 (50.0)	67 (53.6)	27 (58.7)	101 (54.6)
U	3 (21.4)	12 (9.6)	9 (19.6)	24 (13.0)
Y	4 (28.6)	46 (36.8)	10 (21.7)	60 (32.4)
Unspecified	0	2	0	2
Family History-Affective-Siblings				
No. Patients	14	127	46	187
N	10 (71.4)	92 (73.6)	31 (67.4)	133 (71.9)
N/A	0	7 (5.6)	1 (2.2)	8 (4.3)
U	1 (7.1)	6 (4.8)	8 (17.4)	15 (8.1)
Y	3 (21.4)	20 (16.0)	6 (13.0)	29 (15.7)
Unspecified	0	2	0	2
Prior Stimulant Exposure				
No. Patients	14	127	46	187
N	4 (28.6)	38 (30.2)	13 (28.3)	55 (29.6)
Y	10 (71.4)	88 (69.8)	33 (71.7)	131 (70.4)
Unspecified	0	1	0	1
Grade in School				
No. Patients	14	127	46	187
1	0	7 (5.5)	2 (4.3)	9 (4.8)
10	1 (7.1)	5 (3.9)	1 (2.2)	7 (3.7)
11	0	2 (1.6)	2 (4.3)	4 (2.1)
12	0	2 (1.6)	0	2 (1.1)
2	0	19 (15.0)	2 (4.3)	21 (11.2)
3	2 (14.3)	16 (12.6)	8 (17.4)	26 (13.9)
4	2 (14.3)	16 (12.6)	7 (15.2)	25 (13.4)
5	4 (28.6)	17 (13.4)	6 (13.0)	27 (14.4)
6	1 (7.1)	17 (13.4)	7 (15.2)	25 (13.4)
7	2 (14.3)	10 (7.9)	7 (15.2)	19 (10.2)
8	1 (7.1)	14 (11.0)	3 (6.5)	18 (9.6)
9	1 (7.1)	2 (1.6)	1 (2.2)	4 (2.1)

U = Unknown

Population: All Enrolled Patients.

Double Blind or Open Label

Visits 1-11

Atomoxetine hydrochloride

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**Table LYAQ.2. Clinical Global Impressions-Severity Score
Primary Efficacy Analysis
Change from Baseline to Endpoint
Double-Blind Atomoxetine versus Atomoxetine-plus-Fluoxetine
Study Period II**

Treatment Group	n	Baseline		Endpoint		Change		p-Value (a)	p-value (b)
		Mean	SD	Mean	SD	Mean	SD		
Atomoxetine-Fluoxetine	113	5.1	0.8	2.8	1.1	-2.3	1.4	<.001	.065
Placebo-Atomoxetine	44	5.1	0.7	3.2	1.2	-1.9	1.3	<.001	----
Difference(1-sided 95% C.I.)					-0.41(-0.77 , ---)				
Mean Squared Error					1.47				
Effect size(1-sided 95% C.I.)					-0.33(-0.63 , ---)				

Abbreviations: C.I. = Confidence Interval; SD = standard deviation.

(a) p-Value is from Wilcoxon signed-rank test.

(b) Between treatment group p-Values are from mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with term for treatment and pooled investigator.

All qualified patients included.

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Table LYAQ.3. Summary of Secondary Efficacy Analyses
Change from Baseline to Endpoint on Total Scores
All Qualified Patients
Study Period II

Treatment Group	n	Baseline		Endpoint		Change		p-Value (a)	p-value (b)
		Mean	SD	Mean	SD	Mean	SD		
ADHDRS									
Atomoxetine-Fluoxetine	113	40.5	8.7	16.4	11.2	-24.0	13.6	<.001	.139
Placebo-Atomoxetine	44	41.5	8.4	21.0	12.5	-20.5	12.9	<.001	----
95% C.I.: (-8.23 , 1.16)									
CDI									
Atomoxetine-Fluoxetine	81	14.7	8.4	5.9	6.1	-8.8	8.1	<.001	.060
Placebo-Atomoxetine	33	14.4	10.9	9.0	8.1	-5.4	10.0	<.001	----
95% C.I.: (-7.02 , 0.15)									
CDRS									
Atomoxetine-Fluoxetine	113	44.4	12.5	24.0	6.4	-20.4	13.6	<.001	.238
Placebo-Atomoxetine	44	43.9	11.1	26.3	7.9	-17.6	11.8	<.001	----
95% C.I.: (-7.37 , 1.85)									
GSAS									
Atomoxetine-Fluoxetine	112	21.8	5.1	9.2	5.3	-12.6	6.9	<.001	.245
Placebo-Atomoxetine	44	22.5	4.8	11.3	6.3	-11.3	6.8	<.001	----
95% C.I.: (-3.82 , 0.98)									

(continued)

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**Table LYAQ.3. Summary of Secondary Efficacy Analyses
Change from Baseline to Endpoint on Total Scores
All Qualified Patients
Study Period II (concluded)**

Treatment Group	n	Baseline		Endpoint		Change		p-Value (a)	p-value (b)
		-----		-----		-----			
		Mean	SD	Mean	SD	Mean	SD		

MASC									
Atomoxetine-Fluoxetine	109	48.1	19.5	34.7	17.2	-13.4	16.0	<.001	.512
Placebo-Atomoxetine	42	49.4	20.4	38.1	23.1	-11.3	19.0	<.001	----
95% C.I.: (-8.10 , 4.06)									

Abbreviations: ADHDRS = Attention Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:

Investigator Administered and Scored; CDI = Children's Depression Inventory;

CDRS = Children's Depression Rating Scale; GSAS = Global Severity Assessment of Affective, Anxiety and Attentional Symptoms; MASC = Multidimensional Anxiety Scale for Children.

(a) p-Value is from Wilcoxon signed-rank test.

(b) Between treatment group p-Values are from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator, treatment. All qualified patients included.

**Table LYAQ.4. Summary of Treatment-Emergent Adverse Events
with Incidence $\geq 5\%$ by Phenotype
Study Period II**

Event Classification	PHENO_PM (N=51)		PHENO_EM (N=97)		Total (N=148)		p-Value*
	n	(%)	n	(%)	n	(%)	
PATIENTS WITH ≥ 1 TESS	38	(74.5)	63	(64.9)	101	(68.2)	.269
PATIENTS WITH NO TESS	13	(25.5)	34	(35.1)	47	(31.8)	.269
ANOREXIA	13	(25.5)	11	(11.3)	24	(16.2)	.035
HEADACHE	4	(7.8)	16	(16.5)	20	(13.5)	.206
ASTHENIA	7	(13.7)	11	(11.3)	18	(12.2)	.792
INSOMNIA	9	(17.6)	9	(9.3)	18	(12.2)	.185
ABDOMINAL PAIN	6	(11.8)	8	(8.2)	14	(9.5)	.558
ACCIDENTAL INJURY	5	(9.8)	7	(7.2)	12	(8.1)	.752
SOMNOLENCE	7	(13.7)	4	(4.1)	11	(7.4)	.048
NAUSEA	5	(9.8)	5	(5.2)	10	(6.8)	.314
RASH	4	(7.8)	5	(5.2)	9	(6.1)	.496
RHINITIS	3	(5.9)	5	(5.2)	8	(5.4)	1.00
DYSPEPSIA	2	(3.9)	5	(5.2)	7	(4.7)	1.00
NERVOUSNESS	2	(3.9)	5	(5.2)	7	(4.7)	1.00
VOMITING	4	(7.8)	3	(3.1)	7	(4.7)	.234
ALLERGIC REACTION	1	(2.0)	5	(5.2)	6	(4.1)	.665
DIZZINESS	1	(2.0)	5	(5.2)	6	(4.1)	.665
PHARYNGITIS	3	(5.9)	3	(3.1)	6	(4.1)	.415
CHEST PAIN	3	(5.9)	1	(1.0)	4	(2.7)	.118
TREMOR	3	(5.9)	0		3	(2.0)	.039

Population: Phenotypic EMs AND Phenotypic PMs

Double Blind or Open Label

Baseline: Visits 1-4, Endpoint: Visits 5 - 9

* Frequencies are analyzed using a Fisher's Exact test.

**Table LYAQ.5. Summary of Treatment-Emergent Adverse Events
Incidence ≥5% by Treatment Group
Study Period II**

Event Classification	OL_ATXFL (N=14)		DB_ATXFL (N=115)		DB_ATXPL (N=44)		Total (N=173)	
	n	(%)	n	(%)	n	(%)	n	(%)
PATIENTS WITH ≥ 1 TESS	10	(71.4)	81	(70.4)	25	(56.8)	116	(67.1)
PATIENTS WITH NO TESS	4	(28.6)	34	(29.6)	19	(43.2)	57	(32.9)
ANOREXIA	1	(7.1)	23	(20.0)	3	(6.8)	27	(15.6)
HEADACHE	3	(21.4)	17	(14.8)	6	(13.6)	26	(15.0)
INSOMNIA	1	(7.1)	16	(13.9)	5	(11.4)	22	(12.7)
ASTHENIA	1	(7.1)	14	(12.2)	5	(11.4)	20	(11.6)
ABDOMINAL PAIN	2	(14.3)	13	(11.3)	3	(6.8)	18	(10.4)
ACCIDENTAL INJURY	0		9	(7.8)	3	(6.8)	12	(6.9)
SOMNOLENCE	0		11	(9.6)	1	(2.3)	12	(6.9)
NAUSEA	3	(21.4)	6	(5.2)	2	(4.5)	11	(6.4)
RHINITIS	1	(7.1)	8	(7.0)	2	(4.5)	11	(6.4)
RASH	1	(7.1)	7	(6.1)	1	(2.3)	9	(5.2)
NERVOUSNESS	1	(7.1)	5	(4.3)	2	(4.5)	8	(4.6)
VOMITING	1	(7.1)	7	(6.1)	0		8	(4.6)
DIZZINESS	1	(7.1)	3	(2.6)	3	(6.8)	7	(4.0)
DYSPEPSIA	0		6	(5.2)	1	(2.3)	7	(4.0)
PHARYNGITIS	2	(14.3)	2	(1.7)	3	(6.8)	7	(4.0)
ALLERGIC REACTION	0		3	(2.6)	3	(6.8)	6	(3.5)
COUGH INCREASED	1	(7.1)	4	(3.5)	0		5	(2.9)
CHEST PAIN	1	(7.1)	2	(1.7)	1	(2.3)	4	(2.3)
EMOTIONAL LABILITY	1	(7.1)	2	(1.7)	1	(2.3)	4	(2.3)
HYPERTENSION	1	(7.1)	3	(2.6)	0		4	(2.3)
INFECTION	1	(7.1)	2	(1.7)	1	(2.3)	4	(2.3)
TREMOR	1	(7.1)	3	(2.6)	0		4	(2.3)
AMBLYOPIA	1	(7.1)	2	(1.7)	0		3	(1.7)
TACHYCARDIA	2	(14.3)	1	(0.9)	0		3	(1.7)
APATHY	1	(7.1)	0		0		1	(0.6)
EYE PAIN	1	(7.1)	0		0		1	(0.6)
FLU SYNDROME	1	(7.1)	0		0		1	(0.6)
POSTURAL HYPOTENSION	1	(7.1)	0		0		1	(0.6)
TWITCHING	1	(7.1)	0		0		1	(0.6)

Population: All Enrolled Patients who received at least 1 dose of atomoxetine.
Double Blind or Open Label
Baseline: Visits 1-4, Endpoint: Visits 5 - 9

**Table LYAQ.6. Summary of Laboratory Data
Analytes With a Statistically Significant
Between-Group Difference,
Phenotypic PM Patients versus Phenotypic EM Patients
Study Period II**

	MEAN CHANGE TO ENDPOINT		PERCENT HIGH/LOW	
	Patients			
	All	High-dose	All	High-dose
GGT				
pPM	-1.42	-1.49	0/0	0/0
p-val	.028	.080	na/na	na/na
pEM	-0.10	-0.20	0/0	0/0
URIC ACID				
pPM	-17.2	-17.5	0/0	0/0
p-val	.042	.086	na/.552	na/.551
pEM	+1.66	+2.14	1.1/3.2	1.2/3.5
BILIRIBIN				
pPM	-0.97	-0.74	0/0	0/0
p-val	.002	.015	na/na	na/na
pEM	+1.71	+1.76	1.1/0	1.2/0
BICARBONATE				
pPM	+0.75	+1.14	0/2.0	0/2.6
p-val	.075	.014	na/1.0	na/.525
pEM	-0.26	-0.29	0/1.1	0/1.1

Note: p-values comparing PMs and EMs are based on an analysis of variance on ranks of change from baseline scores with terms for treatment and phenotype.
Abbreviations: EM = extensive metabolizer; GGT = gamma glutamyltransferase;
PM = poor metabolizer; pEM = phenotypic extensive metabolizer;
pPM = phenotypic poor metabolizer; p-val = p-value.

**Table LYAQ.7. Summary of Laboratory Data
 Analytes With a Statistically Significant
 Between Group Difference,
 Double Blind Phase, Study Period II**

	Mean Change to Endpoint	Percent Low/High
ALKPH (U/L)		
DB_ATXFL	-25.4	0/3.1
p-val	<.001	na/1.00
DB_ATXPL	-0.15	0/2.9
OL_ATXFL	-25.3	0/0
CPK (U/L)		
DB_ATXFL	+20.85	0/1.9
p-val	.463	na/.046
DB_ATXPL	+9.15	0/10.3
OL_ATXFL	-24.1	0/0
CHOL (mmol/L)		
DB_ATXFL	+0.09	0/5.0
p-val	.214	.001/.322
DB_ATXPL	-0.02	13.9/0
OL_ATXFL	+0.06	0/10.0

Abbreviations: ALT=alanine aminotransferase, ALKPH=alkaline phosphatase, CPK=creatine phosphokinase, CHOL=cholesterol
 p-val=p-value

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**Table LYAQ.8. Summary of Vital Signs
Change from Baseline to Endpoint
Phenotypic PM Patients versus Phenotypic EM Patients
Study Period II**

Measure	Subgroup	N	-----Baseline-----		-----Change-----		within p-value (a)	Subgroup p-value (b)
			Mean	SD	Mean	SD		
Diastolic BP	PM Patients	51	64.93	7.14	4.97	9.97	<.001	.917
	EM Patients	97	67.43	7.70	4.03	9.50	<.001	
Systolic BP	PM Patients	51	105.1	7.57	4.65	9.03	<.001	.072
	EM Patients	97	108.1	9.25	1.12	8.78	.179	
Pulse	PM Patients	51	78.34	11.06	13.19	10.22	<.001	.432
	EM Patients	97	80.73	11.71	11.10	13.21	<.001	
Weight (kg)	PM Patients	51	38.86	12.07	-1.10	1.35	<.001	.832
	EM Patients	97	45.36	14.42	-1.03	1.82	<.001	
Height (cm)	PM Patients	43	142.4	12.44	0.56	1.41	.003	.140
	EM Patients	81	149.5	17.09	1.12	1.75	<.001	
Temperature	PM Patients	51	36.50	0.49	-0.12	0.62	.203	.132
	EM Patients	97	36.52	0.46	-0.02	0.54	.982	

Abbreviations: BP = blood pressure; EM = extensive metabolizer; PM = poor metabolizer.

(a) Within group p-values are based on Wilcoxon's Signed Rank Test.

(b) Subgroup p-values comparing PMs and EMs are based on an ANOVA on change from baseline scores with terms for treatment and subgroup.

Population: Phenotypic PMs and EMs.

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**Table LYAQ.9. Summary of Vital Signs
Change from Baseline to Endpoint
Phenotypic PM Patients versus Phenotypic EM Patients
Who Received ≥ 1.2 mg/kg/day of Atomoxetine
Study Period II**

Measure	Subgroup	N	-----Baseline-----		-----Change-----		within p-value (a)	Subgroup p-value (b)
			Mean	SD	Mean	SD		
Diastolic BP	PM Patients	40	64.39	7.40	5.39	9.86	<.001	.815
	EM Patients	89	67.56	7.51	3.80	9.54	<.001	
Systolic BP	PM Patients	40	104.5	7.63	5.54	9.17	<.001	.037
	EM Patients	89	108.2	9.42	1.05	9.00	.221	
Pulse	PM Patients	40	78.99	11.27	12.26	9.92	<.001	.458
	EM Patients	89	80.76	11.77	10.17	12.79	<.001	
Weight (kg)	PM Patients	40	38.02	11.44	-0.94	1.18	<.001	.485
	EM Patients	89	44.70	14.26	-1.00	1.87	<.001	
Height (cm)	PM Patients	36	141.4	11.87	0.53	1.49	.019	.147
	EM Patients	73	149.0	17.55	1.13	1.80	<.001	
Temperature	PM Patients	40	36.49	0.52	-0.18	0.65	.111	.081
	EM Patients	89	36.51	0.45	-0.03	0.54	.865	

Abbreviations: BP = blood pressure; EM = extensive metabolizer; PM = poor metabolizer.

(a) Within group p-values are based on Wilcoxon's Signed Rank Test.

(b) Subgroup p-values comparing PMs and EMs are based on an ANOVA on change from baseline scores with terms for treatment and subgroup.

Population: Phenotypic PMs and EMs who received at least 1.2 mg/kg/day.

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**Table LYAQ.10. Summary of Vital Signs
Change from Baseline to Endpoint
All Enrolled Patients
By Treatment Group**

Measure	Subgroup	N	-----Baseline-----		-----Change-----		within p-value (a)	Between p-value (b)	Between p-value (c)
			Mean	SD	Mean	SD			
Diastolic BP	DB Atx+Flx	114	66.56	7.79	5.16	9.44	<.001	.008	.682
	DB Atx+Pla	44	67.41	7.56	0.30	9.09	.726		
	OL Atx+Flx	14	66.25	8.36	4.18	12.10	.281		
Systolic BP	DB Atx+Flx	114	107.0	8.75	3.07	8.90	<.001	.070	.572
	DB Atx+Pla	44	106.7	8.08	-0.14	9.33	.975		
	OL Atx+Flx	14	108.4	7.67	3.11	7.96	.211		
Pulse	DB Atx+Flx	114	79.66	11.04	11.88	11.25	<.001	.008	.577
	DB Atx+Pla	44	81.90	11.83	6.48	15.46	.015		
	OL Atx+Flx	14	78.71	12.89	17.07	11.85	<.001		
Weight (kg)	DB Atx+Flx	114	42.21	14.27	-1.05	1.70	<.001	.009	.883
	DB Atx+Pla	44	41.34	12.42	-0.38	1.27	.049		
	OL Atx+Flx	14	52.16	13.35	-1.74	1.25	<.001		
Height (cm)	DB Atx+Flx	92	146.5	16.28	0.79	1.37	<.001	.086	.605
	DB Atx+Pla	34	145.8	17.02	1.22	2.24	<.001		
	OL Atx+Flx	10	153.3	13.06	0.92	1.50	.172		
Temperature	DB Atx+Flx	114	36.51	0.45	-0.04	0.54	.622	.147	.173
	DB Atx+Pla	44	36.63	0.47	-0.20	0.59	.014		
	OL Atx+Flx	14	36.25	0.46	0.17	0.52	.238		

Abbreviations: BP = blood pressure; DB Atx+Flx = double-blind atomoxetine plus fluoxetine;

DB Atx+Pla = double-blind atomoxetine plus placebo; OL Atx+Flx = open-label atomoxetine plus fluoxetine.

(a) Within group p-values are based on Wilcoxon's Signed Rank Test.

(b,c) Between treatment group p-values are based on an ANOVA on change from baseline scores with terms for investigator and treatment. P-value(b) is for comparison between double-blinded atomox.+fluox. and atomox.+placebo.

P-value(c) is for comparison between double-blinded and open-label atomox.+fluox.

Population: enrolled patients with both baseline and at least one post-baseline measurement.

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Table LYAQ.11. Summary of ECG Data
Change from Baseline to Endpoint
All Phenotypic PM Patients versus Phenotypic EM Patients
Study Period II

Measure	Subgroup	N	-----Baseline-----		-----Change-----		within p-value (a)	Subgroup p-value (b)
			Mean	SD	Mean	SD		
PR Interval	PM Patients	51	132.6	18.35	-4.24	9.24	.003	.577
	EM Patients	97	134.1	16.42	-6.10	10.02	<.001	
QRS Interval	PM Patients	51	84.63	8.99	1.88	7.35	.089	.866
	EM Patients	97	85.77	8.33	1.53	5.70	.005	
QT Interval	PM Patients	51	381.7	26.88	-21.0	23.86	<.001	.148
	EM Patients	97	376.0	25.63	-13.6	20.93	<.001	
QTcB	PM Patients	51	419.0	17.13	10.25	17.44	<.001	.610
	EM Patients	97	417.1	15.15	7.46	16.66	<.001	
QTcF	PM Patients	51	406.2	14.04	-1.14	12.64	.598	.163
	EM Patients	97	403.0	14.63	-0.21	12.27	.957	
QTcD	PM Patients	51	410.6	14.06	2.62	13.27	.168	.263
	EM Patients	97	407.8	14.09	2.33	12.97	.060	
Heart Rate	PM Patients	51	73.69	12.60	13.04	13.68	<.001	.361
	EM Patients	97	74.98	10.55	8.78	11.95	<.001	

Abbreviations: EM = extensive metabolizer; PM = poor metabolizer; QTcB = QT interval Bazett correction; QTcD = QT interval data correction; QTcF = QT interval Fridericia correction.

(a) Within group p-values are based on Wilcoxon's Signed Rank Test.

(b) Subgroup p-values comparing PMs and EMs are based on an ANOVA on change from baseline scores with terms for treatment and subgroup.

Population: Phenotypic PM and EM patients.

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**Table LYAQ.12. Summary of ECG Data
Change from Baseline to Endpoint
Phenotypic PM Patients versus Phenotypic EM Patients
Who Received ≥ 1.2 mg/kg/day of Atomoxetine
Study Period II**

Measure	Subgroup	N	-----Baseline-----		-----Change-----		within p-value (a)	Subgroup p-value (b)
			Mean	SD	Mean	SD		
PR Interval	PM Patients	40	132.5	18.63	-4.40	9.62	.007	.817
	EM Patients	89	134.2	16.77	-5.89	9.84	<.001	
QRS Interval	PM Patients	40	84.30	9.17	2.10	7.79	.116	.925
	EM Patients	89	85.75	8.53	1.48	5.70	.008	
QT Interval	PM Patients	40	379.6	28.08	-20.4	25.75	<.001	.309
	EM Patients	89	376.1	26.44	-13.8	21.25	<.001	
QTcB	PM Patients	40	420.0	18.50	10.03	18.13	.002	.782
	EM Patients	89	417.0	15.33	6.72	17.01	<.001	
QTcF	PM Patients	40	406.1	15.28	-1.04	12.76	.731	.359
	EM Patients	89	403.0	14.90	-0.76	12.56	.653	
QTcD	PM Patients	40	410.9	15.36	2.65	13.44	.182	.484
	EM Patients	89	407.9	14.30	1.72	13.27	.208	
Heart Rate	PM Patients	40	74.95	13.14	12.88	14.90	<.001	.429
	EM Patients	89	74.97	10.85	8.54	12.11	<.001	

Abbreviations: EM = extensive metabolizer; PM = poor metabolizer; QTcB = QT interval Bazett correction; QTcD = QT interval data correction; QTcF = QT interval Fridericia correction.

(a) Within group p-values are based on Wilcoxon's Signed Rank Test.

(b) Subgroup p-values comparing PMs and EMs are based on an ANOVA on change from baseline scores with terms for treatment and subgroup.

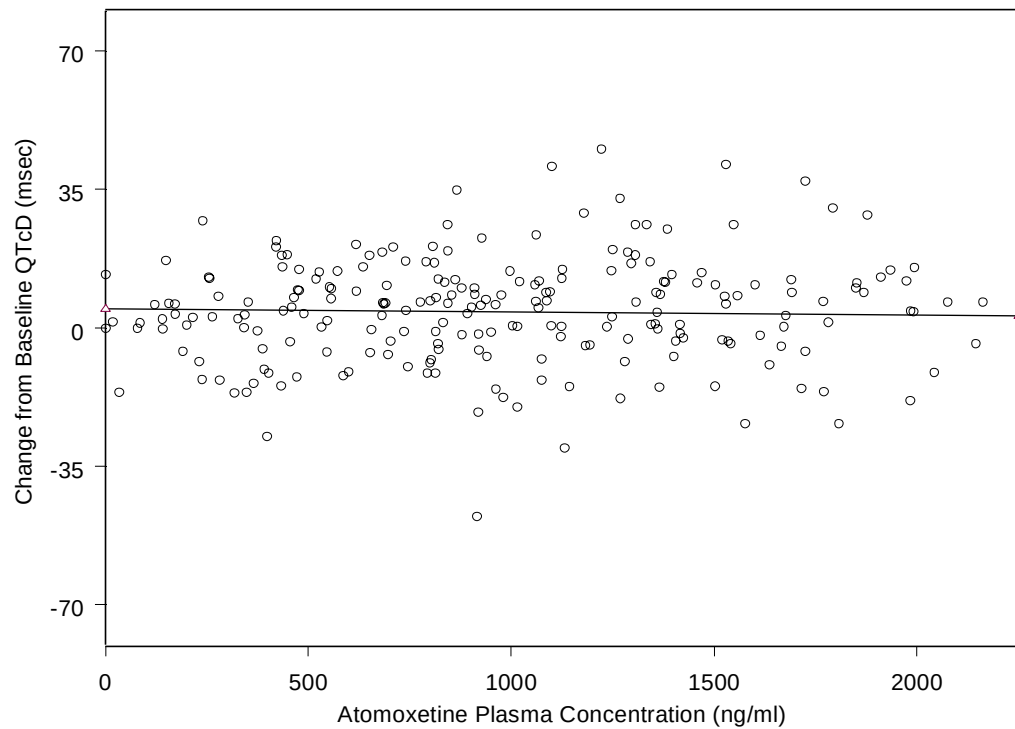
Population: Phenotypic PMs and EMs.

Table LYAQ.13. **Mean Change in QTcD**
During Atomoxetine Treatment in Different Groups
B4Z-MC-LYAQ

Group	Mean Δ QTcD in msec (SD)	p-value
All Patients administered atomoxetine and either fluoxetine or placebo		
Atomoxetine + Placebo (n=41)	-3.36 (12.7)	p<.001
Atomoxetine + Fluoxetine (n=125)	+4.64 (12.5)	
EM and PM Patients co-administered fluoxetine and atomoxetine		
Fluoxetine+Atomoxetine; Phenotypic EM Patients (n=76)	5.63 (11.97)	p=.235
Fluoxetine+Atomoxetine; Phenotypic PM Patients (n=49 ^a)	3.12 (13.25)	

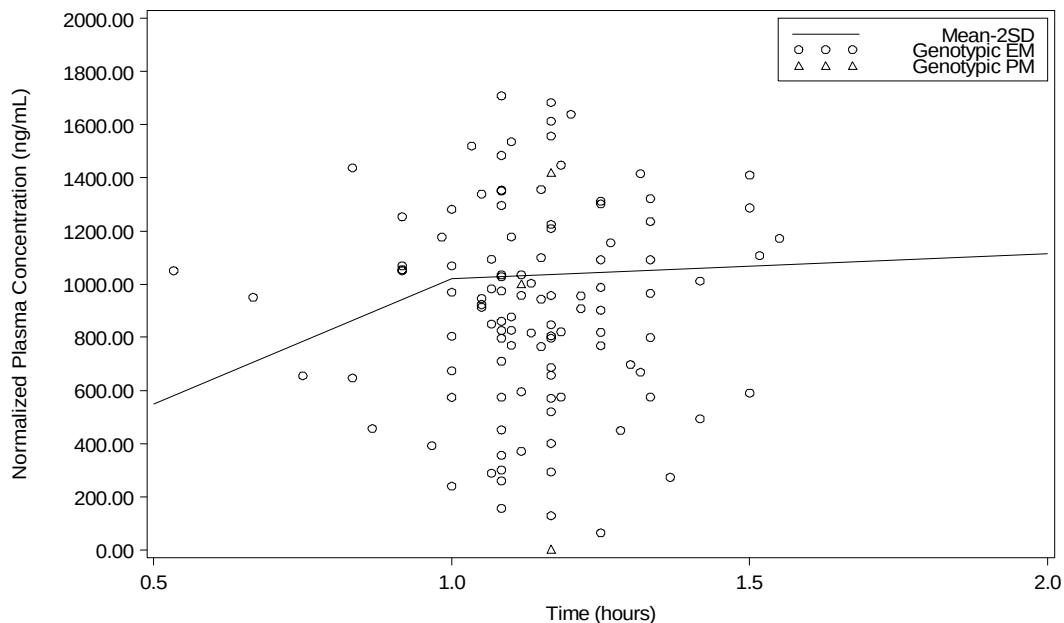
^a Only PM patients converted genotypic EM status by fluoxetine

Abbreviations: EM=extensive metabolizer; n = number of patients; PM=poor metabolizer;
QTcD=data-corrected QT interval; SD = standard deviation.



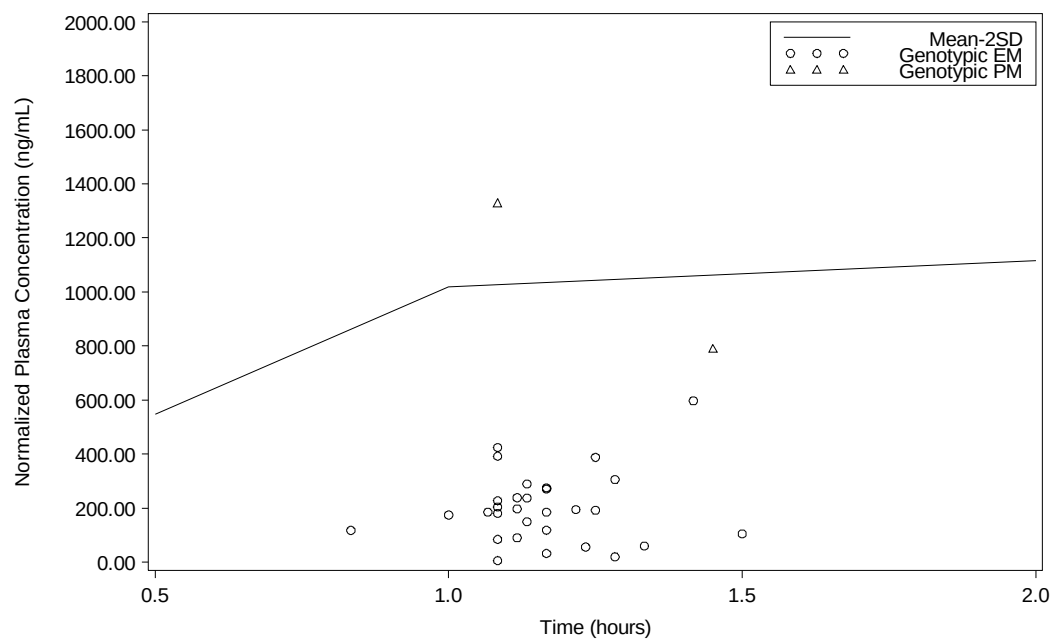
Fitted line is a least square line from a regression model with effects for baseline and plasma concentration

Figure LYAQ.1. Change from data-corrected QT (QTcD) interval by plasma atomoxetine concentration, patients taking fluoxetine and atomoxetine.



Plasma concentrations were normalized to a 1.2 mg/kg/day dose.
 Mean - 2SD was based on data from genotypic PM adult subjects from previous studies.

Figure LYAQ.2. Peak atomoxetine plasma concentration data, for patients who received atomoxetine plus fluoxetine.



Plasma concentrations were normalized to a 1.2 mg/kg/day dose.
Mean - 2SD was based on data from genotypic PM adult subjects from previous studies.

Figure LYAQ.3. Peak atomoxetine plasma concentration data, for patients who received atomoxetine only.

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Table LYAQ.14. Summary of Correlation between Atomoxetine Plasma Concentration (Peak and Trough) and ECG Measurements at Visit 8 Patients who Received Atomoxetine Plus Fluoxetine

Visit	A	B	Sample Time	Sample Size (n)	Correlation Coefficient between A & B	p-value*
8/9	Atomoxetine plasma Concentration	Change of QTcB	Peak	115	-0.1	.312
		Change of QTcD		115	-0.07	.473
		Change of QTcF		115	-0.04	.636
		Change of QTcB	Trough	116	.227	.014
		Change in QTcD		116	.156	.095
		Change in QTcF		116	.093	.318

Abbreviations: n=number of patients with a baseline and at least one postbaseline measurement;

QTcB = QT Interval Bazett Correction; QTcD = QT Interval Data Correction; QTcF = QT Interval Fridericia Correction.
Baseline: Visit 1-4, Endpoint: Visit 5-9.

* p-value is the significance probability of the correlation and is calculated based on a test for nonzero Pearson Correlation Coefficient.

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Table LYAQ.15. Summary of Correlation between Atomoxetine Plasma Concentration (Peak and Trough) and ECG Measurements at Visit 8 Patients who Received Atomoxetine Only

Visit	A	B	Sample Time	Sample Size (n)	Correlation Coefficient between A & B	p-value*
8/9	Atomoxetine plasma Concentration	Change of QTcB	Peak	33	.093	.607
		Change of QTcD		33	-0.04	.816
		Change of QTcF		33	-0.13	.467
		Change of QTcB	Trough	35	-0.13	.440
		Change in QTcD		35	-0.17	.330
		Change in QTcF		35	-0.18	.305

Abbreviations: n=number of patients with a baseline and at least one postbaseline measurement;

QTcB = QT Interval Bazett Correction; QTcD = QT Interval Data Correction; QTcF = QT Interval Fridericia Correction.
Baseline: Visit 1-4, Endpoint: Visit 5-9.

* p-value is the significance probability of the correlation and is calculated based on a test for nonzero Pearson Correlation Coefficient.

Summary ID# 4671

Clinical Study Summary: Study B4Z-MC-LYAR

Long-Term, Open-Label Safety Study of Atomoxetine Hydrochloride in Adult Outpatients with DSM-IV Attention-Deficit/Hyperactivity Disorder

Date summary approved by Lilly: 19 June 2006

Brief Summary of Results

The primary objective of this study was to assess the long-term safety and tolerability of treatment with atomoxetine in adult outpatients with ADHD who were enrolled in a previous atomoxetine study. A total of 385 patients entered Study B4Z-MC-LYAR (LYAR) after completing one of two acute, placebo-controlled atomoxetine trials conducted in adults (B4Z-MC-LYAA [Summary ID# 2556], B4Z-MC-LYAO [Summary ID# 4642]). Of this total, 384 patients were enrolled, 383 took at least one dose of study drug, and 69 (18%) completed the study.

Safety evaluations were based on treatment-emergent adverse events (TEAEs); discontinuations due to adverse events (AEs); and analyses of laboratory data, vital signs, and electrocardiograms (ECGs). No deaths were reported in this study. Of the 383 enrolled patients who took at least one dose of study drug, 16 (4.2%) patients reported a serious adverse event (SAE). Three of the 16 patients who reported an SAE discontinued from the study due to the event. Of the 383 patients who took at least one dose of study drug, a total of 47 (12.3%) patients discontinued treatment because of an AE. The most frequently reported AEs that led to study discontinuation were erectile dysfunction (n=5), depression (n=4), and constipation (n=3).

Efficacy was a secondary objective of this open-label study. The primary efficacy measure was the Conners' Adult ADHD Rating Scale-Investigator Rated:Screening Version (CAARS-Inv:SV) ADHD Symptom score. A statistically significant ($p<.001$) mean score reduction from baseline to LOCF endpoint was shown on the CAARS-Inv:SV Total ADHD Symptom score. All three subscale scores also showed statistically significant symptom improvement in mean change from baseline to endpoint.

Analyses of health outcome measures from the Sheehan Disability Scale showed statistically significant mean reduction in disruption of the respective areas of life. No statistically significant change from baseline to endpoint was shown on the Psychological General Well-Being Schedule (PGWBS) Total score. There was a statistically significant improvement in mean change from baseline to LOCF endpoint on several of the PGWBS subscale scores.

Results of the Arizona Sexual (Experiences) Scale, Male and Female versions (ASEX) Total score mean change from baseline to endpoint for males showed a statistically significant increase in sexual dysfunction. A statistically significant change was not observed for females.

Title of Study: Long-Term, Open-Label Safety Study of Atomoxetine Hydrochloride in Adult Outpatients with DSM-IV Attention-Deficit/Hyperactivity Disorder	
Investigator(s): This multicenter study included 31 principal investigators.	
Study Center(s): This study was conducted at 31 study centers in two countries.	
Length of Study 4 years, 5 months. Date of first patient enrolled: 15 November 2000. Date of last patient: 19 April 2005.	Phase of Development: 3
Objectives: The primary objective of this open-label extension study was to assess long-term safety and tolerability in adult outpatients who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for Attention-Deficit/Hyperactivity Disorder (ADHD), and who had been enrolled in a previous atomoxetine study. The secondary objective was to assess efficacy during long-term therapy, as measured by the Conners' Adult ADHD Rating Scale-Investigator Rated:Screening Version (CAARS-Inv:SV).	
Study Design: Study B4Z-MC-LYAR (LYAR) was a Phase 3, adult outpatient, open-label study of atomoxetine.	
Number of Patients: Planned: Up to 600 patients. Entered: 385. Enrolled: 384 atomoxetine. Completed: 69 atomoxetine.	
Diagnosis and Main Criteria for Inclusion: Patients who were at least 18 years of age at Visit 1, who met the DSM-IV diagnostic criteria for adult ADHD and the criteria for a historical diagnosis of ADHD during childhood, and who participated in a previous atomoxetine study within 30 days of entry into Study LYAR. Diagnostic criteria were assessed by the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAAR-D) and Structured Clinical Interview for DSM-IV Axis Disorder-Modified (SCID).	
Test Product, Dose, and Mode of Administration: Atomoxetine: beginning at 25 mg twice a day (BID) and adjusted up or down by one dose level to any of three dosages: 50 mg once daily or 25 mg BID; 80 mg once daily or 40 mg BID; or 120 mg once daily or 60 mg BID. Dose was based on changes in symptoms or tolerability. Atomoxetine was administered as hydrochloride salt, with doses expressed as atomoxetine free base in capsules supplied in blister cards and/or bottles.	
Reference Therapy, Dose, and Mode of Administration: None.	
Duration of Treatment: Planned: Approximately 3 years.	

Variables:

Efficacy: Efficacy was a secondary objective in this study. The 18-item CAARS-Inv:SV Total ADHD Symptom score (the sum of the inattention and hyperactivity/impulsivity subscales) was considered the primary efficacy measure, while the other subscale scores and symptom counts were considered secondary efficacy measures. The Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity (CGI-ADHD-S) was also administered as a secondary efficacy variable. Efficacy was determined by mean changes from baseline to endpoint in the efficacy variables.

Safety: Long-term safety and tolerability assessment was the primary objective of this study. Variables included treatment-emergent adverse events (TEAEs), discontinuations due to TEAEs, vital signs, laboratory analytes, and electrocardiograms (ECGs).

Health Outcomes: Change from baseline to endpoint on the following measures: Arizona Sexual (Experiences) Scale, Male and Female versions (ASEX); Psychological General Well-Being Schedule (PGWBS); and Sheehan Disability Scale.

Methods:

Statistical: Change from baseline to endpoint was computed, with baseline defined as Visit 1 and endpoint defined as the last nonmissing measurement following Visit 1, for the total and subscale scores of the primary and secondary efficacy measures. Summary statistics were computed on change scores and included the mean, standard deviation, and 2-sided 95% confidence interval. Change from baseline to endpoint scores for laboratory data, vital signs, and ECG intervals were computed. The Wilcoxon signed-rank test assessed whether mean change was significantly different from zero.

Results:

Patient Demographics

Table LYAR.1 summarizes the demographics and other patient characteristics for all enrolled patients from Visit 1 through the end of the study. The majority of patients were male (64.1%), Caucasian (92.2%), and had not used stimulants previously (53.1%). The mean age was 42.4 years (SD 11.2). The most common ADHD diagnosis was the Combined subtype (67.7%), followed by the Predominantly Inattentive subtype (30.5%).

**Table LYAR.1. Summary of Demographics and
Other Patient Characteristics
All Enrolled Patients**

Patient Characteristics Overall ADHD Analysis Group	
Atomoxetine N=384 n (%)	
Gender:	
Female	138 (35.9%)
Male	246 (64.1%)
Origin:	
African Descent	8 (2.1%)
Western Asian	2 (0.5%)
Caucasian	354 (92.2%)
East/Southeast	4 (1.0%)
Hispanic	14 (3.6%)
Other	2 (0.5%)
Age:	
Mean	42.4
Median	42.6
Std.	11.2
CYP2D6 Genotype:	
EXTN	361 (94.0%)
SLOW	23 (6.0%)
Subtype	
MIXED	260 (67.7%)
HYP/IMP	7 (1.8%)
INATTV	117 (30.5%)
Prior Stimulant Exposure	
N	204 (53.1%)
Y	180 (46.9%)

Population: All enrolled patients

Abbreviations: EXTN=extensive, Std= standard deviation,

Patient Disposition

Table LYAR.2 summarizes patient disposition and the primary reasons for study discontinuation for all entered patients. A total of 385 patients entered Study LYAR after completing treatment with either atomoxetine or placebo in 1 of the 2 acute, placebo-controlled trials conducted in adults (Study B4Z-MC-LYAO or Study B4Z-MC-LYAA). Of this total, 384 patients were enrolled, 383 took at least one dose of study drug, and 69 (18%) completed the study. A high discontinuation rate was seen in Study LYAR due in part to the study design. Study LYAR was designed to assess the safety of atomoxetine in patients who were defined as responders. At the end of Visit 8, only patients who had attained a CGI-ADHD-S score ≤ 3 were permitted to continue in the study. A total of 18.7% of patients discontinued from the study on or before Visit 8 due to lack of efficacy. Overall, other common reasons for discontinuation were personal conflict or other patient decision (66 [17.2%]) and unable to contact patient (61 [15.9%]). A total of 47 (12.2%) patients discontinued due to an AE.

Table LYAR.2. Summary of Patient Disposition and Primary Reason for Study Discontinuation All Entered Patients

Patient Disposition	N	%
Entered	385	100
Discontinued (Personal conflict or other pat decision)	1	0.003
Enrolled	384	99.7
Enrolled and took at least one dose of study drug	383	99.5
Discontinued (all enrolled)	315	82.0
Study completed	69	18
Primary Reason for discontinuation (all enrolled)	384	100
Personal conflict or other patient decision	66	17.2
Unable to contact patient (lost to follow-up)	61	15.9
Lack of efficacy, patient perception	59	15.4
Adverse event	47	12.2
Lack of efficacy, patient and physician perception	41	10.7
Protocol Violation	20	5.2
Patient moved	13	3.4
Physician decision	7	1.8
Lack of efficacy, physician perception	1	0.3

Primary Objective Results:

Long-Term Safety and Tolerability Assessments:

Deaths and SAEs: There were no patient deaths in this study. Table LYAR.3 provides a summary of SAEs using MedDRA Preferred Terms for all patients who took at least one

dose of study drug. One enrolled patient did not take study drug. Of all enrolled patients who took at least one dose of study drug 16 (4.2%) patients reported an SAE. Three of these patients discontinued due to the event and are noted in the SAE summary table.

Frequencies of TEAEs: Table LYAR.4 presents the TEAEs that occurred in at least 5% of total patients during the study. Of the 383 enrolled patients who took at least one dose of study drug, a total of 355 (92.7%) patients reported at least one TEAE. The most commonly ($\geq 10\%$) reported AEs were: dry mouth (93 [24.3%]); headache (84 [21.9%]); insomnia (74 [19.3%]); erectile dysfunction (44/245 males [18%]), nausea (62 [16.2%]); constipation (54 [14.1%]); upper respiratory tract infection (41 [10.7%]); and nasopharyngitis (39 [10.2%]).

Discontinuations due to adverse events: Table LYAR.5 summarizes adverse events leading to patient discontinuation for all enrolled patients who took at least one dose of study drug. The most common reasons for study discontinuation related to an adverse event were: erectile dysfunction, 5 patients (2.0%); depression, 4 patients (1.0%); and constipation, 3 patients (0.8%).

Table LYAR.3. Summary of Serious Adverse Events Using MedDRA Terms for All Patients Who Took at Least One Dose of Study Drug

ACTUAL TERM / PREFERRED TERM (GROUPED BY PATIENT)
Diverticulitis / DIVERTICULITIS
Diverticulitis / DIVERTICULITIS
Diverticulitis / DIVERTICULITIS
Severe Allergic Reaction / HYPERSENSITIVITY
Fractured Ankle / ANKLE FRACTURE
Flu-Like Symptoms / INFLUENZA LIKE ILLNESS
Right Renal Cell Carcinoma-Type One / RENAL CELL CARCINOMA STAGE 1
Shingles / HERPES ZOSTER
Pneumonia / PNEUMONIA
*Calculus Renal NOS / NEPHROLITHIASIS
Coronary Artery Disease / CORONARY ARTERY DISEASE
Diabetes / DIABETES MELLITUS
Kidney Infection / KIDNEY INFECTION
*Coma / COMA
Contusions Arms and Right Leg / CONTUSION
Epistaxis / EPISTAXIS
Fractured Ribs (three) / RIB FRACTURE
Loss of Consciousness / LOSS OF CONSCIOUSNESS
Multiple Lacerations / LACERATION
Open Wound on Right Thigh / WOUND
Right Craniotomy with Evacuation of Subdural Hematoma / SUBDURAL HAEMATOMA EVACUATION
Right Subdural Hematoma with Delayed Intraparenchymal Bleed / SUBDURAL HAEMATOMA
Scalp Hematoma / HAEMATOMA
Transverse Process Fractures to T4, T9, T10 / SPINAL FRACTURE
*Left Breast Malignancy / BREAST CANCER
Chest Pain / CHEST PAIN
Shortness of Breath / DYSPNOEA
Unstable Angina / ANGINA UNSTABLE

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities™ Version 8;

NOS = not otherwise specified.

*patients who discontinued from the study due to this SAE

Table LYAR.4. **Summary of Treatment-Emergent Adverse Events**
Incidence $\geq$ 5% Using MedDRA Preferred Terms
Patients who took at Least One Dose of Study Drug

Event	N=383 n (%)
Total -- Any sign or symptom	355 (92.7)
Dry mouth	93 (24.3)
Headache	84 (21.9)
Insomnia	74 (19.3)
Erectile dysfunction**	44 (18.0)
Nausea	62 (16.2)
Constipation	54 (14.1)
Upper respiratory tract infection	41 (10.7)
Nasopharyngitis	39 (10.2)
Urinary hesitation	35 (9.1)
Irritability	33 (8.6)
Back pain	32 (8.4)
Influenza	32 (8.4)
Sinusitis	32 (8.4)
Dysmenorrhoea*	11 (8.0)
Anxiety	30 (7.8)
Fatigue	30 (7.8)
Dizziness	28 (7.3)
Dyspepsia	28 (7.3)
Arthralgia	26 (6.8)
Cough	25 (6.5)
Depression	25 (6.5)
Libido decreased	24 (6.3)
Abnormal dreams	23 (6.0)
Decreased appetite	23 (6.0)
Nasal congestion	20 (5.2)
Pharyngolaryngeal pain	20 (5.2)
Sleep disorder	20 (5.2)
Diarrhoea	19 (5.0)
Hyperhidrosis	19 (5.0)
Initial insomnia	19 (5.0)
Middle insomnia	19 (5.0)

Population: all enrolled patients who took at least one dose of atomoxetine).

**Denominator based on males only (N=245)

*Denominator based on females only (N=138)

Table LYAR.5. Adverse Events Leading to Patient Discontinuation
All Enrolled Patients Who Took at Least One Dose of Study
Drug
(Events Ordered by Decreasing Frequency)

Event	Atomoxetine
	N=383 n (%)
Total -- Any sign or symptom	47 (12.3)
Erectile dysfunction**	5 (2.0)
Depression	4 (1.0)
Constipation	3 (0.8)
Menstruation irregular*	1 (0.7)
Pregnancy*	1 (0.7)
Pregnancy test positive*	1 (0.7)
Dizziness	2 (0.5)
Dry mouth	2 (0.5)
Dyspepsia	2 (0.5)
Hypertension	2 (0.5)
Insomnia	2 (0.5)
Urinary hesitation	2 (0.5)
Anxiety	1 (0.3)
Bladder cancer stage I, with cancer in situ	1 (0.3)
Blood pressure increased	1 (0.3)
Breast cancer	1 (0.3)
Change of bowel habit	1 (0.3)
Chest discomfort	1 (0.3)
Coma	1 (0.3)
Emotional disorder	1 (0.3)
Headache	1 (0.3)
Heart rate increased	1 (0.3)
Hyperhidrosis	1 (0.3)
Hypoaesthesia	1 (0.3)

Population: all enrolled patients who took at least one dose of atomoxetine.

* Denominator based on females only (N=138).

** Denominator based on males only (N=245).

Laboratory Values: Table LYAR.6 summarizes all statistically significant mean change from baseline to endpoint values for laboratory analytes of patients who took at least one dose of atomoxetine and who had a baseline and at least one postbaseline measurement. At endpoint, the mean value for each analyte was in the normal range for that analyte.

Table LYAR.6. Laboratory Analyte Values with Statistically Significant Mean Change from Baseline to LOCF Endpoint All Patients Who Took at Least One Dose of Study Drug

Analyte	Baseline Mean (SD)	Change Mean (SD)	p-Value ^a
albumin	42.44 (3.2)	0.76 (3.04)	<.001
alkaline phosphatase	70.2 (19.5)	1.81 (10.3)	.001
alanine aminotransferase	28.38 (16.6)	-1.67 (14.6)	.036
aspartate aminotransferase	25.19 (9.6)	-1.78 (9.5)	<.001
cholesterol	5.19 (0.97)	0.09 (0.76)	.027
creatine phosphokinase	165.9 (345)	-39.6 (335)	.031
inorganic phosphorus	1.20 (0.19)	-0.04 (0.21)	<.001
basophils	0.05 (0.03)	.007 (0.04)	<.001
erythrocyte count	4.82 (0.42)	0.07 (0.25)	<.001
hematocrit	0.42 (0.03)	0.02 (0.03)	<.001
hemoglobin	9.00 (0.76)	0.13 (0.46)	<.001
lymphocytes	2.12 (0.57)	-0.1 (.48)	<.001
mean cell hemoglobin concentration (MCHC)	21.53 (0.9)	-0.53 (1.02)	<.001
mean cell volume	87.42 (5.01)	2.05 (3.83)	<.001
platelet count	264.4 (58.4)	10.61 (41.1)	<.001
sodium	141.3 (1.92)	0.72 (2.91)	<.001

Abbreviations: SD = standard deviation.

^a p-values are from paired T-test of change from baseline.

Population: all enrolled patients who took at least one dose of study drug.

Vital Signs: Table LYAR.7 summarizes the mean change from baseline to endpoint in vital sign measurements. There was a statistically significant increase from baseline to endpoint in mean diastolic blood pressure (mean change: 1.6 mm Hg, SD 9.4, p=.001), systolic blood pressure (mean change: 2.0 mm Hg, SD 11.8, p=.002), and pulse (mean change 4.4 bpm, SD 11.4, p<.001). A statistically significant decrease (p<.001) was shown for mean change (-0.94 kg, SD 4.3) from baseline (84.1 kg SD 18.8) to LOCF endpoint for weight.

Table LYAR.8 summarizes the categorical analysis of changes in blood pressure, heart rate (pulse), and weight. The criteria used in the analysis are included in a footnote in the table. For each criterion, the percentage of patients meeting the criterion at endpoint was computed. Patients meeting the criteria at baseline were excluded from the analysis. Twenty three percent (23%) of patients met the criteria for weight loss (decrease of at least 7%). No patients discontinued from the study due to weight loss.

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Table LYAR.7. Summary of Vital Sign Data
Mean Change from Baseline to LOCF Endpoint
All Enrolled Patients Who Took At Least One Dose of Study Drug

Treatment		Baseline		Endpoint		Change				p-value*
								Lower Confidence Interval	Upper Confidence Interval	
Atomoxetine	N	Mean	SD	Mean	SD	Mean	SD			
Pulse Average (bpm)	373	73.4	10.2	77.8	11.6	4.4	11.4	3.2	5.5	<.001
Systolic BP Average (mm Hg)	373	120.7	11.5	122.7	12.9	2.0	11.8	0.8	3.2	.002
Diastolic BP Average (mm Hg)	373	77.6	8.7	79.2	9.9	1.6	9.4	0.6	2.5	.001
Weight (kg)	373	84.1	18.8	83.2	19.0	-0.94	4.3	-1.4	-0.5	<.001

*p-Value is from Wilcoxon's signed-rank test.

Abbreviations: LOCF = last observation carried forward; N = number of patients with a baseline and at least one postbaseline measurement; SD = standard deviation; BP= blood pressure

Change = endpoint-baseline; Lower, Upper Confidence Interval = 95% 2-sided Confidence Interval of Change.

Baseline: Visit 1; Endpoint: Visits 2-24.

**Table LYAR.8. Summary of Vital Sign Data
Categorical Changes in Blood Pressure,
Heart Rate (Pulse), and Weight**

		N	n (%)
Heart Rate (Pulse)	High	373	2 (0.5)
	Low	373	3 (0.8)
Systolic BP	High	373	30 (8.0)
	Low	373	2 (0.5)
Diastolic BP	High	373	28 (7.5)
	Low	373	0 (0.0)
Weight	Gain	373	28 (7.5)
	Loss	373	87 (23.3)

Abbreviations: BP = blood pressure; bpm = beats per minute; N = total number of patients; n = number of patients within category.

Criteria:

Pulse-High: Increase of at least 15 bpm to at least 120 bpm.

Pulse-Low: Decrease of at least 15 bpm to at most 50 bpm.

Systolic BP-High: Increase of at least 10 mm Hg to at least 150 mm Hg.

Systolic BP-Low: Decrease of at least 20 mm Hg to at most 90 mm Hg.

Diastolic BP-High: Increase of at least 10 mm Hg to at least 100 mm Hg.

Diastolic BP-Low: Decrease of at least 15 mm Hg to at most 50 mm Hg.

Weight-Gain: Increase of at least 7%.

Weight-Loss: Decrease of at least 7%.

The criteria for the analysis of weight and pulse were based on the criteria used in the current label for atomoxetine.

Electrocardiogram: Table LYAR.9 summarizes the mean change from baseline to LOCF endpoint in ECG interval and heart rate. Atomoxetine showed a statistically significant mean decrease from baseline to endpoint in the QT interval ($p < .001$) and Fridericia corrected QT interval ($p = .013$). A statistically significant increase in mean change from baseline to endpoint was observed in Bazette corrected QT interval ($p < .001$). Bazett's QT correction is known to overcorrect the QT interval in cases where there is an increase in heart rate (Funk-Brentano and Jouillon 1993). No statistically significant mean change was seen in data-corrected QT interval. A statistically significant decrease in mean change from baseline to endpoint was seen in PR ($p < .001$) and QRS ($p = .006$) intervals. Heart rate measured from ECG showed a statistically significant ($p < .001$) mean increase (5.5 bpm SD 11.9) from baseline (68.8 bpm SD 12.1) to LOCF endpoint.

Table LYAR.10 summarizes the percentage of patients who met the criteria for potentially clinically significant changes in the data corrected QT interval following baseline. One patient (0.29%) had a ≥ 60 msec increase in data corrected QT interval. One patient (0.29%) had a final data corrected QT interval ≥ 500 msec.

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Table LYAR.9. Summary of ECG Data
Mean Change from Baseline to LOCF Endpoint
All Enrolled Patients Who Took At Least One Dose of Study Drug

Treatment		Baseline		Endpoint		Change				p-value*
								Lower Confidence Interval	Upper Confidence Interval	
Atomoxetine	N	Mean	SD	Mean	SD	Mean	SD			
QT/Interval	339	408.1	17.6	406.5	17.1	-1.6	13.2	-3.0	-0.2	.013
-Fridericia (MSEC)										
QT Interval	339	416.1	19.2	419.8	18.0	3.8	16.1	2.1	5.5	<.001
-Bazette (MSEC)										
QT Interval (MSEC)	339	392.5	30.4	380.9	29.6	-11.6	25.7	-14.3	-8.9	<.001
PR Interval (MSEC)	338	156.6	21.2	152.6	21.0	-4.0	13.6	-5.4	-2.5	<.001
QRS Interval (MSEC)	339	92.0	11.7	91.1	11.7	-0.8	5.7	-1.4	-0.2	.006
RR Interval (MSEC)	339	897.0	148.1	828.6	134.6	-68.4	138.0	-83.1	-53.7	<.001
Heart Rate (BPM)	339	68.8	12.1	74.3	11.9	5.5	11.9	4.2	6.8	<.001
QT Data Corrected **	339	26.0	1.1	26.0	1.0	0.0	0.8	-0.1	0.1	.536

* p-Value is from Wilcoxon signed-rank test.

** QTCD=QT/(RR**0.40)

Abbreviations: LOCF = last observation carried forward; N = number of patients with a baseline and at least one postbaseline measurement; SD = standard deviation;

Change = endpoint-baseline; Lower, Upper Confidence Interval = 95% 2-sided Confidence Interval of Change;

Baseline: Visit 1; Endpoint: Visits 2-24

Table LYAR.10. Incidence of Potentially Clinically Significant Changes in Data Corrected QT (QTc) Interval

N = 342		
Criteria	Increase n (%)	Decrease n (%)
Change $\geq$ 30 msec	13 (3.80%)	8 (2.34%)
Change $\geq$ 60 msec	1 (0.29%)	0 (0.0%)
Final $\geq$ 500 msec	1 (0.29%)	NA

Criteria:

Increase or decrease $\geq$ 30
Increase or decrease $\geq$ 60.
Increases to $>$ 500.

Secondary Objective Results:

Primary Efficacy Analysis:

Efficacy was a secondary objective in this open-label study. The primary efficacy measure was the CAARS-Inv:SV Total ADHD Symptom score. Table LYAR.11 summarizes mean baseline, LOCF endpoint, and change from baseline to endpoint for all patients who had a baseline and at least one postbaseline measurement. Baseline was defined as Visit 1. Endpoint was defined as the last nonmissing postbaseline measurement (Visit 2 through Visit 24). A statistically significant ($p < .001$) improvement in mean change score was shown on the CAARS-Inv:SV Total ADHD Symptom score (mean change -8.8, SD 10.9).

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**Table LYAR.11. CAARS-Inv:SV 18-item Total ADHD Symptom Score
Change from Baseline to LOCF Endpoint**

Treatment		Baseline		Endpoint		Change				p-value*
								Lower Confidence Interval	Upper Confidence Interval	
Atomoxetine	N	Mean	SD	Mean	SD	Mean	SD			
Total ADHD Score	372	29.1	11.0	20.4	10.8	-8.8	10.9	-9.9	-7.7	<.001

*p-Value is from Wilcoxon's signed-rank test.

Abbreviations: ADHD = Attention-Deficit/Hyperactivity Disorder; CAARS-Inv:SV = Conners' Adult ADHD Rating Scale-Investigator Rated:Screening Version; LOCF = last observation carried forward; N = number of patients with a baseline and at least one postbaseline measurement; SD = standard deviation.

Change = endpoint-baseline; Lower, Upper Confidence Interval = 95% 2-sided Confidence Interval of Change.

Baseline: Visit 1; Endpoint: Visits 2-24.

Secondary Efficacy Analyses:

Table LYAR.12 summarizes the CAARS-Inv:SV Subscale Scores. A statistically significant improvement ($p < .001$) was shown in mean change from baseline to LOCF endpoint on the ADHD Index Subscale Score (mean change -5.1, SD 6.9), the Hyperactive/Impulsive Subscale Score (mean change -4.2, SD 5.6), and the Inattention Subscale Score (mean change -4.5, SD 6.0).

Table LYAR.13 summarizes the mean baseline, LOCF endpoint, and change from baseline on the CGI-ADHD-S score. This analysis included all patients with a baseline and at least one postbaseline measurement. A statistically significant ($p < .001$) mean score reduction from baseline to endpoint was shown (mean change -1.1 SD 1.3).

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**Table LYAR.12. CAARS-Inv:SV Subscale Scores
Change from Baseline to LOCF Endpoint**

Treatment		Baseline		Endpoint		Change				p-value*
								Lower Confidence Interval	Upper Confidence Interval	
Atomoxetine	N	Mean	SD	Mean	SD	Mean	SD			
ADHD Index Subscale	372	18.3	7.2	13.2	7.2	-5.1	6.9	-5.8	-4.4	<.001
Hyperactive/Impulsive Subscale	372	12.8	6.2	8.5	5.5	-4.2	5.6	-4.8	-3.7	<.001
Inattention Subscale	372	16.4	6.3	11.9	6.5	-4.5	6.0	-5.1	-3.9	<.001

*p-Value is from Wilcoxon's signed-rank test.

Abbreviations: ADHD = Attention-Deficit/Hyperactivity Disorder; CAARS-Inv:SV = Conners' Adult ADHD Rating Scale-Investigator Rated:Screening Version; LOCF = last observation carried forward; N = number of patients with a baseline and at least one postbaseline measurement; SD = standard deviation.

Change = endpoint-baseline; Lower, Upper Confidence Interval = 95% 2-sided Confidence Interval of Change.

Baseline: Visit 1; Endpoint: Visits 2-24.

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Table LYAR.13. **CGI-ADHD-S**
Change from Baseline to LOCF endpoint

Treatment		Baseline		Endpoint		Change				p-value*
		Mean	SD	Mean	SD	Mean	SD	Lower Confidence Interval	Upper Confidence Interval	
Atomoxetine	N									
CGI ADHD Severity	372	4.3	1.1	3.2	1.3	-1.1	1.3	-1.2	-0.9	<.001

*p-Value is from Wilcoxon signed-rank test

Abbreviations: CGI-ADHD-S = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity
 LOCF = last observation carried forward
 N = number of patients with a baseline and at least one postbaseline measurement; SD = standard deviation.
 Change = endpoint-baseline; Lower, Upper Confidence Interval = 95% 2-sided Confidence Interval of Change.
 Baseline: Visit 1; Endpoint: Visits 2-24.

Health Outcomes:

As shown in Table LYAR.14, the mean change from baseline to LOCF endpoint on the Sheehan Disability Total score and Work, Social Life, and Family subscale scores showed a statistically significant ($p<.001$) mean reduction in disruption of the respective areas of life.

Table LYAR.15 summarizes results of the Arizona Sexual Experience Scale (ASEX) (male and female versions). The Male Total mean score change showed a statistically significant ($p<.001$) increase in sexual dysfunction from baseline to LOCF endpoint (mean change 1.0, SD 3.6). No statistically significant change was observed in the mean Female Total score.

Table LYAR.16 summarizes the mean change scores from baseline to LOCF endpoint of the Psychological General Well-Being Schedule (PGWBS) Total score and subscale scores. No statistically significant changes from baseline to endpoint were shown on the PGWBS Total score. Several subscale scores did show statistically significant improvement in mean change from baseline to LOCF endpoint scores: Anxiety ($p<.001$), Positive Well-Being ($p<.001$), and Self Control ($p<.001$).

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**Table LYAR.14. Sheehan Disability Scale
Change from Baseline to LOCF endpoint**

Treatment		Baseline		Endpoint		Change				p-value*
						Mean		Lower Confidence Interval	Upper Confidence Interval	
Atomoxetine	N	Mean	SD	Mean	SD	Mean	SD			
Sheehan Disability Total	334	15.0	7.2	11.3	7.6	-3.8	7.8	-4.6	-2.9	<.001
Symptoms Disrupted WORK	334	5.2	2.8	4.0	2.8	-1.2	3.1	-1.5	-0.9	<.001
Symptoms Disrupted SOCIAL LIFE	334	4.5	2.7	3.3	2.8	-1.2	2.9	-1.5	-0.9	<.001
Symptoms Disrupted FAMILY LIFE	334	5.4	2.7	4.0	2.7	-1.4	2.9	-1.7	-1.1	<.001

* p-Value is from Wilcoxon signed-rank test

Abbreviations: LOCF = last observation carried forward; N = number of patients with a baseline and at least one postbaseline measurement; SD = standard deviation.

Change = endpoint-baseline; Lower, Upper Confidence Interval = 95% 2-sided Confidence Interval of Change.

Baseline: Visit 1; Endpoint: Visits 2-24.

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**Table LYAR.15. Arizona Sexual Experience Scale
Change from Baseline to LOCF Endpoint**

Treatment		Baseline		Endpoint		Change				p-value*
								Lower Confidence Interval	Upper Confidence Interval	
Atomoxetine	N	Mean	SD	Mean	SD	Mean	SD			
Female Total Score	83	15.2	4.1	14.8	4.9	-0.4	3.2	-1.1	0.3	.185
Male Total Score	195	12.4	3.8	13.5	4.2	1.0	3.6	0.5	1.6	<.001

* p-Value is from Wilcoxon signed-rank test

Abbreviations: LOCF = last observation carried forward; N = number of patients with a baseline and at least one postbaseline measurement; SD = standard deviation.

Change = endpoint-baseline; Lower, Upper Confidence Interval = 95% 2-sided Confidence Interval of Change.

Baseline: Visit 1; Endpoint: Visits 2-24.

Note: higher scores indicate higher sexual dysfunction

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**Table LYAR.16. Psychological General Well-Being Schedule
Change from Baseline to LOCF endpoint**

Treatment		Baseline		Endpoint		Change				
								Lower Confidence Interval	Upper Confidence Interval	p-value*
Atomoxetine	N	Mean	SD	Mean	SD	Mean	SD			
Psychological Well-Being Total	325	77.7	4.6	78.0	4.5	0.2	5.0	-0.3	0.8	.625
Anxiety Score	335	15.5	4.6	16.7	4.5	1.2	4.4	0.7	1.7	<.001
Depressed Mood Score	335	12.0	2.5	12.2	2.6	0.2	2.7	-0.1	0.5	.054
Positive WellBeing Score	332	11.4	3.7	12.1	4.0	0.7	3.4	0.3	1.0	<.001
Self Control Score	335	11.1	2.9	11.8	2.8	0.7	2.7	0.4	1.0	<.001
General Health Score	336	11.3	2.3	11.1	2.7	-0.2	2.7	-0.5	0.1	.476
Vitality Score	331	12.0	3.8	12.2	3.9	0.2	3.3	-0.1	0.6	.146

*p-Value is from Wilcoxon signed-rank test

Abbreviations: LOCF = last observation carried forward; N = number of patients with a baseline and at least one postbaseline measurement; SD = standard deviation.

Change = endpoint-baseline; Lower, Upper Confidence Interval = 95% 2-sided Confidence Interval of Change.

Baseline: Visit 1; Endpoint: Visits 2-24

References:

Funck-Brentano C, Jaillon P. 1993. Rate-corrected QT interval: techniques and limitations. AM J Cardiol 72(6):172B-22B

Summary ID#4908

Clinical Study Summary: Study B4Z-MC-LYAS

Title of Study: A Randomized, Double-Blind Study of Tomoxetine Hydrochloride and Placebo in Pediatric Outpatients with Attention-Deficit/Hyperactivity Disorder and Comorbid Tic Disorders	
Investigators: This multicenter study included 15 principal investigators.	
Study Centers: This study was conducted at 14 study centers in the US. (One study center had coinvestigators; hence the 15 primary investigators at 14 study centers.)	
Length of Study: 19 months Date first patient enrolled: 17 July 2001 Date last patient completed: 21 February 2003	Phase of Development: 3
Objectives: The primary objective was to test the hypothesis that acute treatment for approximately 18 weeks with atomoxetine (formerly called tomoxetine) did not worsen tics in subjects diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD) with comorbid Tourette's Disorder or chronic motor tics. Assessment of noninferiority was measured by last-observation-carried-forward (LOCF), mean change from baseline-to-endpoint, on the Yale Global Tic Severity Scale (YGTSS) Total score. The secondary objectives of the study were as follows: • To assess the efficacy of atomoxetine as compared to placebo for the treatment of tics in children/adolescents with ADHD with mild to moderately severe comorbid Tourette's Disorder or chronic motor tics. Secondary efficacy measures included the Clinical Global Impressions-Overall-Severity (CGI-Overall-S) scale, the Clinical Global Impressions-Tic/Neurological-Severity (CGI-Tic/Neuro-S) scale, and Tic Symptom Self-Report (TSSR). • To assess the efficacy of atomoxetine as compared to placebo for the treatment of ADHD symptoms in children/adolescents with ADHD with comorbid Tourette's Disorder or chronic motor tics. Efficacy measures included the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv), Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder/Psychiatric-Severity (CGI-ADHD/Psych-S) scale, Daily Parent Ratings of Evening and Morning Behavior (DPREMB), and the Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R:S). • To assess the efficacy of atomoxetine as compared to placebo for the treatment of other common comorbid symptoms in children/adolescents with ADHD with comorbid Tourette's Disorder or chronic motor tics. Efficacy measures included the Children's Depression Rating Scale: Revised (CDRS-R), the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), the Social Skills Rating System-Parent Form (SSRS-P), Children's Depression Inventory (CDI), and Multidimensional Anxiety Scale for Children (MASC). • To assess the effectiveness of atomoxetine as compared to placebo at reducing parental stress with children/adolescents with ADHD with comorbid Tourette's Disorder or chronic motor tics. Parental stress was measured using the Parenting Stress Inventory (PSI). • To demonstrate that atomoxetine is safe and well tolerated in children and adolescents with ADHD with comorbid Tourette's Disorder or chronic motor tics as assessed through the collection of clinical data and data concerning adverse events.	

Study Design: Study B4Z-MC-LYAS (LYAS) was a multicenter, randomized, double-blind investigation of the acute safety and efficacy of atomoxetine in subjects who were at least 7 years of age but less than 17 years and 6 months of age, and who had met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for ADHD with comorbid Tourette's Disorder or chronic motor tics. Subjects who completed the acute treatment period (approximately 18 weeks) and continued onto the discontinuation phase (Study Period III, Visit 12) may have been eligible to enter the long-term, open-label atomoxetine Study B4Z-MC-LYAI (LYAI) if all entry criteria were met for Study LYAI at that time.

The study consisted of three Study Periods:

- Study Period I: A 10- to 18-day screening and assessment period (Visit 1 and Visit 2) during which each patient's present and lifetime diagnosis of ADHD and tic disorders were made by clinical assessment, and baseline efficacy and safety measurements were taken according to the Study Schedule. At the end of Visit 2, all eligible patients were randomly assigned to treatment.
- Study Period II: An 18-week (approximately) double-blind, acute treatment period (beginning at the end of Visit 2 and lasting through Visit 11), during which atomoxetine or placebo was administered to all patients. Efficacy and safety measures were completed per the protocol.
- Study Period III: A 10-to 18-day study drug discontinuation period at which time all routine assessments, efficacy measures, and safety measures were completed to assess whether or not tic symptoms returned after discontinuing treatment.

Number of Patients:

Planned: 140 subjects, randomized to placebo or atomoxetine in a 1:1 ratio

Randomized: 76 atomoxetine, 72 placebo

Completed or enrolled into LYAI: 65 atomoxetine, 62 placebo

Diagnosis and Main Criteria for Inclusion: Patients were at least 7 years of age but less than 17 years and 6 months of age. Patients met DSM-IV diagnostic criteria for ADHD with comorbid Tourette's Disorder or chronic motor tics. This diagnosis was confirmed during the screening visit by administration of the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL). Each patient's score from the ADHDRS-IV-Parent:Inv must have been at least 1.5 standard deviations above the age/gender norm for his or her diagnostic subtype, or the Total score for the combined subtype (if the child met DSM-IV criteria for the combined subtype) using published norms for the ADHDRS-IV-Parent:Inv at both Visit 1 and Visit 2. In addition, each patient's score from the YGTSS Total score must have been at least 5 at both Visit 1 and Visit 2. Prior to Visit 1, patients must not have taken any medication used to treat ADHD or tic disorders for either 5 half-lives of the medication or 28 days (whichever was less).

Test Product, Dose, and Mode of Administration: Atomoxetine: 0.5 mg/kg/day to 1.5 mg/kg/day; given twice a day; atomoxetine capsules; 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, and 40 mg dose.

Duration of Treatment: 18 weeks.

Reference Therapy, Dose, and Mode of Administration: Placebo, given twice a day.

Variables:

Efficacy: Treatment differences on the following measures: YGTSS, TSSR, CGI-Overall-S, CGI-ADHD/Psych-S, CGI-Tic/Neuro-S: ADHDRS-IV-Parent:Inv, DPREMB, CTRS-R:S, CDRS-R, CDI, CY-BOCS, MASC, and the SSRS-P.

Safety: Treatment-emergent adverse events, vital signs, height and weight, laboratory measures, and electrocardiograms (ECGs).

Health Outcomes: Stress level in parent-child systems using the PSI.

Evaluation Methods:

Statistical: The primary efficacy analysis was a noninferiority comparison of the difference (placebo minus atomoxetine) in mean change from baseline to endpoint (LOCF) YGTSS Total scores, using a one-sided lower 95% confidence interval in those randomized with at least one postbaseline visit. The mean square error for the analysis of variance (ANOVA) model with terms for treatment and investigator was

used as the estimate of the variance in the calculation of the one-sided confidence interval. The prespecified acceptable clinical cut off between atomoxetine and placebo was -3.7. If the lower bound interval was greater than -3.7, then atomoxetine was noninferior to placebo. For secondary efficacy and safety measures, treatment differences in mean change scores from continuous measures were assessed using ANOVA, while Fisher's exact test was used to assess treatment differences in categorical data.

Summary:

Patient Disposition: Beginning at Visit 9 (12 weeks on atomoxetine or placebo), patients meeting the criteria for "clinical nonresponder" (CGI-Overall-S ≥ 4) at two consecutive visits (Visit 9 or later) were eligible to discontinue this trial and to enter an open-label extension study with atomoxetine (Study LYAI). Sites were instructed that patients meeting these criteria were to be identified on the case report forms (CRFs) as having discontinued due to lack of efficacy.

At Visit 2, 72 patients were randomized to placebo and 76 patients were randomized to atomoxetine. Of the 148 patients randomized, 103 (69.6%) of these patients discontinued the study. The primary reason for discontinuation in both the atomoxetine (38 of 76 patients, 50.0%) and placebo (45 of 72 patients, 62.5%) treatment groups was identified as lack of efficacy, with the majority of the patients discontinuing at Visit 9 (12 weeks on atomoxetine or placebo). Visit 9 was the first visit where patients could meet the criteria for "clinical nonresponder" and were eligible to discontinue the trial and enter an open-label extension study with atomoxetine (Study LYAI). A total of 83 patients (40 from the atomoxetine-treatment group and 43 from the placebo-treatment group) entered the open-label extension before completing the study.

Only 3 patients (2 atomoxetine patients and 1 placebo patient) discontinued the study due to adverse events. There were no statistically significant differences between treatment groups for any reason for discontinuation.

Patient Demographics: Table LYAS.1 summarizes demographic characteristics for all patients who were randomized to treatment. Of the 148 randomized patients, 88.5% were male, 87.8% were Caucasian, and the mean age was 11.2 (range 7.0 to 17.3) years, with 68.2% having been previously exposed to stimulants. The majority (60.8%) of the patients met diagnostic criteria for ADHD combined subtype, while 35.8% were classified as inattentive and 3.4% as hyperactive/impulsive. The only statistically significant demographic difference observed was for mean (standard deviation) weight (atomoxetine 39.9 [13.1], placebo 44.8 [15.3]; $p=.037$).

Efficacy: This study examined patients diagnosed with ADHD with comorbid Tourette's Disorder or chronic motor tics. For this population, ADHD was moderate to marked in severity, with tic disorders in the mild to moderate severity range. At baseline, approximately 80% of these patients were diagnosed with having comorbid Tourette's Disorder.

The protocol-specified primary outcome measure was a noninferiority comparison of atomoxetine and placebo with respect to worsening of tics as assessed by the investigator-rated YGTSS Total score. Table LYAS.2 summarizes mean change from baseline to endpoint using the LOCF approach in YGTSS Total score during the acute treatment phase for all randomized patients with at least one postbaseline visit. This table includes the primary efficacy analysis of the lower bound one-sided 95% confidence interval for the difference in mean change in YGTSS Total scores (placebo minus atomoxetine) to determine noninferiority versus placebo, which was greater than the predefined delta of -3.7. This means that the study's primary objective was achieved. However, the two-sided 95% confidence interval included 0 in the range, indicating that atomoxetine was not superior to placebo for this measure ($p=.063$). In a subgroup of patients with Tourette's Disorder (60 patients in the atomoxetine group and 56 patients in the placebo group), atomoxetine was superior to placebo ($p=.027$) in reducing tic severity on the primary outcome measure.

For the motor and phonic subscales of the YGTSS, no differences were shown between treatment groups in the overall population ($p=.119$ and $p=.168$, respectively). In the subgroup of patients with Tourette's Disorder, however, there was a statistically significantly greater improvement in the motor subscale of the YGTSS (a mean change for atomoxetine-treated patients of -2.7 versus a mean change for placebo-treated

patients of -0.9; $p=.039$), although not in the phonic subscale ($p=.126$). In both the overall population and the subgroup of patients with Tourette's Disorder, atomoxetine treatment showed a statistically significantly greater improvement in the YGTSS Overall Impairment score, a measure of patient functioning. For the overall population, the mean change on the YGTSS Overall Impairment score for atomoxetine-treated patients was -6.4 versus a mean change of -1.9 for placebo-treated patients ($p=.004$). For the subgroup of patients with Tourette's Disorder, the mean change for atomoxetine-treated patients was -6.3 versus a mean change of -1.8 for placebo-treated patients ($p=.019$).

Further analysis of tic measures included the TSSR and CGI-Tic/Neuro-S scales. No differences between treatment groups were shown for the TSSR. However, in the CGI-Tic/Neuro-S, atomoxetine treatment showed a statistically significantly greater improvement compared with placebo for both the study population as a whole and for the subgroup with Tourette's Disorder (Table LYAS.3 and Table LYAS.4, respectively).

On the CGI-Overall-S, atomoxetine treatment showed a statistically significantly greater improvement compared with placebo for the study population as a whole and for the subgroup with Tourette's Disorder (Table LYAS.5 and Table LYAS.6). As Table LYAS.7 and Table LYAS.8 illustrate, statistically significantly greater improvements were seen for both groups on the ADHDRS-IV-Parent:Inv as well. For all randomized patients, those treated with atomoxetine showed a statistically significantly greater improvement in the CGI-ADHD/Psych-S score compared with placebo (Table LYAS.9). In the subgroup of patients with Tourette's Disorder, the change in the CGI-ADHD/Psych-S did not reach statistical significance ($p=.072$). For the DPREMB, a greater numerical reduction in Total score, as well as the Morning and Evening Behavior scores was observed in the atomoxetine treatment group compared with the placebo treatment group (Table LYAS.10). On the SSRS-P, patients on atomoxetine had statistically significantly greater improvement in their social skill standard and raw scores than did patients on placebo (Table LYAS.11). No differences were shown between treatment groups on the CTRS-R:S (only around half of the CTRS-R:S forms were returned).

The CDRS-R and the CDI were used to rate depression, although few patients met the diagnostic criteria for depression at baseline. Placebo-treated patients showed a statistically significant improvement from baseline to endpoint in CDRS-R Total score during the acute treatment phase compared with atomoxetine-treated patients ($p=.011$; Table LYAS.12). Improvement in CDI Total score was identical in the two treatment groups.

Table LYAS.13 summarizes the mean change from baseline to endpoint in MASC Physical Symptoms, Social Anxiety, Harm Avoidance, Separation/Panic, and Total T-scores during the acute treatment phase. Mean baseline scores for the MASC Total and Subscale T-scores were close to normal values for patients in both treatment groups. These scores are consistent with few patients meeting diagnostic criteria for anxiety disorders. A greater numerical reduction in mean scores was observed for the placebo-treated patients compared with the atomoxetine group for the Total and all subscale scores, with a significant treatment difference seen for the Harm Avoidance T-score ($p=.025$).

No statistically significant difference between treatment groups was shown on the scale rating obsessive-compulsive disorder (the CY-BOCS).

Upon discontinuation of study drug, the YGTSS Total, ADHDRS-IV-Parent:Inv Total, and CGI-Overall-S final scores for both treatment groups returned towards baseline but did not exceed their baseline scores from Study Period I.

Overall, it was shown that atomoxetine did not worsen tics in patients with ADHD and comorbid tics disorders, and actually improved tics in patients with Tourette's Disorder.

Safety: A total of 148 patients were randomized to either atomoxetine ($n=76$) or placebo ($n=72$) for approximately 18 weeks of acute double-blind treatment.

The mean maximum dose was 1.41 mg/kg/day and did not exceed 110 mg/day regardless of patient's weight. The top dose of 1.5 mg/kg/day was chosen before atomoxetine became approved in any countries. Furthermore, due to the multiple comorbidities of patients taking part in the study, a more conservative

maximum dose was chosen.

Table LYAS.14 summarizes treatment-emergent adverse events (TEAEs) and preferred terms in order of decreasing frequency. This summary only includes TEAEs that were reported in at least 5% of randomized patients who had taken at least one dose of study medication. There were 81.6% of patients in the atomoxetine-treatment group, and 75.0% of patients in the placebo-treatment group that reported at least 1 TEAE. The most commonly reported adverse events ($\geq 10\%$) for atomoxetine treated patients were headache, vomiting, appetite decreased, nausea, and fatigue. For placebo treated patients, the most common adverse events were headache, abdominal pain, cough, pharyngitis, and diarrhea. A statistically significantly greater percentage of atomoxetine-treated patients compared with placebo-treated patients reported appetite decreased and nausea.

One serious adverse event was reported (constipation) by one atomoxetine-treated patient. The total rate of discontinuations due to adverse events was low (2.0% [placebo, n=1 and atomoxetine, n=2]).

Table LYAS.15 summarizes mean changes from baseline to endpoint for each laboratory analyte during Study Period II for all randomized patients. Statistically significant mean change treatment differences between the atomoxetine-treatment group and placebo-treatment group were observed for alkaline phosphatase, hemoglobin, monocytes, AST/SGOT, ALT/SGPT, creatine phosphokinase, uric acid, and bicarbonate.

Table LYAS.16 summarizes the mean change from baseline to endpoint in vital signs for all randomized patients. There was a statistically significant ($p < .001$) difference between atomoxetine- and placebo-treated patients for weight change. The data showed a baseline to endpoint mean decrease (0.91 kg) in weight for the atomoxetine treatment group and a mean increase (1.64 kg) in weight in the placebo treatment group. Additionally, there was a statistically significant ($p < .001$) difference between atomoxetine- and placebo-treated patients for pulse. The data showed a baseline to endpoint mean increase (8.29 bpm) in pulse for the atomoxetine-treatment group and a mean decrease (1.21 bpm) in pulse for the placebo-treatment group. Although the pulse increase in patients treated with atomoxetine was statistically significantly greater compared with placebo-treated patients, the mean pulse at endpoint was well within the normal range. There were no statistically significant treatment group differences in mean change in blood pressure values between treatment groups.

Table LYAS.17 summarizes change from baseline to endpoint for heart rate and ECG intervals (RR, PR, QRS, QT, and QT corrected using Bazett's and Fridericia's methods) for all randomized patients. Statistically significant differences between the atomoxetine and placebo treatment groups were found for the RR interval, PR interval, QT interval, Fridericia QTc interval, and heart rate. Relative to placebo, atomoxetine treatment was associated with a mean decrease of the RR, PR, QT, and Fridericia QTc intervals, and a mean increase in heart rate. The decrease in RR interval would be expected with an elevation of heart rate.

Health Outcomes: Table LYAS.18 summarizes the mean change from baseline to endpoint PSI Total and subscale scores during the acute treatment phase.

**Table LYAS.1. Patient Demographics and Other Characteristics
Comparison of Treatment Groups at Baseline
Randomized Patients, Study Period II**

Variable	ATOMOX (N=76)	PLACEBO (N=72)	Total (N=148)	p-Value
Sex: No. (%)				
No. Patients	76	72	148	.200*
Female	6 (7.9)	11 (15.3)	17 (11.5)	
Male	70 (92.1)	61 (84.7)	131 (88.5)	
Origin: No. (%)				
No. Patients	76	72	148	.785*
African Descent	5 (6.6)	2 (2.8)	7 (4.7)	
Caucasian	65 (85.5)	65 (90.3)	130 (87.8)	
East/Southeast A	1 (1.3)	0	1 (0.7)	
Hispanic	3 (3.9)	3 (4.2)	6 (4.1)	
Other	2 (2.6)	2 (2.8)	4 (2.7)	
Age: yrs.				
No. Patients	76	72	148	.126**
Mean	10.87	11.49	11.17	
Median	10.32	11.38	10.75	
Standard Dev.	2.49	2.40	2.45	
Minimum	7.00	7.08	7.00	
Maximum	17.00	17.31	17.31	
CYP2D6				
No. Patients	76	72	148	.740*
EXTN	71 (94.7)	66 (93.0)	137 (93.8)	
SLOW	4 (5.3)	5 (7.0)	9 (6.2)	
Unspecified	1	1	2	
Height: cm				
No. Patients	76	72	148	.110**
Mean	144.13	148.08	146.05	
Median	141.00	147.50	144.00	
Standard Dev.	15.43	14.38	15.01	
Minimum	119.00	118.00	118.00	
Maximum	181.50	182.00	182.00	
Weight: kg				
No. Patients	76	72	148	.037**
Mean	39.86	44.78	42.25	
Median	36.00	41.60	39.75	
Standard Dev.	13.10	15.33	14.39	
Minimum	20.40	22.00	20.40	
Maximum	77.30	79.00	79.00	
DSM-IV ADHD Subtype				
No. Patients	76	72	148	.487*
HYP/IMP	2 (2.6)	3 (4.2)	5 (3.4)	
INATTV	24 (31.6)	29 (40.3)	53 (35.8)	
MIXED	50 (65.8)	40 (55.6)	90 (60.8)	
Family History-ADHD-Mother				
No. Patients	76	72	148	.921*
N	56 (73.7)	55 (76.4)	111 (75.0)	
U	7 (9.2)	5 (6.9)	12 (8.1)	
Y	13 (17.1)	12 (16.7)	25 (16.9)	

(continued)

**Table LYAS.1. Patient Demographics and Other Characteristics
Comparison of Treatment Groups at Baseline
Randomized Patients, Study Period II (concluded)**

Variable	ATOMOX (N=76)	PLACEBO (N=72)	Total (N=148)	p-Value

Family History-ADHD-Father				
No. Patients	76	72	148	.454*
N	42 (55.3)	47 (65.3)	89 (60.1)	
U	14 (18.4)	9 (12.5)	23 (15.5)	
Y	20 (26.3)	16 (22.2)	36 (24.3)	
Family History-ADHD-Grandparents				
No. Patients	76	72	148	.909*
N	52 (68.4)	47 (65.3)	99 (66.9)	
U	15 (19.7)	15 (20.8)	30 (20.3)	
Y	9 (11.8)	10 (13.9)	19 (12.8)	
Family History-ADHD-Siblings				
No. Patients	76	72	148	.882*
N	47 (61.8)	44 (61.1)	91 (61.5)	
N/A	3 (3.9)	5 (6.9)	8 (5.4)	
U	6 (7.9)	6 (8.3)	12 (8.1)	
Y	20 (26.3)	17 (23.6)	37 (25.0)	
Prior Stimulant Exposure				
No. Patients	76	72	148	.293*
N	21 (27.6)	26 (36.1)	47 (31.8)	
Y	55 (72.4)	46 (63.9)	101 (68.2)	
Grade in School				
No. Patients	76	72	148	.801*
1	4 (5.3)	1 (1.4)	5 (3.4)	
10	4 (5.3)	3 (4.2)	7 (4.7)	
11	1 (1.3)	1 (1.4)	2 (1.4)	
12	1 (1.3)	1 (1.4)	2 (1.4)	
2	6 (7.9)	5 (6.9)	11 (7.4)	
3	15 (19.7)	7 (9.7)	22 (14.9)	
4	12 (15.8)	11 (15.3)	23 (15.5)	
5	12 (15.8)	13 (18.1)	25 (16.9)	
6	8 (10.5)	9 (12.5)	17 (11.5)	
7	6 (7.9)	10 (13.9)	16 (10.8)	
8	4 (5.3)	7 (9.7)	11 (7.4)	
9	3 (3.9)	4 (5.6)	7 (4.7)	

Population: All Enrolled Patients.

Initial Visit ONLY

Input data from RMP.SAS.B4ZM.L.MCLYASSW

Output stored as RMP.B4Z0.LYASCTRM.FINAL(DE146002)

* Frequencies are analyzed using a Fishers-Exact test.

** Means are analyzed using a Type III Sum of Squares analysis of variance

(ANOVA): PROC GLM model=treatment.

XDES0001

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Approved: 19 April 2005

**Table LYAS.2. YGTSS Total Score
 Change from Baseline to Endpoint
 All Randomized Patients, Study Period II**

Treatment Group	n	Baseline		Endpoint		Change		Within p-Value(A)	Between p-value(B)
		Mean	SD	Mean	SD	Mean	SD		
YGTSS Total Score									
Atomox.	74	21.7	7.8	16.2	9.8	-5.5	6.9	<.001	.063
PLACEBO	71	22.2	8.3	19.2	10.0	-3.0	8.7	.007	----
			One sided 95% C.I. lower bound: 0.27 Two sided 95% C.I.: (-0.13 , 4.88)						

(A) Within p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator and treatment. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAS.SASPGM(EFYGTK1)

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Approved: 19 April 2005

Table LYAS.3. CGI-Tic/Neuro-S Score
Mean Change from Baseline to Endpoint
All Randomized Patients, Study Period II

Treatment Group	n	Baseline		Endpoint		Change		Within p-Value(A)	Between p-value(B)
		Mean	SD	Mean	SD	Mean	SD		
CGI-Tic/Neuro-Severity Score									
Atomox.	74	3.7	0.9	3.0	1.2	-0.7	1.2	<.001	.002
PLACEBO	71	3.6	0.8	3.5	1.2	-0.1	1.0	.367	----
Two sided 95% C.I.: (0.23 , 0.98)									

(A) Within p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator and treatment. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAS.SASPGM(EFCGIK2)

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Table LYAS.4. CGI-Tic/Neuro-S Score
Mean Change from Baseline to Endpoint
Patients with Tourette's Disorder, Study Period II

Treatment Group	n	Baseline		Endpoint		Change		Within p-Value(A)	Between p-value(B)
		Mean	SD	Mean	SD	Mean	SD		
CGI-Tic/Neuro-Severity Score									
Atomox.	60	3.8	0.9	3.1	1.1	-0.7	1.2	<.001	.003
PLACEBO	56	3.7	0.9	3.7	1.1	0.0	1.0	.901	----
Two sided 95% C.I.: (0.23 , 1.09)									

(A) Within p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator and treatment. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAS.SASPGM(EFCGIK2B)

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Table LYAS.5. CGI-Overall-S Score
Mean Change from Baseline to Endpoint
Randomized Patients, Study Period II

Treatment Group	n	Baseline		Endpoint		Change		Within p-Value(A)	Between p-value(B)
		Mean	SD	Mean	SD	Mean	SD		
CGI-Overall-Severity									
Atomox.	74	4.5	0.7	3.9	1.1	-0.6	1.1	<.001	.014
PLACEBO	71	4.3	0.7	4.1	1.1	-0.2	0.9	.060	----
Two sided 95% C.I.: (0.09 , 0.76)									

(A) Within p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator and treatment. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAS.SASPGM(EFCGIK1)

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Table LYAS.6. CGI-Overall-S Score
Mean Change from Baseline to Endpoint
Patients with Tourette's Disorder, Study Period II

Treatment Group	n	Baseline		Endpoint		Change		Within p-Value(A)	Between p-value(B)
		-----		-----		-----			
		Mean	SD	Mean	SD	Mean	SD		
CGI-Overall-Severity									
Atomox.	60	4.6	0.7	4.0	1.1	-0.6	1.2	<.001	.032
PLACEBO	56	4.4	0.7	4.3	0.9	-0.1	0.8	.364	----
Two sided 95% C.I.: (0.04 , 0.79)									

(A) Within p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator and treatment. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAS.SASPGM(EFCGIK1B)

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Table LYAS.7. ADHDRS-IV-Parent:Inv Total Score and Subscale Scores
Mean Change from Baseline to Endpoint
All Randomized Patients, Study Period II

Treatment Group	n	Baseline		Endpoint		Change		Within p-Value(A)	Between p-value(B)
		Mean	SD	Mean	SD	Mean	SD		
Total Score									
Atomox.	74	38.9	9.1	28.0	12.6	-10.9	10.9	<.001	.002
PLACEBO	71	35.0	9.5	30.2	13.5	-4.9	10.3	<.001	----
Two sided 95% C.I.: (2.02 , 9.00)									
Inattentive Subscale									
Atomox.	74	21.6	4.1	15.9	7.1	-5.7	6.7	<.001	.019
PLACEBO	71	20.5	5.0	17.7	7.1	-2.7	6.8	.005	----
Two sided 95% C.I.: (0.44 , 4.73)									
Hyperactive Subscale									
Atomox.	74	17.2	6.8	12.1	7.1	-5.2	5.3	<.001	.002
PLACEBO	71	14.6	7.2	12.5	8.3	-2.1	4.8	<.001	----
Two sided 95% C.I.: (0.94 , 4.28)									

(A) Within p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator treatment and baseline. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAS.SASPGM(EFAD4K1)

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Table LYAS.8. ADHDRS-IV-Parent:Inv Total Score and Subscale Scores
Mean Change from Baseline to Endpoint
Patients with Tourette's Disorder, Study Period II

Treatment Group	n	Baseline		Endpoint		Change		Within p-Value(A)	Between p-value(B)
		Mean	SD	Mean	SD	Mean	SD		
Total Score									
Atomox.	60	40.0	9.1	29.5	12.4	-10.4	11.0	<.001	.011
PLACEBO	56	35.7	9.5	31.3	13.3	-4.4	9.9	.004	----
Two sided 95% C.I.: (1.17 , 9.03)									
Inattentive Subscale									
Atomox.	60	22.1	4.2	16.7	7.0	-5.4	6.3	<.001	.038
PLACEBO	56	20.5	5.0	18.2	7.0	-2.3	6.4	.025	----
Two sided 95% C.I.: (0.14 , 4.84)									
Hyperactive Subscale									
Atomox.	60	17.9	6.9	12.8	7.0	-5.1	5.7	<.001	.017
PLACEBO	56	15.2	6.8	13.1	8.0	-2.1	4.8	.001	----
Two sided 95% C.I.: (0.44 , 4.36)									

(A) Within p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator treatment and baseline. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAS.SASPGM(EFAD4K1B)

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Table LYAS.9. CGI-ADHD/Psych-S Score
Mean Change from Baseline to Endpoint
All Randomized Patients, Study Period II

Treatment Group	n	Baseline		Endpoint		Change		Within p-Value(A)	Between p-value(B)
		Mean	SD	Mean	SD	Mean	SD		
CGI-ADHD/Psych-Severity Score									
Atomox.	74	4.7	0.8	3.9	1.2	-0.8	1.1	<.001	.015
PLACEBO	71	4.5	0.8	4.1	1.2	-0.3	1.0	.008	----
Two sided 95% C.I.: (0.09 , 0.80)									

(A) Within p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator and treatment. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAS.SASPGM(EFCGIK3)

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Table LYAS.10. Daily Parent Rating Scale of Evening and Morning Behavior-Revised (DPREMB-Revised)
Total and Subscores
Change from Baseline to Endpoint
Study Period II

Treatment Group	n	Baseline		Endpoint		Change		Within p-Value(A)	Between p-value(B)
		Mean	SD	Mean	SD	Mean	SD		
Total Score									
Atomox.	56	16.3	8.5	11.1	7.7	-5.2	7.7	<.001	.553
PLACEBO	49	12.8	7.4	9.8	6.4	-2.9	6.3	.003	----
Two sided 95% C.I.: (-1.69 , 3.13)									
AM Subtotal Score									
Atomox.	56	3.9	2.7	2.8	2.0	-1.1	2.8	.009	.638
PLACEBO	49	3.1	2.2	2.4	1.8	-0.7	2.1	.087	----
Two sided 95% C.I.: (-0.88 , 0.55)									
PM Subtotal Score									
Atomox.	56	12.4	6.4	8.3	6.1	-4.1	5.4	<.001	.324
PLACEBO	49	9.7	5.6	7.4	5.1	-2.3	4.8	.002	----
Two sided 95% C.I.: (-0.92 , 2.75)									

(A) Within p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator, treatment and baseline. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAS.SASPGM(EFDEPK1)

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Table LYAS.11. SSRS-P Scores
Mean Change from Baseline to Endpoint
Randomized Patients, Study Period II

Treatment Group	n	Baseline		Endpoint		Change		Within p-Value(A)	Between p-value(B)
		Mean	SD	Mean	SD	Mean	SD		
Social Skill Raw Score									
Atomox.	71	41.6	10.1	45.9	11.0	4.3	9.2	<.001	.042
PLACEBO	65	46.0	10.5	47.4	10.1	1.4	8.0	.095	----
Two sided 95% C.I.: (-6.01 , -0.12)									
Social Skill Standard Score									
Atomox.	71	83.7	13.7	90.1	16.1	6.4	13.4	<.001	.037
PLACEBO	65	89.2	14.8	91.2	14.5	2.0	11.4	.091	----
Two sided 95% C.I.: (-8.83 , -0.28)									
Problem Behaviors Raw Score									
Atomox.	71	19.7	6.6	17.3	6.8	-2.4	5.4	<.001	.203
PLACEBO	65	16.3	7.2	15.0	7.1	-1.3	4.6	.025	----
Two sided 95% C.I.: (-0.61 , 2.85)									
Problem Behaviors Standard Score									
Atomox.	71	119.7	13.3	113.5	14.6	-6.3	12.7	<.001	.193
PLACEBO	65	113.5	15.7	110.0	14.9	-3.5	11.7	.020	----
Two sided 95% C.I.: (-1.42 , 6.95)									

(A) Within p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator and treatment. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAS.SASPGM(EFSSRK1)

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Table LYAS.12. CDRS-R Total Score
Mean Change from Baseline to Endpoint
Randomized Patients, Study Period II

Treatment Group	n	Baseline		Endpoint		Change		Within p-Value(A)	Between p-value(B)
		-----		-----		-----			
		Mean	SD	Mean	SD	Mean	SD		
CDRS-R Total Score									
Atomox.	74	22.7	4.9	23.4	5.3	0.8	5.7	.571	.011
PLACEBO	68	24.2	5.9	22.5	5.0	-1.7	5.6	.006	----
Two sided 95% C.I.: (-4.47 , -0.59)									

(A) Within p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator and treatment. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAS.SASPGM(EFCDRK1)

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Table LYAS.13. MASCC Total and Subscale T-scores
Mean Change from Baseline to Endpoint
Randomized Patients, Study Period II

Treatment Group	n	Baseline		Endpoint		Change		Within p-Value(A)	Between p-value(B)
		Mean	SD	Mean	SD	Mean	SD		
Total T-Score									
Atomox.	69	51.0	12.8	49.4	13.0	-1.6	9.3	.428	.119
PLACEBO	64	50.2	11.4	46.2	11.3	-4.1	9.0	<.001	----
Two sided 95% C.I.: (-5.72 , 0.66)									
Anxiety Disorders Index T-Score									
Atomox.	71	48.6	12.5	45.0	11.4	-3.6	10.1	.002	.663
PLACEBO	68	48.0	11.2	43.8	10.4	-4.2	9.5	.001	----
Two sided 95% C.I.: (-4.02 , 2.57)									
Harm Avoidance T-Score									
Atomox.	70	46.9	10.7	48.9	11.8	2.0	8.0	.057	.025
PLACEBO	68	46.6	9.6	45.3	11.6	-1.3	8.6	.185	----
Two sided 95% C.I.: (-6.04 , -0.40)									
Physical Symptoms T-Score									
Atomox.	72	50.4	11.0	48.3	10.1	-2.1	10.0	.115	.110
PLACEBO	69	49.9	8.8	45.5	9.0	-4.5	7.5	<.001	----
Two sided 95% C.I.: (-5.43 , 0.56)									

(continued)

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Table LYAS.13. MASC Total and Subscale T-scores
Mean Change from Baseline to Endpoint
Randomized Patients, Study Period II (concluded)

Treatment Group	n	Baseline		Endpoint		Change		Within p-Value(A)	Between p-value(B)
		Mean	SD	Mean	SD	Mean	SD		
Separation T-Score									
Atomox.	74	55.0	14.0	55.5	14.5	0.5	9.3	.518	.479
PLACEBO	67	52.4	11.0	51.8	12.5	-0.7	9.1	.591	----
Two sided 95% C.I.: (-4.21 , 1.99)									
Social Anxiety T-Score									
Atomox.	74	50.9	13.0	47.7	10.2	-3.2	10.6	.017	.656
PLACEBO	68	52.0	11.0	48.4	10.5	-3.6	9.1	.002	----
Two sided 95% C.I.: (-4.08 , 2.58)									

(A) Within p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator and treatment. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAS.SASPGM(EFMASK2)

**Table LYAS.14. Summary of Treatment-Emergent Adverse Events
with Incidence $\geq 5\%$ Using MedDRA™ Preferred Terms
All Randomized Patients
Study Period II**

Preferred Term	ATOMOX (N=76) n (%)	PLACEBO (N=72) n (%)	Total (N=148) n (%)	p-Value*
PATIENTS WITH ≥ 1 TESS	62 (81.6)	54 (75.0)	116 (78.4)	.425
PATIENTS WITH NO TESS	14 (18.4)	18 (25.0)	32 (21.6)	.425
Headache	16 (21.1)	14 (19.4)	30 (20.3)	.840
Vomiting NOS	12 (15.8)	6 (8.3)	18 (12.2)	.211
Abdominal pain upper	7 (9.2)	9 (12.5)	16 (10.8)	.601
Appetite decreased NOS	12 (15.8)	2 (2.8)	14 (9.5)	.010
Cough	4 (5.3)	9 (12.5)	13 (8.8)	.151
Nausea	12 (15.8)	1 (1.4)	13 (8.8)	.002
Fatigue	9 (11.8)	3 (4.2)	12 (8.1)	.131
Nasopharyngitis	6 (7.9)	6 (8.3)	12 (8.1)	1.00
Pharyngitis	3 (3.9)	9 (12.5)	12 (8.1)	.073
Pyrexia	6 (7.9)	6 (8.3)	12 (8.1)	1.00
Diarrhoea NOS	3 (3.9)	8 (11.1)	11 (7.4)	.123
Somnolence	5 (6.6)	3 (4.2)	8 (5.4)	.720
Initial insomnia	3 (3.9)	4 (5.6)	7 (4.7)	.714
Irritability	4 (5.3)	2 (2.8)	6 (4.1)	.682
Rhinorrhoea	2 (2.6)	4 (5.6)	6 (4.1)	.433
Tic	4 (5.3)	2 (2.8)	6 (4.1)	.682

Population: Enrolled patients who took at least 1 dose of study drug.

Baseline: Visits 1-2, Endpoint: Visits 3 - 11

Input data from RMP.SAS.B4ZM.L.MCLYASSW

Output stored as RMP.B4Z0.LYASCTRM.FINAL(AE219007)

* Frequencies are analyzed using a Fisher's Exact test.

XAES0002 MEDDRA VERSION: 5.1

Table LYAS.15. Summary of Laboratory Data
Mean Change from Baseline to Endpoint by Analyte
Study Period II
All Randomized Patients

Lab Test	Lab Unit	Therapy	n	Mean	SD	Mean	SD	Therapy
HCT	1	ATOMOX	63	0.393	0.033	0.004	0.029	.192
		PLACEBO	60	0.393	0.029	-0.003	0.024	
HGB	mmL/L-Fe	ATOMOX	63	8.357	0.643	0.153	0.441	.007
		PLACEBO	60	8.395	0.610	-0.031	0.349	
RBC	TI/L	ATOMOX	63	4.752	0.385	0.052	0.251	.290
		PLACEBO	60	4.757	0.324	0.008	0.202	
WBC	GI/L	ATOMOX	63	7.146	1.975	-0.332	1.897	.239
		PLACEBO	60	7.223	1.770	0.174	2.307	
BANDS	GI/L	ATOMOX	63	0.000	0.000	0.003	0.020	.963
		PLACEBO	60	0.000	0.000	0.005	0.041	
POLYS	GI/L	ATOMOX	63	3.762	1.423	-0.305	1.428	.182
		PLACEBO	60	3.875	1.351	0.238	2.063	
LYMPHS	GI/L	ATOMOX	63	2.627	0.724	0.050	0.621	.297
		PLACEBO	60	2.649	0.709	-0.070	0.628	
MONOS	GI/L	ATOMOX	63	0.437	0.191	-0.038	0.149	.031
		PLACEBO	60	0.412	0.104	0.024	0.132	
EOSN	GI/L	ATOMOX	63	0.258	0.244	-0.032	0.236	.537
		PLACEBO	60	0.229	0.177	-0.017	0.156	
BASO	GI/L	ATOMOX	63	0.051	0.024	0.002	0.031	.249
		PLACEBO	60	0.058	0.037	-0.008	0.044	
MCV	fL	ATOMOX	63	82.841	6.091	-0.143	3.914	.582
		PLACEBO	60	82.733	4.364	-0.583	3.797	
PLTCT	GI/L	ATOMOX	61	301.459	72.342	1.443	50.044	.385
		PLACEBO	60	305.200	64.372	-3.417	50.472	
U-SPGR	NO UNITS	ATOMOX	61	1.024	0.007	0.002	0.009	.333
		PLACEBO	62	1.026	0.008	0.000	0.009	
AST	U/L	ATOMOX	64	28.313	7.167	-2.953	5.818	.015
		PLACEBO	58	26.776	5.205	-0.466	3.705	
ALT	U/L	ATOMOX	64	17.984	8.056	-3.281	6.968	.007
		PLACEBO	59	17.508	6.015	-0.153	6.125	
CPK	U/L	ATOMOX	64	139.484	64.328	-24.563	69.790	.002
		PLACEBO	59	139.339	68.878	1.576	56.344	
ALKPH	U/L	ATOMOX	64	244.344	77.130	-17.156	40.140	.004
		PLACEBO	59	239.661	87.198	6.102	48.043	
GGT	U/L	ATOMOX	64	12.516	3.290	-1.016	3.089	.580
		PLACEBO	59	13.847	5.010	-0.576	3.701	
BUN	mmol/L	ATOMOX	64	4.814	1.233	-0.050	1.180	.448
		PLACEBO	59	4.750	1.210	0.115	1.385	
CALC	mmol/L	ATOMOX	64	2.488	0.085	-0.011	0.087	.440
		PLACEBO	59	2.484	0.073	-0.000	0.089	
PHOS	mmol/L	ATOMOX	64	1.647	0.187	-0.055	0.206	.131
		PLACEBO	59	1.620	0.206	0.007	0.221	
SODIUM	mmol/L	ATOMOX	64	142.406	2.556	-1.063	2.666	.449
		PLACEBO	59	142.610	2.659	-0.661	3.198	
POTAS	mmol/L	ATOMOX	64	4.217	0.295	-0.103	0.441	.736
		PLACEBO	58	4.350	0.380	-0.103	0.429	

(continued)

Table LYAS.15. Summary of Laboratory Data
Mean Change from Baseline to Endpoint by Analyte
Study Period II
All Randomized Patients (continued)

Lab Test	Lab Unit	Therapy	n	Mean	SD	Mean	SD	Therapy
CHLOR	mmol/L	ATOMOX	64	104.531	2.443	0.172	3.016	.656
		PLACEBO	59	104.458	2.555	0.525	2.706	
TPROT	g/L	ATOMOX	64	72.766	4.556	-0.609	3.490	.192
		PLACEBO	59	73.644	3.580	-1.373	3.600	
ALBUM	g/L	ATOMOX	64	44.938	3.275	-0.344	2.674	.628
		PLACEBO	59	44.695	2.660	-0.339	3.214	
NFGLU	mmol/L	ATOMOX	64	5.104	0.839	0.083	1.103	.768
		PLACEBO	59	5.117	0.854	0.109	0.973	
UR AC	umol/L	ATOMOX	64	250.560	69.507	-16.543	43.276	.017
		PLACEBO	59	264.434	77.712	3.226	45.838	
CHOL	mmol/L	ATOMOX	64	4.382	0.816	-0.101	0.464	.363
		PLACEBO	59	4.225	0.744	-0.174	0.475	
BICARB	mmol/L	ATOMOX	64	21.084	1.956	1.002	2.337	.030
		PLACEBO	59	21.812	1.864	0.102	2.430	
CREAT	umol/L	ATOMOX	64	50.554	12.449	1.519	10.395	.395
		PLACEBO	59	52.591	14.161	-1.049	9.861	
T.BILI	umol/L	ATOMOX	52	7.761	4.673	0.395	2.548	.581
		PLACEBO	47	6.549	3.895	0.400	2.576	

Population: All Enrolled Patients.

Baseline: Visits 1-2, Endpoint: Visits 3 - 11

Input data from RMP.SAS.B4ZM.L.MCLYASSW

Output stored as RMP.B4Z0.LYASCTRM.FINAL(LS6S1008)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks:
PROC GLM model=treatment.

Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.

XLAS0006

Table LYAS.15. **Summary of Laboratory Data**
Mean Change from Baseline to Endpoint by Analyte
Study Period II
All Randomized Patients (concluded)

Legend of Lab Test Code Abbreviations:

Abbrev.	Description
HCT	HEMATOCRIT
HGB	HEMOGLOBIN
RBC	ERYTHROCYTE COUNT
WBC	LEUKOCYTE COUNT
BANDS	BANDS
POLYS	NEUTROPHILS, SEGMENTED
LYMPHS	LYMPHOCYTES
MONOS	MONOCYTES
EOSN	EOSINOPHILS
BASO	BASOPHILS
MCV	MEAN CELL VOLUME (MCV)
PLTCT	PLATELET COUNT
U-SPGR	UA-SPECIFIC GRAVITY
AST	AST/SGOT
ALT	ALT/SGPT
CPK	CREATINE PHOSPHOKINASE
ALKPH	ALKALINE PHOSPHATASE
GGT	GGT (GGPT/SGGT/YGGT)
BUN	UREA NITROGEN
CALC	CALCIUM
PHOS	INORGANIC PHOSPHORUS
SODIUM	SODIUM
POTAS	POTASSIUM
CHLOR	CHLORIDE
TPROT	TOTAL PROTEIN
ALBUM	ALBUMIN
NFGLU	GLUCOSE, NON-FASTING
UR AC	URIC ACID
CHOL	CHOLESTEROL
BICARB	BICARBONATE, HCO ₃
CREAT	CREATININE
T.BILI	BILIRUBIN, TOTAL

Table LYAS.16.

Vital Signs
Change from Baseline to Endpoint
All Randomized Patients

		-----Baseline-----			Change to -----Endpoint-----		p-Values
Variables	Therapy	n	Mean	SD	Mean	SD	Therapy
DIASAVG	ATOMOX	75	61.500	8.964	3.307	10.950	.083
	PLACEBO	70	63.421	8.722	0.507	8.047	
SYSAVG	ATOMOX	75	104.700	10.144	2.900	10.385	.147
	PLACEBO	70	107.064	10.837	0.364	10.546	
PULSAVG	ATOMOX	75	82.253	11.172	8.293	11.967	<.001
	PLACEBO	70	84.143	12.377	-1.214	12.671	
WEIGHT	ATOMOX	75	40.275	13.294	-0.909	1.949	<.001
	PLACEBO	70	45.443	15.657	1.644	2.323	
HEIGHT	ATOMOX	69	143.535	14.978	1.923	3.698	.647
	PLACEBO	66	148.382	14.700	1.698	1.507	
TEMP	ATOMOX	75	36.600	0.468	-0.037	0.655	.865
	PLACEBO	70	36.674	0.537	-0.056	0.641	

Population: All Enrolled Patients.

Baseline: Visits 1-2, Endpoint: Visits 3 - 11

Input data from RMP.SAS.B4ZM.L.MCLYASSW

Output stored as RMP.B4Z0.LYASCTRM.FINAL(VI6L1008)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=treatment.

Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.XLAS0006

Legend of Variable Abbreviations:

Abbrev.	Description
DIASAVG	Diastolic BP Average
HEIGHT	Height in CM
PULSAVG	Heart Rate Average
SYSAVG	Systolic BP Average
TEMP	Temperature in Centigrade
WEIGHT	Weight in KG

**Table LYAS.17. Electrocardiogram Intervals and Heart Rate
Mean Change from Baseline to Endpoint
All Randomized Patients**

		-----Baseline-----		Change to -----Endpoint-----		- p-Values -	
Variables Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy Pair- (Int*1) wse*2
RR	ATOMOX	75	814.729	133.580	-88.046	120.047	<.001
	PLACEBO	69	789.705	114.733	18.637	111.643	<.001
PR	ATOMOX	75	134.240	16.794	-2.933	10.912	.002
	PLACEBO	69	137.130	17.985	1.768	10.984	.002
QRS	ATOMOX	75	83.840	10.814	0.000	5.882	.169
	PLACEBO	69	82.841	8.405	0.928	5.001	.169
QT	ATOMOX	75	375.840	29.661	-19.520	24.832	<.001
	PLACEBO	69	367.565	25.249	2.812	21.078	<.001
QTCB	ATOMOX	75	417.627	15.495	2.307	14.747	.237
	PLACEBO	69	414.565	16.448	-1.232	15.074	.237
QTCF	ATOMOX	75	403.222	15.521	-5.735	12.446	<.001
	PLACEBO	69	398.371	15.115	0.160	12.328	<.001
HR	ATOMOX	75	75.533	11.967	9.733	13.076	<.001
	PLACEBO	69	77.478	10.725	-1.464	10.390	<.001

Population: All Enrolled Patients.

Baseline: Visits 1-2, Endpoint: Visits 3 - 11

Input data from RMP.SAS.B4ZM.L.MCLYASSW

Output stored as RMP.B4Z0.LYASCTRM.FINAL(EC6L4008)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks:
PROC GLM model=treatment.

*2 Least-squares mean option in PROC GLM from the ANOVA on the ranks using the
mean square for error.XLAS0006

Legend of Variable Abbreviations:

Abbrev.	Description
HR	ECG Heart Rate
PR	PR Interval
QRS	QRS Interval
QT	QT Interval
QTCB	Bazett QTC Interval
QTCF	Fridericia QTC Interval
RR	RR Interval

Atomoxetine hydrochloride
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Approved: 19 April 2005

**Table LYAS.18. PSI Total and Subscale Scores
 Mean Change from Baseline to Endpoint
 Randomized Patients
 Study Period II**

Treatment Group	n	Baseline		Endpoint		Change		Within p-Value(A)	Between p-value(B)
		Mean	SD	Mean	SD	Mean	SD		
Total Score									
Atomox.	73	247.1	47.6	231.9	50.2	-15.2	32.9	<.001	.517
PLACEBO	68	230.0	51.5	219.0	48.7	-11.1	32.4	.020	----
Two sided 95% C.I.: (-7.36 , 14.54)									
Total Child Score									
Atomox.	73	133.0	26.8	120.6	26.8	-12.4	21.4	<.001	.449
PLACEBO	68	125.0	28.6	115.2	26.8	-9.8	16.5	<.001	----
Two sided 95% C.I.: (-3.90 , 8.77)									
Total Parent Score									
Atomox.	73	114.0	28.1	111.3	28.8	-2.8	18.6	.068	.725
PLACEBO	68	105.0	27.3	103.7	25.9	-1.3	20.2	.985	----
Two sided 95% C.I.: (-5.35 , 7.66)									

(A) Within p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator and treatment. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAS.SASPGM(EFPSIK1)

Summary ID# 5001

Clinical Study Summary: Study B4Z-MC-LYAU

A Double-Blind Crossover Study of Tomoxetine Hydrochloride and Methylphenidate Effects on Neural Activity in Attention-Deficit/Hyperactivity Disorder

Date summary approved by Lilly: 16 February 2007

Brief Summary of Results

This was a 16-week (approximately), double-blind, crossover comparison of tomoxetine and methylphenidate in children aged at least 6 years and <13 years with Attention-Deficit/Hyperactivity Disorder (ADHD) who had not been on treatment for at least 3 weeks prior to starting the study. The primary objective of Study B4Z-MC-LYAU (LYAU) was to test the hypothesis that regional neuronal activation of prefrontal cortical and subcortical areas after approximately 6 weeks of treatment with tomoxetine in children with ADHD was greater than baseline neural activity.

Due to a malfunction of the functional Magnetic Resonance Imaging (fMRI) equipment at the investigative site during data recording, an analysis of the efficacy of tomoxetine on regional neuronal activation of prefrontal cortical and subcortical areas is unavailable. The following summary provides the available data from this trial.

Title of Study: A Double-Blind Crossover Study of Tomoxetine Hydrochloride and Methylphenidate Effects on Neural Activity in Attention-Deficit/Hyperactivity Disorder	
Investigators: This single-center study included 3 principal investigators.	
Study Center: This study was conducted at 1 study center in 1 region.	
Length of Study: 1 year 7 months First patient enrolled (assigned to therapy): 16 February 2002 Last patient completed: 20 September 2003	Phase of Development: 3
Objectives: The primary objective of Study LYAU was to test the hypothesis that regional neuronal activation of prefrontal cortical and subcortical areas after approximately 6 weeks of treatment with tomoxetine (maximum total daily dose 1.8 mg/kg/day given as a twice-daily [BID] dose, not to exceed 120-mg dose regardless of weight) in children with ADHD was greater than baseline neural activity. Extent of activation was measured during 3 cognitive tasks (probes of attention, working memory, and inhibitory	

control) which were performed while undergoing blood oxygenation level dependent (BOLD), fMRI before treatment (baseline scan) in comparison with posttreatment with tomoxetine.

The secondary objectives of the study were as follows:

- To test the hypothesis that the percentage of increase in activity during specific cognitive performance tasks in prefrontal cortical and subcortical areas after approximately 6 weeks of treatment with tomoxetine in children with ADHD was greater than baseline (unmedicated condition). The 3 cognitive tasks are probes of attention, working memory, and inhibitory control performed while undergoing BOLD fMRI.
- To test the hypothesis that the extent of neuronal activation and percentage of increase in activation in prefrontal cortical and subcortical areas following approximately 6 weeks of treatment with tomoxetine were different from those following 6 weeks of treatment with methylphenidate (Ritalin®) (maximum total daily dose 1.5 mg/kg given as a 3 times daily [TID] dose). The extent (volume of activation) and percentage increase in activity of frontal and subcortical structures were measured during 3 cognitive tasks: probes of attention, working memory, and inhibitory control performed while undergoing BOLD fMRI before treatment (baseline scan) in comparison with posttreatment with tomoxetine and methylphenidate.
- To test the hypothesis that changes in percentage of neural activation (and/or decreased activation volume) of dorso lateral prefrontal cortex (DLPFC) were correlated with changes in working memory and inhibitory control task performance
- To test the hypothesis that changes in percentage of neural activation (and/or decreased activation volume) of DLPFC were correlated with changes in clinical measures of ADHD symptomatology including the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv), Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity (CGI-ADHD-S), and others
- To assess the safety and tolerability of tomoxetine through the collection of data on adverse events (AEs), vital signs, laboratory tests, and electrocardiograms (ECGs).

The investigator requested an addendum to the protocol to gather baseline data in healthy controls. The addition of control subjects without ADHD enabled determinations as to whether there were any practice effects associated with multiple administrations of the cognitive battery. In addition, it was possible to test the hypothesis that ADHD children exhibited more diffuse activation and less striatal activation during task performance compared to normal children.

Other objectives that were tested by the inclusion of normal controls included:

- To test the hypothesis that unmedicated ADHD children exhibited more diffuse task-related activation when compared with normal children
- To test the hypothesis that task-related activation in medicated ADHD children approximated task-related activation when compared to normal children
- To test the hypothesis that task-related activation in medicated ADHD children did not vary significantly when the tasks were repeated 5 to 6 weeks apart.

Study Design: This study was a 16-week (approximately), double-blind, crossover comparison of tomoxetine and methylphenidate in children aged at least 6 years and <13 years with ADHD who had not been on treatment for at least 3 weeks prior to starting the study. Study Period I was the screening, medication washout, and assessment phase. Study Period II consisted of the double-blind, acute treatment period. Study Period III was the study drug washout period, where patients crossed over, leading into Study Period IV, a second double-blind, acute treatment period. Study Period V was the discontinuation of study drug phase [See Figure 1].

For the study addendum, there was a maximum of 4 visits completed by at least half the children: Visit 1 (Screening), Visit 2 (Practice Session in Mock Scanner), Visit 3 (Scanning Procedure and tests) and Visit 4 (Scanning Procedure and tests). Visits 1 and 2 procedures could be performed on the same day if time allowed. One-half of the sample was asked to repeat the scan session about 5 to 6 weeks after the first scan in order to assess for practice effects. Control children and parents were screened using the same structured interview [Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children, (KSADS)] completed by the ADHD children and parents. Control children completed the same task training as ADHD children. They also underwent a scan session identical to the scan session used with the ADHD sample. The ADHDRS assessment and CGI-ADHD-S were performed at Visit 1 only.

Number of Patients:

Planned Completers: 16

Randomized: 8 tomoxetine then methylphenidate, 8 methylphenidate then tomoxetine

Completed: 5 tomoxetine then methylphenidate, 6 methylphenidate then tomoxetine

Main Criteria for Inclusion: Subjects must be right-handed and meet the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria for ADHD as assessed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version: Behavioral Disorders Supplement (K-SADS-PL:Behavioral) at Visit 1 and by investigator assessment using DSM-IV criteria. In addition, all subjects must have scored at least 1.0 standard deviation above norms for age and sex on either subscale or the combined scale for his or her diagnostic subtype of the ADHDRS-IV-Parent:Inv at Visit 1.

Inclusion criteria for the study addendum required subjects to be right-handed, at least 6 years of age, but <13 years of age, who had not yet reached Tanner Stage II, and who were generally healthy without a history of neurological illness, seizures, or head trauma.

Test Product, Dose, and Mode of Administration: Tomoxetine: Administered as divided (BID) dose beginning at .5 mg/kg/day and with a maximum dose of 1.8 mg/kg/day, supplied in 2.5-, 5-, 10-, 20-, 25-, and 40-mg capsules. Placebo: Placebo capsules, given once-daily (QD; noontime).

Note: patients randomized to tomoxetine received 2 doses of tomoxetine *and* 1 dose of placebo per day.

Comparator Dose and Mode of Administration: Methylphenidate: 0.45 to 1.8 mg/kg/day TID; Methylphenidate capsules, 5 mg and 10 mg.

Duration of Treatment: 12 weeks of active treatment (approximately 16 weeks of study participation).

Variables:

Efficacy: fMRI, ADHDRS-IV-Parent:Inv, CGI-ADHD-S, Task Performance

Safety: AEs, laboratory analytes, vital signs, ECGs

Note: Subjects in the study addendum were not treated with tomoxetine or methylphenidate; therefore, data from this group is not included in this summary.

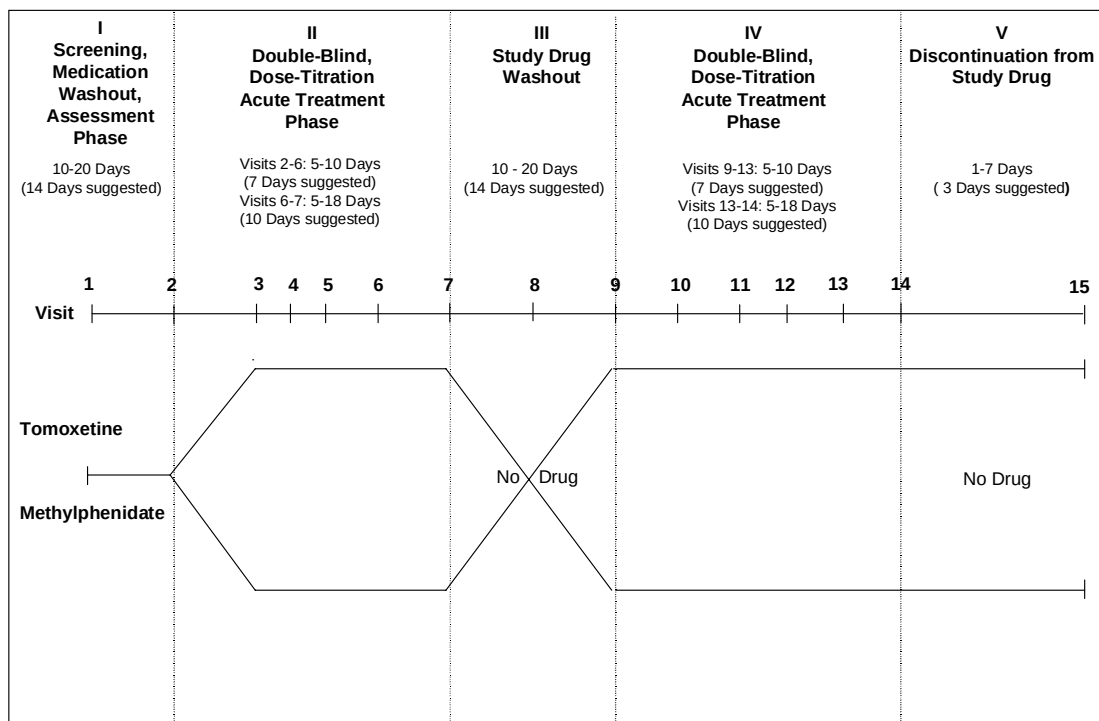
Evaluation Methods:

Primary Efficacy: A whole-brain, 2-way (Treatment X Order), within-subject, repeated-measures analysis of variance (ANOVA) for each task activation map using an *a priori* threshold of $p=.002$ was used to identify those regions whose activation was associated with a tomoxetine and methylphenidate treatment. Alternatively, regions of interest (ROI) analysis utilized a mean baseline activation map as a mask to define activated ROIs for each subject. The resultant activation mask was applied to each treatment condition yielding mean percent and extent of activation for each condition within the ROI.

Secondary Efficacy: Changes in secondary efficacy measures were summarized by sequence group and treatment period. The sum and difference of the scores for each period for each subject was computed. The test for carryover effect was performed by comparing the sum score values between the 2 sequence groups using the Wilcoxon rank sum test. The test for treatment effect (assuming no carryover effect) was performed using the difference score values between the 2 sequence groups using the Wilcoxon rank sum test. If a statistically significant carryover effect was found ($p<.10$) for a variable, then a treatment comparison was performed using the Wilcoxon rank sum test only on data from the first crossover period. Treatment group comparisons were performed only on subjects who did not discontinue prior to entering the second treatment period.

Safety: For treatment-emergent computations (AEs and abnormal, high, or low laboratory values), Visits 1 and 2 were used as baseline. Categorical safety parameters were analyzed by first placing subjects into 1 of 4 classifications based on their response in each treatment period (subjects experiencing no incidence in either Period I or II [0,0], no incidence in Period I and incidence in Period II [0,1], incidence in Period I and no incidence in Period II [1,0], and incidence in both Periods I and II [1,1]). The frequency of subjects in each classification was then obtained for each sequence group. Carryover effect was determined by combining the [0,1] and [1,0] classifications within each sequence group and performing a chi-square test on the resulting 2 by 3 contingency table. Treatment effect was assessed by comparing the [1,0] and [0,1] categories for each sequence group using a chi-square test on the 2 by 2 contingency table. Changes in vital signs and laboratory data were analyzed similar to the secondary efficacy measures.

Study Design



Note: Visits 2, 7, and 14 will have an fMRI administered.

Figure 1. Illustration of study design for Study B4Z-MC-LYAU.

Patient Disposition

A total of 16 patients were randomized in this trial, 8 patients who were initially randomized to tomoxetine and then crossed over to methylphenidate, and 8 patients initially randomized to methylphenidate who crossed over to tomoxetine. Thirteen patients completed Study Period II, and 11 patients completed the entire study.

Primary Efficacy Measures

Due to a malfunction of the fMRI equipment at the investigative site during data recording, an analysis of the efficacy of tomoxetine on regional neuronal activation of prefrontal cortical and subcortical areas is unavailable.

Secondary Efficacy Measures

Both methylphenidate and tomoxetine were associated with symptomatic improvement on the ADHDRS-IV-Parent:Inv total and subscales and the CGI-ADHD-S score compared with study baseline. For the ADHDRS-IV-Parent:Inv rating scale score, a responder to either tomoxetine or methylphenidate was considered to be a patient who achieved at the end of the treatment period for the relevant drug a $\geq 25\%$ decrease from baseline.

Safety

Adverse Events

There were no deaths or serious adverse events (SAEs) in this study. During Study Period II, 10 patients experienced at least 1 treatment-emergent adverse event (TEAE). The most common TEAEs were decreased appetite, headache, initial insomnia, and irritability. Three patients reported at least 1 TEAE during Study Period IV. The most common TEAEs were decreased appetite and irritability. In the entire study, 2 patients discontinued due to AEs. There were no statistically significant differences between treatment groups for TEAEs and discontinuations due to AEs.

Vital Signs

There were no statistically significant differences in vital signs or ECG measurements (including QT intervals) between treatment groups.

Summary ID# 5002

Clinical Study Summary: Study B4Z-US-LYAV

Sleep and Cognitive/Neuropsychological Function in Children with Attention-Deficit/Hyperactivity Disorder Before and During Treatment with Tomoxetine Hydrochloride and Stimulants

Date summary approved by Lilly: 14 March 2007

Brief Summary of Results

Atomoxetine hydrochloride, formerly known as tomoxetine or tomoxetine hydrochloride, was changed in agreement with the United States Adopted Names (USAN) council to minimize the possibility of confusion with tamoxifen, which is often used in the treatment of breast cancer. However, this summary uses tomoxetine (instead of atomoxetine) to be consistent with the wording of the protocol that was written prior to the name change.

Efficacy

For the primary measure, time to onset of persistent sleep, tomoxetine was statistically superior to methylphenidate ($p < .001$). For tomoxetine, the reported mean change was a 12.1-minute increase in time to onset of persistent sleep versus a 39.2-minute increase for methylphenidate.

Polysomnography data collected in a laboratory setting showed statistically significantly less time to onset of persistent sleep, less time to onset of first sleep epoch, increase in time in Stage 2 sleep, lower decrease in number of awakenings, less time in rapid eye movement (REM) sleep, greater increase in REM latency, and greater increase in sleep efficiency, for tomoxetine compared with methylphenidate.

Safety and Tolerability

There were no deaths reported in this study. Overall, there were 10 discontinuations: 5 patients discontinued while being treated with methylphenidate and 5 patients

discontinued while being treated with tomoxetine. One patient discontinued due to an adverse event (AE) while being treated with methylphenidate. Other reasons for discontinuation included lost to follow-up (4), protocol violation (2), and patient decision (3).

Treatment-emergent adverse events (TEAEs) were reported. There were no serious adverse events (SAEs) reported. Insomnia ($p < .001$), initial insomnia ($p = .062$), and anorexia ($p = .03$) were reported more often when patients were treated with methylphenidate. Compared to patients treated with methylphenidate, patients in the tomoxetine group reported more somnolence ($p = .057$), fatigue ($p = .121$) and abdominal pain ($p = .248$). There were no significant differences in gastrointestinal events between treatments. No AEs were reported with significantly greater frequency when patients were treated with tomoxetine than with methylphenidate.

Treatment with tomoxetine resulted in significant increases in diastolic blood pressure ($p = .001$) compared with methylphenidate (Study Period II: tomoxetine = +4.99 mmHg, methylphenidate = +3.28 mmHg; Study Period III: tomoxetine = +9.65 mmHg, methylphenidate = +2.38 mmHg). There was a trend ($p = .056$) toward greater increase in pulse for tomoxetine compared with methylphenidate (Study Period II: tomoxetine = +8.26 bpm, methylphenidate = +3.31 bpm; Study Period III: tomoxetine = +1.36 bpm, methylphenidate = -0.89 bpm). There were no other significant differences in vital signs. With both treatments, patients showed a decrease in weight but there was no significant difference between methylphenidate and tomoxetine.

Title of Study: Sleep and Cognitive/Neuropsychological Function in Children with Attention-Deficit/Hyperactivity Disorder Before and During Treatment with Tomoxetine Hydrochloride and Stimulants	
Investigator(s): This multicenter study included 2 principal investigators.	
Study Center(s): This study was conducted at 2 study centers.	
Length of Study: 1 year 4 months Date of first patient enrolled: 22 June 2001 Date of last patient completed: 23 October 2002	Phase of Development: 4
Objectives: The primary objective of this study was to test the hypothesis that the effects of tomoxetine on sleep differ from those of methylphenidate as assessed by time to onset of persistent sleep as measured by actigraphy. The secondary objectives of the study were as follows: • To compare the effects of tomoxetine and methylphenidate on sleep in children with Attention-Deficit/Hyperactivity Disorder (ADHD) as assessed by sleep efficiency (time asleep/time in bed), number of awakenings, time in Stage III or IV sleep, rapid-eye movement (REM) latency, and the total number of REM episodes. • To compare sleep in children with ADHD and that in healthy controls as assessed by sleep efficiency (time asleep/time in bed), number of awakenings, time in Stage III or IV sleep, REM latency, and the total number of REM episodes. • To assess the relationship between symptom change assessed by the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent-Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) and the bedtime-specific items on the Daily Parent Ratings of Evening and Morning Behavior (DPREMB) and time to onset of persistent sleep. • To compare the effects of tomoxetine and methylphenidate on neuropsychological function as assessed by the: Dual Working Memory Task, Stop Signal Task, Stroop, Trail Making Test (Trails A and B), and California Verbal Learning Test® (CVLT). • To compare the efficacy of tomoxetine and methylphenidate in children with ADHD as assessed by change from baseline to endpoint on the ADHDRS-IV-Parent:Inv, Clinical Global Impressions-Severity (CGI-S), DPREMB, Social Skills Rating System-Parent Questionnaire (SSRS-P), and Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) scales. • To compare subjects diagnosed with ADHD with healthy controls on measures of sleep as assessed by actigraph measurements. • To compare the safety and tolerability of tomoxetine and methylphenidate as assessed through collection of data concerning AEs, laboratory analyses, and electrocardiograms (ECGs).	
Study Design: This was a multicenter, Phase 4, double-blind, order-randomized crossover study of tomoxetine and methylphenidate in children and adolescents with ADHD. The active treatment period was approximately 6 weeks for each treatment.	
Number of Patients: Planned: 60 randomized patients who completed both study periods – anticipated that it would require 86 patients randomized. The investigators planned for 40 healthy volunteers as well. Evaluated: Approximately 60 ADHD subjects who received both treatments and 40 healthy control (non-ADHD) subjects who received no treatment and were evaluated at baseline only. Study Period II: 44 patients were randomized to tomoxetine and 41 patients were randomized to methylphenidate. Study Period III: 37 patients were randomized to crossover treatment with tomoxetine and 42 patients were randomized to crossover treatment with methylphenidate. Healthy control subjects: 46 subjects were evaluated at baseline.	

Diagnosis and Main Criteria for Inclusion: Patients with ADHD were male and female patients at least 6 years old but <15 years of age at Visit 1 with Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) diagnosis of ADHD who had to have ADHD-Rating Scale (ADHD-RS) scores at least 1.0 standard deviation above age and gender norms for their subtype at Visits 1 and 3. Healthy subjects were male and female patients at least 6 years old but <15 years of age at Visit 1 with no current or past psychiatric illness (including ADHD) who had to have scores on the ADHD-RS <1.0 standard deviation above age and gender norms for their subtype and no history of sleep disorder.

Test Product, Dose, and Mode of Administration: Tomoxetine administered orally twice daily. Mean final dose: 1.58 mg/kg (Study Period II), 1.53 mg/kg (Study Period III).

Reference Therapy, Dose, and Mode of Administration: Methylphenidate was administered orally 3 times daily. Mean final dose: 1.14 mg/kg (Study Period II), 1.10 mg/kg (Study Period III).

Duration of Treatment: Approximately 6 weeks for each active treatment period.

Variables:

Efficacy: The primary efficacy assessment was based on the change from baseline to endpoint in time to onset of persistent sleep as measured by actigraphy. Polysomnography was performed in a lab setting on a subset of patients to capture data on other sleep-related secondary efficacy measures including: sleep efficiency, number of awakenings, number of arousals, time in each sleep stage, time to onset of first sleep epoch, total time in bed, REM latency, and the total number of REM episodes. Bedtime-specific behaviors using the DPREMB were also collected via daily parent ratings using electronic data capture and from the patient and parent via a paper diary.

Secondary measures that assessed the severity of ADHD and depressive symptoms were: ADHDRS-IV-Parent:Inv, Clinical Global Impressions-ADHD Severity (CGI-ADHD-S), Clinical Global Impressions-Improvement (CGI-I), CPRS-R:S, and the Children's Depression Rating Scale Revised (CDRS-R).

Other secondary efficacy measures were the SSRS-P and the Assessment of Affective Range (AAR).

Cognitive measures included: the Dual Working Memory Task, the Stop Signal Task, Trails A and B, Stroop, CVLT, and the Wechsler Intelligence Scale for Children- 3rd Edition-Revised (WISC III-R) working memory and mazes.

Safety: Safety was evaluated through the collection and reporting of discontinuation rates, TEAEs, laboratory analytes, ECGs, and vital signs.

Evaluation Methods:

Statistical Methods: Since this study had a crossover design, the population of completer patients using data over both crossover periods was considered primary for analyses of efficacy. The study was designed with sufficient washout period to prevent carryover effects; therefore, data were combined from both crossover periods to assess treatment differences. To test for treatment differences in continuous data, the sums and differences of change scores were computed. Safety analyses included all randomized patients who had taken at least 1 dose of study drug and incorporated data from both crossover periods.

All analyses were conducted on an intent-to-treat (ITT) basis unless otherwise specified. Treatment effects were evaluated based on a 2-sided significance level of 0.05. No adjustments for multiple comparisons were made. For all total scores calculated from individual items, if any of the individual items were missing, the corresponding total score was considered missing. For analyses of the diary and actigraphy, patients were required to have 70% of all possible scores during each visit interval to be included.

After datalock, it was noted that 4 patients had actiwatches that were not functioning properly. Their data was excluded from analysis. For comparison of ADHD and healthy control data, the rank scores rather than the raw scores were analyzed due to nonnormality of the data.

To adjust for variability in responses, the DPREMB was averaged according to the following algorithm. Three averages were computed: average scores over a 14-day window, an average of the first 7 days of the 14-day window, and an average of the last 7 days of the 14-day window. For the average to have been computed, a patient was required to have scores for at least 9 of 14 days for the 14-day window average or 4 of the 7 days for a 7-day window average. The required completion rate for the DPREMB was lowered from the 70% in the original protocol due to the lower number of patients with 70% or more responses. The weekly window approach was determined after examining the variability in the visit interval for patients. Polysomnographic data was collected over 2 consecutive days during each crossover period. The average of the 2 scores for each crossover period was used in analysis rather than either of the 2 individual measures.

The test for treatment difference was performed by testing whether the sequence term was significant in an analysis of variance (ANOVA) model on the crossover differences in change scores incorporating terms for sequence and investigator.

The analysis method of Nagelkerke was used to analyze incidence of TEAEs. In this method, each subject was categorized according to patient or subject response in each treatment period into one of the following 4 classifications:

- | | | |
|-----|-------|--|
| [1] | (0,0) | 'Failure' in treatment Period I and 'Failure' in treatment Period II |
| [2] | (0,1) | 'Failure' in treatment Period I and 'Success' in treatment Period II |
| [3] | (1,0) | 'Success' in treatment Period I and 'Failure' in treatment Period II |
| [4] | (1,1) | 'Success' in treatment Period I and 'Success' in treatment Period II |

The frequency of subjects in each classification was obtained for each sequence group.

Treatment effects were assessed by combining the (1,1) and (0,0) categories and then performing a chi-square test with 2 degrees of freedom for homogeneity on the resulting 2×3 contingency table. Patients with ADHD and healthy controls were compared using repeated-measures ANOVA with terms for diagnostic group, visit, and group by investigator interaction with an unstructured covariance matrix.

Results:

Patient Demographics

Table 1 provides the baseline demographics for this study.

Table 1. Baseline Demographics

GENDER	NON		MPH		TMX	
	N	PERCENT	N	PERCENT	N	PERCENT
F	26	38.23 %	8	19.51 %	14	31.81 %
M	42	61.76 %	33	80.48 %	30	68.18 %

ORIGIN	NON		MPH		TMX	
	N	PERCENT	N	PERCENT	N	PERCENT
AF	6	8.82 %	8	19.51 %	13	29.54 %
AS	2	2.94 %	0	0.00 %	0	0.00 %
CA	58	85.29 %	32	78.04 %	30	68.18 %
EA	2	2.94 %	0	0.00 %	0	0.00 %
O	0	0.00 %	1	2.43 %	1	2.27 %

PATIENT INFORMATION		N	MEAN	MEDIAN	STD	MAX	MIN
AGE	NON	68	10.407	10.790	2.384	14.833	6.050
	MPH	41	10.282	10.184	2.199	14.989	6.633
	TMX	44	9.984	9.881	1.704	13.281	6.390
BMIV1	NON	66	19.026	17.809	4.112	31.713	11.796
	MPH	41	18.484	17.449	2.964	27.301	15.175
	TMX	43	18.766	18.852	2.649	25.208	14.486
HEIGHTV1	NON	67	140.025	140.000	14.311	166.000	113.500
	MPH	41	142.188	141.000	11.577	168.500	119.000
	TMX	43	140.212	137.000	11.729	166.800	119.000
WEIGHTV1	NON	67	38.319	35.500	13.780	67.600	15.600
	MPH	41	37.817	34.200	9.784	63.000	25.300
	TMX	44	37.527	37.250	9.759	57.000	25.000

Abbreviations: F=female, M=male, AF=African Descent, AS=Western Asian, CA=Caucasian, EA=East/Southeast Asian, O=other.

Patient Disposition

There were no deaths reported in this study. Overall there were 10 discontinuations (see Table 2), 5 patients discontinued while being treated with methylphenidate and 5 patients discontinued while being treated with tomoxetine. One patient discontinued due to an AE while being treated with methylphenidate. Other reasons for discontinuation included lost to follow-up (4), protocol violation (2), and patient decision (3).

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Table 2. Patient Disposition

SUMMARY OF PATIENT DISPOSITION DURING SP II

	MPH			TMX			EXACT			FISHER'S
		N	N	%	N	N	%	P-VALUE		
ADVERSE EVENT	41	1	2.4%	44	0	0.0%	.482			
DEATH	41	0	0.0%	44	0	0.0%				
LACK OF EFFICACY	41	0	0.0%	44	0	0.0%				
LOST TO FOLLOW-UP	41	2	4.9%	44	0	0.0%	.230			
PATIENT DECISION	41	0	0.0%	44	2	4.5%	.495			
PHYSICIAN DECISION	41	0	0.0%	44	0	0.0%				
PROTOCOL VIOLATION	41	1	2.4%	44	0	0.0%	.482			
SATISFACTORY RESPONSE	41	0	0.0%	44	0	0.0%				
SPONSOR DECISION	41	0	0.0%	44	0	0.0%				
STUDY PERIOD II COMPLETE	41	37	90.2%	44	42	95.5%	.423			
TOTAL	41	41	100%	44	44	100%				

POPULATION: ALL ENROLLED PATIENTS

(continued)

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Table 2. Patient Disposition (Concluded)

SUMMARY OF PATIENT DISPOSITION DURING SP III

	MPH			TMX			FISHER'S EXACT
	N	N	%	N	N	%	P-VALUE
ADVERSE EVENT	42	0	0.0%	37	0	0.0%	
DEATH	42	0	0.0%	37	0	0.0%	
LACK OF EFFICACY	42	0	0.0%	37	0	0.0%	
LOST TO FOLLOW-UP	42	0	0.0%	37	2	5.4%	.216
PATIENT DECISION	42	0	0.0%	37	1	2.7%	.468
PHYSICIAN DECISION	42	0	0.0%	37	0	0.0%	
PROTOCOL VIOLATION	42	1	2.4%	37	0	0.0%	1.00
SATISFACTORY RESPONSE	42	0	0.0%	37	0	0.0%	
SPONSOR DECISION	42	0	0.0%	37	0	0.0%	
STUDY PERIOD III COMPLETE	42	41	97.6%	37	34	91.9%	.336
TOTAL	42	42	100%	37	37	100%	

POPULATION: ALL RANDOMIZED PATIENTS WHO ENTERED STUDY PERIOD III

Abbreviations: TMX = tomoxetine; MPH = methylphenidate.

Primary Efficacy Measure

On the primary measure (time to onset of persistent sleep), tomoxetine was statistically superior to methylphenidate ($p < .001$). For tomoxetine, the reported mean change was a 12.1-minute increase in time to onset of persistent sleep versus a 39.2-minute increase for methylphenidate (Table 3). Actigraphy measurements also captured significant differences in assumed sleep time, interrupted sleep time, and number of sleep interruptions with tomoxetine patients showing lower decreases in assumed sleep time ($p < .05$) and greater interrupted sleep time ($p < .05$) compared to methylphenidate. Tomoxetine-treated patients reported a statistically significantly lower decrease in number of sleep interruptions compared with methylphenidate-treated patients (an approximate decrease of 1.31 wake bouts compared with a decrease of 4.36 wake bouts for methylphenidate) (Table 4).

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**Table 3. Actigraph—Sleep Onset Latency (In Minute)
Mean Change from Baseline to Endpoint**

		PERIOD II						PERIOD III							
SEQUENCE	N	BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2		OVERALL		TREATMENT	P-VALUE
		-----		-----		-----		-----		-----		-----			-----
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEDIAN	
SLEEP ONSET LATENCY															
ATX/MPH	27	32.46	28.49	44.35	35.36	11.90	32.25	71.57	49.50	39.11	46.98	12.06#	27.07#	8.62#	<.001
MPH/ATX	23	27.36	20.36	66.75	37.07	39.39	33.06	39.61	27.10	12.25	20.07	39.24*	40.77*	31.78*	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (6.49 , 12.82)															
EFFECT SIZE IS -0.785															

P-VALUE IS BASED ON AN ANOVA MODEL WITH TERMS FOR INVESTIGATOR AND SEQUENCE

TESTING SEQUENCE EFFECT IS EQUAL TO TESTING TREATMENT EFFECT

*: MPH TREATMENT GROUP #: ATX TREATMENT GROUP

RANKED SCORES ARE APPLIED IN THE ANALYSIS DUE TO VIOLATION OF NORMALITY ASSUMPTION

ONLY THOSE PATIENTS WHO COMPLETED BOTH PERIODS AND HAD >=70% DATA SINCE PREVIOUS VISIT ARE INCLUDED IN THE ANALYSIS

POPULATION: ALL RANDOMIZED PATIENTS EXCEPT 7194,7195,7196,7198 ARE INCLUDED

FOUR PATIENTS WERE NOT INCLUDED DUE TO MALFUNCTION OF ACTIWATCH ON THOSE PATIENTS

Abbreviations: ATX = atomoxetine; MPH = methylphenidate; N = number of patients; SD = standard deviation.

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Table 4. Actigraphy Mean Change from Baseline to Endpoint

		PERIOD II						PERIOD III						
SEQUENCE	N	BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2		OVERALL TREATMENT		P-VALUE
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
ASSUMED SLEEP TIME														
MPH/TMX	23	451.11	39.52	428.09	38.91	-23.02	34.59	439.93	44.78	-11.18	44.46	-29.61*	53.00*	.016
TMX/MPH	27	462.77	53.67	444.02	55.91	-18.75	44.61	427.55	69.89	-35.22	64.88	-15.26#	44.25#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(2.73 , 25.73)				
EFFECT SIZE IS 0.294														
INTERRUPTED SLEEP TIME														
MPH/TMX	23	67.57	20.78	58.85	21.96	-8.72	12.96	60.38	19.01	-7.19	11.78	-6.28*	17.48*	.025
TMX/MPH	27	56.17	20.00	62.78	21.11	6.60	14.76	51.97	19.22	-4.21	20.60	0.26#	15.04#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(0.80 , 11.69)				
EFFECT SIZE IS 0.401														
TOTAL SLEEP INTERVAL														
MPH/TMX	23	518.68	37.69	486.94	44.03	-31.74	38.66	500.31	41.06	-18.37	43.39	-35.89*	56.10*	.004
TMX/MPH	27	518.94	50.06	506.80	58.73	-12.14	47.14	479.51	75.69	-39.43	68.10	-15.00#	45.10#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(6.81 , 34.15)				
EFFECT SIZE IS 0.410														
NUMBER OF SLEEP INTERRUPTION														
MPH/TMX	22	32.59	7.62	28.70	8.42	-3.89	4.05	29.97	10.15	-2.61	6.43	-4.36*	6.33*	.011
TMX/MPH	26	31.09	8.10	30.88	10.84	-0.21	7.09	26.34	10.56	-4.75	7.82	-1.31#	6.83#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(0.70 , 5.19)				
EFFECT SIZE IS 0.463														
TOTAL NAP TIME														
MPH/TMX	22	3.92	6.66	4.94	4.45	1.02	5.85	5.99	4.43	2.07	5.18	3.04*	7.92*	.475
TMX/MPH	28	3.12	4.13	9.52	12.82	6.40	12.93	7.75	8.82	4.63	9.02	4.49#	10.41#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-1.68, 3.55)				
EFFECT SIZE IS 0.157														

P-VALUE IS BASED ON AN ANOVA MODEL WITH TERMS OF INVESTIGATOR AND SEQUENCE

TESTING SEQUENCE GROUPS IS EQUAL TO TESTING TREATMENT EFFECT

*: MPH TREATMENT GROUP #: TMX TREATMENT GROUP

ONLY THOSE PATIENTS WHO COMPLETED BOTH PERIODS AND HAD >=70% DATA SINCE PREVIOUS VISIT ARE INCLUDED IN THE ANALYSIS

FOUR PATIENTS WERE NOT INCLUDED DUE TO MALFUNCTION OF ACTIWATCH ON THOSE PATIENTS

Abbreviations: MPH = methylphenidate; N = number of patients; SD = standard deviation; TMX = tomoxetine.

Secondary Efficacy Measures

Patients with ADHD and healthy controls were compared at baseline to assess whether there were differences in sleep patterns apart from any treatment administration. Actigraphy comparison of sleep parameters of healthy subjects (non-ADHD and no sleep problems) and ADHD patients (Table 5) showed that healthy subjects had a statistically significantly longer total sleep interval (median time 26.27 minutes greater, $p < .001$) compared to children with ADHD, but healthy subjects also exhibited more sleep interruptions (median 12.99 more sleep interruptions, $p < .001$). Although the median time to onset of sleep for healthy patients was 32.43 minutes compared with 25.10 minutes for ADHD patients ($p < .001$), healthy patients had a longer assumed sleep time (median of 495.42 minutes compared with 457.61 minutes, $p < .001$).

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Table 5. Actigraphy Comparison of Sleep Parameters of Healthy Subjects and ADHD Patients

VARCLAS	GROUP	N	MEANB	SDB	PROB	MEDIANB	RANK
ACTIGRAPHY ACTUAL NAP TIME IN MINUTES	ADHD	80	4.02	5.93	.494	1.77	<.001
ACTIGRAPHY ACTUAL NAP TIME IN MINUTES	HEALTHY	45	3.28	3.83		1.82	
ACTIGRAPHY ACTUAL SLEEP IN MINUTES	ADHD	80	460.30	46.86	.001	457.61	<.001
ACTIGRAPHY ACTUAL SLEEP IN MINUTES	HEALTHY	45	489.39	39.22		495.42	
ACTIGRAPHY NOCTURNAL MOVEMENT TIME IN MINS	ADHD	80	56.70	19.64	.002	53.00	<.001
ACTIGRAPHY NOCTURNAL MOVEMENT TIME IN MINS	HEALTHY	45	44.49	17.93		40.67	
ACTIGRAPHY NUMBER OF AWAKE BOUTS/BODY MOVEMENT	ADHD	80	35.33	12.10	<.001	32.68	<.001
ACTIGRAPHY NUMBER OF AWAKE BOUTS/BODY MOVEMENT	HEALTHY	45	44.45	14.41		45.67	
ACTIGRAPHY TIME TO ONSET OF SLEEP IN MINUTES	ADHD	80	31.44	23.07	.795	25.10	<.001
ACTIGRAPHY TIME TO ONSET OF SLEEP IN MINUTES	HEALTHY	45	32.94	17.39		32.43	
ACTIGRAPHY TOTAL SLEEP IN MINUTES	ADHD	80	517.01	46.19	.056	519.48	<.001
ACTIGRAPHY TOTAL SLEEP IN MINUTES	HEALTHY	45	533.88	40.80		545.75	
ACTIGRAPHY TOTAL TIME IN BED	ADHD	80	548.45	47.53	.045	552.18	<.001
ACTIGRAPHY TOTAL TIME IN BED	HEALTHY	45	566.82	40.58		571.75	

POPULATION:ALL ENTERED HEALTHY SUBJECTS AND ADHD PATIENTS AT BASELINE EXCLUDES

FOUR PATIENTS WHICH ARE NOT INCLUDED FOR THE PURPOSE OF SENSITIVITY ANALYSIS

VISIT LEVEL AVERAGE IS IMPUTED IF THE PATIENT HAVE MORE THAN 70% OF NONMISSING DATA ON EACH VISIT INTERVAL

TOTAL SLEEP TIME IS SUMMATION OF ACTUAL SLEEP TIME AND ACTUAL AWAKE TIME

TOTAL TIME IN BED IS SUMMATION OF TOTAL SLEEP TIME AND TIME TO ONSET OF SLEEP

PROB IS FROM AN ANOVA MODEL WITH TERM FOR INVESTIGATOR AND GROUP

PROB_RANK IS FROM SEMI-PARAMETRIC METHOD WITH THE SAME TERMS FOR INVESTIGATOR AND GROUP

Abbreviations: ADHD = attention-deficit hyperactivity disorder; MEANB = baseline mean; MEDIANB = baseline median; MINS = minutes; N = number of patients; SDB = baseline standard deviation.

Polysomnography data collected for tomoxetine-treated patients compared with methylphenidate-treated patients (Table 6) in a laboratory setting showed: statistically significantly less time to onset of persistent sleep, less time to onset of first sleep epoch, increase in time in Stage 2 sleep, lower decrease in number of awakenings, less time in REM sleep, greater increase in REM latency, and greater increase in sleep efficiency.

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Table 6. Polysomnography Mean Change from Baseline to Endpoint

		PERIOD II						PERIOD III				OVERALL		EFFECT SIZE	P-VALUE
		BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2		TREATMENT			
SEQUENCE	N	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD		
TIME TO ONSET OF FIRST SLEEP EPOCH															
ATX/MPH	21	13.38	10.50	15.29	12.86	1.90	11.84	26.71	25.27	13.33	20.14	-0.31#	11.93#	-0.95	<.001
MPH/ATX	18	19.33	13.43	40.17	32.83	20.83	25.20	16.44	11.39	-2.89	11.83	16.79*	22.63*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(9.41 , 25.84)					
TIME TO ONSET OF PERSISTENT SLEEP															
ATX/MPH	21	15.57	10.58	18.05	14.52	2.48	12.44	28.57	24.65	13.00	18.86	-0.22#	12.98#	-0.99	<.001
MPH/ATX	18	23.64	14.66	44.89	33.48	21.25	22.33	20.28	12.85	-3.36	13.22	16.81*	20.68*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(9.23 , 25.88)					
PERCENTAGE OF TIME IN SLEEP STAGE1															
ATX/MPH	21	0.05	0.05	0.04	0.05	-0.01	0.05	0.03	0.03	-0.02	0.03	-0.01#	0.04#	0.08	.910
MPH/ATX	18	0.03	0.03	0.03	0.07	0.00	0.04	0.03	0.02	-0.00	0.01	-0.01*	0.04*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.01 , 0.01)					
PERCENTAGE OF TIME IN SLEEP STAGE2															
ATX/MPH	21	0.47	0.08	0.51	0.07	0.05	0.10	0.52	0.06	0.06	0.07	0.06#	0.10#	0.28	.042
MPH/ATX	18	0.47	0.07	0.47	0.08	0.00	0.11	0.54	0.09	0.07	0.10	0.03*	0.09*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.06 , -0.00)					
PERCENTAGE OF TIME IN SLEEP STAGE3/STAGE4															
ATX/MPH	21	0.29	0.07	0.26	0.06	-0.03	0.07	0.25	0.05	-0.04	0.06	-0.04#	0.08#	-0.03	.771
MPH/ATX	18	0.30	0.08	0.27	0.07	-0.03	0.07	0.25	0.08	-0.04	0.09	-0.03*	0.06*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.01 , 0.02)					
PERCENTAGE OF TIME IN REM SLEEP															
ATX/MPH	21	0.19	0.06	0.18	0.04	-0.00	0.06	0.19	0.05	0.00	0.04	-0.01#	0.06#	-0.47	.007
MPH/ATX	18	0.20	0.06	0.23	0.06	0.03	0.06	0.18	0.05	-0.02	0.06	0.01*	0.05*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(0.01 , 0.05)					
TOTAL TIME IN SLEEP															
ATX/MPH	21	502.48	41.40	503.98	47.54	1.50	30.38	503.24	42.12	0.76	37.38	1.54#	29.49#	0.19	.165
MPH/ATX	18	493.11	49.03	482.31	45.23	-10.81	28.43	494.69	43.77	1.58	29.29	-4.58*	33.63*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-16.73 , 2.96)					
TOTAL TIME IN BED															
ATX/MPH	21	537.00	50.68	532.81	54.38	-4.19	19.77	537.67	51.90	0.67	32.52	-2.38#	16.95#	-0.16	.276
MPH/ATX	18	527.81	52.47	529.44	46.58	1.64	16.23	527.53	46.78	-0.28	13.20	1.12*	25.98*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-2.87 , 9.75)					

(continued)

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Table 6. Polysomnography Mean Change from Baseline to Endpoint (Concluded)

		PERIOD II						PERIOD III				OVERALL TREATMENT		EFFECT SIZE	P-VALUE
		BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2					
SEQUENCE	N	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD		
NUMBER OF AWAKENINGS															
ATX/MPH	21	14.26	12.26	8.00	4.03	-6.26	12.21	6.02	3.68	-8.24	12.90	-4.41#	9.62#	0.24	.002
MPH/ATX	18	9.36	4.30	4.44	2.76	-4.92	3.08	7.11	4.05	-2.25	4.71	-6.71*	9.73*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-3.81 , -0.90)					
NUMBER OF AROUSALS															
ATX/MPH	21	161.64	100.66	131.60	92.14	-30.05	52.90	140.48	82.13	-21.17	79.41	-6.00#	76.66#	0.02	.872
MPH/ATX	18	118.42	73.26	126.78	92.27	8.36	66.32	140.47	101.73	22.06	91.08	-7.54*	74.22*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-26.10, 22.22)					
REM LATENCY															
ATX/MPH	21	168.29	51.48	211.57	55.83	43.29	72.69	182.69	60.50	14.40	52.34	35.17#	70.27#	0.64	.001
MPH/ATX	18	179.36	45.29	154.86	37.77	-24.50	37.55	205.06	63.58	25.69	68.16	-3.55*	49.59*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-64.53, -17.82)					
SLEEP EFFICIENCY															
ATX/MPH	21	0.94	0.04	0.95	0.03	0.01	0.04	0.94	0.05	0.00	0.04	0.01#	0.04#	0.38	.022
MPH/ATX	18	0.94	0.04	0.91	0.06	-0.02	0.05	0.94	0.05	0.00	0.05	-0.01*	0.05*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.03 , -0.00)					
AROUSAL INDEX															
ATX/MPH	21	19.02	11.26	15.38	10.01	-3.64	5.86	16.40	9.01	-2.63	8.58	-0.87#	8.99#	-0.00	.999
MPH/ATX	18	14.45	8.96	15.68	11.45	1.23	8.19	16.81	11.54	2.36	10.94	-0.85*	8.52*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-2.74 , 2.74)					

P-VALUE IS BASED ON AN ANOVA MODEL WITH TERMS OF INVESTIGATOR AND SEQUENCE
TESTING SEQUENCE GROUPS IS EQUAL TO TESTING TREATMENT EFFECT

*: MPH TREATMENT GROUP #: ATX TREATMENT GROUP

POPULATION: ALL RANDOMIZED PATIENTS WHO FINISHED BOTH OF THE TREATMENT PERIODS

Abbreviations: ATX = atomoxetine; MPH = methylphenidate; SD = standard deviation.

Child sleep diary data (Table 7) indicated that tomoxetine treatment resulted in statistically significant improvement compared with methylphenidate in quality of sleep, time to fall asleep, and ease in getting up in the morning.

Compared to methylphenidate, tomoxetine treatment resulted in statistically significant improvement in morning behaviors as measured by the morning subscores of the DPREMB ($p < .001$) and parent diary morning items ($p < .001$) (Table 8 and Table 9).

Parent and child sleep diaries showed statistically significant differences in sleep characteristics between healthy subjects and patients; children with ADHD and parents of ADHD children reported statistically significantly worse scores on items that assessed: falling sleep, being sleepy, quality of sleep, getting up in the morning, getting ready in the morning, arguing in the morning and evening, losing temper in the morning and evening, completing homework and other tasks in the evening, remaining still at dinner, playing quietly in the evening, inattention in the evening, transitioning activities in the evening, and settling down for bed (Table 8).

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**Table 7. Sleep and Cognitive/Neuropsychological Function in Children with ADHD Before and During Treatment with Tomoxetine Hydrochloride and Stimulant
B4Z-US-LYAV: DPREMB Score from Diary Dataset – Mean Change from Baseline to Endpoint**

		PERIOD II						PERIOD III						
SEQUENCE	N	BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2		OVERALL TREATMENT		P-VALUE
		-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
DPREMB EVENING SCORE														
MPH/TMX	17	8.74	4.97	7.31	4.48	-1.43	3.77	5.15	3.07	-3.58	4.50	-2.79*	4.00*	.003
TMX/MPH	28	10.99	5.31	5.86	3.63	-5.12	4.50	7.37	4.80	-3.61	3.98	-4.54#	4.51#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-2.86 , -0.65)				
DPREMB MORNING SCORE														
MPH/TMX	23	2.47	1.89	2.62	1.80	0.15	1.67	1.47	0.99	-1.00	1.72	-0.41*	1.62*	<.001
TMX/MPH	34	2.89	1.62	1.59	1.44	-1.30	1.43	2.10	1.64	-0.78	1.50	-1.18#	1.55#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-1.20 , -0.45)				
TOTAL DPREMB SCORE														
MPH/TMX	13	12.58	6.50	9.50	6.04	-3.07	4.16	7.04	4.09	-5.53	5.47	-3.65*	5.07*	.003
TMX/MPH	21	14.03	6.27	7.48	4.85	-6.55	5.81	10.02	6.43	-4.01	5.63	-6.16#	5.62#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-4.03 , -0.90)				

P-VALUE IS BASED ON AN ANOVA MODEL WITH TERMS OF INVESTIGATOR AND SEQUENCE

TESTING SEQUENCE GROUPS IS EQUAL TO TESTING TREATMENT EFFECT

*: MPH TREATMENT GROUP #: TMX TREATMENT GROUP

POPULATION: PATIENTS HAVING MORE THAN 4 RECORDS PER WEEK PERIOD ARE INCLUDED

WEEKLY AVERAGE SCORE IS IMPUTED BASED ON THE RECORDS IN THAT WEEK.

Abbreviations: MPH = methylphenidate; N = number of patients; SD = standard deviation; TMX = tomoxetine.

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Table 8. Sleep Diary Mean Change from Baseline to Endpoint

SEQUENCE	N	PERIOD II						PERIOD III				OVERALL TREATMENT		EFFECT SIZE	P-VALUE
		BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2		MEAN	SD		
		-----	-----	-----	-----	-----	-----								
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD						
EASY GETTING UP-BY CHILD															
ATX/MPH	32	25.20	19.46	21.93	18.28	-3.27	12.90	28.73	21.77	3.53	23.41	-3.09#	18.04#	-0.37	.004
MPH/ATX	24	28.27	19.12	34.09	23.19	5.82	23.22	25.43	18.60	-2.84	23.54	4.51*	23.15*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(2.77 , 14.04)					
SLEEPY-BY CHILD															
ATX/MPH	33	31.89	23.46	29.35	20.71	-2.54	24.55	32.31	24.30	0.42	27.43	-0.09#	21.76#	0.06	.135
MPH/ATX	24	30.33	22.57	26.06	22.03	-4.27	16.41	33.61	22.49	3.28	17.13	-1.55*	23.36*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-7.23 , 1.00)					
TIME TO FALL ASLEEP-BY CHILD															
ATX/MPH	36	30.84	22.85	30.44	25.47	-0.40	19.18	44.31	27.57	13.47	26.11	-0.02#	20.61#	-0.57	.001
MPH/ATX	24	38.16	26.08	52.03	30.14	13.87	28.05	38.71	25.49	0.55	23.01	13.63*	26.66*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(5.54 , 20.81)					
HOW WELL SLEEP-BY CHILD															
ATX/MPH	36	75.15	17.23	76.58	17.38	1.43	16.11	70.51	18.32	-4.64	17.74	1.12#	16.48#	0.29	.045
MPH/ATX	24	75.39	17.48	72.32	23.94	-3.06	19.77	76.03	18.54	0.65	17.36	-4.01*	18.43*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-9.81 , -0.11)					
NUMBER OF TIMES WAKE-BY PARENT															
ATX/MPH	33	0.35	0.42	0.30	0.39	-0.05	0.39	0.36	0.52	0.01	0.49	-0.02#	0.39#	-0.22	.080
MPH/ATX	23	0.23	0.26	0.39	0.42	0.16	0.46	0.24	0.31	0.01	0.40	0.07*	0.48*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.01 , 0.24)					
DIFFICULT GETTING UP-BY PARENT															
ATX/MPH	34	0.74	0.69	0.43	0.48	-0.31	0.67	0.63	0.58	-0.11	0.62	-0.28#	0.61#	-0.50	<.001
MPH/ATX	23	0.58	0.55	0.81	0.70	0.23	0.52	0.35	0.38	-0.23	0.52	0.03*	0.60*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(0.17 , 0.48)					

(continued)

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Table 8. Sleep Diary Mean Change from Baseline to Endpoint (Continued)

		PERIOD II						PERIOD III				OVERALL TREATMENT		EFFECT SIZE	P-VALUE
		BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2					
SEQUENCE	N	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD		
DIFFICULT GETTING READY-BY PARENT															
ATX/MPH	34	1.12	0.64	0.60	0.53	-0.53	0.54	0.74	0.55	-0.38	0.55	-0.46#	0.50#	-0.44	<.001
MPH/ATX	23	0.76	0.45	0.77	0.65	0.01	0.58	0.39	0.33	-0.37	0.43	-0.22*	0.59*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(0.12 , 0.41)					
ARGUING-BY PARENT															
ATX/MPH	34	0.57	0.48	0.29	0.41	-0.28	0.44	0.40	0.48	-0.17	0.46	-0.25#	0.53#	-0.23	.056
MPH/ATX	23	0.62	0.62	0.52	0.48	-0.09	0.51	0.40	0.39	-0.21	0.64	-0.14*	0.47*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.00 , 0.24)					
LOSE TEMPER-BY PARENT															
ATX/MPH	34	0.46	0.49	0.28	0.49	-0.18	0.37	0.33	0.44	-0.13	0.45	-0.19#	0.47#	-0.25	.032
MPH/ATX	23	0.52	0.66	0.54	0.45	0.03	0.55	0.33	0.33	-0.19	0.59	-0.07*	0.49*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(0.01 , 0.24)					
DIFFICULT TASKS-BY PARENT															
ATX/MPH	29	1.52	0.84	0.78	0.76	-0.74	0.56	0.92	0.77	-0.59	0.61	-0.65#	0.61#	-0.07	.998
MPH/ATX	19	1.22	0.61	0.60	0.57	-0.62	0.66	0.71	0.55	-0.51	0.68	-0.60*	0.62*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.20 , 0.20)					
STILL AT DINNER-BY PARENT															
ATX/MPH	30	1.08	0.78	0.48	0.57	-0.61	0.83	0.56	0.63	-0.52	0.68	-0.54#	0.76#	-0.13	.238
MPH/ATX	20	0.84	0.66	0.49	0.56	-0.35	0.56	0.39	0.28	-0.45	0.64	-0.45*	0.63*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.06 , 0.23)					

(continued)

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Table 8. Sleep Diary Mean Change from Baseline to Endpoint (Concluded)

		PERIOD II						PERIOD III				OVERALL TREATMENT		EFFECT SIZE	P-VALUE
		BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2					
SEQUENCE	N	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD		
LATE PLAY QUIETLY--BY PARENT															
ATX/MPH	30	1.27	0.96	0.64	0.60	-0.63	0.88	0.75	0.78	-0.52	0.74	-0.57#	0.80#	-0.07	.780
MPH/ATX	19	1.16	0.84	0.65	0.58	-0.51	0.61	0.69	0.55	-0.47	0.65	-0.52*	0.69*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.17 , 0.23)					
LATE INATTENTIVE--BY PARENT															
ATX/MPH	30	1.56	0.80	0.76	0.74	-0.80	0.66	0.90	0.72	-0.66	0.63	-0.67#	0.68#	-0.18	.304
MPH/ATX	20	1.17	0.61	0.77	0.59	-0.40	0.55	0.69	0.49	-0.48	0.68	-0.55*	0.61*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.09 , 0.28)					
LATE ARGUING--BY PARENT															
ATX/MPH	30	1.03	0.67	0.55	0.54	-0.48	0.66	0.60	0.55	-0.43	0.64	-0.49#	0.69#	-0.12	.316
MPH/ATX	20	1.20	0.80	0.82	0.60	-0.38	0.70	0.70	0.51	-0.50	0.75	-0.41*	0.66*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.07 , 0.21)					
LATE LOSE TEMPER--BY PARENT															
ATX/MPH	30	0.75	0.58	0.41	0.44	-0.35	0.56	0.50	0.46	-0.25	0.50	-0.37#	0.62#	-0.16	.185
MPH/ATX	20	1.04	0.75	0.74	0.64	-0.31	0.63	0.63	0.49	-0.41	0.72	-0.27*	0.55*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.04 , 0.22)					
LATE TRANSITION--BY PARENT															
ATX/MPH	30	1.23	0.78	0.67	0.61	-0.56	0.56	0.77	0.72	-0.46	0.55	-0.51#	0.56#	-0.17	.276
MPH/ATX	19	0.85	0.70	0.52	0.56	-0.33	0.57	0.43	0.36	-0.42	0.57	-0.41*	0.55*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.07 , 0.22)					
SETTLING DOWN--BY PARENT															
ATX/MPH	30	0.99	0.68	0.54	0.59	-0.46	0.46	0.69	0.69	-0.30	0.66	-0.35#	0.45#	-0.48	<.001
MPH/ATX	20	0.81	0.55	1.10	0.86	0.29	0.61	0.63	0.45	-0.19	0.38	-0.06*	0.70*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(0.15 , 0.49)					
NIGHT FALLING ASLEEP--BY PARENT															
ATX/MPH	30	1.30	0.83	1.16	0.84	-0.14	0.72	1.54	0.92	0.24	0.79	-0.12#	0.75#	-0.67	<.001
MPH/ATX	20	1.06	0.70	1.73	0.84	0.68	0.84	0.98	0.62	-0.08	0.81	0.41*	0.83*		—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(0.29 , 0.84)					

P-VALUE IS BASED ON AN ANOVA MODEL WITH TERMS OF INVESTIGATOR AND SEQUENCE

TESTING SEQUENCE GROUPS IS EQUAL TO TESTING TREATMENT EFFECT

*: MPH TREATMENT GROUP #: ATX TREATMENT GROUP

POPULATION: ALL RANDOMIZED PATIENTS WHO FINISHED BOTH OF THE TREATMENT PERIODS

Abbreviations: MPH = methylphenidate; N = number of patients; SD = standard deviation; TMX = tomoxetine.

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Table 9. Daily Parent Rating of Evening and Morning Behavior Scores – Second to Last Week Average Mean Change from Baseline to Endpoint

		PERIOD II						PERIOD III				P-VALUE (A)	P-VALUE (B)
		BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2			
SEQUENCE	GROUP												
	N	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD		
TOTAL SCORE													
TMX/MPH	17	12.34	5.21	6.31	4.34	-6.03	4.13	8.29	5.96	-4.06	4.77		
MPH/TMX	5	9.63	3.24	7.49	3.27	-2.14	1.23	5.22	3.33	-4.41	2.04	.164	.088
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:								(-4.16, 0.32)					
MORNING SCORE													
TMX/MPH	24	2.47	1.27	1.35	1.10	-1.12	1.08	1.96	1.32	-0.51	1.37		
MPH/TMX	13	1.66	1.26	1.99	1.45	0.32	0.65	1.07	0.93	-0.60	0.70	.045	<.001
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:								(-1.14, -0.41)					
EVENING SCORE													
TMX/MPH	23	8.99	4.79	5.04	3.68	-3.95	4.43	5.75	4.40	-3.24	3.57		
MPH/TMX	16	6.46	3.26	4.18	2.74	-2.27	3.01	3.41	2.03	-3.05	2.92	.230	.230
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:								(-1.67, 0.42)					

A) P-VALUE IS TESTING FOR CARRYOVER EFFECT BY COMPARING 2 SEQUENCE GROUPS USING SUM SCORE

B) P-VALUE IS TESTING FOR TREATMENT EFFECT BY COMPARING 2 SEQUENCE GROUPS USING DIFFERENCE SCORE

SEQUENCE GROUP COMPARISON ARE USING ANOVA MODEL WITH TERMS FOR INVESTIGATOR AND SEQUENCE

ONLY THOSE PATIENTS WHO COMPLETED TWO STUDY PERIODS, HAD ≥4 DAYS DATA OVER 7-DAY-PERIOD AT BASELINE

AND ≥4 DAYS DATA OVER SECOND-TO-LAST 7-DAY-PERIOD AT POSTBASELINE ARE INCLUDED IN THE ANALYSIS

Abbreviations: MPH = methylphenidate; N = number of patients; SD = standard deviation; TMX = tomoxetine.

As shown in Table 10, evaluation of treatment effects on measures of overall index of severity of depression and depressive symptoms showed no statistically significant difference between tomoxetine and methylphenidate.

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Table 10. Children's Depression Rating Scale Mean Change from Baseline to Endpoint

		PERIOD II						PERIOD III						
SEQUENCE	N	BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2		OVERALL TREATMENT		P-VALUE
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
CDRS RAW TOTAL SCORE														
MPH/TMX	34	26.79	4.91	25.35	4.99	-1.44	4.61	22.35	3.40	-4.44	5.78	-0.96*	6.30*	.084
TMX/MPH	41	24.37	4.36	23.78	6.33	-0.59	6.20	23.80	7.92	-0.56	7.46	-2.33#	6.28#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-2.87, 0.18)				
CDRS T-SCORE														
MPH/TMX	34	48.87	5.52	47.25	5.61	-1.62	5.18	43.88	3.82	-4.99	6.50	-1.08*	7.08*	.084
TMX/MPH	41	46.14	4.90	45.48	7.11	-0.66	6.97	45.51	8.89	-0.63	8.38	-2.62#	7.06#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-3.22, 0.21)				

P-VALUE IS BASED ON AN ANOVA MODEL WITH TERMS OF INVESTIGATOR AND SEQUENCE
TESTING SEQUENCE GROUPS IS EQUAL TO TESTING TREATMENT EFFECT

*: MPH TREATMENT GROUP #: TMX TREATMENT GROUP

POPULATION: ALL RANDOMIZED PATIENTS WHO FINISHED BOTH TREATMENT PERIODS
ONLY THOSE PATIENTS WHO COMPLETE BOTH PERIODS ARE INCLUDED IN THE ANALYSIS

Abbreviations: MPH = methylphenidate; N = number of patients; SD = standard deviation; TMX = tomoxetine.

Preliminary analyses showed the only statistically significant treatment differences as measured by change from baseline to endpoint on cognitive assessments were greater increase on Stroop color score (improvement) (Table 11) and increase in some CVLT perseveration (worsening) and number correct items (improvement) (Table 12) for methylphenidate compared with tomoxetine.

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Table 11. Stroop Color and Word Test Mean Change from Baseline to Endpoint

		PERIOD II						PERIOD III						
SEQUENCE	N	BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2		OVERALL TREATMENT		P-VALUE
		-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
COLOR AGE CORRECTED RAW SCORE														
MPH/TMX	33	67.52	9.37	71.58	10.03	4.06	7.79	70.85	7.92	3.33	7.25	3.66*	8.46*	.021
TMX/MPH	40	70.75	11.80	71.03	10.99	0.28	8.22	74.08	11.23	3.33	9.06	1.66#	7.89#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-3.77, -0.32)				
COLOR RAW SCORE														
MPH/TMX	33	44.88	11.74	50.12	12.49	5.24	6.06	49.79	12.94	4.91	7.54	5.05*	6.74*	.005
TMX/MPH	41	45.32	12.47	46.46	13.22	1.15	7.12	50.22	13.61	4.90	7.31	2.82#	7.50#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-3.67, -0.66)				
COLOR T-SCORE														
MPH/TMX	33	42.12	6.67	44.85	6.17	2.73	5.56	43.70	5.53	1.58	5.67	2.52*	5.71*	.004
TMX/MPH	40	43.50	8.00	43.80	7.26	0.30	5.29	45.85	7.57	2.35	5.89	0.88#	5.47#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-2.85, -0.56)				
COLOR WORD AGE CORRECTED SCORE														
MPH/TMX	33	41.45	5.83	43.94	7.76	2.48	5.73	44.58	7.02	3.12	6.06	1.40*	13.61*	.882
TMX/MPH	40	44.48	16.83	44.10	6.79	-0.38	16.19	44.98	7.71	0.50	17.70	1.21#	12.70#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-1.64, 1.41)				

(continued)

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Table 11. Stroop Color and Word Test Mean Change from Baseline to Endpoint (Concluded)

		PERIOD II						PERIOD III						
SEQUENCE	N	BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2		OVERALL TREATMENT		P-VALUE
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
COLOR WORD RAW SCORE														
MPH/TMX	33	26.09	8.27	29.42	9.07	3.33	4.62	30.21	9.04	4.12	5.74	3.78*	5.76*	.704
TMX/MPH	41	24.98	7.33	27.80	7.02	2.83	4.52	29.12	8.71	4.15	6.57	3.41#	5.10#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-1.53, 1.04)				
WORD AGE CORRECTED SCORE														
MPH/TMX	33	95.79	13.31	98.33	16.36	2.55	12.60	99.33	13.34	3.55	14.86	3.88*	13.62*	.764
TMX/MPH	40	97.78	13.71	102.43	12.74	4.65	9.26	102.75	14.66	4.98	14.47	4.15#	12.04#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-2.59, 3.52)				
WORD RAW SCORE														
MPH/TMX	33	63.82	16.41	67.85	17.57	4.03	9.62	69.27	21.09	5.45	14.30	4.84*	10.19*	.980
TMX/MPH	40	64.60	13.27	68.43	16.20	3.83	7.50	70.10	15.41	5.50	10.71	4.56#	11.05#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-2.70, 2.77)				
WORD T-SCORE														
MPH/TMX	33	43.64	6.57	45.39	6.94	1.76	5.49	45.82	6.55	2.18	7.10	1.84*	5.81*	.727
TMX/MPH	40	45.15	5.78	47.00	6.39	1.85	4.35	47.05	7.56	1.90	6.13	2.00#	5.72#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-1.16, 1.66)				

P-VALUE IS BASED ON AN ANOVA MODEL WITH TERMS OF INVESTIGATOR AND SEQUENCE

TESTING SEQUENCE GROUPS IS EQUAL TO TESTING TREATMENT EFFECT

*: MPH TREATMENT GROUP #: TMX TREATMENT GROUP

POPULATION: ALL RANDOMIZED PATIENTS WHO FINISHED BOTH TREATMENT PERIODS

ONLY THOSE PATIENTS WHO COMPLETE BOTH PERIODS ARE INCLUDED IN THE ANALYSIS

Abbreviations: MPH = methylphenidate; N = number of patients; SD = standard deviation; TMX = tomoxetine.

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Table 12. California Verbal Learning Test Mean Change from Baseline to Endpoint

		PERIOD II						PERIOD III						
		BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2		OVERALL TREATMENT		P-VALUE
SEQUENCE	N	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
TRIAL 1 TOTAL CORRECT														
MPH/TMX	34	6.00	1.65	8.26	2.51	2.26	2.43	9.24	2.27	3.24	2.35	2.51*	2.36*	.386
TMX/MPH	41	5.90	2.08	8.00	2.06	2.10	2.19	8.61	2.53	2.71	2.32	2.61#	2.32#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.30, 0.77)				
TRIAL 1 TOTAL PERSEVERATION														
MPH/TMX	34	0.18	0.46	0.53	0.75	0.35	0.88	0.53	0.86	0.35	1.07	0.37*	1.08*	.408
TMX/MPH	41	0.20	0.46	0.29	0.56	0.10	0.49	0.59	1.18	0.39	1.22	0.21#	0.81#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.36, 0.15)				
TRIAL 1 TOTAL INTRUSION														
MPH/TMX	34	0.62	0.78	0.50	1.26	-0.12	1.34	0.44	0.61	-0.18	1.00	-0.13*	1.15*	.724
TMX/MPH	41	0.54	0.78	0.34	0.73	-0.20	1.05	0.39	0.59	-0.15	0.99	-0.19#	1.02#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.29, 0.20)				
TRIAL 2 TOTAL CORRECT														
MPH/TMX	34	8.09	2.26	9.88	2.41	1.79	2.68	10.12	2.33	2.03	2.87	2.11*	2.53*	.368
TMX/MPH	41	8.29	2.42	9.88	2.79	1.59	2.24	10.66	2.38	2.37	2.40	1.79#	2.53#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.83, 0.31)				

(continued)

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Table 12. California Verbal Learning Test Mean Change from Baseline to Endpoint (Continued)

		PERIOD II						PERIOD III						
SEQUENCE	N	BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2		OVERALL TREATMENT		P-VALUE
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
TRIAL 2 TOTAL PERSEVERATION														
MPH/TMX	34	0.53	0.71	1.18	1.34	0.65	1.47	0.65	0.81	0.12	1.07	0.40*	1.26*	.037
TMX/MPH	41	0.73	0.84	0.78	0.96	0.05	1.05	0.93	0.98	0.20	1.03	0.08#	1.05#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.68, -0.02)				
TRIAL 2 TOTAL INTRUSION														
MPH/TMX	34	0.56	1.02	0.38	0.74	-0.18	1.06	0.59	1.13	0.03	1.47	-0.19*	0.90*	.264
TMX/MPH	41	0.44	0.63	0.24	0.54	-0.20	0.78	0.24	0.49	-0.20	0.75	-0.09#	1.14#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.10, 0.36)				
TRIAL 3 TOTAL CORRECT														
MPH/TMX	34	9.44	2.35	10.41	2.60	0.97	2.35	11.06	2.20	1.62	2.00	1.44*	2.31*	.834
TMX/MPH	41	9.66	2.82	10.85	2.64	1.20	2.17	11.49	2.73	1.83	2.22	1.39#	2.09#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.42, 0.52)				
TRIAL 3 TOTAL PERSEVERATION														
MPH/TMX	34	0.79	1.07	1.03	0.90	0.24	1.42	0.82	0.94	0.03	1.45	0.08*	1.58*	.233
TMX/MPH	41	1.12	1.19	0.88	1.03	-0.24	1.46	1.07	1.15	-0.05	1.72	-0.12#	1.45#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.50, 0.12)				

(continued)

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Table 12. California Verbal Learning Test Mean Change from Baseline to Endpoint (Continued)

		PERIOD II						PERIOD III						
SEQUENCE	N	BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2		OVERALL TREATMENT		P-VALUE
		-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
TRIAL 3 TOTAL INTRUSION														
MPH/TMX	34	0.50	0.71	0.38	0.65	-0.12	0.77	0.29	0.52	-0.21	0.69	-0.05*	0.68*	.610
TMX/MPH	41	0.27	0.50	0.41	0.87	0.15	0.85	0.27	0.50	0.00	0.59	-0.01#	0.80#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.13, 0.21)				
TRIAL 4 TOTAL CORRECT														
MPH/TMX	34	10.50	2.35	11.35	1.87	0.85	1.84	11.21	2.41	0.71	2.37	1.01*	2.14*	.686
TMX/MPH	41	10.66	2.66	11.63	2.35	0.98	2.38	11.80	2.63	1.15	2.37	0.85#	2.36#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.50, 0.33)				
TRIAL 4 TOTAL PERSEVERATION														
MPH/TMX	34	1.44	2.09	1.29	1.43	-0.15	2.19	0.88	1.12	-0.56	2.19	-0.07*	2.17*	.008
TMX/MPH	41	1.41	1.79	0.88	1.17	-0.54	2.23	1.41	1.47	0.00	2.18	-0.55#	2.20#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.86, -0.13)				
TRIAL 4 TOTAL INTRUSION														
MPH/TMX	34	0.21	0.41	0.35	0.60	0.15	0.56	0.32	0.53	0.12	0.59	0.04*	0.65*	.642
TMX/MPH	41	0.29	0.64	0.20	0.51	-0.10	0.70	0.24	0.54	-0.05	0.71	0.00#	0.66#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.19, 0.12)				

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Table 12. California Verbal Learning Test Mean Change from Baseline to Endpoint (Continued)

		PERIOD II						PERIOD III						
SEQUENCE	N	BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2		OVERALL TREATMENT		P-VALUE
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
TRIAL 5 TOTAL CORRECT														
MPH/TMX	34	10.38	2.42	11.38	2.02	1.00	1.95	11.26	2.37	0.88	2.25	1.33*	2.13*	.034
TMX/MPH	41	10.68	2.38	11.46	2.45	0.78	2.40	12.29	2.47	1.61	2.26	0.83#	2.32#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.95, -0.04)				
TRIAL 5 TOTAL PERSEVERATION														
MPH/TMX	34	0.88	1.01	1.68	1.72	0.79	1.70	1.03	1.03	0.15	1.44	0.53*	1.80*	.011
TMX/MPH	41	1.00	1.12	0.95	1.09	-0.05	1.36	1.32	1.65	0.32	1.86	0.04#	1.39#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.86, -0.12)				
TRIAL 5 TOTAL INTRUSION														
MPH/TMX	34	0.35	0.54	0.35	0.65	0.00	0.70	0.47	0.96	0.12	0.81	-0.08*	0.67*	.523
TMX/MPH	41	0.32	0.61	0.12	0.33	-0.20	0.64	0.17	0.44	-0.15	0.65	-0.05#	0.73#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.11, 0.21)				

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Table 12. California Verbal Learning Test Mean Change from Baseline to Endpoint (Continued)

		PERIOD II						PERIOD III						
SEQUENCE	N	BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2		OVERALL TREATMENT		P-VALUE
		-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
SHORT DELAY FREE TOTAL CORRECT														
MPH/TMX	34	9.09	2.71	10.91	2.38	1.82	2.52	10.68	2.78	1.59	2.46	1.89*	2.41*	.210
TMX/MPH	41	9.07	2.90	10.66	2.79	1.59	2.56	11.02	3.23	1.95	2.34	1.59#	2.50#	
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.69, 0.15)				
SHORT DELAY FREE TOTAL PERSEVERATION														
MPH/TMX	34	0.29	0.68	0.88	1.15	0.59	1.13	0.47	0.66	0.18	0.72	0.53*	1.29*	.017
TMX/MPH	41	0.56	0.81	0.66	0.91	0.10	1.04	1.05	1.40	0.49	1.42	0.13#	0.91#	
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.70, -0.07)				
SHORT DELAY FREE TOTAL INTRUSION														
MPH/TMX	34	0.44	0.75	0.35	0.69	-0.09	0.67	0.32	0.68	-0.12	1.01	-0.11*	0.81*	.725
TMX/MPH	41	0.41	0.87	0.34	0.73	-0.07	0.79	0.29	0.46	-0.12	0.93	-0.09#	0.89#	
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.16, 0.22)				
SHORT DELAY CUED TOTAL CORRECT														
MPH/TMX	34	9.26	2.27	11.65	2.44	2.38	2.47	11.68	2.06	2.41	1.97	2.37*	2.32*	.052
TMX/MPH	41	9.51	2.72	11.10	2.72	1.59	1.94	11.88	2.93	2.37	2.22	1.96#	1.98#	
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.77, 0.00)				

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Table 12. California Verbal Learning Test Mean Change from Baseline to Endpoint (Continued)

SEQUENCE	N	PERIOD II						PERIOD III				OVERALL TREATMENT		P-VALUE
		BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2		MEAN	SD	
		-----	-----	-----	-----	-----	-----							
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD			
SHORT DELAY CUED TOTAL PERSEVERATION														
MPH/TMX	34	0.09	0.29	0.12	0.41	0.03	0.52	0.18	0.39	0.09	0.51	0.00*	0.46*	.916
TMX/MPH	41	0.10	0.30	0.02	0.16	-0.07	0.35	0.07	0.35	-0.02	0.42	0.00#	0.43#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.10, 0.11)				
SHORT DELAY CUED TOTAL INTRUSION														
MPH/TMX	34	0.56	1.16	0.53	0.79	-0.03	1.03	0.56	0.93	0.00	1.33	-0.13*	0.91*	.542
TMX/MPH	41	0.59	0.77	0.39	0.77	-0.20	0.95	0.37	0.62	-0.22	0.79	-0.11#	1.13#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.12, 0.22)				
LONG DELAY FREE TOTAL CORRECT														
MPH/TMX	34	9.29	2.36	11.24	2.54	1.94	2.23	10.59	3.12	1.29	2.54	2.03*	2.17*	.105
TMX/MPH	41	9.15	2.82	11.00	2.93	1.85	2.60	11.24	2.80	2.10	2.15	1.60#	2.57#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.99, 0.10)				
LONG DELAY FREE TOTAL PERSEVERATION														
MPH/TMX	34	0.59	1.02	0.76	1.02	0.18	1.29	0.59	0.74	0.00	1.15	0.20*	1.19*	.221
TMX/MPH	41	0.49	0.71	0.54	0.84	0.05	0.84	0.71	0.90	0.22	1.11	0.03#	0.99#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.42, 0.10)				
LONG DELAY FREE TOTAL INTRUSION														
MPH/TMX	34	0.56	0.79	0.32	0.64	-0.24	0.65	0.35	0.95	-0.21	1.09	-0.25*	1.01*	.663
TMX/MPH	41	0.71	1.08	0.29	0.64	-0.41	1.22	0.44	0.71	-0.27	1.25	-0.32#	1.16#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.26, 0.17)				

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Table 12. California Verbal Learning Test Mean Change from Baseline to Endpoint (Continued)

		PERIOD II						PERIOD III						
SEQUENCE	N	BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2		OVERALL TREATMENT		P-VALUE
		-----						-----				-----		-----
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
LONG DELAY CUED TOTAL CORRECT														
MPH/TMX	34	9.68	2.52	11.88	2.32	2.21	2.48	12.03	2.35	2.35	1.95	2.11*	2.12*	.195
TMX/MPH	41	10.12	2.69	11.46	2.91	1.34	2.25	12.15	2.73	2.02	1.80	1.80#	2.17#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.63, 0.13)				
LONG DELAY CUED TOTAL PERSEVERATION														
MPH/TMX	34	0.09	0.29	0.09	0.29	0.00	0.35	0.06	0.24	-0.03	0.39	0.08*	0.43*	.395
TMX/MPH	41	0.02	0.16	0.10	0.30	0.07	0.35	0.17	0.44	0.15	0.48	0.03#	0.37#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.15, 0.06)				
LONG DELAY CUED TOTAL INTRUSION														
MPH/TMX	34	0.88	1.39	0.56	0.93	-0.32	0.94	0.47	0.71	-0.41	1.35	-0.28*	0.88*	.660
TMX/MPH	41	0.71	0.84	0.46	0.81	-0.24	0.92	0.46	0.67	-0.24	0.83	-0.32#	1.13#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.21, 0.14)				
TRIAL 1-5 TOTAL CORRECT														
MPH/TMX	34	44.41	9.07	51.29	9.69	6.88	7.61	52.88	9.39	8.47	7.70	8.40*	7.50*	.501
TMX/MPH	41	45.20	10.19	51.83	10.53	6.63	7.27	54.85	11.20	9.66	7.27	7.47#	7.47#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-2.19, 1.08)				

(continued)

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Table 12. California Verbal Learning Test Mean Change from Baseline to Endpoint (Concluded)

SEQUENCE	N	PERIOD II						PERIOD III				OVERALL TREATMENT		P-VALUE
		BASELINE		ENDPOINT 1		CHANGE 1		ENDPOINT 2		CHANGE 2				
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD			
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD			
TRIAL 1-5 T-SCORE														
MPH/TMX	34	46.29	10.76	53.32	10.40	7.03	12.85	57.76	9.89	11.47	10.68	10.71*	12.47*	.616
TMX/MPH	41	47.07	11.64	55.02	12.30	7.95	13.14	60.83	10.28	13.76	11.43	9.55#	12.14#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-3.11, 1.86)				
TOTAL NUMBER CORRECT LIST A														
MPH/TMX	34	13.12	2.14	13.94	1.46	0.82	2.28	13.79	1.74	0.68	2.25	0.44*	1.93*	.990
TMX/MPH	41	13.71	1.54	13.95	1.61	0.24	1.70	13.83	1.61	0.12	1.54	0.44#	1.97#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.37, 0.38)				
TOTAL NUMBER FALSE POSITIVES														
MPH/TMX	34	13.12	2.14	13.94	1.46	0.82	2.28	13.79	1.74	0.68	2.25	0.44*	1.93*	.990
TMX/MPH	41	13.71	1.54	13.95	1.61	0.24	1.70	13.83	1.61	0.12	1.54	0.44#	1.97#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:										(-0.37, 0.38)				

P-VALUE IS BASED ON AN ANOVA MODEL WITH TERMS OF INVESTIGATOR AND SEQUENCE TESTING SEQUENCE GROUPS
IS EQUAL TO TESTING TREATMENT EFFECT
*: MPH TREATMENT GROUP #: TMX TREATMENT GROUP
POPULATION: ALL RANDOMIZED PATIENTS WHO FINISHED BOTH TREATMENT PERIODS
ONLY THOSE PATIENTS WHO COMPLETE BOTH PERIODS ARE INCLUDED IN THE ANALYSIS

Abbreviations: MPH = methylphenidate; N = number of patients; SD = standard deviation; TMX = tomoxetine.

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Table 13. ADHDRS-IV-Parent:Inv Score And CGI-S Scores Mean Change From Baseline To Endpoint

		PERIOD II								PERIOD III				
SEQUENCE	N	BASELINE 1		ENDPOINT 1		CHANGE 1		BASELINE 2		ENDPOINT 2		CHANGE 2		P-VALUE
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
		-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	
TOTAL SCORE														
TMX/MPH	41	38.00	11.01	23.98	14.04	-14.02	12.02	33.34	13.60	22.85	14.12	-10.49	15.86	0.847*
MPH/TMX	34	36.12	8.31	22.76	12.39	-13.35	11.06	32.79	10.81	20.35	10.56	-12.44	10.94	0.427**
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-5.32 , 2.28)														
INATTENTATIVE SUBSCORE														
TMX/MPH	41	22.00	4.64	14.02	7.39	-7.98	7.10	19.27	6.69	12.78	7.12	-6.49	8.65	0.761*
MPH/TMX	34	20.88	3.78	13.38	6.97	-7.50	6.01	18.53	5.32	12.06	5.51	-6.47	5.81	0.736**
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-2.42 , 1.72)														
HYP/IMP SUBSCORE														
TMX/MPH	41	16.00	7.95	9.95	7.71	-6.05	6.30	14.07	8.35	10.07	7.62	-4.00	8.09	0.498*
MPH/TMX	34	15.24	6.70	9.38	6.57	-5.85	6.20	14.26	7.03	8.29	6.29	-5.97	5.98	0.245**
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-3.16 , 0.82)														

(continued)

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Table 13. ADHDRS-IV-Parent:Inv Score And CGI-S Scores Mean Change From Baseline To Endpoint (Concluded)

		PERIOD II								PERIOD III				
SEQUENCE	N	BASELINE 1		ENDPOINT 1		CHANGE 1		BASELINE 2		ENDPOINT 2		CHANGE 2		P-VALUE
		-----	-----	-----	-----	-----	-----	-----	-----	-----	-----			
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
TOTAL T-SCORE														
TMX/MPH	40	79.89	13.65	64.45	15.54	-15.44	12.94	74.90	15.50	63.62	16.27	-11.28	16.55	0.924*
MPH/TMX	33	75.99	8.56	61.65	12.77	-14.34	11.16	72.48	11.40	59.43	10.63	-13.05	11.43	0.423**
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-5.79 , 2.46)														
INATTENTATIVE T-SUBSCORE														
TMX/MPH	41	81.16	10.29	65.84	14.36	-15.32	13.39	76.07	14.11	63.72	14.88	-12.36	16.45	0.8*
MPH/TMX	33	77.44	7.36	62.77	12.39	-14.68	10.97	72.99	10.00	60.66	9.82	-12.32	10.90	0.772**
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-4.57 , 3.40)														
HYP/IMP T-SUBSCORE														
TMX/MPH	40	74.01	17.80	61.27	16.75	-12.75	13.35	69.69	17.53	61.39	16.23	-8.30	16.14	0.611*
MPH/TMX	34	70.63	12.67	59.15	13.22	-11.48	12.23	69.08	14.14	56.96	11.99	-12.12	12.32	0.197**
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-6.88 , 1.45)														
CGI-S SCORE														
TMX/MPH	41	5.10	0.83	3.39	1.43	-1.71	1.38	4.37	1.09	3.10	1.36	-1.27	1.38	0.397*
MPH/TMX	34	4.76	0.74	3.21	1.23	-1.56	1.19	4.18	0.97	3.00	1.26	-1.18	1.11	0.779**
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.43 , 0.32)														

** : P-VALUE IS TESTING FOR TREATMENT EFFECT BY COMPARING 2 SEQUENCE GROUPS USING DIFFERENCE OF CHANGE SCORE

* : P-VALUE IS TESTING FOR CARRYOVER EFFECT BY COMPARING 2 SEQUENCE GROUPS USING SUMMATION OF CHANGE SCORE

SEQUENCE GROUP COMPARISONS ARE USING ANOVA MODEL WITH TERMS FOR INVESTIGATOR AND SEQUENCE

ONLY THOSE PATIENTS WHO COMPLETE BOTH PERIODS ARE INCLUDED IN THE ANALYSIS

Abbreviations: MPH = methylphenidate; N = number of patients; SD = standard deviation; TMX = tomoxetine.

Safety:

Table 14 summarizes the following results. Treatment with tomoxetine resulted in statistically significant increases in diastolic blood pressure ($p=.001$) compared with methylphenidate (Study Period II: tomoxetine = +4.99 mmHg, methylphenidate = +3.28 mmHg, Study Period III: tomoxetine = +9.65 mmHg, methylphenidate = +2.38 mmHg). There was a trend ($p=.056$) toward greater increase in pulse for tomoxetine compared with methylphenidate (Study Period II: tomoxetine = +8.26 bpm, methylphenidate = +3.31 bpm, Study Period III: tomoxetine = +1.36 bpm, methylphenidate = -0.89 bpm). There were no other statistically significant differences in vital signs. While both treatment groups showed a decrease in weight, overall there was no significant difference between methylphenidate and tomoxetine.

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Table 14. Vital Signs and Weight–Mean Change From Baseline To Endpoint

PERIOD II															PERIOD III				P-VALUE
SEQUENCE	N	BASELINE 1		ENDPOINT 1		CHANGE 1		BASELINE 2		ENDPOINT 2		CHANGE 2							
		-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----							
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD						
SYSTOLIC BP																			
TMX/MPH	42	103.19	10.22	107.82	9.71	4.63	11.02	102.71	11.22	107.83	10.94	5.12	10.68	0.096*					
MPH/TMX	36	102.14	9.36	107.72	12.64	5.58	11.41	103.61	12.38	113.82	11.01	10.21	12.07	0.274**					
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-1.61, 5.58)																			
DIASTOLIC BP																			
TMX/MPH	42	63.51	7.68	68.50	6.31	4.99	7.94	64.85	7.02	67.23	7.10	2.38	6.87	0.077*					
MPH/TMX	36	62.74	6.90	66.01	8.04	3.28	8.09	63.38	6.32	73.03	10.41	9.65	10.65	0.001**					
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (1.88 , 6.77)																			
PULSE																			
TMX/MPH	42	80.12	10.53	88.38	7.82	8.26	11.18	85.68	7.39	84.79	10.99	-0.89	12.40	0.559*					
MPH/TMX	36	78.82	8.89	82.13	6.61	3.31	7.79	86.32	10.08	87.68	13.01	1.36	14.31	0.056**					
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.10, 7.20)																			
TEMPERATURE																			
TMX/MPH	42	36.56	0.43	36.59	0.50	0.03	0.51	36.66	0.46	36.74	0.46	0.08	0.58	0.082*					
MPH/TMX	36	36.57	0.37	36.51	0.39	-0.06	0.47	36.51	0.38	36.45	0.41	-0.06	0.43	0.75**					
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.19, 0.14)																			
WEIGHT																			
TMX/MPH	42	38.08	10.12	37.23	9.79	-0.85	1.67	38.00	9.85	37.62	9.97	-0.37	1.34	0.994*					
MPH/TMX	36	37.28	8.86	36.43	8.90	-0.84	1.05	37.24	9.03	36.79	8.85	-0.45	0.88	0.786**					
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.46, 0.35)																			

** : P-VALUE IS TESTING FOR TREATMENT EFFECT BY COMPARING 2 SEQUENCE GROUPS USING SUMMATION OF CHANGE SCORE.

* : P-VALUE IS TESTING FOR CARRYOVER EFFECT BY COMPARING 2 SEQUENCE GROUPS USING DIFFERENCE OF CHANGE SCORE.

SEQUENCE GROUP COMPARISONS ARE USING ANOVA MODEL WITH TERMS FOR INVESTIGATOR AND SEQUENCE.

THOSE PATIENTS WHO ENTERED STUDY AND TOOK AT LEAST ONE DOSE OF STUDY DRUG ARE INCLUDED IN THE ANALYSIS

Abbreviations: MPH = methylphenidate; N = number of patients; SD = standard deviation; TMX = tomoxetine.

None of the changes in laboratory analytes (Table 15) or ECG (Table 16) were considered clinically significant.

No clinically significant AEs or deaths occurred during this study. Table 17 shows TEAEs by System Organ Class.

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Table 15. Laboratory Test Mean Change From Baseline To Endpoint Combining Two Treatment Periods Together

		PERIOD II						PERIOD III								
SEQUENCE	N	BASELINE1		ENDPOINT 1		CHANGE 1		BASELINE2		ENDPOINT 2		CHANGE 2		OVERALL	TREATMENT	P-VALUE
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
ALBUMIN																
MPH/TMX	35	44.51	2.48	45.31	2.68	0.80	2.46	43.89	2.17	45.97	2.53	2.09	2.27	1.31*	3.10*	.876
TMX/MPH	40	44.35	2.78	44.65	2.38	0.30	2.91	43.28	2.59	45.03	2.90	1.75	3.54	1.13#	2.76#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-1.01 , 0.86)																
ALKALINE PHOSPHATASE																
MPH/TMX	35	252.34	65.71	254.74	71.27	2.40	34.46	238.49	58.84	254.86	68.63	16.37	36.15	2.65*	34.40*	.149
TMX/MPH	40	260.28	72.66	262.90	73.48	2.63	27.09	242.18	68.14	245.05	68.03	2.88	34.77	9.04#	32.17#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-2.65 , 17.07)																
ALT/SGPT																
MPH/TMX	34	17.00	5.05	14.26	2.61	-2.74	4.49	16.82	5.34	17.91	17.46	1.09	17.80	-2.77*	5.66*	.377
TMX/MPH	40	17.58	5.50	14.03	3.08	-3.55	5.67	17.55	7.27	14.75	2.98	-2.80	6.54	-1.42#	12.88#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-1.75 , 4.58)																
AST/SGOT																
MPH/TMX	34	26.24	4.77	26.35	3.56	0.12	3.66	27.62	4.70	27.35	6.61	-0.26	6.40	-0.69*	4.42*	.780
TMX/MPH	37	26.78	4.89	26.11	3.34	-0.68	4.16	27.16	5.36	25.73	3.98	-1.43	4.95	-0.48#	5.32#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-1.34 , 1.78)																
BANDS																
MPH/TMX	35	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00*	0.00*	.430
TMX/MPH	41	0.00	0.01	0.00	0.00	-0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	-0.00#	0.01#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.00 , 0.00)																

(continued)

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Table 15. Laboratory Test Mean Change From Baseline To Endpoint Combining Two Treatment Periods Together (Continued)

		PERIOD II						PERIOD III								
SEQUENCE	N	BASELINE1		ENDPOINT 1		CHANGE 1		BASELINE2		ENDPOINT 2		CHANGE 2		OVERALL	TREATMENT	P-VALUE
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
BASOPHILS																
MPH/TMX	35	0.05	0.02	0.06	0.04	0.01	0.03	0.05	0.02	0.06	0.04	0.01	0.03	0.00*	0.03*	.813
TMX/MPH	41	0.05	0.04	0.05	0.04	-0.00	0.03	0.06	0.03	0.05	0.03	-0.01	0.03	0.00#	0.03#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.01 ,0.01)																
BICARBONATE, HCO3																
MPH/TMX	35	22.56	1.91	24.04	2.03	1.49	1.80	23.77	2.32	23.32	1.72	-0.46	1.80	0.20*	2.48*	.859
TMX/MPH	40	22.31	1.89	23.44	1.58	1.12	1.75	23.86	2.43	22.94	1.92	-0.93	2.45	0.39#	1.93#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.60 ,0.71)																
BILIRUBIN, TOTAL																
MPH/TMX	28	5.92	2.77	8.00	3.23	2.08	3.17	6.96	3.60	8.24	4.49	1.28	2.70	1.49*	3.48*	.807
TMX/MPH	33	7.15	3.54	8.55	4.76	1.40	3.32	6.74	3.92	7.72	4.04	0.98	3.70	1.35#	3.03#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-1.37 ,1.07)																
CALCIUM																
MPH/TMX	35	2.53	0.08	2.57	0.10	0.04	0.10	2.48	0.08	2.55	0.09	0.07	0.09	0.03*	0.11*	.750
TMX/MPH	40	2.53	0.10	2.53	0.10	0.00	0.10	2.50	0.09	2.53	0.08	0.02	0.12	0.03#	0.10#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.03 ,0.04)																
CHLORIDE																
MPH/TMX	35	104.63	2.28	104.89	1.84	0.26	2.28	104.31	1.69	104.20	1.95	-0.11	2.59	0.20*	2.66*	.345
TMX/MPH	40	104.68	1.44	104.40	1.77	-0.28	2.15	104.90	1.77	105.05	2.19	0.15	2.97	-0.20#	2.35#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-1.25 ,0.44)																

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Table 15. Laboratory Test Mean Change From Baseline To Endpoint Combining Two Treatment Periods Together (Continued)

		PERIOD II						PERIOD III								
SEQUENCE	N	BASELINE1		ENDPOINT 1		CHANGE 1		BASELINE2		ENDPOINT 2		CHANGE 2		OVERALL	TREATMENT	P-VALUE
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
CHOLESTEROL																
MPH/TMX	35	4.30	0.61	4.30	0.54	-0.00	0.42	4.41	0.62	4.44	0.58	0.04	0.51	-0.08*	0.49*	.174
TMX/MPH	41	4.39	0.65	4.41	0.69	0.02	0.60	4.45	0.64	4.30	0.68	-0.15	0.54	0.03#	0.55#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.05 ,0.26)																
CREATINE PHOSPHOKINASE																
MPH/TMX	35	126.94	55.36	140.83	58.34	13.89	40.22	129.83	49.61	121.37	52.86	-8.46	39.84	12.19*	53.63*	.240
TMX/MPH	40	140.73	56.73	153.23	92.49	12.50	84.61	140.23	59.29	150.93	71.15	10.70	63.57	2.72#	67.92#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-30.21 ,7.68)																
CREATININE																
MPH/TMX	35	51.02	15.02	53.80	9.91	2.78	12.82	47.48	12.14	52.03	11.89	4.55	9.68	2.79*	10.33*	.450
TMX/MPH	41	50.88	9.43	54.55	10.81	3.67	9.68	48.73	9.30	51.53	10.44	2.80	7.77	4.07#	9.62#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-1.99 ,4.43)																
EOSINOPHILS																
MPH/TMX	35	0.27	0.60	0.28	0.67	0.00	0.11	0.21	0.25	0.24	0.46	0.03	0.26	-0.03*	0.11*	.085
TMX/MPH	41	0.20	0.15	0.20	0.18	-0.00	0.10	0.21	0.17	0.16	0.15	-0.05	0.11	0.01#	0.19#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.00 ,0.08)																
ERYTHROCYTE COUNT																
MPH/TMX	35	4.71	0.30	4.88	0.30	0.17	0.23	4.60	0.33	4.87	0.34	0.27	0.31	0.17*	0.26*	.096
TMX/MPH	41	4.67	0.30	4.86	0.34	0.19	0.21	4.61	0.32	4.79	0.38	0.17	0.28	0.23#	0.26#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.01 ,0.15)																

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Table 15. Laboratory Test Mean Change From Baseline To Endpoint Combining Two Treatment Periods Together (Continued)

		PERIOD II						PERIOD III								
		BASELINE1		ENDPOINT 1		CHANGE 1		BASELINE2		ENDPOINT 2		CHANGE 2		OVERALL	TREATMENT	P-VALUE
SEQUENCE	N	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
GGT (GGPT/SGGT/YGGT)																
MPH/TMX	35	12.34	2.96	12.46	2.55	0.11	2.04	12.23	2.94	13.03	2.95	0.80	2.54	-0.08*	2.22*	.760
TMX/MPH	40	12.60	3.26	11.88	2.92	-0.73	2.46	12.33	3.29	12.08	2.94	-0.25	2.37	-0.01#	2.60#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.65 ,0.88)																
GLUCOSE, NON-FASTING																
MPH/TMX	35	5.10	0.44	5.41	0.70	0.30	0.72	5.21	0.60	5.20	0.60	-0.01	0.66	0.12*	0.86*	.555
TMX/MPH	38	5.10	0.71	5.23	0.73	0.13	0.74	5.20	0.72	5.15	0.66	-0.06	0.96	0.06#	0.70#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.33 ,0.18)																
HEMATOCRIT																
MPH/TMX	35	0.38	0.02	0.40	0.02	0.02	0.02	0.38	0.02	0.41	0.03	0.02	0.03	0.02*	0.02*	.201
TMX/MPH	41	0.38	0.02	0.40	0.03	0.02	0.02	0.38	0.02	0.39	0.03	0.01	0.03	0.02#	0.03#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.00 ,0.01)																
HEMOGLOBIN																
MPH/TMX	35	8.26	0.45	8.51	0.46	0.25	0.36	8.06	0.52	8.60	0.64	0.53	0.62	0.28*	0.42*	.125
TMX/MPH	41	8.17	0.49	8.43	0.59	0.26	0.41	8.06	0.47	8.37	0.53	0.31	0.47	0.38#	0.53#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.03 ,0.27)																
INORGANIC PHOSPHORUS																
MPH/TMX	35	1.64	0.18	1.52	0.18	-0.12	0.22	1.61	0.21	1.49	0.17	-0.12	0.18	-0.13*	0.22*	.455
TMX/MPH	38	1.61	0.19	1.52	0.20	-0.09	0.23	1.64	0.20	1.50	0.25	-0.15	0.22	-0.10#	0.20#	—

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Table 15. Laboratory Test Mean Change From Baseline To Endpoint Combining Two Treatment Periods Together (Continued)

		PERIOD II						PERIOD III								
SEQUENCE	N	BASELINE1		ENDPOINT 1		CHANGE 1		BASELINE2		ENDPOINT 2		CHANGE 2		OVERALL TREATMENT		P-VALUE
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.04 ,0.10)																
LEUKOCYTE COUNT																
MPH/TMX	35	6.64	2.12	6.07	2.23	-0.57	1.98	6.55	2.24	5.85	1.70	-0.70	1.57	-0.95*	1.87*	.835
TMX/MPH	41	7.05	1.84	6.02	1.53	-1.03	1.94	7.10	1.59	5.83	1.38	-1.27	1.74	-0.87#	1.77#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.48 ,0.60)																
LYMPHOCYTES																
MPH/TMX	35	2.62	0.80	2.43	0.81	-0.19	0.59	2.48	0.90	2.26	0.77	-0.23	0.65	-0.18*	0.58*	.419
TMX/MPH	41	2.75	0.76	2.45	0.68	-0.29	0.54	2.63	0.66	2.45	0.67	-0.18	0.58	-0.26#	0.59#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.24 ,0.10)																
MEAN CELL VOLUME (MCV)																
MPH/TMX	35	81.06	3.41	82.94	4.39	1.89	2.88	83.06	4.39	83.17	4.55	0.11	2.97	0.97*	2.89*	.376
TMX/MPH	41	80.93	5.43	81.98	5.92	1.05	3.35	82.22	5.83	82.41	5.04	0.20	2.70	0.62#	3.19#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-1.54 ,0.59)																
MONOCYTES																
MPH/TMX	35	0.41	0.14	0.33	0.09	-0.08	0.11	0.37	0.14	0.35	0.12	-0.02	0.11	-0.10*	0.14*	.015
TMX/MPH	41	0.39	0.14	0.34	0.15	-0.05	0.18	0.43	0.15	0.31	0.11	-0.12	0.16	-0.04#	0.15#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (0.01 ,0.11)																
NEUTROPHILS, SEGMENTED																
MPH/TMX	35	3.30	1.51	2.97	1.64	-0.32	1.80	3.44	1.82	2.95	1.12	-0.49	1.22	-0.64*	1.67*	.871
TMX/MPH	41	3.65	1.40	2.98	1.20	-0.66	1.69	3.78	1.40	2.86	0.89	-0.91	1.52	-0.58#	1.49#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.43 ,0.50)																

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Table 15. Laboratory Test Mean Change From Baseline To Endpoint Combining Two Treatment Periods Together (Continued)

		PERIOD II						PERIOD III								
SEQUENCE	N	BASELINE1		ENDPOINT 1		CHANGE 1		BASELINE2		ENDPOINT 2		CHANGE 2		OVERALL	TREATMENT	P-VALUE
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
PLATELET COUNT																
MPH/TMX	34	302.41	62.45	289.59	49.39	-12.82	53.66	278.15	50.29	295.56	53.76	17.41	52.43	-12.10*	50.71*	.147
TMX/MPH	39	314.00	66.02	291.82	56.37	-22.18	47.38	310.82	70.87	299.36	62.88	-11.46	48.70	-3.74#	53.29#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-3.51 , 22.99)																
POTASSIUM																
MPH/TMX	34	4.86	0.46	4.97	0.48	0.11	0.48	4.56	0.42	4.85	0.59	0.28	0.63	0.13*	0.47*	.787
TMX/MPH	37	4.78	0.52	4.72	0.42	-0.06	0.47	4.58	0.48	4.73	0.55	0.15	0.46	0.11#	0.58#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.19 , 0.15)																
SODIUM																
MPH/TMX	35	143.14	2.17	141.89	2.10	-1.26	2.19	142.06	2.11	141.86	1.72	-0.20	2.48	-0.68*	2.39*	.641
TMX/MPH	40	142.80	1.86	141.18	2.29	-1.63	2.80	142.50	2.11	142.33	2.12	-0.18	2.47	-0.96#	2.73#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-1.08 , 0.67)																
TOTAL PROTEIN																
MPH/TMX	35	73.34	3.60	74.11	3.63	0.77	3.96	72.00	3.17	75.26	4.31	3.26	3.57	1.05*	4.13*	.136
TMX/MPH	40	73.68	4.93	74.30	3.99	0.63	3.97	72.90	4.15	74.20	4.27	1.30	4.32	1.85#	3.99#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.31 , 2.22)																
UA-SPECIFIC GRAVITY																
MPH/TMX	35	1.02	0.01	1.03	0.01	0.00	0.01	1.03	0.01	1.03	0.01	0.00	0.01	0.00*	0.01*	.644
TMX/MPH	42	1.03	0.01	1.03	0.01	0.00	0.01	1.03	0.01	1.03	0.01	0.00	0.01	0.00#	0.01#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.00 , 0.00)																

(continued)

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Table 15. Laboratory Test Mean Change From Baseline To Endpoint Combining Two Treatment Periods Together (Concluded)

		PERIOD II						PERIOD III								
		BASELINE1		ENDPOINT 1		CHANGE 1		BASELINE2		ENDPOINT 2		CHANGE 2		OVERALL TREATMENT		P-VALUE
SEQUENCE	N	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
UREA NITROGEN																
MPH/TMX	35	4.88	1.23	4.54	1.06	-0.34	1.15	4.92	1.27	4.55	1.24	-0.37	1.06	-0.32*	1.28*	.374
TMX/MPH	41	4.83	1.20	4.93	1.27	0.10	1.24	5.08	1.29	4.76	1.35	-0.31	1.39	-0.12#	1.17#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-0.21 ,0.56)																
URIC ACID																
MPH/TMX	35	222.63	50.37	227.72	52.16	5.10	40.24	232.99	52.56	227.55	60.66	-5.44	49.75	2.54*	38.60*	.264
TMX/MPH	40	231.82	51.19	225.58	49.37	-6.25	46.83	239.11	51.40	239.41	56.17	0.30	37.47	-5.87#	47.89#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE: (-23.71 ,6.59)																
P-VALUE IS BASED ON AN ANOVA MODEL WITH TERMS OF INVESTIGATOR AND SEQUENCE																
TESTING SEQUENCE GROUPS IS EQUAL TO TESTING TREATMENT EFFECT																
*: MPH TREATMENT GROUP #: TMX TREATMENT GROUP																
POPULATION: ALL RANDOMIZED PATIENTS WHO TOOK AT LEAST ONE DOSE OF STUDY DRUG ARE INCLUDED																

Abbreviations: MPH = methylphenidate; N = number of patients; SD = standard deviation; TMX = tomoxetine.

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Table 16. ECG – Mean Change From Baseline to Endpoint Combining Two Treatment Periods Together

		PERIOD II						PERIOD III									
		BASELINE1		ENDPOINT 1		CHANGE 1		BASELINE2		ENDPOINT 2		CHANGE 2		OVERALL TREATMENT		P-VALUE	
SEQUENCE	N	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD		
ECG HEART RATE																	
MPH/TMX	35	73.26	8.26	72.17	8.54	-1.09	8.97	77.54	10.28	81.97	15.60	4.43	14.06	-1.18*	11.58*	<.001	
TMX/MPH	42	75.21	8.32	83.19	8.70	7.98	9.71	81.71	9.19	80.45	11.77	-1.26	13.49	6.36#	11.93#	—	
											95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:		(3.30 ,11.40)				
ECG RR INTERVAL																	
MPH/TMX	35	829.31	94.52	843.38	105.71	14.07	104.93	788.53	115.90	756.01	133.09	-32.52	114.30	16.16*	117.30*	<.001	
TMX/MPH	42	807.28	89.29	729.13	77.96	-78.15	93.12	743.72	86.93	761.61	112.63	17.90	127.94	-57.41#	105.10#	—	
											95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:		(-109.80,-33.49)				
ECG PR INTERVAL																	
MPH/TMX	34	136.47	16.76	129.06	16.07	-7.41	8.07	131.29	14.95	129.29	16.50	-2.00	9.91	-2.83*	9.40*	.382	
TMX/MPH	42	131.98	22.63	130.10	19.54	-1.88	10.05	128.74	18.60	129.62	18.36	0.88	8.81	-1.93#	9.92#	—	
											95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:		(-1.69 ,4.35)				
ECG QRS INTERVAL																	
MPH/TMX	35	82.74	7.62	85.14	6.48	2.40	3.78	84.23	8.17	85.14	7.80	0.91	5.91	1.71*	4.56*	.595	
TMX/MPH	42	82.00	7.81	83.62	9.47	1.62	6.25	82.10	8.20	83.24	7.56	1.14	5.10	1.30#	6.07#	—	
											95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:		(-2.18 ,1.26)				
ECG QT INTERVAL																	
MPH/TMX	35	378.06	21.90	382.29	23.13	4.23	20.37	370.06	24.97	361.94	28.49	-8.11	25.57	2.49*	21.94*	.001	
TMX/MPH	42	369.81	16.56	359.14	18.54	-10.67	16.99	361.33	18.29	362.38	23.98	1.05	23.31	-9.51#	21.21#	—	
											95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:		(-19.52 ,-4.96)				

(continued)

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Table 16. ECG – Mean Change From Baseline to Endpoint Combining Two Treatment Periods Together (Concluded)

		PERIOD II						PERIOD III								
		BASELINE1		ENDPOINT 1		CHANGE 1		BASELINE2		ENDPOINT 2		CHANGE 2		OVERALL	TREATMENT	P-VALUE
SEQUENCE	N	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	
FRIDERICIA QTC INTERVAL																
MPH/TMX	35	402.80	13.37	405.14	14.06	2.34	13.07	401.25	14.62	398.47	16.16	-2.77	16.16	0.06*	12.65*	.646
TMX/MPH	42	397.79	13.59	399.44	13.20	1.65	14.64	399.39	13.39	397.56	12.76	-1.83	12.11	-0.36#	15.40#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:											(-5.41 , 3.38)					
DATABASE CORRECTED QTC INTERVAL																
MPH/TMX	35	407.22	12.90	409.22	13.73	2.00	13.37	406.89	14.25	405.18	15.95	-1.71	16.19	-0.37*	13.14*	.634
TMX/MPH	42	402.81	14.47	406.78	13.28	3.97	15.80	406.31	13.89	403.96	12.35	-2.34	12.78	1.39#	16.13#	—
95% CONFIDENCE INTERVAL FOR TREATMENT DIFFERENCE:											(-3.48 , 5.68)					

P-VALUE IS BASED ON AN ANOVA MODEL WITH TERMS OF INVESTIGATOR AND SEQUENCE TESTING SEQUENCE GROUPS

IS EQUAL TO TESTING TREATMENT EFFECT

*: MPH TREATMENT GROUP #: TMX TREATMENT GROUP

POPULATION: ALL RANDOMIZED PATIENTS WHO TOOK AT LEAST ONE DOSE OF STUDY DRUG ARE INCLUDED

Abbreviations: MPH = methylphenidate; N = number of patients; SD = standard deviation; TMX = tomoxetine.

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Table 17. Treatment-Emergent Adverse Events By System Organ Class

SOC Name=Ear and labyrinth disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over Treatment	
		n	n	n	n	P-value	P-value

PATIENT >= 1 TEAE							
	MPH/TMX	34	1	2	0		
	TMX/MPH	39	0	3	0	1.00	.821
Ear pain							
	MPH/TMX	35	0	2	0		
	TMX/MPH	40	0	2	0	1.00	1.00
Motion sickness							
	MPH/TMX	36	1	0	0		
	TMX/MPH	41	0	1	0	1.00	.721

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PAIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Eye disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value
PATIENT >= 1 TEAE							
	MPH/TMX	34	1	2	0		
	TMX/MPH	40	1	1	0	.661	.796
Blepharospasm	MPH/TMX	36	0	1	0		
	TMX/MPH	41	1	0	0	1.00	.721
Eye irritation	MPH/TMX	36	1	0	0		
	TMX/MPH	41	0	1	0	1.00	.721
Eye pain	MPH/TMX	36	0	1	0		
	TMX/MPH	42	0	0	0	.468	.468
Conjunctivitis	MPH/TMX	37	0	0	0		
	TMX/MPH	42	0	0	0		

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Gastrointestinal disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value

PATIENT >= 1 TEAE							
	TMX/MPH	22	3	9	8	.073	.935
	MPH/TMX	24	4	8	1		
Abdominal pain upper	TMX/MPH	34	0	7	1	.628	.248
	MPH/TMX	33	1	3	0		
Nausea	TMX/MPH	35	1	4	2	.642	.1.000
	MPH/TMX	33	1	3	0		
Vomiting NOS	TMX/MPH	37	1	3	1	.1.000	.1.000
	MPH/TMX	34	1	2	0		
Abdominal discomfort	TMX/MPH	39	1	2	0	1.00	.508
	MPH/TMX	35	2	0	0		
Diarrhoea NOS	TMX/MPH	39	2	1	0	.618	.746
	MPH/TMX	36	0	1	0		
Lip dry	TMX/MPH	42	0	0	0	.468	.468
	MPH/TMX	36	1	0	0		
Abdominal pain NOS	TMX/MPH	37	3	2	0	.057	.121
	MPH/TMX						

(continued)

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III
(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III
(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III
(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III
POPULATION: ALL RANDOMIZED PAIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Gastrointestinal disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value
Abdominal pain NOS	MPH/TMX	37	0	0	0		
Chapped lips	TMX/MPH	41	1	0	0	1.00	1.00
	MPH/TMX	37	0	0	0		
Constipation	TMX/MPH	39	0	3	0	.243	.243
	MPH/TMX	37	0	0	0		
Dry mouth	TMX/MPH	41	1	0	0	1.00	1.00
	MPH/TMX	37	0	0	0		
Dyspepsia	TMX/MPH	40	1	1	0	.496	1.00
	MPH/TMX	37	0	0	0		
Gastrointestinal upset	TMX/MPH	41	0	1	0	1.00	1.00
	MPH/TMX	37	0	0	0		
Glossitis	TMX/MPH	41	1	0	0	1.00	1.00
	MPH/TMX	37	0	0	0		
Toothache	TMX/MPH	41	0	1	0	1.00	1.00
	MPH/TMX	37	0	0	0		

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=General disorders and administration site conditions

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value
PATIENT >= 1 TEAE							
Fatigue	MPH/TMX	14	10	8	5		
	TMX/MPH	24	4	10	4	.236	.128
Unexpected therapeutic drug effect	MPH/TMX	29	6	2	0		
	TMX/MPH	38	1	3	0	.209	.121
Pyrexia	MPH/TMX	30	1	4	2		
	TMX/MPH	32	2	7	1	.535	.718
Asthenia	MPH/TMX	31	2	3	1		
	TMX/MPH	38	2	1	1	.729	.637
Chest discomfort	MPH/TMX	36	0	1	0		
	TMX/MPH	41	0	1	0	1.00	1.00
Chest pain	MPH/TMX	36	1	0	0		
	TMX/MPH	42	0	0	0	.468	.468
Feeling jittery	MPH/TMX	36	0	1	0		
	TMX/MPH	42	0	0	0	.468	.468
	MPH/TMX	36	1	0	0		
	TMX/MPH	42	0	0	0	.468	.468

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III
(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III
(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III
(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III
POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=General disorders and administration site conditions

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value
Feeling jittery	TMX/MPH	42	0	0	0	.468	.468
Gait abnormal	MPH/TMX	36	0	1	0		
	TMX/MPH	42	0	0	0	.468	.468
Inflammation localised	MPH/TMX	36	1	0	0		
	TMX/MPH	42	0	0	0	.468	.468
Lethargy	MPH/TMX	36	1	0	0		
	TMX/MPH	41	0	1	0	1.00	.721
Pain NOS	MPH/TMX	36	0	1	0		
	TMX/MPH	40	1	1	0	1.00	.1.000

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PAIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Infections and infestations

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value
PATIENT >= 1 TEAE							
Hand-foot-and-mouth disease	MPH/TMX	35	1	1	0		
	TMX/MPH	36	2	3	1	.438	.711
Localised infection	MPH/TMX	36	1	0	0		
	TMX/MPH	42	0	0	0	.468	.468
Dermatophytosis NOS	MPH/TMX	36	0	1	0		
	TMX/MPH	42	0	0	0	.468	.468
Herpes simplex	MPH/TMX	37	0	0	0		
	TMX/MPH	41	0	1	0	1.00	1.00
Influenza	MPH/TMX	37	0	0	0		
	TMX/MPH	40	0	2	0	.496	.496
Pharyngitis streptococcal	MPH/TMX	37	0	0	0		
	TMX/MPH	41	1	0	0	1.00	1.00
Skin infection	MPH/TMX	37	0	0	0		
	TMX/MPH	41	0	1	0	1.00	1.00
(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III (0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III (1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III (1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III POPULATION: ALL RANDOMIZED PAIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III							

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Infections and infestations

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value
Skin infection							
	TMX/MPH	41	1	0	0	1.00	1.00
Upper respiratory tract infection NOS							
	MPH/TMX	37	0	0	0		
	TMX/MPH	41	1	0	0	1.00	1.00

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Injury, poisoning and procedural complications

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value

PATIENT >= 1 TEAE							
	MPH/TMX	33	2	2	0		
	TMX/MPH	39	2	1	0	.700	.846
Abrasion NOS	MPH/TMX	36	1	0	0		
	TMX/MPH	41	1	0	0	1.00	1.00
Arthropod sting	MPH/TMX	36	1	0	0		
	TMX/MPH	42	0	0	0	.468	.468
Radius fracture	MPH/TMX	36	0	1	0		
	TMX/MPH	42	0	0	0	.468	.468
Upper limb fracture NOS	MPH/TMX	36	0	1	0		
	TMX/MPH	42	0	0	0	.468	.468
Skin laceration	MPH/TMX	37	0	0	0		
	TMX/MPH	41	1	0	0	1.00	1.00
Wound NOS	MPH/TMX	37	0	0	0		
	TMX/MPH	41	0	1	0	1.00	1.00

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Investigations

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value

PATIENT >= 1 TEAE							
	MPH/TMX	36	1	0	0		
	TMX/MPH	41	1	0	0	1.00	1.00
Blood pressure increased	MPH/TMX	36	1	0	0		
	TMX/MPH	42	0	0	0	.468	.468
Heart rate increased	MPH/TMX	36	1	0	0		
	TMX/MPH	41	1	0	0	1.00	1.00

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Metabolism and nutrition disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value

PATIENT >= 1 TEAE							
	MPH/TMX	16	1	16	4		
	TMX/MPH	19	8	13	2	.653	.058
Anorexia	MPH/TMX	22	0	13	2		
	TMX/MPH	31	4	7	0	.154	.030
Appetite decreased NOS	MPH/TMX	31	1	5	0		
	TMX/MPH	29	5	6	2	.252	.357
Appetite increased NOS	MPH/TMX	34	2	1	0		
	TMX/MPH	41	0	1	0	.336	.463
Polydipsia	MPH/TMX	36	0	1	0		
	TMX/MPH	42	0	0	0	.468	.468

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Musculoskeletal and connective tissue disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value

PATIENT >= 1 TEAE							
Arthralgia	MPH/TMX	32	0	5	0		
	TMX/MPH	39	2	1	0	.463	.060
Neck pain	MPH/TMX	35	0	2	0		
	TMX/MPH	42	0	0	0	.216	.216
Pain in limb	MPH/TMX	35	0	2	0		
	TMX/MPH	42	0	0	0	.216	.216
Chest wall pain	MPH/TMX	36	0	1	0		
	TMX/MPH	40	2	0	0	1.00	.350
Local swelling	MPH/TMX	37	0	0	0		
	TMX/MPH	41	0	1	0	1.00	1.00
	MPH/TMX	37	0	0	0		
	TMX/MPH	41	1	0	0	1.00	1.00

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Nervous system disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value

PATIENT >= 1 TEAE							
	TMX/MPH	20	5	16	1	.001	.009
	MPH/TMX	21	3	4	9		
Headache	TMX/MPH	29	4	9	0	.159	.698
	MPH/TMX	26	3	5	3		
Somnolence	TMX/MPH	35	1	6	0	.775	.057
	MPH/TMX	29	6	2	0		
Dizziness	TMX/MPH	39	0	3	0	.700	.700
	MPH/TMX	33	0	4	0		
Disturbance in attention	TMX/MPH	40	0	2	0	1.00	1.00
	MPH/TMX	35	0	2	0		
Psychomotor hyperactivity	TMX/MPH	40	1	1	0	1.00	.788
	MPH/TMX	35	0	2	0		
Memory impairment	TMX/MPH	41	1	0	0	1.00	1.00
	MPH/TMX	36	1	0	0		
Repetitive speech	TMX/MPH	42	0	0	0	.468	.468

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III							
(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III							
(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III							
(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III							
POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III							

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Nervous system disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value
Repetitive speech							
	MPH/TMX	36	0	1	0		
Sedation	TMX/MPH	42	0	0	0	.468	.468
	MPH/TMX	36	1	0	0		
Visual field defect NOS							
	TMX/MPH	42	0	0	0	.468	.468
	MPH/TMX	36	0	1	0		
Dysgraphia							
	TMX/MPH	41	0	1	0	1.00	1.00
	MPH/TMX	37	0	0	0		

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III
 (0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III
 (1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III
 (1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III
 POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=OVERALL

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value
PATIENT >= 1 TEAE							
	MPH/TMX	0	2	8	27		
	TMX/MPH	2	1	5	34	.175	.379

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III
 (0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III
 (1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III
 (1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III
 POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Psychiatric disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value
PATIENT >= 1 TEAE							
Irritability	MPH/TMX	8	4	18	7		
	TMX/MPH	14	8	5	15	.036	.001
Insomnia	MPH/TMX	26	3	8	0		
	TMX/MPH	34	2	4	2	.111	.263
Initial insomnia	MPH/TMX	28	0	8	1		
	TMX/MPH	27	11	3	1	.547	<.001
Mood swings	MPH/TMX	28	3	6	0		
	TMX/MPH	33	7	1	1	.885	.062
Decreased activity	MPH/TMX	33	0	3	1		
	TMX/MPH	39	0	2	1	.829	.661
Impulsive behaviour NOS	MPH/TMX	35	1	0	1		
	TMX/MPH	42	0	0	0	.216	.468
Social avoidant behaviour	MPH/TMX	35	1	1	0		
	TMX/MPH	40	1	1	0	1.00	.1.000
	MPH/TMX	35	2	0	0		

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III
(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III
(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III
(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Psychiatric disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value
Social avoidant behaviour							
	TMX/MPH	42	0	0	0	.216	.216
Abnormal behaviour NOS							
	MPH/TMX	36	1	0	0		
	TMX/MPH	42	0	0	0	.468	.468
Affect lability							
	MPH/TMX	36	0	1	0		
	TMX/MPH	40	1	1	0	1.00	.1.000
Anger							
	MPH/TMX	36	0	1	0		
	TMX/MPH	41	1	0	0	1.00	.721
Belligerence							
	MPH/TMX	36	1	0	0		
	TMX/MPH	42	0	0	0	.468	.468
Crying							
	MPH/TMX	36	0	1	0		
	TMX/MPH	40	0	2	0	1.00	1.00
Disinhibition							
	MPH/TMX	36	0	1	0		
	TMX/MPH	42	0	0	0	.468	.468
Early morning awakening							
	MPH/TMX	36	1	0	0		
	TMX/MPH	42	0	0	0	.468	.468

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PAIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Psychiatric disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value
Emotional disturbance NOS							
	MPH/TMX	36	0	1	0		
	TMX/MPH	41	0	1	0	1.00	1.00
Flat affect							
	MPH/TMX	36	1	0	0		
	TMX/MPH	41	1	0	0	1.00	1.00
Logorrhoea							
	MPH/TMX	36	0	1	0		
	TMX/MPH	40	1	1	0	1.00	.1.000
Middle insomnia							
	MPH/TMX	36	1	0	0		
	TMX/MPH	42	0	0	0	.468	.468
Nervousness							
	MPH/TMX	36	0	1	0		
	TMX/MPH	39	3	0	0	.618	.169
Nightmare							
	MPH/TMX	36	0	1	0		
	TMX/MPH	42	0	0	0	.468	.468
Panic attack							
	MPH/TMX	36	0	1	0		
	TMX/MPH	41	1	0	0	1.00	.721
Suicidal ideation							
	MPH/TMX	36	0	1	0		

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Psychiatric disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value
Suicidal ideation							
	TMX/MPH	42	0	0	0	.468	.468
Tearfulness							
	MPH/TMX	36	0	1	0		
	TMX/MPH	40	1	1	0	1.00	.1.000
Tic							
	MPH/TMX	36	0	1	0		
	TMX/MPH	41	0	1	0	1.00	1.00
Aggression							
	MPH/TMX	37	0	0	0		
	TMX/MPH	41	1	0	0	1.00	1.00
Agitation							
	MPH/TMX	37	0	0	0		
	TMX/MPH	42	0	0	0		
Anxiety							
	MPH/TMX	37	0	0	0		
	TMX/MPH	41	0	1	0	1.00	1.00
Confusional state							
	MPH/TMX	37	0	0	0		
	TMX/MPH	41	0	1	0	1.00	1.00
Euphoric mood							
	MPH/TMX	37	0	0	0		
	TMX/MPH	41	0	1	0	1.00	1.00

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Psychiatric disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value
Learning disorder NOS							
	MPH/TMX	37	0	0	0		
	TMX/MPH	41	0	1	0	1.00	1.00
Negativism							
	MPH/TMX	37	0	0	0		
	TMX/MPH	40	1	1	0	.496	1.00
Restlessness							
	MPH/TMX	37	0	0	0		
	TMX/MPH	40	1	1	0	.496	1.00
Sleep disorder NOS							
	MPH/TMX	37	0	0	0		
	TMX/MPH	41	0	1	0	1.00	1.00

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Renal and urinary disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over Treatment	
		n	n	n	n	P-value	P-value
PATIENT >= 1 TEAE							
	MPH/TMX	34	0	3	0	.336	.098
	TMX/MPH	41	1	0	0		
Dysuria	MPH/TMX	36	0	1	0	.468	.468
	TMX/MPH	42	0	0	0		
Polyuria	MPH/TMX	36	0	1	0	.468	.468
	TMX/MPH	42	0	0	0		
Urinary frequency	MPH/TMX	36	0	1	0	.468	.468
	TMX/MPH	42	0	0	0		
Terminal dribbling	MPH/TMX	37	0	0	0	1.00	1.00
	TMX/MPH	41	1	0	0		

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Reproductive system and breast disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value

PATIENT >= 1 TEAE							
	MPH/TMX	37	0	0	0		
	TMX/MPH	41	0	1	0	1.00	1.00
Penile disorder NOS							
	MPH/TMX	37	0	0	0		
	TMX/MPH	41	0	1	0	1.00	1.00

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Respiratory, thoracic and mediastinal disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value

PATIENT >= 1 TEAE							
	TMX/MPH	17	7	13	5	.200	.090
	MPH/TMX	22	7	4	4		
Pharyngitis	TMX/MPH	29	5	8	0	.187	.173
	MPH/TMX	31	4	2	0		
Nasal congestion	TMX/MPH	32	6	3	1	.886	.912
	MPH/TMX	30	4	2	1		
Cough	TMX/MPH	33	2	5	2	.718	.625
	MPH/TMX	32	2	2	1		
Sneezing	TMX/MPH	39	3	0	0	1.00	.083
	MPH/TMX	35	0	2	0		
Asthma NOS	TMX/MPH	40	0	2	0	.496	.496
	MPH/TMX	37	0	0	0		
Nasopharyngitis	TMX/MPH	42	0	0	0		
	MPH/TMX	37	0	0	0		
Pharyngolaryngeal pain	TMX/MPH	41	1	0	0	1.00	1.00

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Respiratory, thoracic and mediastinal disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value

Pharyngolaryngeal pain	MPH/TMX	37	0	0	0		
Respiratory disorder NOS	TMX/MPH	40	1	1	0	.496	1.00
	MPH/TMX	37	0	0	0		
Rhinorrhoea	TMX/MPH	37	1	4	0	.057	.118
	MPH/TMX	37	0	0	0		
Upper respiratory tract congestion	TMX/MPH	41	1	0	0	1.00	1.00
	MPH/TMX	37	0	0	0		

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III
 (0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III
 (1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III
 (1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III
 POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Skin and subcutaneous tissue disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value

PATIENT >= 1 TEAE							
	MPH/TMX	34	1	2	0		
	TMX/MPH	35	2	5	0	.322	.575
Dermatitis contact							
	MPH/TMX	36	0	1	0		
	TMX/MPH	42	0	0	0	.468	.468
Eczema							
	MPH/TMX	36	1	0	0		
	TMX/MPH	42	0	0	0	.468	.468
Rash NOS							
	MPH/TMX	36	0	1	0		
	TMX/MPH	40	0	2	0	1.00	1.00
Ecchymosis							
	MPH/TMX	37	0	0	0		
	TMX/MPH	41	1	0	0	1.00	1.00
Pruritus							
	MPH/TMX	37	0	0	0		
	TMX/MPH	41	0	1	0	1.00	1.00
Rash pruritic							
	MPH/TMX	37	0	0	0		
	TMX/MPH	41	0	1	0	1.00	1.00
Urticaria NOS							
	MPH/TMX	37	0	0	0		

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PAIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Skin and subcutaneous tissue disorders

-----		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over Treatment	
TEAE: BY DESCENDING FREQUENCY							
		n	n	n	n	P-value	P-value

Urticaria NOS							
	TMX/MPH	40	1	1	0	.496	1.00

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PAIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Continued)

SOC Name=Social circumstances

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value

PATIENT >= 1 TEAE							
	MPH/TMX	35	1	0	1		
	TMX/MPH	41	0	1	0	.731	.721
Treatment noncompliance							
	MPH/TMX	35	2	0	0		
	TMX/MPH	42	0	0	0	.216	.216
Illiteracy							
	MPH/TMX	36	0	1	0		
	TMX/MPH	42	0	0	0	.468	.468
Educational problem							
	MPH/TMX	37	0	0	0		
	TMX/MPH	41	0	1	0	1.00	1.00

(0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III

(0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III

(1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III

(1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

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Table 17. Treatment-Emergent Adverse Events By System Organ Class (Concluded)

SOC Name=Vascular disorders

TEAE: BY DESCENDING FREQUENCY		(0,0)	(0,1)	(1,0)	(1,1)	Cross-over	Treatment
		n	n	n	n	P-value	P-value

PATIENT >= 1 TEAE							
	MPH/TMX	37	0	0	0		
	TMX/MPH	41	0	1	0	1.00	1.00
Haematoma NOS							
	MPH/TMX	37	0	0	0		
	TMX/MPH	41	0	1	0	1.00	1.00

 (0,0) is 'Event Absent' in treatment period II and 'Event Absent' in treatment period III
 (0,1) is 'Event Absent' in treatment period II and 'Event Present' in treatment period III
 (1,0) is 'Event Present' in treatment period II and 'Event Absent' in treatment period III
 (1,1) is 'Event Present' in treatment period II and 'Event Present' in treatment period III

POPULATION: ALL RANDOMIZED PATIENTS HAVING AT LEAST ONE DOSE OF STUDY DRUG AND ENTERING INTO STUDY PERIOD III

Abbreviations: MPH = methylphenidate; n = number of patients; NOS = nonorgan specific; SD = standard deviation; SOC = system organ class; TEAE = treatment-emergent adverse event; TMX = tomoxetine.

Summary ID#5003

Clinical Study Summary: Study B4Z-MC-LYAW

Title of Study: A Double-Blind, Placebo-Controlled Trial of Atomoxetine Hydrochloride to Evaluate Efficacy in the School Setting in Children Ages 8 to 12 Years with Attention-Deficit/Hyperactivity Disorder – Acute Treatment Period (Visit 1 through Visit 7)	
Investigators: This multicenter study included 11 principal investigators.	
Study Centers: This study was conducted at 11 study centers in 2 countries.	
Length of Study: Approximately 5 months Date first patient enrolled: 22 January 2002 Date last patient completed Study Period II: 14 June 2002	Phase of Development: 3
Objectives: The primary objective of this study was to test the hypothesis that acute treatment for approximately 7 weeks with atomoxetine (titrated to a maximum dose of 1.8 mg/kg/day and given once a day in the morning) provides superior efficacy compared with placebo in children with Attention-Deficit/Hyperactivity Disorder (ADHD) diagnosed using the <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</i> (DSM-IV) criteria. Efficacy was measured by comparing the differences in the treatment at the end of approximately 7 weeks using the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Teacher Version: Investigator-Administered and Scored (ADHDRS-IV-Teacher:Inv) Total score. The secondary objectives of the study were to compare the change in parent-reported outcomes (quality of life) between atomoxetine and placebo as assessed by the Child Health Questionnaire-Parent-Completed Full Length (CHQ-PF50); to compare the change in symptoms associated with ADHD in children achieved by atomoxetine versus placebo, with improvement defined by a >40% reduction in the ADHDRS-IV-Teacher:Inv Total score; to compare the change in academic performance and school social functioning between atomoxetine and placebo as assessed by the total and subscale scores of the Academic Performance Rating Scale (APRS), the Social Skills Rating System-Teacher Form (SSRS-T), the Brown Attention-Deficit Disorder Scales: Teacher Form (Brown ADD Scales: Teacher), and the Conners' Global Index-Teacher; to compare the change in school behavior between atomoxetine and placebo as assessed by the Behavioral Grade Measure; and to compare the change in parent-reported symptoms of ADHD between atomoxetine and placebo as assessed by the mean total and subscale scores for the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S).	
Study Design: Study B4Z-MC-LYAW (LYAW) was a multicenter, double-blind, randomized, placebo-controlled study of children and adolescents aged 8 to 12 years who met DSM-IV criteria for ADHD, as assessed by investigators and based on reports from parents and the patient's primary classroom teacher. The study consisted of three periods: • Study Period I: A 10- to 28-day diagnostic assessment phase during which patients were screened (Visit 1) for eligibility and all baseline efficacy, health outcomes, and safety measures (Visit 2 and Visit 3) were obtained according to the Study Schedule. At the end of Visit 3, eligible patients were randomly assigned to treatment with atomoxetine or placebo. • Study Period II: A 35- to 74-day (approximately 7-week) acute, double-blind treatment period consisting of four visits. During this study period, patients received a titrated dose (increase or decrease) based on weight and a prespecified dose titration schedule. The initial atomoxetine dose was 0.8 mg/kg/day. The highest total daily dose in this study was 1.8 mg/kg/day, and did not exceed	

120 mg/day regardless of patient's weight. Dose was adjusted based on response, safety and tolerability, and the investigator's clinical judgment. One dose reduction was permitted during this study period. Patients who required more than one dose reduction for safety or tolerability concerns at any time during Study Period II were discontinued from treatment but remained eligible to enroll in Study Period III. Patients assigned to placebo were given study medication that was identical in appearance to atomoxetine, and dose was evaluated and adjusted in the same double-blind manner for both treatment groups. Efficacy, quality of life, and safety measures were completed according to the Study Schedule.

- Study Period III: The open-label extension-until-launch phase of the study may extend for up to 2 years. Data from this study period will be presented in a later report.

Number of Patients:

Planned: 106 atomoxetine, 53 placebo
Randomized: 101 atomoxetine, 52 placebo
Completed: 84 atomoxetine, 48 placebo

Diagnosis and Main Criteria for Inclusion: Patients were at least 8 years but no more than 12 years of age prior to Visit 7. Patients met DSM-IV diagnostic criteria for ADHD. The diagnosis was confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School aged Children-Present and Lifetime Version: Behavioral Disorders Supplement (K-SADS-PL:Behavioral). At Visit 2 and Visit 3, all patients had a mean ADHDRS-IV-Teacher:Inv Total score that was at least 1.0 standard deviations above age and sex norms. In addition, at both Visit 2 and Visit 3, each patient's mean CPRS-R:S ADHD Index score was at least 1.5 standard deviations above age and sex norms. Patients' ADHD symptoms were confirmed at Visit 2 by the Children's Academic Performance, Attention, Behavior, and Learning Evaluation: Teacher Telephone Interview (CAPABLE-TTI) and the ADHDRS-IV-Teacher:Inv.

Test Product, Dose, and Mode of Administration: Atomoxetine: 0.8 mg/kg/day to 1.8 mg/kg/day, given once daily; atomoxetine capsules, 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, and 40 mg.

Duration of Treatment: Approximately 7 weeks.

Reference Therapy, Dose, and Mode of Administration: Placebo: once daily.

Variables:

Efficacy: Treatment differences on the following measures: ADHDRS-IV-Teacher:Inv, APRS, SSRS-Teacher, Brown ADD Scales: Teacher, Conners' Global Index-Teacher, Behavioral Grade Measure, CPRS-R:S, Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity (CGI-ADHD-S), and Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Improvement (CGI-ADHD-I).

Safety: Treatment-emergent adverse events, vital signs, height and weight, laboratory analytes, and electrocardiograms (ECGs).

Health Outcomes: Physical and psychosocial well being using the Child Health Questionnaire.

Evaluation Methods:

Statistical: The primary efficacy analysis was the comparison of least-square means across treatment at the final week of the double-blind treatment phase (Visit 7). The repeated measures analysis was based on the restricted maximum likelihood method assuming an unstructured covariance matrix. The independent effects in the model were investigator, treatment, visit, cytochrome P450 2D6 (CYP2D6) metabolism status, baseline ADHDRS-IV-Teacher:Inv Total score, baseline ADHDRS-IV-Teacher:Inv Total score-by-visit interaction, and treatment-by-visit interaction. Baseline was defined as scores obtained for Visit 3. Mean changes were also compared by using analysis of covariance (ANCOVA) on the last-observation-carried-forward (LOCF) change from baseline to endpoint observation. The independent effects in the ANCOVA model were investigator, treatment, CYP2D6 metabolism status, and baseline score. The percentages of responders during the double-blind acute phase were compared across treatment groups using Fisher's exact test. Treatment differences in the percentages of treatment-emergent adverse events were assessed using Fisher's exact test. Treatment differences in continuous safety data were assessed using ANOVA with investigator and treatment as independent effects in the model.

Summary:

Patient Disposition: Patients were randomized to treatment with atomoxetine or placebo in a 2:1 ratio. At Visit 3, 52 patients were randomized to the placebo treatment group and 101 patients were randomized to the atomoxetine treatment group. Of the 153 patients who were randomized, 132 (86.3%) completed Study Period II. Overall, completion rates were high for both treatment groups.

Patient Demographics: Table LYAW.1 summarizes demographic characteristics for all randomized patients. Of the 153 randomized patients, 80.4% were male; 60.1% were Caucasian; 40.1% had no prior stimulant exposure, and 2.6% were determined to be cytochrome P450 2D6 (CYP2D6) poor metabolizer (PM) patients. The mean age was 9.94 years (range of 7.38 years to 12.79 years) and 69.3% of the patients were in the third through fifth grades in school.

Patients were required to meet DSM-IV criteria for ADHD following clinical examination. The diagnosis was confirmed by the K-SADS-PL:Behavioral. The presence of symptoms at school was also documented using the CAPABLE-TTI and the ADHDRS-IV-Teacher:Inv. Of the randomized patients, 72.5% met criteria for the combined ADHD subtype on the K-SADS-PL:Behavioral, with 26.8% classified as predominantly Inattentive and 0.7% as Hyperactive-Impulsive. At baseline, the two treatment groups were comparable on all baseline measures.

Efficacy: Symptom reduction in the atomoxetine group in Study Period II was numerically superior compared to placebo as assessed by both repeated measures analysis and mean change on the primary outcome measure, the ADHDRS-IV-Teacher:Inv Total score. As Table LYAW.2 illustrates, for the ADHDRS-IV-Teacher:Inv Total score at Visit 7 (the primary analysis visit), the mean score for atomoxetine-treated patients from the repeated measures analysis was 20.13 compared to 27.89 for placebo-treated patients, giving a mean treatment difference of 7.76 ($p < .001$). As Table LYAW.3 shows, the mean change from baseline to endpoint for atomoxetine-treated patients was -14.5 compared to a mean change of -7.2 for placebo-treated patients ($p = .001$).

Statistically significant differences in mean change from baseline to endpoint were observed for some, but not all, secondary efficacy measures from teachers. Results from the secondary efficacy measures (percentage of responders, Conners' Global Index-Teacher, Behavioral Grade Measure [Classroom Behaviors and Lunchroom/Playground Behaviors], SSRS-T, Brown ADD Scales: Teacher, APRS, CPRS-R:S, CGI-ADHD-S, and CGI-ADHD-I) are presented in Table LYAW.4 through Table LYAW.13. The following reasons may explain the differential results on the secondary efficacy measures: First, in contrast to the primary efficacy measure, which was administered during telephone interviews with teachers, most secondary efficacy measures were collected by faxing forms to and from teachers – a process that resulted in roughly 20% missing data. In addition, this study was designed to have adequate statistical power to detect a treatment effect using the ADHDRS-IV-Teacher:Inv, but not specifically powered to detect differences in the secondary efficacy measures. Some secondary efficacy measures may have been less sensitive measures of treatment effect than the ADHDRS-IV-Teacher:Inv. As a result, this study may not have been adequately powered to detect treatment effects using the less sensitive measures.

A review of the secondary efficacy measures used in this 7-week trial suggests that teacher measures of disruptive behaviors may have been somewhat more sensitive to treatment effects than teacher measures of academic performance, emotions, and prosocial behaviors. The combination of the presence of missing data, different levels of sensitivity to treatment effects for some measures, and a higher observed placebo response rate in this study may have contributed to the failure to detect a statistically significant difference between treatment effects on some secondary efficacy measures from teachers.

This study used dose-titration based on clinical response, with a final mean dose of 1.33 mg/kg/day.

Symptoms of ADHD at school are a major impediment to academic success and are one of the most common reasons that families of affected children seek treatment. The results of this study demonstrate that once-daily atomoxetine is effective at reducing ADHD symptoms in children who were assessed in a school setting.

Safety: There were no deaths or serious adverse events (SAEs) reported in this study. Six patients (6.0%) discontinued due to an adverse event and all were assigned to the atomoxetine treatment group; 2 reported abdominal pain, 1 reported emotional lability, 1 reported feeling abnormal, 1 reported increased irritability, and 1 reported vomiting.

Table LYAW.14 summarizes treatment-emergent adverse events by system organ class and preferred term that were reported in $\geq 1\%$ of drug-treated patients who had taken at least one dose of study medication. Among treatment-emergent adverse events, “appetite decreased” and “somnolence” were reported statistically significantly more often among atomoxetine-treated patients than placebo-treated patients.

Table LYAW.15 summarizes mean change from baseline to endpoint for each analyte during Study Period II. Statistically significant treatment differences in mean change scores between atomoxetine and placebo were observed for erythrocyte count, lymphocytes, aspartate transaminase/serum glutamic oxaloacetic transaminase, alanine transaminase/serum glutamic pyruvic transaminase, creatine phosphokinase, total protein, and albumin.

Table LYAW.16 summarizes the mean change from baseline to endpoint in vital sign measures from Study Period II. There was a statistically significant difference between atomoxetine and placebo for weight change ($p < .001$). There was a mean decrease (0.7 kg) in weight for the atomoxetine treatment group and a mean increase (1.2 kg) in weight in the placebo treatment group. Thirty-five (35) atomoxetine-treated patients (35.4%) experienced at least a 3.5% decrease in weight compared to two placebo-treated patients (3.9%). Although not statistically significant ($p = .067$), patients taking atomoxetine had a mean pulse increase of 3.3 bpm, while those in the placebo group had a mean decrease of 0.1 bpm. There were no statistically significant treatment group differences in mean change in blood pressure values.

Table LYAW.17 summarizes the mean change from Study Period II baseline-to-endpoint ECG intervals and heart rate. Statistically significant differences between atomoxetine and placebo were found for heart rate and the RR intervals. Relative to placebo, atomoxetine was associated with a mean decrease of the RR interval (mean change for atomoxetine-treated patients = -53.853, mean change for placebo-treated patients = -11.285; $p = .012$) and a mean increase in heart rate (mean change for atomoxetine-treated patients = 6.267, mean change for placebo-treated patients = 0.878; $p = .006$). The decrease in RR interval would be expected with an elevation of heart rate. There was no evidence of QTc prolongation.

Health Outcomes: Table LYAW.18 summarizes the LOCF analysis of the change from baseline-to-endpoint analysis of the 12 subscales of the CHQ. The atomoxetine treatment group had statistically significantly greater mean improvement scores compared with the placebo treatment group ($p = .013$) on the General Behavior subscale.

**Table LYAW.1. Patient Demographics and Other Characteristics
Comparison of Treatment Groups at Baseline
All Randomized Patients**

Variable	ATOMOX (N=101)	PLACEBO (N=52)	Total (N=153)	p-Value
Sex: No. (%)				
No. Patients	101	52	153	.520*
Female	18 (17.8)	12 (23.1)	30 (19.6)	
Male	83 (82.2)	40 (76.9)	123 (80.4)	
Origin: No. (%)				
No. Patients	101	52	153	.270*
African Descent	10 (9.9)	4 (7.7)	14 (9.2)	
Western Asian	3 (3.0)	0	3 (2.0)	
Caucasian	61 (60.4)	31 (59.6)	92 (60.1)	
East/Southeast A	1 (1.0)	0	1 (0.7)	
Hispanic	25 (24.8)	13 (25.0)	38 (24.8)	
Other	1 (1.0)	4 (7.7)	5 (3.3)	
Age: yrs.				
No. Patients	101	52	153	.899**
Mean	9.94	9.92	9.94	
Median	9.80	9.59	9.71	
Standard Dev.	1.37	1.26	1.33	
Minimum	7.38	7.96	7.38	
Maximum	2.79	12.47	12.79	
CYP2D6				
No. Patients	101	52	153	.116*
EXTN	99 (99.0)	49 (94.2)	148 (97.4)	
SLOW	1 (1.0)	3 (5.8)	4 (2.6)	
Unspecified	1	0	1	
Height: cm				
No. Patients	101	52	153	.948**
Mean	137.95	137.80	137.90	
Median	136.50	135.00	136.00	
Standard Dev.	10.20	9.07	9.80	
Minimum	117.00	121.00	117.00	
Maximum	164.00	158.00	164.00	
Weight: kg				
No. Patients	101	52	153	.906**
Mean	35.05	35.16	35.09	
Median	33.00	33.05	33.00	
Standard Dev.	9.44	9.38	9.39	
Minimum	21.20	22.70	21.20	
Maximum	61.40	61.80	61.80	
DSM-IV ADHD Subtype				
No. Patients	101	52	153	.355*
HYP/IMP	0	1 (1.9)	1 (0.7)	
INATTV	26 (25.7)	15 (28.8)	41 (26.8)	
MIXED	75 (74.3)	36 (69.2)	111 (72.5)	
Family History-ADHD-Mother				
No. Patients	101	52	153	1.00*
N	77 (76.2)	40 (76.9)	117 (76.5)	
U	10 (9.9)	5 (9.6)	15 (9.8)	
Y	14 (13.9)	7 (13.5)	21 (13.7)	

(continued)

**Table LYAW.1. Patient Demographics and Other Characteristics
Comparison of Treatment Groups at Baseline
All Randomized Patients (Concluded)**

Variable	ATOMOX (N=101)	PLACEBO (N=52)	Total (N=153)	p-Value
Family History-ADHD-Father				
No. Patients	101	52	153	.964*
N	72 (71.3)	36 (69.2)	108 (70.6)	
U	12 (11.9)	7 (13.5)	19 (12.4)	
Y	17 (16.8)	9 (17.3)	26 (17.0)	
Family History-ADHD-Grandparents				
No. Patients	101	52	153	.944*
N	78 (77.2)	42 (80.8)	120 (78.4)	
U	18 (17.8)	8 (15.4)	26 (17.0)	
Y	5 (5.0)	2 (3.8)	7 (4.6)	
Family History-ADHD-Siblings				
No. Patients	101	52	153	.132*
N	56 (55.4)	38 (73.1)	94 (61.4)	
N/A	5 (5.0)	3 (5.8)	8 (5.2)	
U	8 (7.9)	3 (5.8)	11 (7.2)	
Y	32 (31.7)	8 (15.4)	40 (26.1)	
Prior Stimulant Exposure				
No. Patients	101	52	153	.489*
N	38 (38.0)	23 (44.2)	61 (40.1)	
Y	62 (62.0)	29 (55.8)	91 (59.9)	
Unspecified	1	0	1	
Grade in School				
No. Patients	101	52	153	.907*
1	0	1 (1.9)	1 (0.7)	
2	15 (14.9)	8 (15.4)	23 (15.0)	
3	29 (28.7)	14 (26.9)	43 (28.1)	
4	23 (22.8)	12 (23.1)	35 (22.9)	
5	19 (18.8)	9 (17.3)	28 (18.3)	
6	11 (10.9)	7 (13.5)	18 (11.8)	
7	4 (4.0)	1 (1.9)	5 (3.3)	

Population: All Enrolled Patients.

Initial Visit ONLY

NOTE: Pooled Investigator Used in Analysis

Input data from RMP.SAS.B4ZM.L.MCLYAWSW

Output stored as RMP.B4Z0.LYAWCTRM.ACUTE(DE12500A)

* Frequencies are analyzed using a Fishers-Exact test.

** Means are analyzed using a Type III Sum of Squares analysis of variance
(ANOVA): PROC GLM model=investigator and treatment.

XDES0001

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**Table LYAW.2. ADHDRS-IV-Teacher:Inv Total Score - Imputed
 Repeated Measures Least-Squares Means
 Study Period II**

Visit	Atomoxetine			Placebo			Treatment Difference		
	LS Mean	SE	p-val a	LS Mean	SE	p-val a	LS Mean	SE	p-val b
4	26.59	2.48	<.001	30.38	2.47	<.001	3.80	1.78	.035
5	22.74	2.55	<.001	29.73	2.58	<.001	6.99	1.99	<.001
6	21.35	2.54	<.001	29.76	2.52	<.001	8.41	1.88	<.001
7	20.13	2.59	<.001	27.89	2.62	<.001	7.76	2.09	<.001
95% Confidence Interval on Change from Baseline to Visit 7									
(-22.99 , -12.76)				(-15.28, -4.95)					
Summary of Model Parameters			F-Value	P-Value c					
Baseline			69.59	<.001					
Treatment			18.96	<.001					
Visit			1.62	.187					
Investigator			0.64	.764					
CYP2D6			1.37	.243					
Treatment*Visit			1.71	.168					
Baseline*Visit			0.64	.592					

Results based on a mixed model with a term for visit, baseline, treatment, CYP2D6, investigator, treatment by visit interaction, and baseline by visit interaction using an unstructured covariance matrix to model correlations within patient across visits.

a P-values are from tests for a nonzero least squares mean at the given visit.

b P-values are from tests for a treatment difference in least squares means at the given visit.

c P-values are from F-tests for a nonzero coefficient estimate.

Program: RMP.B4ZSLYAW.SASPGM(EFF1A)

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**Table LYAW.3. ADHDRS-IV-Teacher:Inv Total Score
 Change from Baseline to Endpoint
 Study Period II**

Treatment Group	n	Baseline		Endpoint		Change		p-Value(A)	p-value(B)
		Mean	SD	Mean	SD	Mean	SD		
Total Score									
Atomox.	100	38.9	7.2	24.4	13.4	-14.5	12.3	<.001	.001
Placebo	51	36.7	8.4	29.5	13.4	-7.2	9.7	<.001	----
95% C.I.: (-10.8 , -2.79)									

(A) p-Value is from Wilcoxon signed-rank test.

(B) Between treatment group p-Values are from pairwise tests of treatment differences versus placebo in mean change from baseline to endpoint (LOCF) scores using least squares means from an ANCOVA model with terms for investigator, treatment, CYP2D6 status and baseline covariate. All enrolled patients with a baseline and at least one postbaseline measurement included.

Program: RMP.B4ZSLYAW.SASPGM(EFFTRGR1)

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**Table LYAW.4. Percentages of Responders
 All Randomized Patients
 Study Period II**

Treatment	Response(A)			
	N	n	%	p-value(B)
Atomox.	100	48	(48.0)	.057
Placebo	51	16	(31.4)	----

(A) Responder is defined as having a 40% or greater decrease from baseline to endpoint in the ADHDRS-IV-Teacher:Inv total score-Imputed.

(B) p-values are for between treatment differences using a Fishers exact test.

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**Table LYAW.5. Conners' Global Index-Teacher
 Change from Baseline to Endpoint
 Study Period II**

Treatment Group	n	Baseline		Endpoint		Change		p-Value (a)	p-value (b)
		Mean	SD	Mean	SD	Mean	SD		
Total Index									
Atomox.	74	16.1	6.8	12.4	6.4	-3.7	6.0	<.001	.008
Placebo	42	16.4	5.9	15.6	6.8	-0.8	6.0	.640	----
95% C.I.: (-5.13 , -0.77)									
Emotional Lability									
Atomox.	78	3.8	3.5	3.1	2.9	-0.8	2.4	.005	.199
Placebo	45	3.9	3.3	3.7	3.2	-0.2	2.6	.908	----
95% C.I.: (-1.33 , 0.28)									
Restless Impulsivity									
Atomox.	74	12.4	4.3	9.4	4.3	-3.0	4.4	<.001	.002
Placebo	42	12.7	3.7	12.0	4.4	-0.8	4.2	.509	----
95% C.I.: (-4.04 , -0.93)									

(a) p-Value is from Wilcoxon signed-rank test.

(b) Between treatment group p-Values are from baseline to endpoint (LOCF) scores using least squares means from an ANCOVA model with terms for investigator, treatment, CYP2D6, and baseline covariate.

Program: RMP.B4ZSLYAW.SASPGM(EFFSC14A)

Table LYAW.6. **Behavioral Grade Measure**
Classroom Behaviors
Change from Baseline to Endpoint
Study Period II

Baseline Score=Unsatisfactory				
	Total at Baseline	Endpoint Score		
		U	S	E
Atomox.	81	45	34	2
Placebo	43	35	7	1
Baseline Score=Satisfactory				
	Total at Baseline	Endpoint Score		
		U	S	E
Atomox.	18	4	14	0
Placebo	6	1	5	0

van Elterens Test stratified by Baseline Score: p =.011

Results based on a Van Elterens test.

Program: RMP.B4ZSLYAW.SASPGM(EFFVELT1)

Table LYAW.7. Behavioral Grade Measure
Lunchroom/Playground Behaviors
Change from Baseline to Endpoint
Study Period II

Baseline Score=Unsatisfactory				
	Total at Baseline	Endpoint Score		
		U	S	E
Atomox.	38	17	19	2
Placebo	21	14	6	1
Baseline Score=Satisfactory				
	Total at Baseline	Endpoint Score		
		U	S	E
Atomox.	53	10	38	5
Placebo	27	6	19	2
Baseline Score=Excellent				
	Total at Baseline	Endpoint Score		
		U	S	E
Atomox.	1	0	1	0
Placebo	1	0	1	0
van Elterens Test stratified by Baseline Score: p =.175				

Results based on a Van Elterens test.

Program: RMP.B4ZSLYAW.SASPGM(EFFVELT2)

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**Table LYAW.8. Social Skills Rating System-Teacher Form
 Change from Baseline to Endpoint
 Using Standard Scores
 Study Period II**

Treatment Group	n	Baseline		Endpoint		Change		p-Value (a)	p-value (b)
		Mean	SD	Mean	SD	Mean	SD		
Problem Behavior Standard Score									
Atomox.	76	115.8	11.7	110.5	13.6	-5.3	8.8	<.001	.025
Placebo	45	116.4	10.1	114.4	13.2	-2.0	10.3	.382	----
95% C.I.: (-7.55 , -0.51)									
Social Skills Standard Score									
Atomox.	74	85.7	10.8	89.7	12.0	4.0	9.0	<.001	.196
Placebo	44	84.3	10.6	86.7	11.9	2.4	10.0	.219	----
95% C.I.: (-1.20 , 5.79)									

(a) p-Value is from Wilcoxon signed-rank test.

(b) Between treatment group p-Values are from baseline to endpoint (LOCF) scores using least squares means from an ANCOVA model with terms for investigator, treatment, CYP2D6, and baseline covariate.

Program: RMP.B4ZSLYAW.SASPGM(EFFSC14D)

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**Table LYAW.9. Brown Attention Deficit Disorder Scales: Teacher Form
 Change from Baseline to Endpoint
 Using Standardized Total Scores
 Study Period II**

Treatment Group	n	Baseline		Endpoint		Change		p-Value (a)	p-value (b)
		Mean	SD	Mean	SD	Mean	SD		
Combined T-Score									
Atomox.	79	64.1	7.6	59.1	8.3	-5.0	7.0	<.001	.072
Placebo	46	64.4	6.6	61.5	7.7	-2.9	7.7	.016	----
				95% C.I.: (-4.80 , 0.21)					
Activation T-Score									
Atomox.	79	62.6	9.0	58.6	9.6	-4.1	7.7	<.001	.231
Placebo	46	63.7	7.6	60.9	7.9	-2.9	7.8	.012	----
				95% C.I.: (-4.28 , 1.04)					
Focus T-Score									
Atomox.	79	63.8	6.6	58.8	8.1	-5.0	7.5	<.001	.169
Placebo	46	64.0	6.6	60.8	8.2	-3.2	8.9	.019	----
				95% C.I.: (-4.72 , 0.83)					
Effort T-Score									
Atomox.	79	63.8	8.2	59.2	8.6	-4.6	7.5	<.001	.046
Placebo	46	63.6	7.8	61.7	7.9	-1.9	8.8	.194	----
				95% C.I.: (-5.53 , -0.05)					
Emotion T-Score									
Atomox.	79	58.8	10.7	55.6	10.7	-3.2	7.9	<.001	.528
Placebo	46	59.9	9.5	57.3	9.0	-2.5	8.3	.086	----
				95% C.I.: (-3.72 , 1.92)					

(continued)

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**Table LYAW.9. Brown Attention Deficit Disorder Scales: Teacher Form
 Change from Baseline to Endpoint
 Using Standardized Total Scores
 Study Period II (concluded)**

Treatment Group	n	Baseline		Endpoint		Change		p-Value(a)	p-value(b)
		Mean	SD	Mean	SD	Mean	SD		
Memory T-Score									
Atomox.	79	61.7	9.0	57.4	8.3	-4.3	7.5	<.001	.109
Placebo	46	61.9	9.9	59.5	9.6	-2.4	9.2	.029	----
				95% C.I.: (-4.69 , 0.48)					
Action T-Score									
Atomox.	76	64.9	11.1	59.2	11.2	-5.7	8.8	<.001	.052
Placebo	46	65.3	9.8	62.5	11.6	-2.9	7.4	.022	----
				95% C.I.: (-6.03 , 0.03)					
Inattention T-Score									
Atomox.	79	63.2	7.6	58.6	8.2	-4.6	6.8	<.001	.118
Placebo	46	63.7	7.1	60.8	7.6	-2.9	8.2	.020	----
				95% C.I.: (-4.50 , 0.51)					

(a) p-Value is from Wilcoxon signed-rank test.

(b) Between treatment group p-Values are from baseline to endpoint (LOCF) scores using least squares means from an ANCOVA model with terms for investigator, treatment, CYP2D6, and baseline covariate.

Program: RMP.B4ZSLYAW.SASPGM(EFFSC14C)

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**Table LYAW.10. Academic Performance Rating Scale Total Score
 Change from Baseline to Endpoint
 Study Period II**

Treatment Group	n	Baseline		Endpoint		Change		p-Value(a)	p-value(b)
		Mean	SD	Mean	SD	Mean	SD		
Total Score									
Atomox.	70	35.1	10.8	39.9	10.4	4.8	9.2	<.001	.106
Placebo	36	35.9	11.8	38.1	11.7	2.2	9.6	.260	----
				95% C.I.: (-0.64 , 6.53)					
Academic Success									
Atomox.	73	14.1	4.8	15.6	4.9	1.6	3.9	<.001	.257
Placebo	38	14.2	5.6	15.0	5.6	0.8	3.7	.352	----
				95% C.I.: (-0.65 , 2.42)					
Impulse Control									
Atomox.	80	4.3	2.2	4.8	2.5	0.5	2.1	.016	.474
Placebo	45	4.6	2.1	4.8	2.2	0.2	2.2	.461	----
				95% C.I.: (-0.47 , 1.01)					
Academic Productivity									
Atomox.	71	22.5	9.0	26.2	8.1	3.7	7.7	<.001	.108
Placebo	37	23.4	8.2	24.8	8.8	1.4	6.8	.400	----
				95% C.I.: (-0.50 , 4.98)					

(a) p-Value is from Wilcoxon signed-rank test.

(b) Between treatment group p-Values are from baseline to endpoint (LOCF) scores using least squares means from an ANCOVA model with terms for investigator, treatment, CYP3D6, and baseline covariate.

Program: RMP.B4ZSLYAW.SASPGM(EFFSC14B)

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**Table LYAW.11. Conners' Parent Rating Scale-Revised: Short Form
 Change from Baseline to Endpoint
 Study Period II**

Treatment Group	n	Baseline		Endpoint		Change		p-Value(a)	p-value(b)
		Mean	SD	Mean	SD	Mean	SD		
T-Score Index									
Atomox.	99	74.6	8.5	62.5	11.0	-12.1	12.7	<.001	<.001
Placebo	51	75.2	8.5	71.1	11.0	-4.1	7.6	<.001	----
				95% C.I.: (-11.4 , -4.43)					
Cognitive Problems T-Score									
Atomox.	99	73.3	10.0	61.5	11.4	-11.8	13.1	<.001	<.001
Placebo	51	75.2	10.5	71.4	11.4	-3.8	8.3	.001	----
				95% C.I.: (-12.0 , -5.03)					
Hyperactive T-Score									
Atomox.	99	76.5	17.1	64.3	15.3	-12.2	16.6	<.001	<.001
Placebo	51	78.3	16.8	74.0	18.1	-4.2	9.3	<.001	----
				95% C.I.: (-13.0 , -4.22)					
Oppositional T-Score									
Atomox.	99	66.0	14.9	60.6	14.0	-5.4	14.9	.002	.276
Placebo	51	64.2	15.0	62.6	14.3	-1.6	11.1	.347	----
				95% C.I.: (-6.22 , 1.79)					

(a) p-Value is from Wilcoxon signed-rank test.

(b) Between treatment group p-Values are from baseline to endpoint (LOCF) scores using least squares means from an ANCOVA model with terms for investigator, treatment, CYP2D6, and baseline covariate.

Program: RMP.B4ZSLYAW.SASPGM(EFFSC14F)

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**Table LYAW.12. CGI-ADHD-S Rating Scale
 Change from Baseline to Endpoint
 Study Period II**

Treatment Group	n	Baseline		Endpoint		Change		p-Value(a)	p-value(b)
		Mean	SD	Mean	SD	Mean	SD		
CGI ADHD Severity									
Atomox.	99	4.9	0.8	3.4	1.3	-1.5	1.2	<.001	.001
Placebo	51	4.9	0.8	4.1	1.1	-0.7	1.0	<.001	----
				95% C.I.: (-1.06 , -0.27)					

(a) p-Value is from Wilcoxon signed-rank test.

(b) Between treatment group p-Values are from baseline to endpoint (LOCF) scores using least squares means from an ANCOVA model with terms for investigator, treatment, CYP2D6, and baseline covariate.

Program: RMP.B4ZSLYAW.SASPGM(EFFS14E1)

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**Table LYAW.13. CGI-ADHD-I Rating Scale
 Change from Baseline to Endpoint
 Study Period II**

Treatment Group	n	Baseline		Endpoint		Change		p-Value(a)
		Mean	SD	Mean	SD	Mean	SD	
CGI ADHD Improvement								
Atomox.	99			2.6	1.0			<.001
Placebo	51			3.4	1.0			----
				95% C.I.: (-1.12 , -0.42)				

(a) Between treatment group p-Values are from endpoint (LOCF) scores using least squares means from an ANOVA model with terms for investigator, treatment, and CYP2D6.
 Program: RMP.B4ZSLYAW.SASPGM(EFFS14E2)

**Table LYAW.14. Summary of Treatment-Emergent Adverse Events
by System Organ Class Using MedDRA Preferred Terms
All Randomized Patients, Study Period II**

System Organ Class: Overall

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	89 (89.0)	31 (59.6)	120 (78.9)	<.001
PATIENTS WITH NO TESS	11 (11.0)	21 (40.4)	32 (21.1)	<.001

System Organ Class: Blood and lymphatic system disorders

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	2 (2.0)	0	2 (1.3)	.547
PATIENTS WITH NO TESS	98 (98.0)	52 (100)	150 (98.7)	.547
Lymphadenitis NOS	2 (2.0)	0	2 (1.3)	.547

System Organ Class: Cardiac disorders

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	1 (1.0)	0	1 (0.7)	1.00
PATIENTS WITH NO TESS	99 (99.0)	52 (100)	151 (99.3)	1.00
Palpitations	1 (1.0)	0	1 (0.7)	

System Organ Class: Congenital, familial and genetic disorders

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	1 (1.0)	1 (1.9)	2 (1.3)	1.00
PATIENTS WITH NO TESS	99 (99.0)	51 (98.1)	150 (98.7)	1.00
Pigmented naevus	1 (1.0)	0	1 (0.7)	
Tourette's disorder	0	1 (1.9)	1 (0.7)	

System Organ Class: Ear and labyrinth disorders

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	1 (1.0)	1 (1.9)	2 (1.3)	1.00
PATIENTS WITH NO TESS	99 (99.0)	51 (98.1)	150 (98.7)	1.00
Ear pain	1 (1.0)	0	1 (0.7)	
Fluid in middle ear	0	1 (1.9)	1 (0.7)	

(continued)

**Table LYAW.14. Summary of Treatment-Emergent Adverse Events
by System Organ Class Using MedDRA Preferred Terms
All Randomized Patients, Study Period II (continued)**

System Organ Class: Eye disorders

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	1 (1.0)	1 (1.9)	2 (1.3)	1.00
PATIENTS WITH NO TESS	99 (99.0)	51 (98.1)	150 (98.7)	1.00
Conjunctivitis NOS	1 (1.0)	0	1 (0.7)	
Vision blurred	0	1 (1.9)	1 (0.7)	

System Organ Class: Gastrointestinal disorders

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	43 (43.0)	14 (26.9)	57 (37.5)	.055
PATIENTS WITH NO TESS	57 (57.0)	38 (73.1)	95 (62.5)	.055
Abdominal pain upper	15 (15.0)	5 (9.6)	20 (13.2)	.452
Vomiting NOS	14 (14.0)	2 (3.8)	16 (10.5)	.057
Pharyngolaryngeal pain	6 (6.0)	4 (7.7)	10 (6.6)	.736
Abdominal pain NOS	8 (8.0)	1 (1.9)	9 (5.9)	.167
Nausea	7 (7.0)	1 (1.9)	8 (5.3)	.265
Dyspepsia	3 (3.0)	0	3 (2.0)	.551
Diarrhoea NOS	0	1 (1.9)	1 (0.7)	
Dry mouth	1 (1.0)	0	1 (0.7)	
Lip ulceration	1 (1.0)	0	1 (0.7)	
Mouth ulceration	0	1 (1.9)	1 (0.7)	

System Organ Class: General disorders and administration site conditions

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	21 (21.0)	8 (15.4)	29 (19.1)	.515
PATIENTS WITH NO TESS	79 (79.0)	44 (84.6)	123 (80.9)	.515
Fatigue	9 (9.0)	1 (1.9)	10 (6.6)	.165
Pyrexia	6 (6.0)	4 (7.7)	10 (6.6)	.736
Unexpected therapeutic drug effect	3 (3.0)	1 (1.9)	4 (2.6)	1.00
Chest pain	1 (1.0)	1 (1.9)	2 (1.3)	1.00
Feeling hot	2 (2.0)	0	2 (1.3)	.547
Lethargy	2 (2.0)	0	2 (1.3)	.547
Malaise	1 (1.0)	1 (1.9)	2 (1.3)	1.00
Feeling abnormal	1 (1.0)	0	1 (0.7)	
Influenza like illness	1 (1.0)	0	1 (0.7)	
Pain trauma activated	1 (1.0)	0	1 (0.7)	
Rigors	1 (1.0)	0	1 (0.7)	
Thirst	1 (1.0)	0	1 (0.7)	
Weakness	0	1 (1.9)	1 (0.7)	

(continued)

**Table LYAW.14. Summary of Treatment-Emergent Adverse Events
by System Organ Class Using MedDRA Preferred Terms
All Randomized Patients, Study Period II (continued)**

System Organ Class: Immune system disorders

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	1 (1.0)	0	1 (0.7)	1.00
PATIENTS WITH NO TESS	99 (99.0)	52 (100)	151 (99.3)	1.00
Hypersensitivity NOS	1 (1.0)	0	1 (0.7)	

System Organ Class: Infections and infestations

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	20 (20.0)	11 (21.2)	31 (20.4)	1.00
PATIENTS WITH NO TESS	80 (80.0)	41 (78.8)	121 (79.6)	1.00
Upper respiratory tract infection NOS	8 (8.0)	2 (3.8)	10 (6.6)	.495
Nasopharyngitis	6 (6.0)	2 (3.8)	8 (5.3)	.716
Pharyngitis NOS	0	3 (5.8)	3 (2.0)	.039
Influenza	1 (1.0)	1 (1.9)	2 (1.3)	1.00
Tinea pedis	2 (2.0)	0	2 (1.3)	.547
Bronchitis NOS	0	1 (1.9)	1 (0.7)	
Croup infectious	0	1 (1.9)	1 (0.7)	
Ear infection NOS	1 (1.0)	0	1 (0.7)	
Folliculitis	1 (1.0)	0	1 (0.7)	
Gastroenteritis viral NOS	1 (1.0)	0	1 (0.7)	
Otitis media NOS	1 (1.0)	0	1 (0.7)	
Sinusitis NOS	1 (1.0)	0	1 (0.7)	
Viral infection NOS	0	1 (1.9)	1 (0.7)	

System Organ Class: Injury, poisoning and procedural complications

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	7 (7.0)	2 (3.8)	9 (5.9)	.719
PATIENTS WITH NO TESS	93 (93.0)	50 (96.2)	143 (94.1)	.719
Arthropod bite	1 (1.0)	1 (1.9)	2 (1.3)	1.00
Joint sprain	1 (1.0)	1 (1.9)	2 (1.3)	1.00
Back injury NOS	1 (1.0)	0	1 (0.7)	
Face injury	1 (1.0)	0	1 (0.7)	
Laceration	1 (1.0)	0	1 (0.7)	
Scratch	1 (1.0)	0	1 (0.7)	
Sunburn	1 (1.0)	0	1 (0.7)	
Upper limb fracture NOS	1 (1.0)	0	1 (0.7)	

System Organ Class: Investigations

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	3 (3.0)	0	3 (2.0)	.551
PATIENTS WITH NO TESS	97 (97.0)	52 (100)	149 (98.0)	.551
Weight decreased	3 (3.0)	0	3 (2.0)	.551

(continued)

**Table LYAW.14. Summary of Treatment-Emergent Adverse Events
by System Organ Class Using MedDRA Preferred Terms
All Randomized Patients, Study Period II (continued)**

System Organ Class: Metabolism and nutrition disorders

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	28 (28.0)	4 (7.7)	32 (21.1)	.003
PATIENTS WITH NO TESS	72 (72.0)	48 (92.3)	120 (78.9)	.003
Appetite decreased NOS	24 (24.0)	2 (3.8)	26 (17.1)	.001
Anorexia	3 (3.0)	0	3 (2.0)	.551
Appetite increased NOS	1 (1.0)	2 (3.8)	3 (2.0)	.270

System Organ Class: Musculoskeletal and connective tissue disorders

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	2 (2.0)	3 (5.8)	5 (3.3)	.339
PATIENTS WITH NO TESS	98 (98.0)	49 (94.2)	147 (96.7)	.339
Arthralgia	0	2 (3.8)	2 (1.3)	.116
Neck pain	2 (2.0)	0	2 (1.3)	.547
Back pain	1 (1.0)	0	1 (0.7)	
Pain in limb	0	1 (1.9)	1 (0.7)	

System Organ Class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	1 (1.0)	0	1 (0.7)	1.00
PATIENTS WITH NO TESS	99 (99.0)	52 (100)	151 (99.3)	1.00
Skin papilloma	1 (1.0)	0	1 (0.7)	

System Organ Class: Nervous system disorders

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	37 (37.0)	9 (17.3)	46 (30.3)	.015
PATIENTS WITH NO TESS	63 (63.0)	43 (82.7)	106 (69.7)	.015
Headache NOS	18 (18.0)	5 (9.6)	23 (15.1)	.234
Somnolence	17 (17.0)	2 (3.8)	19 (12.5)	.020
Dizziness (excl vertigo)	5 (5.0)	1 (1.9)	6 (3.9)	.665
Sedation	6 (6.0)	0	6 (3.9)	.095
Frequent headaches	0	1 (1.9)	1 (0.7)	
Increased activity	1 (1.0)	0	1 (0.7)	
Reflexes abnormal	1 (1.0)	0	1 (0.7)	

(continued)

**Table LYAW.14. Summary of Treatment-Emergent Adverse Events
by System Organ Class Using MedDRA Preferred Terms
All Randomized Patients, Study Period II (continued)**

System Organ Class: Psychiatric disorders

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	25 (25.0)	5 (9.6)	30 (19.7)	.031
PATIENTS WITH NO TESS	75 (75.0)	47 (90.4)	122 (80.3)	.031
Irritability	11 (11.0)	2 (3.8)	13 (8.6)	.221
Aggression	5 (5.0)	0	5 (3.3)	.166
Emotional disturbance NOS	5 (5.0)	0	5 (3.3)	.166
Mood swings	3 (3.0)	0	3 (2.0)	.551
Tearfulness	1 (1.0)	1 (1.9)	2 (1.3)	1.00
Abnormal behaviour NOS	1 (1.0)	0	1 (0.7)	
Abnormal dreams	1 (1.0)	0	1 (0.7)	
Anger	0	1 (1.9)	1 (0.7)	
Anxiety NEC	1 (1.0)	0	1 (0.7)	
Crying	1 (1.0)	0	1 (0.7)	
Decreased activity	1 (1.0)	0	1 (0.7)	
Early morning awakening	1 (1.0)	0	1 (0.7)	
Encopresis	0	1 (1.9)	1 (0.7)	
Insomnia	1 (1.0)	0	1 (0.7)	
Middle insomnia	1 (1.0)	0	1 (0.7)	
Negativism	0	1 (1.9)	1 (0.7)	
Short-term memory loss	1 (1.0)	0	1 (0.7)	
Tic	1 (1.0)	0	1 (0.7)	

System Organ Class: Renal and urinary disorders

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	2 (2.0)	0	2 (1.3)	.547
PATIENTS WITH NO TESS	98 (98.0)	52 (100)	150 (98.7)	.547
Enuresis	1 (1.0)	0	1 (0.7)	
Urinary frequency	1 (1.0)	0	1 (0.7)	

System Organ Class: Reproductive system and breast disorders

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	2 (2.0)	0	2 (1.3)	.547
PATIENTS WITH NO TESS	98 (98.0)	52 (100)	150 (98.7)	.547
Dysmenorrhoea	1 (1.0)	0	1 (0.7)	
Gynaecomastia	1 (1.0)	0	1 (0.7)	

(continued)

**Table LYAW.14. Summary of Treatment-Emergent Adverse Events
by System Organ Class Using MedDRA Preferred Terms
All Randomized Patients, Study Period II (concluded)**

System Organ Class: Respiratory, thoracic and mediastinal disorders

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	15 (15.0)	8 (15.4)	23 (15.1)	1.00
PATIENTS WITH NO TESS	85 (85.0)	44 (84.6)	129 (84.9)	1.00
Cough	10 (10.0)	5 (9.6)	15 (9.9)	1.00
Nasal congestion	5 (5.0)	2 (3.8)	7 (4.6)	1.00
Rhinorrhoea	2 (2.0)	1 (1.9)	3 (2.0)	1.00
Hypoventilation	0	1 (1.9)	1 (0.7)	
Nasal turbinate hypertrophy	0	1 (1.9)	1 (0.7)	
Rhinitis NOS	1 (1.0)	0	1 (0.7)	
Tonsillar hypertrophy	0	1 (1.9)	1 (0.7)	
Wheezing	0	1 (1.9)	1 (0.7)	

System Organ Class: Skin and subcutaneous tissue disorders

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	5 (5.0)	3 (5.8)	8 (5.3)	1.00
PATIENTS WITH NO TESS	95 (95.0)	49 (94.2)	144 (94.7)	1.00
Contusion	1 (1.0)	1 (1.9)	2 (1.3)	1.00
Dermatitis contact	1 (1.0)	0	1 (0.7)	
Erythema	1 (1.0)	0	1 (0.7)	
Face oedema	0	1 (1.9)	1 (0.7)	
Rash pruritic	1 (1.0)	0	1 (0.7)	
Skin hyperpigmentation	0	1 (1.9)	1 (0.7)	
Sweating increased	1 (1.0)	0	1 (0.7)	

System Organ Class: Surgical and medical procedures

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	1 (1.0)	0	1 (0.7)	1.00
PATIENTS WITH NO TESS	99 (99.0)	52 (100)	151 (99.3)	1.00
Wart excision	1 (1.0)	0	1 (0.7)	

System Organ Class: Vascular disorders

Preferred Term	ATOMOX (N=100) n (%)	PLACEBO (N=52) n (%)	Total (N=152) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	0	1 (1.9)	1 (0.7)	.342
PATIENTS WITH NO TESS	100 (100)	51 (98.1)	151 (99.3)	.342
Flushing	0	1 (1.9)	1 (0.7)	

Population: Enrolled patients who took at least 1 dose of study drug.

Baseline: Visits 1-3, Endpoint: Visits 4-7

Input data from RMP.SAS.B4ZM.L.MCLYAWSW

Output stored as RMP.B4Z0.LYAWCTRM.ACUTE(AE213003)

* Frequencies are analyzed using a Fisher's Exact test.

XAES0002 MEDDRA VERSION: 4.0

Table LYAW.15. Summary of Laboratory Data
Mean Change from Baseline to Endpoint by Analyte
Study Period II

Lab Test	Lab Unit	Therapy	n	-----Baseline-----		Change to -----Endpoint-----		p-Values
				Mean	SD	Mean	SD	
HCT	1	ATOMOX	82	0.377	0.024	0.013	0.023	.172
		PLACEBO	42	0.379	0.021	0.007	0.024	
HGB	mmL/L-Fe	ATOMOX	83	8.152	0.436	0.114	0.428	.285
		PLACEBO	42	8.117	0.457	0.004	0.491	
RBC	TI/L	ATOMOX	83	4.639	0.287	0.047	0.224	.050
		PLACEBO	42	4.669	0.302	-0.031	0.244	
WBC	GI/L	ATOMOX	83	7.052	1.715	-0.331	1.790	.747
		PLACEBO	42	7.142	1.661	-0.436	1.860	
BANDS	GI/L	ATOMOX	83	0.000	0.000	0.000	0.000	.153
		PLACEBO	42	0.000	0.000	0.002	0.011	
POLYS	GI/L	ATOMOX	83	3.633	1.231	-0.017	1.561	.159
		PLACEBO	42	3.834	1.300	-0.421	1.488	
LYMPHS	GI/L	ATOMOX	83	2.722	0.707	-0.251	0.585	.009
		PLACEBO	42	2.660	0.713	0.015	0.634	
MONOS	GI/L	ATOMOX	83	0.400	0.132	-0.028	0.113	.861
		PLACEBO	42	0.395	0.136	-0.021	0.107	
EOSN	GI/L	ATOMOX	83	0.247	0.157	-0.036	0.093	.286
		PLACEBO	42	0.204	0.129	-0.012	0.098	
BASO	GI/L	ATOMOX	83	0.048	0.022	0.002	0.025	.323
		PLACEBO	42	0.051	0.021	-0.001	0.033	
MCV	fL	ATOMOX	82	81.512	4.152	1.902	2.674	.938
		PLACEBO	42	81.190	4.221	2.024	2.322	
PLTCT	GI/L	ATOMOX	82	320.512	65.816	-23.378	49.844	.473
		PLACEBO	41	319.634	70.905	-11.049	62.817	
U-SPGR	NO UNITS	ATOMOX	82	1.025	0.007	0.001	0.008	.280
		PLACEBO	39	1.025	0.007	-0.001	0.007	
AST	U/L	ATOMOX	82	28.866	6.675	-1.305	5.550	.038
		PLACEBO	42	29.333	6.863	1.405	8.076	
ALT	U/L	ATOMOX	83	17.627	6.982	-2.422	7.066	.003
		PLACEBO	43	17.884	6.400	3.209	19.016	
CPK	U/L	ATOMOX	83	138.928	56.919	-3.301	65.160	.022
		PLACEBO	43	135.837	59.579	14.767	72.161	
ALKPH	U/L	ATOMOX	83	231.205	60.192	-2.494	35.018	.094
		PLACEBO	43	233.465	51.838	10.233	32.661	
GGT	U/L	ATOMOX	83	12.349	3.753	-0.157	2.217	.515
		PLACEBO	43	12.442	3.750	0.349	2.785	
BUN	mmol/L	ATOMOX	83	4.749	1.117	0.077	1.148	.227
		PLACEBO	43	4.981	1.113	-0.199	1.276	

(continued)

Table LYAW.15. Summary of Laboratory Data
Mean Change from Baseline to Endpoint by Analyte
Study Period II (continued)

Lab Test	Lab Unit	Therapy	n	-----Baseline-----		Change to -----Endpoint-----		p-Values
				Mean	SD	Mean	SD	
CALC	mmol/L	ATOMOX	83	2.471	0.088	0.013	0.104	.438
		PLACEBO	43	2.475	0.094	-0.009	0.092	
PHOS	mmol/L	ATOMOX	83	1.597	0.167	-0.028	0.190	.134
		PLACEBO	43	1.588	0.167	0.018	0.177	
SODIUM	mmol/L	ATOMOX	83	142.337	2.563	-0.711	2.540	.824
		PLACEBO	43	142.233	2.409	-0.791	3.106	
POTAS	mmol/L	ATOMOX	83	4.311	0.406	-0.086	0.377	.558
		PLACEBO	43	4.323	0.395	-0.051	0.458	
CHLOR	mmol/L	ATOMOX	83	104.265	2.384	-0.434	2.591	.154
		PLACEBO	43	103.860	2.088	0.116	2.519	
TPROT	g/L	ATOMOX	83	72.892	4.303	0.169	3.847	.013
		PLACEBO	43	74.140	4.121	-1.558	3.666	
ALBUM	g/L	ATOMOX	83	44.301	2.649	0.072	2.541	.037
		PLACEBO	43	44.930	3.418	-1.116	3.311	
NFGLU	mmol/L	ATOMOX	83	5.005	0.880	0.072	0.998	.421
		PLACEBO	43	4.784	0.800	0.266	0.969	
UR AC	umol/L	ATOMOX	83	218.428	47.541	-4.658	32.882	.901
		PLACEBO	43	222.151	58.938	-3.181	35.531	
CHOL	mmol/L	ATOMOX	83	4.353	0.671	-0.116	0.503	.970
		PLACEBO	43	4.337	0.772	-0.103	0.635	
BICARB	mmol/L	ATOMOX	83	21.540	1.824	1.136	2.363	.172
		PLACEBO	43	21.744	1.794	0.556	2.105	
CREAT	umol/L	ATOMOX	83	48.886	7.728	0.959	8.051	.232
		PLACEBO	43	47.078	8.781	-0.822	9.989	
T.BILI	umol/L	ATOMOX	59	7.246	4.472	-0.232	3.102	.642
		PLACEBO	30	6.156	2.359	0.114	2.197	

Population: Enrolled patients who took at least 1 dose of study drug.

Baseline: Visits 1-3, Endpoint: Visits 4-7

NOTE: Pooled Investigator Used in Analysis

Input data from RMP.SAS.B4ZM.L.MCLYAWSW

Output stored as RMP.B4ZO.LYAWCTRM.ACUTE(LS606003)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDOC2 - Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks:

PROC GLM model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA on the ranks using the
mean square for error.

Note: At least one investigator does not have patients in every treatment group.

(continued)

Table LYAW.15. **Summary of Laboratory Data**
Mean Change from Baseline to Endpoint by Analyte
Study Period II (concluded)

Legend of Lab Test Code Abbreviations:

Abbrev.	Description
HCT	HEMATOCRIT
HGB	HEMOGLOBIN
RBC	ERYTHROCYTE COUNT
WBC	LEUKOCYTE COUNT
BANDS	BANDS
POLYS	NEUTROPHILS, SEGMENTED
LYMPHS	LYMPHOCYTES
MONOS	MONOCYTES
EOSN	EOSINOPHILS
BASO	BASOPHILS
MCV	MEAN CELL VOLUME (MCV)
PLTCT	PLATELET COUNT
U-SPGR	UA-SPECIFIC GRAVITY
AST	AST/SGOT
ALT	ALT/SGPT
CPK	CREATINE PHOSPHOKINASE
ALKPH	ALKALINE PHOSPHATASE
GGT	GGT (GGPT/SGGT/YGGT)
BUN	UREA NITROGEN
CALC	CALCIUM
PHOS	INORGANIC PHOSPHORUS
SODIUM	SODIUM
POTAS	POTASSIUM
CHLOR	CHLORIDE
TPROT	TOTAL PROTEIN
ALBUM	ALBUMIN
NFGLU	GLUCOSE, NON-FASTING
UR AC	URIC ACID
CHOL	CHOLESTEROL
BICARB	BICARBONATE, HCO ₃
CREAT	CREATININE
T.BILI	BILIRUBIN, TOTAL

**Table LYAW.16. Summary of Vital Sign Data
Change from Baseline to Endpoint
Study Period II**

		-----Baseline-----			Change to -----Endpoint-----		p-Values
Variables Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy
DIASAVG	ATOMOX	99	64.010	8.256	2.793	9.533	.399
	PLACEBO	51	63.422	7.870	1.725	8.030	
SYSAVG	ATOMOX	99	103.828	10.741	0.571	9.035	.858
	PLACEBO	51	102.422	9.593	0.853	8.958	
PULSAVG	ATOMOX	99	83.268	11.569	3.318	11.331	.067
	PLACEBO	51	83.794	9.645	-0.098	9.820	
WEIGHT	ATOMOX	99	35.523	9.578	-0.671	1.212	<.001
	PLACEBO	51	34.865	8.769	1.206	1.381	
HEIGHT	ATOMOX	91	138.029	10.194	0.654	0.950	.480
	PLACEBO	46	137.922	9.058	0.800	1.447	
TEMP	ATOMOX	98	36.718	0.483	0.004	0.594	.771
	PLACEBO	51	36.627	0.376	0.047	0.533	

Population: Enrolled patients who took at least 1 dose of study drug.

Baseline: Visits 1-3, Endpoint: Visits 4-7

NOTE: Pooled Investigator Used in Analysis

Input data from RMP.SAS.B4ZM.L.MCLYAWSW

Output stored as RMP.B4ZO.LYAWCTRM.ACUTE(VI6L9003)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDUC1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for
error.

Note: Each investigator has at least one patient in each treatment group.

XLAS0006

Legend of Variable Abbreviations:

Abbrev.	Description
DIASAVG	Diastolic BP Average
HEIGHT	Height in CM
PULSAVG	Heart Rate Average
SYSAVG	Systolic BP Average
TEMP	Temperature in Centigrade
WEIGHT	Weight in KG

Table LYAW.17. Summary of Changes from Baseline ECG Study Period II

		-----Baseline-----		Change to -----Endpoint-----		p-Values	
Variables Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy
RR	ATOMOX	90	780.653	103.852	-53.853	98.076	.012
	PLACEBO	49	780.136	117.451	-11.285	108.789	
PR	ATOMOX	90	135.222	16.641	-3.000	13.107	.079
	PLACEBO	49	133.673	17.163	3.265	16.757	
QRS	ATOMOX	90	76.667	8.611	0.444	8.060	.956
	PLACEBO	49	75.918	8.396	1.020	7.143	
QT	ATOMOX	90	353.111	25.068	-3.111	21.181	.178
	PLACEBO	49	357.551	25.293	1.224	21.855	
QTCB	ATOMOX	90	401.156	24.323	11.367	25.095	.188
	PLACEBO	49	406.633	22.508	4.367	25.175	
QTCF	ATOMOX	90	384.282	21.356	5.936	20.565	.842
	PLACEBO	49	389.345	19.466	3.224	20.199	
QTCD	ATOMOX	90	389.927	21.948	7.678	21.756	.465
	PLACEBO	49	395.119	19.988	3.585	21.483	
HR	ATOMOX	90	78.289	11.097	6.267	10.678	.006
	PLACEBO	49	78.612	11.809	0.878	11.168	

Population: Enrolled patients who took at least 1 dose of study drug.

Baseline: Visits 1-3, Endpoint: Visits 4-7

NOTE: Pooled Investigator Used in Analysis

Input data from RMP.SAS.B4ZM.L.MCLYAWSW

Output stored as RMP.B4ZO.LYAWCTRM.ACUTE(EC6LF003)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDUC1 - Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks:
PROC GLM model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA on the ranks using the
mean square for error.

Note: Each investigator has at least one patient in each treatment group.

XLAS0006

Legend of Variable Abbreviations:

Abbrev.	Description
HR	ECG Heart Rate
PR	PR Interval
QRS	QRS Interval
QT	QT Interval
QTCB	Bazett QTC Interval
QTCD	QT/
QTCF	Fridericia QTC Interval
RR	RR Interval

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**Table LYAW.18. Child Health Questionnaire (CHQ) Subscale Scores
 Change from Baseline to Endpoint
 Study Period II**

Treatment Group	n	Baseline		Endpoint		Change		p-Value(a)	p-value(b)
		Mean	SD	Mean	SD	Mean	SD		
Behavior									
Atomox.	93	43.0	18.5	57.3	19.9	14.3	20.1	<.001	.013
Placebo	49	45.3	18.4	50.6	19.7	5.4	17.5	.081	----
				95% C.I.: (1.67 , 14.05)					
Bodily Pain									
Atomox.	93	85.6	18.4	84.2	19.8	-1.4	21.2	.517	.575
Placebo	49	82.9	21.8	81.4	22.0	-1.4	18.9	.722	----
				95% C.I.: (-4.61 , 8.27)					
Family Activities									
Atomox.	93	50.6	26.3	65.0	23.2	14.4	24.1	<.001	.182
Placebo	49	52.0	24.4	61.0	25.0	9.0	19.7	.002	----
				95% C.I.: (-2.27 , 11.85)					
General Health									
Atomox.	93	76.4	15.1	77.3	16.5	0.9	14.0	.536	.843
Placebo	49	74.7	15.9	76.2	17.8	1.5	14.1	.454	----
				95% C.I.: (-4.23 , 5.18)					
Mental Health									
Atomox.	93	66.9	18.6	69.9	16.9	3.0	18.8	.229	.091
Placebo	49	67.0	17.9	65.4	18.4	-1.6	14.7	.198	----
				95% C.I.: (-0.75 , 9.96)					

(continued)

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**Table LYAW.18. Child Health Questionnaire (CHQ) Subscale Scores
 Change from Baseline to Endpoint
 Study Period II (continued)**

Treatment Group	n	Baseline		Endpoint		Change		p-Value(a)	p-value(b)
		Mean	SD	Mean	SD	Mean	SD		
Parent Impact-Emotion									
Atomox.	93	44.7	19.9	50.5	26.3	5.8	22.1	.014	.385
Placebo	49	47.0	20.8	47.8	19.6	0.8	20.5	.668	----
				95% C.I.: (-3.95 , 10.17)					
Parent Time Impact									
Atomox.	93	63.2	22.5	73.1	22.2	9.9	22.4	<.001	.918
Placebo	49	60.3	25.1	71.2	23.7	10.9	22.8	<.001	----
				95% C.I.: (-7.39 , 6.66)					
Physical Functioning									
Atomox.	92	95.2	13.4	97.1	9.6	1.9	14.8	.177	.401
Placebo	49	93.4	17.5	95.3	11.0	2.0	19.0	.622	----
				95% C.I.: (-2.07 , 5.13)					
Physical Summary Score									
Atomox.	92	55.0	7.6	54.8	7.3	-0.3	8.2	.632	.738
Placebo	49	53.6	10.8	53.7	8.2	0.2	9.2	.775	----
				95% C.I.: (-1.97 , 2.77)					

(continued)

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**Table LYAW.18. Child Health Questionnaire (CHQ) Subscale Scores
 Change from Baseline to Endpoint
 Study Period II (concluded)**

Treatment Group	n	Baseline		Endpoint		Change		p-Value(a)	p-value(b)
		Mean	SD	Mean	SD	Mean	SD		
Psychosocial Summary									
Atomox.	92	32.5	11.4	39.6	11.7	7.1	12.6	<.001	.056
Placebo	49	32.1	10.7	35.8	11.1	3.7	9.4	.002	----
95% C.I.: (-0.09 , 7.14)									
Role-Emotion/Behavior									
Atomox.	92	61.3	34.4	79.0	28.2	17.8	39.1	<.001	.185
Placebo	49	54.3	34.5	70.5	33.7	16.1	31.8	<.001	----
95% C.I.: (-3.36 , 17.16)									
Self Esteem									
Atomox.	93	65.5	21.6	73.1	18.7	7.5	24.2	.013	.108
Placebo	49	62.4	17.5	66.5	17.7	4.1	16.0	.021	----
95% C.I.: (-1.12 , 11.09)									

(a) p-Value is from Wilcoxon signed-rank test.

(b) Between treatment group p-Values are from baseline to endpoint (LOCF) scores using least squares means from an ANCOVA model with terms for investigator, treatment, CYP2D6, and Baseline covariate.

Program: RMP.B4ZSLYAW.SASPGM(EFFSCALE)

Summary ID# 5003

Clinical Study Summary: Study B4Z-MC-LYAW Open-Label Extension Phase

A Double-Blind, Placebo-Controlled Trial of Atomoxetine Hydrochloride to Evaluate Efficacy in the School Setting in Children Ages 8 to 12 Years with Attention-Deficit/Hyperactivity Disorder

Date summary approved by Lilly: 18 October 2006

Brief Summary of Results

This summary provides the results of the open-label extension phase of Study B4Z-MC-LYAW that followed the 7-week, randomized, double-blind, placebo-controlled, acute treatment phase (CT#5003a). The primary purpose of the extension phase was to assess the safety and efficacy of atomoxetine based on prior treatment in the acute phase.

- There were no statistically significant differences in mean change from baseline to endpoint in Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) subscale scores or Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) scores among patients who had been in the atomoxetine treatment group during the acute study period and were continuing atomoxetine treatment in the open-label phase compared with patients who had been treated with atomoxetine during the acute study period and were therefore new to atomoxetine treatment in the open-label phase.
- There were statistically significant within-group reductions in the mean CGI-ADHD-S score and all of the mean CPRS-R:S subscale scores among patients who had been in the placebo treatment group during the acute study period and were therefore new to atomoxetine treatment in the open-label study period.

- There were statistically significant within-group reductions in mean CPRS-R:S ADHD Index and CPRS-R:S Hyperactivity T-scores among patients who had been in the atomoxetine treatment group during the acute study period and were continuing atomoxetine treatment in the open-label period.
- There were statistically significantly greater changes from baseline to endpoint in the Parental Impact-Emotional Subscale of the Child Health Questionnaire (CHQ) among patients who had been in the placebo treatment group during the acute study period and were therefore new to atomoxetine treatment in the open-label period compared with patients who had been in the atomoxetine treatment group during the acute study period and were continuing atomoxetine treatment in the open-label period.
- There were statistically significant within-group changes in mean scores for the Behavior, Family Activities, General Health Perceptions (GGH), Mental Health, Parent Impact-Emotion, Psychosocial Summary, Role-Emotion/Behavior, and Self-Esteem subscales of the CHQ among patients who had been in the placebo treatment group during the acute study period and were therefore new to atomoxetine treatment in the open-label period.
- There were no statistically significant within-group changes in mean score for any of the CHQ subscales among patients who had been in the atomoxetine treatment group during the acute study period and were continuing atomoxetine treatment in the open-label period.
- A total of 120 (90.2%) patients experienced at least 1 treatment-emergent adverse event (TEAE). The most common TEAE, decreased appetite, occurred in statistically significantly more patients who had been in the placebo treatment group during the acute phase and were therefore new to atomoxetine treatment in the open-label phase compared with patients who had been in the atomoxetine treatment group during the acute phase and were continuing atomoxetine treatment during the open-label phase of the study.
- There was a statistically significantly greater increase in mean weight from baseline to endpoint among patients who had been in the atomoxetine treatment group during the acute study phase and were continuing atomoxetine treatment in the open-label phase compared with patients who had been in the placebo treatment group during the acute study phase and were new to atomoxetine treatment in the open-label phase. There was also a statistically significant within-group mean weight increase among patients who had treated with atomoxetine during the acute study phase.
- Seven of the 44 patients (15.9%) who had both baseline and endpoint measures on the optional Tanner Stage Examination advanced at least 1 developmental stage between baseline and endpoint.

Title of Study: A Double-Blind, Placebo-Controlled Trial of Atomoxetine Hydrochloride to Evaluate Efficacy in the School Setting in Children Ages 8 to 12 Years with Attention-Deficit/Hyperactivity Disorder	
Investigator(s): This multicenter study included 11 principal investigators.	
Study Center(s): This study was conducted at 11 study centers in 2 countries.	
Length of Study: 40 months Date first patient enrolled: 22 January 2002 Date last patient completed: 20 May 2005	Phase of Development: 4
Objectives: The primary objective of the acute phase of this study was to test the hypothesis that treatment for approximately 7 weeks with atomoxetine hydrochloride, hereafter referred to as atomoxetine, provides superior efficacy compared with placebo in children with Attention-Deficit/Hyperactivity Disorder (ADHD), as measured by the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Teacher Version: Investigator Administered and Scored (ADHDRS-IV-Teacher:Inv) total score. This summary reports the results of the open-label treatment phase of the study, which assessed the safety and efficacy of atomoxetine based on prior treatment in the acute phase.	
Study Design: Study LYAW was a randomized, double-blind, placebo-controlled comparison in pediatric patients with the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for ADHD. Following the approximate 7-week, randomized, double-blind, placebo-controlled, acute treatment phase, patients were eligible for an optional open-label extension phase that continued for up to 2 years or until atomoxetine was commercially available to the patient. This summary covers the open-label extension phase of the study.	
Number of Patients: Randomized into acute phase: 101 atomoxetine, 52 placebo Completed acute phase: 84 (83.2%) atomoxetine, 48 (92.3%) placebo Entered open-label extension phase: 133 Completed open-label extension phase: 74	
Diagnosis and Main Criteria for Inclusion: Study patients were males and females aged 8 to 13 years at the time of study entry who met the DSM-IV diagnostic criteria for ADHD. Study patients exhibited symptoms of ADHD in the school setting as confirmed at Visit 2 by the Children's Academic Performance, Attention Behavior, and Learning Evaluation: Teacher Telephone Interview (CAPABLE-TTI) and the ADHDRS-IV-Teacher:Inv. Patients had to complete the acute phase of the study in order to enter the open-label extension phase of the study.	
Test Product, Dose, and Mode of Administration: Atomoxetine hydrochloride as 5-mg, 10-mg, 25-mg, and 40-mg capsules given either once a day in the morning or as divided doses twice daily (morning and late afternoon/early evening) at the investigator's discretion. The standard dose was 1.2 mg/kg/day. Dose adjustments were allowed at the investigator's discretion to a minimum dose of 0.8 mg/kg/day and a maximum dose of 1.8 mg/kg/day.	
Duration of Treatment: Up to 2 years or until atomoxetine became commercially available to the patient.	

Variables:

Efficacy: Efficacy was evaluated using the following measures:

- The change in parent-reported symptoms of ADHD from baseline to endpoint, as assessed by the mean total and subscale scores for the CPRS-R:S.
- The change from baseline to endpoint in CGI-ADHD-S scores.

Safety: Safety was assessed using TEAEs, and changes from baseline to endpoint in vital signs, electrocardiograms (ECG), and the Tanner Stage measure.

Health Outcomes: Improvement in patient-reported outcomes (quality of life) was assessed by the change in patient-reported outcomes (quality of life) from baseline to endpoint in CHQ scores.

Evaluation Methods:

Statistical methods utilized during the open-label extension phase included post hoc analysis by the patient's randomized treatment assignment during the acute phase. A Wilcoxon signed-rank test was used to evaluate within-treatment-group differences. Between-treatment-group p-values were calculated using least-squares means from an analysis of covariance model. All analyses were performed using a 2-sided, 0.05 significance level. For categorical analyses, frequencies were evaluated using a chi-square test or Fisher's exact test.

The baseline for all analyses was Visit 7, which was the final visit for the acute phase of the study. For the least-squares means calculations, analyses were adjusted for baseline value and investigator.

Results:

Patient Demographics

Of the 133 patients who entered the open-label phase of the study, 106 (79.7%) were male, 82 (61.7%) were Caucasian, and 75 (56.8%) had reported prior stimulant use. Most patients (73.7%) met the criteria for the Combined ADHD subtype. Of the remaining patients, 25.6% met the criteria for the Inattentive ADHD subtype, and 0.8% met the criteria for the Hyperactive ADHD subtype. Three patients (2.3%) were poor cytochrome P450 2D6 (CYP2D6) metabolizers.

Study patients ranged in age from 7.38 to 12.79 years; the mean age was 9.95 years, and the standard deviation for age was 1.36. Three patients were under the age of 8 when they enrolled in the study. For 2 of these patients, an age exception to the study inclusion criteria was obtained from the Study Sponsor prior to enrollment. The third patient was 5 days from turning 8 years old at the time of receiving study drug.

Patient Disposition

Of the 133 patients who entered the open-label extension phase of the study, a total of 74 completed the study. One of the patients who entered the open-label extension phase had not completed the acute phase of the study but re-entered the study at the beginning of the open-label extension phase (Visit 8). This patient, who had been randomized to the atomoxetine treatment group during the acute phase, had discontinued from the acute phase at Visit 5 due to lack of efficacy.

Of the patients who discontinued from the open-label extension phase of the study, 16 discontinued due to lack of efficacy, and 12 due to an adverse event (AE). Of the patients who discontinued due to lack of efficacy, 6 had been in the placebo treatment group during the acute study phase and were new to atomoxetine treatment in the open-label phase, while 10 had been in the atomoxetine treatment group during the acute study phase and were continuing atomoxetine treatment in the open-label phase. Of the patients who discontinued due to AEs, 3 had been in the placebo treatment group during the acute study phase, and 9 had been treated with atomoxetine during the acute study phase. Three patients discontinued from the open-label study period due to abdominal pain. The other AEs that resulted in discontinuation during the open-label study period included anger, asthenia, depression, feeling abnormal, headache, irritability, mood swings, tearfulness, and vomiting.

Efficacy Measures

Table 1 summarizes the last-observation-carried-forward (LOCF) change from baseline to endpoint in the CPRS-R:S and the CGI-ADHD-S subscales during the open-label extension phase of the study. There were no statistically significant differences between patients who had been treated with atomoxetine during the acute study period compared with those who had been treated with placebo during the acute study period. There were statistically significant reductions in all of the CPRS-R:S subscale scores and the CGI-ADHD-S score for patients who had been in the placebo treatment group during the acute period and were new to atomoxetine treatment in the open-label period. There were statistically significant reductions in the CPRS-R:S ADHD Index and the CPRS-R:S Hyperactive T-scores for patients who had been in the atomoxetine treatment group during the acute period and were continuing atomoxetine treatment in the open-label period.

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Table 1. CPRS-R:S and CGI-ADHD-S Rating Change from Baseline to Endpoint Open-Label Extension Phase

Measure	Acute Treatment	N	Baseline		Endpoint		Change		Within group p-value ^a	Between group p-value ^b
			Mean	SD	Mean	SD	Mean	SD		
CPRS-R:S ADHD Index T-score	Atomoxetine	82	62.0	10.7	59.6	9.5	-2.4	10.6	.036	.236
	Placebo	47	70.4	11.1	61.4	9.7	-9.1	10.4	<.001	
CPRS-R:S Cognitive Problems T-score	Atomoxetine	82	61.1	11.4	59.5	10.0	-1.5	10.9	.294	.378
	Placebo	48	71.1	11.7	62.5	11.4	-8.6	12.0	<.001	
CPRS-R:S Hyperactive T-score	Atomoxetine	83	63.5	15.0	59.2	12.4	-4.4	13.3	.012	.291
	Placebo	48	73.1	18.1	61.4	14.1	-11.7	13.7	<.001	
CPRS-R:S Oppositional T-score	Atomoxetine	83	59.7	13.2	58.7	13.3	-1.0	12.0	.438	.180
	Placebo	48	62.6	14.0	57.7	12.4	-4.9	12.2	.011	
CGI-ADHD-S	Atomoxetine	82	3.3	1.1	3.0	1.1	-0.2	1.3	.107	.117
	Placebo	48	4.0	1.1	2.9	1.2	-1.1	1.5	<.001	

Abbreviations: ADHD = Attention-Deficit Hyperactivity Disorder; CGI-ADHD-S = Clinical Global Impressions ADHD-Severity; CPRS-R:S = Conners' Parent Rating Scale -Revised: Short Form; SD = standard deviation.

All patients entering open-label extension phase; Baseline = Visit 7, Postbaseline = Visits 8-25.

^a p-value is from Wilcoxon's signed-rank test.

^b Between-treatment-group p-values are from baseline to endpoint (LOCF) scores using least-squares means from an analysis of covariance (ANCOVA) model with terms for investigator, treatment, and baseline covariate.

Safety

Dose: The mean final dose was 56.09 mg/day. The mean therapy duration was 305 days, the maximum was 1,119 days, and the minimum was 33 days.

Deaths and Serious Adverse Events: There were no patient deaths during the study. Three patients experienced serious adverse events (SAEs) during the open-label extension phase. Two of these patients experienced appendicitis that required hospitalization and appendectomy, while the third patient was hospitalized for 4 days with depression. In each case, the principal investigator considered the SAEs to be unrelated to study drug or protocol procedures.

Adverse Events: Table 2 presents TEAEs that occurred in $\geq 5\%$ of total patients during the open-label extension phase. A total of 120 (90.2%) patients experienced at least 1 TEAE. The most common TEAE, decreased appetite, occurred in statistically significantly more patients who had been treated with placebo during the acute phase and were new to atomoxetine treatment in the open-label phase than in patients who had been treated with atomoxetine during the acute phase and were continuing atomoxetine treatment in the open-label phase.

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**Table 2. Treatment-Emergent Adverse Events in ≥5% of Patients
Open-Label Extension Phase**

Event Classification Term	ATX/ATX (N=85)		PBO/ATX (N=48)		Total (N=133)		Fisher's Exact p-value
	n	(%)	n	(%)	n	(%)	
Patients with ≥1 TESS	74	(87.1)	46	(95.8)	120	(90.2)	.133
Patients with no TESS	11	(12.9)	2	(4.2)	13	(9.8)	.133
Decreased appetite	15	(17.6)	18	(37.5)	33	(24.8)	.013
Headache	20	(23.5)	7	(14.6)	27	(20.3)	.266
Vomiting	15	(17.6)	9	(18.8)	24	(18.0)	1.000
Abdominal pain upper	10	(11.8)	11	(22.9)	21	(15.8)	.136
Pyrexia	13	(15.3)	5	(10.4)	18	(13.5)	.599
Dizziness	12	(14.1)	3	(6.3)	15	(11.3)	.254
Nausea	9	(10.6)	6	(12.5)	15	(11.3)	.779
Cough	9	(10.6)	4	(8.3)	13	(9.8)	.769
Fatigue	6	(7.1)	7	(14.6)	13	(9.8)	.224
Influenza	7	(8.2)	6	(12.5)	13	(9.8)	.545
Pharyngitis streptococcal	7	(8.2)	5	(10.4)	12	(9.0)	.756
Irritability	7	(8.2)	5	(10.4)	12	(9.0)	.756
Pharyngolaryngeal pain	8	(9.4)	3	(6.3)	11	(8.3)	.745
Upper respiratory tract infection	7	(8.2)	3	(6.3)	10	(7.5)	1.000
Nasopharyngitis	6	(7.1)	4	(8.3)	10	(7.5)	.747
Diarrhoea	7	(8.2)	2	(4.2)	9	(6.8)	.487
Sedation	5	(5.9)	3	(6.3)	8	(6.0)	1.000
Abdominal pain	3	(3.5)	4	(8.3)	7	(5.3)	.252
Rhinorrhoea	4	(4.7)	3	(6.3)	7	(5.3)	.703

Abbreviations: ATX = atomoxetine, N = number of patients, PBO = placebo; TESS = treatment-emergent signs and symptoms.

Population: All patients entering open-label extension phase (Study Period III).

Baseline = Visit 7, Postbaseline = Visits 8-25

MedDRA version: 8.0

Vital Signs and Electrocardiogram Data: Table 3 summarizes the mean change from baseline to endpoint in vital signs during the open-label extension phase. There was a statistically significant increase in mean pulse from baseline to endpoint among patients who had been in the placebo treatment group during the acute study period and were new to atomoxetine treatment in the open-label period. However, this increase was not statistically significantly greater than that experienced by patients who had been in the atomoxetine treatment group during the acute phase and were continuing atomoxetine treatment in the open-label phase.

There was a statistically significantly greater increase in mean weight from baseline to endpoint in patients who had been in the atomoxetine treatment group during the acute phase compared with patients who had been in the placebo treatment group during the acute phase. There was a statistically significant within-group increase in mean weight from baseline to endpoint among patients who had been in the atomoxetine treatment group during the acute phase.

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Table 3. **Condensed Summary of Vital Signs:
Change from Baseline to Endpoint
Open-Label Extension Phase**

Treatment Group	N	Baseline		Endpoint		Change		p-value (a)	p-value (b)
		Mean	SD	Mean	SD	Mean	SD		

Pulse Average									
Atmx/Atmx	83	86.9	12.8	86.9	14.2	-0.1	12.8	.890	.071
Pla/Atmx	48	83.7	10.1	89.0	12.1	5.3	11.5	.002	
				95% C.I.: (-6.81 , 0.29)					
Systolic BP Average									
Atmx/Atmx	83	104.7	9.5	105.0	9.5	0.3	10.5	.679	.731
Pla/Atmx	48	103.3	8.9	105.1	9.1	1.8	9.0	.147	
				95% C.I.: (-3.64 , 2.57)					
Diastolic BP Average									
Atmx/Atmx	83	67.5	9.1	65.4	8.7	-2.0	9.7	.097	.236
Pla/Atmx	48	65.3	8.2	66.9	7.6	1.6	9.4	.350	
				95% C.I.: (-4.25 , 1.06)					
Height (CM)									
Atmx/Atmx	73	138.6	10.4	143.2	12.3	4.6	4.5	<.001	.696
Pla/Atmx	40	137.8	8.6	142.0	10.3	4.1	4.3	<.001	
				95% C.I.: (-1.14 , 1.70)					

(continued)

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**Table 3. Condensed Summary of Vital Signs:
Change from Baseline to Endpoint
Open-Label Extension Phase (Concluded)**

Treatment Group	N	Baseline		Endpoint		Change		p-value (a)	p-value (b)
		Mean	SD	Mean	SD	Mean	SD		

Weight (KG)									
Atmx/Atmx	83	34.8	8.8	37.4	10.9	2.6	4.6	<.001	.004
Pla/Atmx	48	36.2	9.4	36.9	10.0	0.7	3.8	.383	----
95% C.I.: (0.65 , 3.35)									
Temperature (C)									
Atmx/Atmx	81	36.7	0.4	36.6	0.7	-0.1	0.7	.186	.555
Pla/Atmx	47	36.7	0.4	36.5	0.5	-0.2	0.5	.014	----
95% C.I.: (-0.14 , 0.26)									

Abbreviations: Atmx = atomoxetine; BP = blood pressure; Pla = placebo; SD = standard deviation.

Population: All patients entering open-label SP III.

Baseline=Visit 7, Postbaseline=Visits 8-25

(a) p-Value is from Wilcoxon signed-rank test.

(b) Between treatment group p-values are from baseline to endpoint (LOCF) scores using least-squares means from an ANCOVA model with terms for investigator, treatment, and baseline covariate.

Tanner Stage Examination: Table 4 summarizes results of the optional Tanner Stage Examination for patients who entered the open-label extension phase of the study. A total of 44 patients had both baseline and endpoint measurements. Of these patients, 7 advanced at least 1 developmental stage between baseline and endpoint.

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Table 4. Summary of Tanner Staging at Baseline and Endpoint and Number of Patients Advancing at Least One Stage Open-Label Extension Phase

Variable	Atmx/Atmx (N=85)	Pla/Atmx (N=48)	Total (N=133)	P-value

Tanner Score at Baseline				
No.	43	27	70	.686*
Stage1	30 (69.8)	21 (77.8)	51 (72.9)	
Stage2	9 (20.9)	5 (18.5)	14 (20.0)	
Stage3	2 (4.7)	1 (3.7)	3 (4.3)	
Stage4	2 (4.7)	0 (0.0)	2 (2.9)	
Tanner Score at Endpoint				
No.	27	17	44	.228*
Stage1	17 (63.0)	11 (64.7)	28 (63.6)	
Stage2	5 (18.5)	6 (35.3)	11 (25.0)	
Stage3	3 (11.1)	0 (0.0)	3 (6.8)	
Stage4	2 (7.4)	0 (0.0)	2 (4.5)	
Advancing at Least One Stage				
No.	4	3	7	.350*
1 Stage from Stage1	2 (50.0)	3 (100.0)	5 (71.4)	
1 Stage from Stage2	1 (25.0)	0 (0.0)	1 (14.3)	
2 Stages from Stage2	1 (25.0)	0 (0.0)	1 (14.3)	

Abbreviations: Atmx = atomoxetine; No. = number; Pla = placebo.

Population: All patients with a baseline and postbaseline observation.

Baseline=Visit 1 or 2, Postbaseline=Visits 8-25

*FREQUENCIES ARE ANALYZED USING A CHI-SQUARE TEST.

Laboratory Values: Table 5 summarizes the incidence of treatment-emergent abnormal, abnormally high, or abnormally low laboratory values that occurred in $\geq 5\%$ of patients or at statistically significantly different frequencies in the different treatment groups during the open-label extension phase of the study. Patients with low values at baseline of the open-label phase were not included in the analysis of treatment-emergent low laboratory values, and patients with high values at baseline of the open-label phase were not included in the analysis of treatment-emergent high laboratory values. There were statistically significantly higher incidences of high albumin and high AST/SGOT among patients who had been in the placebo treatment group during the acute period and were new to atomoxetine treatment in the open-label period compared with patients who had been in the atomoxetine treatment group during the acute period and were continuing atomoxetine treatment in the open-label period. There were no other statistically significant differences between treatment groups in the incidence of abnormally high, abnormally low, or abnormal laboratory values.

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**Table 5. Treatment-Emergent Abnormal Laboratory Values in ≥5% of Patients
Open-Label Extension Phase**

Lab Test	Direction	-----Atmx/Atmx----- (N=70)			-----Pla/Atmx----- (N=41)			P-value*
		N	n	Percent	N	n	Percent	
ALBUMIN	High	60	7	11.7	37	11	29.7	.033
	Low	70	0	0.0	41	0	0.0	
AST/SGOT	High	69	0	0.0	39	3	7.7	.045
	Low	70	0	0.0	40	0	0.0	
CALCIUM	High	62	7	11.3	38	10	26.3	.061
	Low	70	0	0.0	41	0	0.0	
CHOLESTEROL	High	66	5	7.6	36	5	13.9	.318
	Low	62	1	1.6	36	2	5.6	
CREATININE	High	62	8	12.9	41	4	9.8	.759
	Low	70	0	0.0	41	0	0.0	
EOSINOPHILS	High	69	4	5.8	39	2	5.1	1.000
	Low	70	0	0.0	40	0	0.0	
LEUKOCYTE COUNT	High	70	0	0.0	40	1	2.5	.364
	Low	66	6	9.1	32	2	6.3	
PLATELET COUNT	High	64	4	6.3	36	4	11.1	.454
	Low	69	0	0.0	39	0	0.0	
UA-PROTEIN	Abnormal	68	5	7.4	38	2	5.3	1.000
UA-SPECIFIC GRAVITY	High	68	8	11.8	37	1	2.7	.155
	Low	69	4	5.8	37	4	10.8	

Abbreviations: Atmx = atomoxetine; AST/SGOT = aspartate amino transferase/serum glutamic-oxaloacetic transaminase; Pla = placebo.

Population: All patients entering open-label SP III.

Baseline=Visit 7, Postbaseline=Visits 8-25

Total=Total number of patients in the treatment group having both baseline and endpoint visits.

N = number of at risk Patients with a baseline and postbaseline measurement.

n = number of at risk Patients with the specific lab result (eg, High).

* Frequencies are analyzed using Fisher's exact test.

Health Outcomes

Table 6 summarizes the LOCF change from baseline to endpoint for the CHQ. There were statistically significant changes from baseline to endpoint in mean scores for the Behavior, Family Activities, General Health Perceptions (GGH), Mental Health, Parent Impact-Emotion, Psychosocial Summary, Role-Emotion/Behavior, and Self-Esteem subscales among patients who had been in the placebo treatment group during the acute study period and were new to atomoxetine treatment in the open-label period. There was also a statistically significantly greater change from baseline to endpoint in the Parent Impact-Emotional Subscale among these patients compared with patients who had been in the atomoxetine treatment group during the acute study phase and were continuing atomoxetine treatment in the open-label phase.

There were no statistically significant changes in mean score from baseline to endpoint for patients who had been in the atomoxetine treatment group during the acute study period.

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Table 6. **CHQ – Subscale Scores**
Change from Baseline to Endpoint
Open-Label Extension Phase

Treatment Group	N	Baseline		Endpoint		Change		p-value (a)	p-value (b)
		Mean	SD	Mean	SD	Mean	SD		

Behavior									
Atmx/Atmx	68	59.0	16.8	59.3	19.8	0.3	20.2	.826	.080
Pla/Atmx	42	51.6	19.8	63.0	18.2	11.3	20.0	<.001	
				95% C.I.: (-13.2 , 0.75)					
Bodily Pain									
Atmx/Atmx	68	85.4	18.6	82.8	18.8	-2.6	24.1	.394	.417
Pla/Atmx	42	81.4	22.3	83.8	18.6	2.4	20.2	.552	
				95% C.I.: (-9.83 , 4.10)					
Family Activites									
Atmx/Atmx	67	67.3	20.8	66.2	24.6	-1.0	24.1	.926	.086
Pla/Atmx	42	61.4	24.7	70.3	23.4	8.9	20.9	.013	
				95% C.I.: (-15.0 , 1.02)					
CHQGGH									
Atmx/Atmx	63	92.5	11.7	90.3	12.8	-2.2	13.4	.244	.213
Pla/Atmx	40	86.1	15.7	91.3	10.4	5.1	15.3	.029	
				95% C.I.: (-7.50 , 1.69)					

(continued)

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**Table 6. CHQ – Subscale Scores
Change from Baseline to Endpoint
Open-Label Extension Phase (Continued)**

Treatment Group	N	Baseline		Endpoint		Change		p-value (a)	p-value (b)
		Mean	SD	Mean	SD	Mean	SD		

Mental Health									
Atmx/Atmx	68	70.4	15.3	71.8	16.8	1.4	17.1	.620	.442
Pla/Atmx	42	66.0	17.4	72.7	16.7	6.8	15.8	.004	
				95% C.I.: (-8.22 , 3.62)					
Parent Impact-Emotion									
Atmx/Atmx	68	50.9	25.4	53.8	26.5	2.9	25.8	.394	.017
Pla/Atmx	42	45.9	19.6	61.9	22.5	16.0	21.5	<.001	
				95% C.I.: (-17.5 , -1.74)					
Parent Time Impact									
Atmx/Atmx	67	75.3	20.0	75.1	24.1	-0.1	25.1	.742	.408
Pla/Atmx	42	72.8	23.0	78.7	22.4	5.9	24.8	.117	
				95% C.I.: (-12.4 , 5.08)					
Physical Functioning									
Atmx/Atmx	67	97.3	7.9	95.7	16.2	-1.5	16.5	.919	.671
Pla/Atmx	42	95.8	9.4	95.7	13.6	-0.1	14.5	.530	
				95% C.I.: (-7.23 , 4.67)					

(continued)

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**Table 6. CHQ – Subscale Scores
Change from Baseline to Endpoint
Open-Label Extension Phase (Concluded)**

Treatment Group	N	Baseline		Endpoint		Change		p-value (a)	p-value (b)
		Mean	SD	Mean	SD	Mean	SD		

Physical Summary Score									
Atmx/Atmx	66	55.0	6.2	53.8	8.2	-1.2	8.8	.579	.247
Pla/Atmx	42	53.7	7.9	54.9	7.9	1.2	8.7	.415	
				95% C.I.: (-4.91 , 1.28)					
Psychosocial Summary									
Atmx/Atmx	66	40.3	9.9	40.9	12.1	0.6	11.3	.454	.113
Pla/Atmx	42	36.3	10.4	42.7	11.9	6.4	12.4	<.001	
				95% C.I.: (-7.69 , 0.83)					
Role-Emotion/Behavior									
Atmx/Atmx	67	80.2	25.9	78.5	29.0	-1.7	31.2	.712	.434
Pla/Atmx	42	71.9	32.4	79.7	29.0	7.7	32.8	.040	
				95% C.I.: (-15.3 , 6.62)					
Self Esteem									
Atmx/Atmx	68	73.6	17.1	75.1	16.8	1.5	18.7	.508	.685
Pla/Atmx	42	67.5	16.3	73.9	16.5	6.4	17.7	.020	
				95% C.I.: (-7.46 , 4.92)					

Abbreviations: Atmx = atomoxetine; CHQ = Child Health Questionnaire; CHQGGH = Child Health Questionnaire General Health subscale; SD = standard deviation.

Population: All patients entering open-label SP III

Baseline=Visit 7, Postbaseline=Visits 8-25

(a) p-Value is from Wilcoxon signed-rank test.

(b) Between treatment group p-values are from baseline to endpoint (LOCF) scores using least-squares means from an ANCOVA model with terms for investigator, treatment, and baseline covariate.

Summary ID# 5004

Clinical Study Summary: Study B4Z-MC-LYAX

A Randomized, Double-Blind, Placebo-Controlled Study of Atomoxetine Hydrochloride in Adolescents with Attention-Deficit/Hyperactivity Disorder and Comorbid Depressive Disorder

Date summary approved by Lilly: 26 July 2006

Brief Summary of Results

The primary objective of Study B4Z-MC-LYAX was to assess the efficacy of atomoxetine hydrochloride (hereafter referred to as atomoxetine) given orally at doses of up to 1.8 mg/kg/day for approximately 9 weeks compared to placebo in reducing signs and symptoms of depression in adolescent patients with Attention-Deficit/Hyperactivity Disorder (ADHD), and comorbid depression, as measured by the Child Depression Rating Scale–Revised (CDRS-R) and the ADHD Rating Scale–IV–Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv).

The results were as follows:

- There were no statistically significant differences observed between the atomoxetine-treated and placebo-treated groups based on the CDRS-R repeated measures analysis or the CDRS-R total score with mean change analysis for Study Period II.
- Statistically significant improvement in symptoms of ADHD were demonstrated in the atomoxetine-treated group in the repeated measures analyses for: ADHDRS-IV-Parent:Inv total scores ($p < .001$), total T-scores ($p < .001$), inattention subscale scores ($p \leq .004$), and the hyperactivity-impulsivity subscale scores ($p \leq .002$). In addition, the mean change analyses of: the ADHDRS-IV-Parent:Inv total score, total T-score, inattention subscale score, and the hyperactivity-impulsivity subscale score for Study Period II demonstrated statistically significant ($p < .001$) changes in the atomoxetine treatment groups.

- Atomoxetine was declared noninferior to placebo in reducing scores on the CDRS-R and, therefore, did not worsen depression when compared with placebo.
- There were no patient deaths in Study LYAX. One patient (placebo treatment group) experienced the serious adverse events (SAEs) of worsening major depression and acute psychotic features. During Study Period II, 2 patients discontinued the Study LYAX due to an adverse event (AE); 1 due to nausea (atomoxetine treatment group), and 1 due to an AE prior to taking study drug (placebo treatment group). During Study Period III, 2 patients discontinued due to somnolence, and 1 patient discontinued due to upper abdominal pain. One patient also discontinued due to lethargy the day of randomization to atomoxetine. During Study Period IV, 1 patient discontinued due to anorexia.
- Of the treatment-emergent adverse events (TEAEs) that occurred with $\geq 5\%$ incidence in Study Period II, nausea (22.2%) and decreased appetite (12.5%) occurred at a statistically significantly greater incidence ($p \leq 0.05$) in patients treated with atomoxetine than those of placebo. The most frequently occurring TEAEs with $\geq 5\%$ incidence for patients in Study Periods III/IV were: nausea (22.5%), headache (17.5%), fatigue (15%), decreased appetite (14.2%), abdominal pain–upper (11.7%), weight decrease (11.7%), and unexpected therapeutic drug effect (10.8%).
- In Study Period II, statistically significant ($p < .05$) treatment differences in mean change scores were observed in the atomoxetine treatment group for: monocytes, ALT/SGPT, GGT, BUN, cholesterol, uric acid, creatinine, and platelet count.
- In Study Period II, the mean change and the categorical analyses of vitals including: height, weight, blood pressure (diastolic and systolic), and temperature, indicated no statistically significant differences in the mean changes in the atomoxetine treatment group with the exception of weight ($p < .001$).
- In Study Period II, the mean change analysis of electrocardiogram (ECG) variables showed a statistically significant decrease in: RR interval values ($p < .001$), decrease in QT interval values ($p = .006$), increase in heart rate ($p < .001$), prolongation of QTcB ($p = .045$), and decrease of PR values ($p = .002$) for the mean change in the atomoxetine treatment group when compared to the placebo treatment group when using QTcB. There was not a statistically significant difference when using data corrections or Fridericia correction.

Title of Study: A Randomized, Double-Blind, Placebo-Controlled Study of Atomoxetine Hydrochloride in Adolescents with Attention-Deficit/Hyperactivity Disorder and Comorbid Depressive Disorder	
Investigator(s): This multicenter study included 18 principal investigator(s).	
Study Center(s): This study was conducted at 16 study centers in one country. Two study centers had 2 co-principal investigators, making the total investigators 18.	
Length of Study: Approximately 2 years First patient enrolled (assigned to therapy): 08 July 2002 Date of early study termination: 13 November 2003 Last patient completed: 26 May 2004	Phase of Development: 3
Objectives: The primary objective of Study LYAX was to assess efficacy of atomoxetine given orally at doses up to 1.8 mg/kg/day for approximately 9 weeks compared with placebo in reducing signs and symptoms of depression in adolescent patients with ADHD and comorbid depression as measured by the CDRS-R and the ADHDRS-IV-Parent:Inv. The secondary objectives are: • To test the hypothesis that atomoxetine does not worsen depressive symptoms in adolescents with depression by testing whether atomoxetine is noninferior to placebo in reducing scores on the CDRS-R. • To test the hypothesis that atomoxetine is superior to placebo in improving psychosocial functioning in adolescents with ADHD and depression as assessed by parental reports of change in the CHQ-PF50. • To test the hypothesis that atomoxetine is superior to placebo in reducing the signs and symptoms of depression as assessed by the MADRS. • To test the hypothesis that atomoxetine is superior to placebo in reducing the symptoms of depression as assessed by patient self-report using the RADS. • To test the hypothesis that atomoxetine is superior to placebo in improving psychosocial functioning as assessed by patient self-report using the CHQ-CF87. • To test the hypothesis that atomoxetine will improve overall outcomes (considering both ADHD and depressive symptoms) in patients with ADHD as measured by the CGI-S and the CGI-I when compared to patients receiving placebo. • To test the hypothesis that atomoxetine does not induce manic switching as assessed by the YMRS. • To assess the safety and tolerability of atomoxetine at total daily doses up to 1.8 mg/kg/day.	
Study Design: Study LYAX is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study of atomoxetine in approximately 240 adolescent outpatients with ADHD and comorbid depressive disorder. Study LYAX incorporated 4 Study Periods including an initial (up to 2-week) evaluation period followed by a 1-week, single-blind, placebo-administration period (Period I); a double-blind, acute treatment period of up to 9 weeks, with either atomoxetine or placebo (Period II); and 2 open-label treatment phases of up to 9 months total of extended treatment with atomoxetine (Periods III and IV). All patients, including those from the placebo group, had the opportunity to receive atomoxetine during the study extension periods.	
Number of Patients: Planned: 240 (120 atomoxetine, 120 placebo) patients Study Period II: 142 (72 atomoxetine, 70 placebo) patients were randomized into Study Period II, 120 (59 atomoxetine, 61 placebo) completed Study Period II. Study Period III: 120 patients entered Study Period III, 40 completed Study Period III Study Period IV: 20 patients entered Study Period IV, 2 completed Study Period IV.	

Main Criteria for Inclusion: The child or adolescent was at least 12 years of age, but had not reached their 18th birthday prior to Visit 1, and had to meet DSM-IV criteria for ADHD and major depression. The presence of ADHD and major depression must be confirmed by the K-SADS-PL. The patient's ADHD had to be diagnosed by a physician or psychologist prior to the age of 12. There also must have been some period after the age of 7, of at least 6 months, during which some symptoms of ADHD were present and the patient was not depressed. In addition, to be eligible for randomization at Visit 4, the following criteria must have been met. At Visits 2, 3, and 4, patients must have an ADHDRS-IV-Parent:Inv score at least 1.5 standard deviations above age and gender norms for at least 1 of the 3 following scores: the inattention subscale score, the hyperactivity subscale score or the total scale score, and the attentional symptoms are not, in the investigator's judgment, better accounted for by the affective disorder than by an ADHD spectrum disorder. Additionally, at Visits 1, 2, 3, and 4, patients had to have a CDRS-R score of at least 40.

Study Drug, Dose, and Mode of Administration: Atomoxetine, up to 1.8 mg/kg/day, given once daily, in Study Period II, or as an evenly or unevenly divided doses taken twice daily in Study Periods III and IV; as 2.5, 5, 10, 20, 25, and 40 mg capsules.

Reference Therapy, Dose, and Mode of Administration: Placebo capsules used for the single-blind, placebo lead-in during Study Period I and the double-blind dosing in Study Period II were identical in appearance to atomoxetine capsules. However, during Study Periods III/IV, the study drug was supplied in bottles.

Duration of Treatment: One-week, single-blind, placebo lead-in, with 9 weeks double-blind treatment, and up to 9 months open-label therapy with atomoxetine.

Variables:

Efficacy: Primary efficacy variables were the CDRS-R and ADHDRS-IV-Parent:Inv. The secondary efficacy measures were: MADRS, RADS, CGI-S, CGI-I, and Y-MRS.

Safety: AEs, laboratory data, vital signs, and ECG.

Health Outcomes: CHQ-PF50 and CHQ-CF87.

Evaluation Methods:

Statistical: Efficacy analyses were conducted on the full analysis set. Safety analyses were conducted using all data from all randomized patients taking at least 1 dose of the study drug. For questionnaires such as the ADHDRS-IV-Parent:Inv, if more than 1 item of a subscale was missing, then the score for that subscale was also considered missing. All tests of treatment effects were conducted at a two-sided alpha level of 0.05 unless otherwise stated.

The primary efficacy analysis for the CDRS-R total score and the ADHDRS-IV-Parent:Inv total score was the treatment group comparison of Visit 9 values based on contrasts from a repeated measures analysis for the postbaseline scores (Visit 5 through Visit 9) during Study Period II. To assess the overall robustness of the primary analyses, the CDRS-R total score and the ADHDRS-IV-Parent:Inv total score were also analyzed based on treatment comparisons of change from baseline-to-endpoint scores during Study Period II computed on a last observation carried forward (LOCF) basis. Treatment differences in change scores were assessed using an analysis of covariance (ANCOVA). In addition, the ADHDRS-IV-Parent:Inv inattention subscale, hyperactivity-impulsivity subscale, and T-score were analyzed from a repeated measures analysis and a baseline-to-endpoint change was computed on a LOCF basis.

The secondary efficacy endpoints including: MADRS, RADS, CGI-S, CGI-I, and Y-MRS and health outcomes (CHQ-PF50 and CHQ-CF87) were analyzed based on treatment comparisons of change from baseline-to-endpoint scores during Study Period II and were computed on a LOCF basis. Treatment differences in change scores were assessed using ANCOVA.

Treatment differences in percentages of TEAEs collected by discussion were assessed using the Fisher's exact test. Baseline-to-endpoint changes for laboratory data, vital signs (including height and weight), and ECG intervals were computed. Treatment differences were assessed using ANOVA. Within-group changes were assessed with paired t-tests or the Wilcoxon signed-rank test. Treatment differences in treatment-emergent out-of-range laboratory values were assessed in a similar fashion as TEAEs. Categorical analyses of changes in ECG intervals and vital signs were also performed.

Patient Demographics

The majority of enrolled patients were male (73.2%), Caucasian (82.4%), and had previously used stimulants (81.0%). Most of these patients were also extensive metabolizers (EMs) based on their CYP2D6 genotype. The median age was 14.3 years. The age range was 12.0 to 17.9 years. Most patients were diagnosed with either ADHD inattention subtype (57%) or ADHD combined subtype (43%). See Table LYAX.1 for baseline demographics.

Table LYAX.1. Baseline Demographics

Variable	ATOMOX (N=72)	PLACEBO (N=70)	TOTAL (N=142)	p-Value
Sex: No. (%)				
No. Patients	72	70	142	.851*
Female	20 (27.8)	18 (25.7)	38 (26.8)	
Male	52 (72.2)	52 (74.3)	104 (73.2)	
Origin: No. (%)				
No. Patients	72	70	142	.184*
African Descent	6 (8.3)	11 (15.7)	17 (12.0)	
Caucasian	64 (88.9)	53 (75.7)	117 (82.4)	
East/Southeast A	0	1 (1.4)	1 (0.7)	
Hispanic	2 (2.8)	3 (4.3)	5 (3.5)	
Other	0	2 (2.9)	2 (1.4)	
Age: yrs.				
No. Patients	72	70	142	.183**
Mean	14.59	14.22	14.41	
Median	14.39	13.95	14.26	
Standard Dev	1.76	1.52	1.65	
Height: cm				
No. Patients	72	69	141	.990**
Mean	163.74	163.71	163.73	
Median	163.40	163.00	163.00	
Standard Dev	11.90	9.84	10.90	
Weight: kg				
No. Patients	72	69	141	.039**
Mean	63.10	58.35	60.78	
Median	64.30	56.40	59.50	
Standard Dev	14.32	12.66	13.69	
DSM-IV ADHD Subtype				
No. Patients	72	70	142	.502*
INATTV	39 (54.2)	42 (60.0)	81 (57.0)	
MIXED	33 (45.8)	28 (40.0)	61 (43.0)	
Prior Stimulant Exposure				
No. Patients	72	70	142	.670*
N	15 (20.8)	12 (17.1)	27 (19.0)	
Y	57 (79.2)	58 (82.9)	115 (81.0)	
CYP2D6				
No. Patients	72	70	142	.493*
EXTN	67 (95.7)	64 (92.8)	131 (94.2)	
SLOW	3 (4.3)	5 (7.2)	8 (5.8)	
Unspecified	2	1	3	

* Frequencies are analyzed using a Fishers-Exact test.

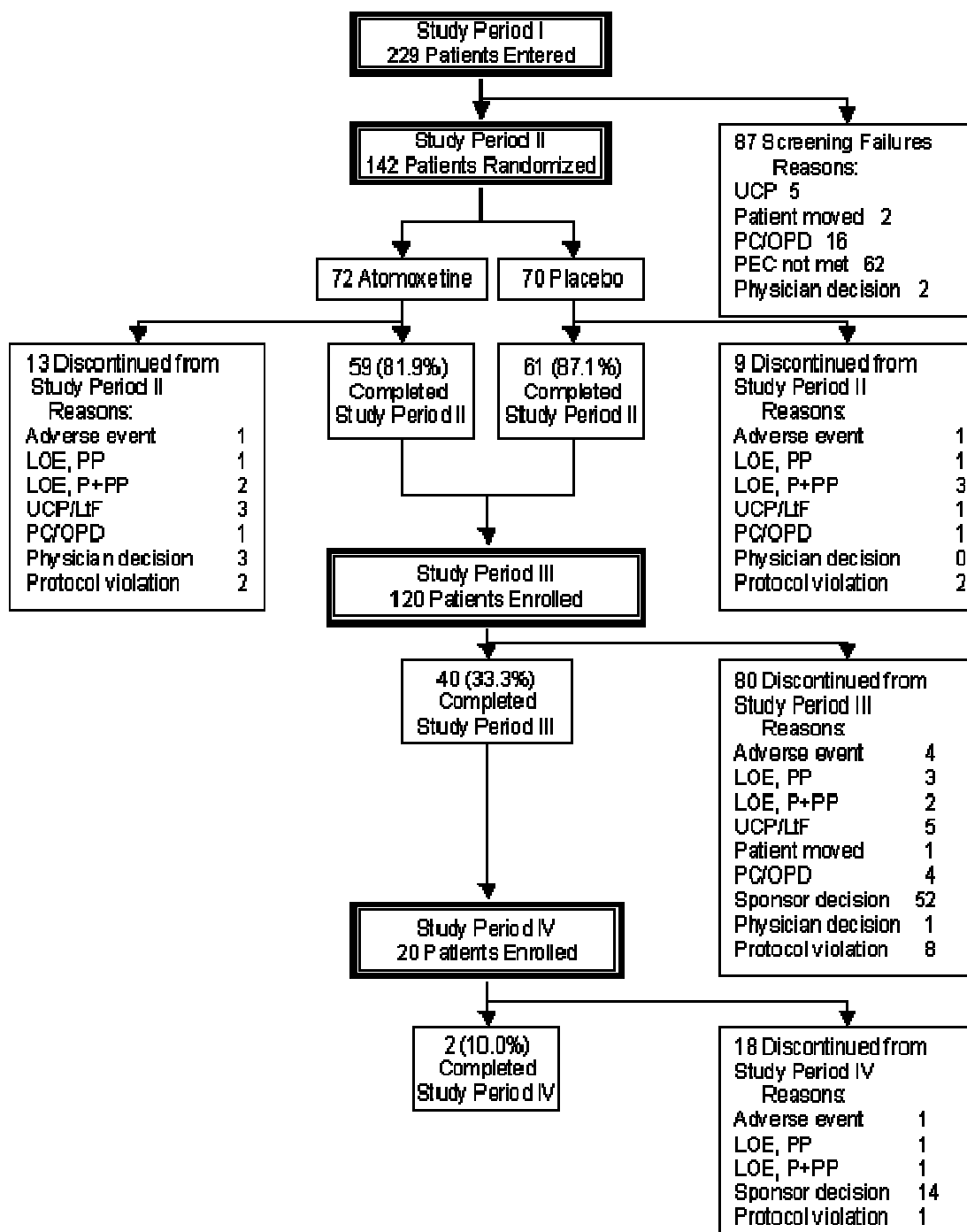
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.

Patient Disposition

Figure LYAX.1 outlines the reasons for study drug discontinuations during each Study Period. Study LYAX had originally planned to enroll approximately 240 patients in Study Period II; however, enrollment was slower than anticipated, and the study was stopped early on 13 November 2003 after enrolling 142 patients. One hundred twenty-nine patients entered Study Period I; 142 patients were randomized in Study Period II (72 to atomoxetine, 70 to placebo); 120 patients enrolled in Study Period III; 20 patients enrolled in Study Period IV; 2 patients completed Study Period IV.

Of the patients who discontinued due to AEs in Study Period II, 1 atomoxetine-treated patient discontinued due to nausea. One patient in the placebo treatment group discontinued due to insomnia, in addition to cold, influenza, and nausea symptoms, and had discontinued Study LYAX before beginning treatment. In addition, 1 patient in the placebo treatment group discontinued due to a lack of efficacy, which was coded as patient and physician perception. The investigator described the lack of efficacy as a worsening in symptoms of depression. The most common reasons for discontinuation were found to be similar between treatment groups.

In Study Periods III/IV, 5 patients discontinued atomoxetine due to AEs: 2 patients discontinued due to somnolence, 1 patient discontinued due to abdominal pain upper, and 1 patient discontinued due to anorexia. In addition, 1 patient discontinued due to lethargy the day of randomization to atomoxetine.



Abbreviations: LOE, P+PP = lack of efficacy, patient and physician perception; LOE, PP = lack of efficacy, patient perception; LtF = lost to follow-up; PC/OPD = personal conflict/other patient decision; PEC = protocol entry criteria; UCP = unable to contact patient.

Figure LYAX.1.

Patient disposition.

Results

Primary Efficacy Measures

The primary objective of Study LYAX was to assess the efficacy of atomoxetine given orally at doses of up to 1.8 mg/kg/day for approximately 9 weeks compared to placebo in reducing signs and symptoms of depression in adolescent patients with ADHD and comorbid depression, as measured by the CDRS-R and the ADHDRS-IV-Parent:Inv.

Analysis of CDRS-R

There were no statistically significant differences between the atomoxetine-treated and placebo-treated groups in mean improvement of depression symptoms at any visit observed on the repeated measures analysis for the postbaseline CDRS-R total scores (Visit 5 through Visit 9) (Table LYAX.2) or the CDRS-R total score with mean change from baseline-to-endpoint analysis for Study Period II (Table LYAX.3).

**Table LYAX.2. CDRS-R Total Score
Repeated Measures Analysis
Randomized Patients
Study Period II**

Treatment	Visit	N	LSMean	SE	Pairwise P-Value
Placebo	5	70	46.54	1.63	.593
Atomoxetine		71	45.75	1.67	
Placebo	6	66	43.33	1.75	.854
Atomoxetine		69	43.65	1.78	
Placebo	7	67	42.28	1.76	.071
Atomoxetine		66	39.10	1.81	
Placebo	8	64	40.25	1.78	.237
Atomoxetine		65	38.14	1.82	
Placebo	9	61	38.28	1.76	.224
Atomoxetine		59	36.15	1.80	

N = Number of randomized subjects with non-missing data at the specified visit.

Model CDRS Total Score = Pooled investigator TRT VISIT CYP2D6 BASELINE trt*VISIT.

Baseline Visit 1-4, Endpoint Visit 5-9.

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Table LYAX.3. CDRS-R Total Score
Mean Change from Baseline to Endpoint
All Randomized Patients
Study Period II

<u>Study Period</u>	<u>Treatment</u>	<u>N</u>	<u>Baseline</u>		<u>Change</u>		<u>95%CI</u>		<u>p-value*</u>
			<u>Mean</u>	<u>SD</u>	<u>Mean*</u>	<u>SD</u>	<u>Lower</u>	<u>Upper%</u>	
II	Atomoxetine	71	53.42	10.86	-14.82	13.26	-4.96	1.74	.342
	Placebo	70	52.01	8.85	-12.79	10.43			

Population: Randomized patients with a baseline and a postbaseline visit.

**p-value is from a t-test on differences in mean changes from baseline to endpoint scores using terms for baseline, pooled investigator, CYP2D6 status and treatment.

***95% CI:2-sided confidence interval of LSmean difference in change score between atomoxetine and placebo.

Analysis of ADHDRS-IV-Parent:Inv

Improvement ($p < .001$) in symptoms of ADHD were demonstrated at each visit in the atomoxetine-treated group compared with the placebo-treated group in the repeated measures analysis for the postbaseline ADHDRS-IV-Parent:Inv total scores (Visit 5 through Visit 9). The least squares means for the placebo-treated group changed very little at each visit (Table LYAX.4). In addition, statistically significant improvement in the ADHDRS-IV-Parent:Inv total T-scores ($p < .001$), inattention subscale scores ($p \leq .004$), and the hyperactivity-impulsivity subscale scores ($p \leq .002$) was also demonstrated at each visit in the atomoxetine-treated group compared with the placebo-treated group in the repeated measures analysis (Table LYAX.5).

The mean change from baseline-to-LOCF endpoint analysis of the ADHDRS-IV-Parent:Inv total score, total T-score, inattention subscale score, and the hyperactivity-impulsivity subscale score for Study Period II demonstrated statistically significant ($p < .001$) change scores in the atomoxetine treatment group compared with the placebo treatment group (Table LYAX.6), which demonstrates ADHD symptom improvement that is consistent with the primary analysis (repeated measures) results observed on the ADHDRS-IV-Parent:Inv total score.

**Table LYAX.4. ADHDRS-IV-Parent:Inv Total Score
Repeated Measures Analysis
Randomized Patients
Study Period II**

Treatment	Visit	N	LSMean	SE	Pairwise P-Value
Placebo	5	70	30.94	1.30	<.001
Atomoxetine		71	26.61	1.34	
Placebo	6	67	30.82	1.35	<.001
Atomoxetine		69	25.01	1.38	
Placebo	7	67	28.77	1.42	<.001
Atomoxetine		66	23.35	1.46	
Placebo	8	63	27.55	1.55	<.001
Atomoxetine		65	21.55	1.58	
Placebo	9	61	28.22	1.54	<.001
Atomoxetine		58	19.91	1.58	

N = Number of randomized subjects with non-missing data at the specified visit.

Model ADHSRS-INV Total Score = Pooled investigator TRT VISIT CYP2D6 BASELINE trt*VISIT.
Baseline Visit 1-4, Endpoint Visit 5-9.

**Table LYAX.5. ADHDRS-IV-Parent:Inv Subscales and Total Tscore
Repeated Measures Analysis
Randomized Patients
Study Period II**

Treatment	Visit	N	LSMean	SE	Pairwise P-Value
ADHDRS-INV Total Tscore					
Placebo	5	70	73.02	1.40	
Atomoxetine		71	68.44	1.43	<.001
Placebo	6	67	72.73	1.46	
Atomoxetine		69	66.40	1.48	<.001
Placebo	7	67	70.40	1.53	
Atomoxetine		66	64.70	1.56	<.001
Placebo	8	63	69.25	1.67	
Atomoxetine		65	62.72	1.69	<.001
Placebo	9	61	70.00	1.65	
Atomoxetine		58	60.83	1.69	<.001
ADHDRS-INV HYP/IMP Score					
Treatment	Visit	N	LSMean	SE	Pairwise P-Value
Placebo	5	70	11.39	0.70	
Atomoxetine		71	9.28	0.72	.001
Placebo	6	67	11.21	0.72	
Atomoxetine		69	8.55	0.74	<.001
Placebo	7	67	10.47	0.71	
Atomoxetine		66	8.20	0.73	<.001
Placebo	8	63	9.88	0.78	
Atomoxetine		65	7.33	0.80	.002
Placebo	9	61	10.54	0.81	
Atomoxetine		58	6.49	0.83	<.001
ADHDRS-INV Inatten Score					
Treatment	Visit	N	LSMean	SE	Pairwise P-Value
Placebo	5	70	19.87	0.82	
Atomoxetine		71	17.73	0.85	.004
Placebo	6	67	19.96	0.86	
Atomoxetine		69	16.85	0.89	<.001
Placebo	7	67	18.65	0.92	
Atomoxetine		66	15.52	0.95	.001
Placebo	8	63	17.99	0.99	
Atomoxetine		65	14.61	1.02	.002
Placebo	9	61	18.01	0.97	
Atomoxetine		58	13.81	1.00	<.001

N = Number of randomized subjects with non-missing data at the specified visit.

Model ADHDRS -INV Total Tscore,inatten score, and HYP/IMP score=pooled investigator TRT VISIT

CYP2D6 BASELINE trt*VISIT

Baseline Visit 1-4, Endpoint Visit 5-9

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Table LYAX.6. ADHDRS-IV-Parent:Inv Total and Subscores Mean Change from Baseline to Endpoint Study Period II

	<u>Treatment</u>	<u>N</u>	<u>Baseline</u>		<u>Change</u>		<u>Lower</u>	<u>Upper%</u>	<u>p-value*</u>
			<u>Mean</u>	<u>SD</u>	<u>Mean*</u>	<u>SD</u>			
ADHDRS -INV Total Score	Atomoxetine	71	34.48	7.74	-13.31	9.97	-10.92	-4.64	<.001
	Placebo	70	33.67	8.82	-5.11	9.90			
ADHDRS -INV Total T-Score	Atomoxetine	71	77.63	9.47	-14.70	11.31	-11.79	-5.07	<.001
	Placebo	70	75.35	10.08	-5.38	10.49			
ADHDRS -INV HYP/IMP Score	Atomoxetine	71	12.42	6.09	-5.59	5.32	-5.30	-2.15	<.001
	Placebo	70	12.20	6.18	-1.66	5.11			
ADHDRS-INV Inatten Score	Atomoxetine	71	22.06	4.28	-7.72	6.38	-6.00	-2.02	<.001
	Placebo	70	21.47	4.78	-3.46	6.20			

Population: Randomized patients with a baseline and a postbaseline visit.

**p-value is from a t-test on differences in mean changes from baseline to endpoint scores using terms for baseline,pooled investigator, CYP2D6 status and treatment.

***95% CI:2-sided confidence interval of LSmean

Secondary Efficacy Measures

Noninferiority Analysis Using the CDRS-R

A noninferiority comparison between atomoxetine and placebo was computed using the least squares means from the CDRS-R total score to construct a 95% confidence interval for the difference between treatments (calculated as atomoxetine–placebo) in mean change from baseline total score. In agreement with the repeated measures analysis, no significant difference between atomoxetine and placebo was observed, and the lower 95% confidence limit for the difference, which was set a priori, was ≤ 2.5 . Atomoxetine was declared noninferior to placebo in reducing scores on the CDRS-R and, therefore, did not worsen depression compared with placebo.

Mean Change from Baseline to LOCF for Secondary Endpoints

The analyses of: CHQ-PF50, MADRS, RADS, CHQ-CF87, CGI-S, CGI-I, and the YMRS were presented using the mean change from baseline-to-LOCF endpoint for Study Period II. CGI-S and CGI-I scores were also presented using the percentage of responders analysis. A responder was defined as having an endpoint score of a 1 or 2 on the CGI-S or CGI-I scale.

There were no statistically significant changes between atomoxetine and placebo treatment groups in the mean change from baseline in:

- Improving psychosocial functioning as measured by the CHQ-PF50 subscales (i.e., psychosocial summary score, mental health, role-emotion/behavior, and self-esteem) or physical functioning subscale scores (Table LYAX.7).
- Improving the signs and symptoms of depression as measured by the MADRS and RADS scores (Table LYAX.8).
- Improving psychosocial functioning as measured by the CHF-CH87 subscales (i.e., mental health, role-emotion, role-behavior, and self-esteem) or physical functioning subscale scores (Table LYAX.9).
- Improving the overall outcomes of both ADHD and depressive symptoms as measured by the CGI-S scale (Table LYAX.10).
- Preventing the induction of manic switching as measured by the YMRS mean scores (Table LYAX.11).

Results of the mean change in CGI-I score analysis demonstrated statistically significant improvement ($p=.003$) in the mean change from baseline in the atomoxetine treatment group compared with placebo group in improving the overall outcomes of both ADHD and depressive symptoms (Table LYAX.12). The responders analysis for the CGI-S and the CGI-I demonstrated that the atomoxetine group was significantly higher ($p<.001$) than the placebo treatment group using the CGI-I scale (Table LYAX.13).

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Table LYAX.7. CHQ-PF50 Subscales
Mean Change from Baseline to LOCF Endpoint
All Randomized Patients
Study Period II

	<u>Treatment</u>	<u>N</u>	<u>Baseline</u>		<u>Change</u>		<u>95%CI</u>		<u>p-value*</u>
			<u>Mean</u>	<u>SD</u>	<u>Mean*</u>	<u>SD</u>	<u>Lower</u>	<u>Upper%</u>	
Mental Health	Atomoxetine	67	49.15	16.40	9.13	20.04	-5.24	5.92	.905
	Placebo	68	53.54	18.48	5.43	18.17			
Psychosocial Summary Score	Atomoxetine	64	25.31	11.27	5.97	13.54	-1.95	5.91	.321
	Placebo	68	26.00	12.63	2.96	11.97			
Role-Emotion/Behave	Atomoxetine	66	58.30	36.17	5.88	40.48	-4.20	17.87	.222
	Placebo	68	53.93	35.16	0.81	36.39			
Self-Esteem	Atomoxetine	67	43.81	21.09	9.57	19.85	-4.68	8.17	.592
	Placebo	68	46.38	20.77	5.63	23.01			
Physical Functioning	Atomoxetine	67	94.82	12.48	0.22	13.09	-3.56	4.28	.856
	Placebo	68	91.74	14.70	1.66	16.45			

Population: Randomized patients with a baseline and a postbaseline visit.

**p-value is from a t-test on differences in mean changes from baseline to endpoint scores using terms for baseline, pooled investigator, CYP2D6 status and treatment.

***95% CI:2-sided confidence interval of LSmean difference in change score between atomoxetine and placebo.

Baseline Visit 1-4, Endpoint Visit 5-9

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Table LYAX.8. MADRS and RADS Total Scores
Mean Change from Baseline to LOCF Endpoint
All Randomized Patients
Study Period II

	<u>Treatment</u>	<u>N</u>	<u>Baseline</u>		<u>Change</u>		<u>95%CI</u>		<u>p-value*</u>
			<u>Mean</u>	<u>SD</u>	<u>Mean*</u>	<u>SD</u>	<u>Lower</u>	<u>Upper%</u>	
MADRS Total Score	Atomoxetine	69	22.83	6.20	-6.94	8.26	-2.43	2.43	.997
	Placebo	68	22.75	7.01	-7.01	8.19			
RADS Total Score	Atomoxetine	66	67.91	14.59	-3.73	15.38	-2.95	6.19	.485
	Placebo	67	61.34	15.52	-2.79	11.02			

Population: Randomized patients with a baseline and a postbaseline visit.

**p-value is from a t-test on differences in mean changes from baseline to endpoint scores using terms for baseline, pooled investigator, CYP2D6 status and treatment.

***95% CI:2-sided confidence interval of LSmean difference in change score between atomoxetine and placebo.

Baseline Visits 1-4, Endpoint Visits 5-9

Atomoxetine

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Table LYAX.9. CHF-CH87 Subscales
Mean Change from Baseline to LOCF Endpoint
All Randomized Patients
Study Period II

	<u>Treatment</u>	<u>N</u>	<u>Baseline</u>		<u>Change</u>		<u>95%CI</u>		<u>p-value*</u>
			<u>Mean</u>	<u>SD</u>	<u>Mean*</u>	<u>SD</u>	<u>Lower</u>	<u>Upper%</u>	
Mental Health	Atomoxetine	67	63.33	17.28	1.32	17.02	-9.95	.24	.061
	Placebo	68	67.52	18.52	4.59	15.73			
Role-Behavior	Atomoxetine	65	73.33	29.58	11.11	30.93	-4.88	10.96	.448
	Placebo	67	79.27	27.14	3.32	30.83			
Role Emotion	Atomoxetine	66	75.84	26.37	4.46	30.21	10.49	6.07	.598
	Placebo	67	72.14	29.55	8.46	33.23			
Self Esteem	Atomoxetine	67	60.22	21.45	5.41	17.25	-4.72	6.50	.754
	Placebo	68	71.45	17.24	0.66				
Physical Functioning	Atomoxetine	67	86.55	15.61	4.16	17.01	-3.83	3.52	.933
	Placebo	68	87.09	17.51	3.65	11.13			

Population: Randomized patients with a baseline and a postbaseline visit.

**p-value is from a t-test on differences in mean changes from baseline to endpoint scores using terms for baseline, pooled investigator, CYP2D6 status and treatment.

***95% CI:2-sided confidence interval of LSmean difference in change score between atomoxetine and placebo.

Baseline Visit 1-4, Endpoint Visit 5-9

Table LYAX.10. CGI Severity
Mean Change from Baseline to LOCF Endpoint
All Randomized Patients
Study Period II

<u>Treatment</u>	<u>N</u>	<u>Baseline</u>		<u>Change</u>		<u>95%CI</u>		<u>p-value*</u>
		<u>Mean</u>	<u>SD</u>	<u>Mean*</u>	<u>SD</u>	<u>Lower</u>	<u>Upper%</u>	
Atomoxetine	71	4.54	0.67	-1.03	1.16	-.54	.08	.144
Placebo	70	4.44	0.61	-0.74	0.81			

Population: Randomized patients with a baseline and a postbaseline visit.

**p-value is from a t-test on differences in mean changes from baseline to endpoint scores using terms for baseline, pooled investigator, CYP2D6 status and treatment.

***95% CI:2-sided confidence interval of LSmean difference in change score between atomoxetine and placebo.

Baseline Visits 1-4, Endpoint Visits 5-9

Table LYAX.11. YMRS Total Score
Mean Change from Baseline to Endpoint
For All Randomized Patients
with Baseline and Postbaseline Visit
Study Period II

<u>Treatment</u>	<u>N</u>	<u>Baseline</u>		<u>Change</u>		<u>95%CI</u>		<u>p-value*</u>
		<u>Mean</u>	<u>SD</u>	<u>Mean*</u>	<u>SD</u>	<u>Lower</u>	<u>Upper%</u>	
Atomoxetine	68	6.38	5.11	-1.51	5.00	-1.75	.95	.560
Placebo	67	5.67	4.26	-0.64	5.59			

Population: Randomized patients with a baseline and a postbaseline visit.

**p-value is from a t-test on differences in mean changes from baseline to endpoint scores using terms for baseline, pooled investigator, CYP2D6 status and treatment.

***95% CI:2-sided confidence interval of LSmean difference in change score between atomoxetine and placebo.

Baseline Visit 1-4, Endpoint Visit 5-9

Table LYAX.12. CGI Improvement
Mean Change from Baseline to Endpoint
All Randomized Patients
Study Period II

<u>Treatment</u>	<u>N</u>	<u>Baseline</u>		<u>Change</u>		<u>95%CI</u>		<u>p-value*</u>
		<u>Mean</u>	<u>SD</u>	<u>Mean*</u>	<u>SD</u>	<u>Lower</u>	<u>Upper%</u>	
Atomoxetine	71	3.90	0.68	-1.07	1.29	-.85	-.17	.003
Placebo	69	3.78	0.59	-0.46	0.99			

Population: Randomized patients with a baseline and a postbaseline visit.

**p-value is from a t-test on differences in mean changes from baseline to endpoint scores using terms for baseline, pooled investigator, CYP2D6 status and treatment.

***95% CI:2-sided confidence interval of LSmean difference in change score between atomoxetine and placebo.

Baseline Visits 1-4, Endpoint Visits 5-9

Table LYAX.13. CGI-I and CGI-S
Percentage of Responders
Study Period II

<u>Treatment</u>	<u>N</u>	<u>CGI Severity</u>		<u>p-value*</u>	<u>N</u>	<u>CGI Improvement</u>		<u>p-value*</u>
		<u>n</u>	<u>%</u>			<u>n</u>	<u>%</u>	
Placebo	67	7	(10.4)	----	67	12	(17.9)	----
Atomoxetine	69	13	(18.8)	.227	69	33	(47.8)	<.001

Responder is defined as having a endpoint score of 1 or 2 on the CGI-ADHD-Severity and CGI-ADHD-Improvement scale.

*p-values for between treatment differences vs. Placebo were found using Fisher's Exact test.

Baseline Visit 1-4, Endpoint Visit 5-9

Safety

Adverse Events

There were no patient deaths in Study LYAX. One patient who had been randomized to placebo experienced SAEs of worsening major depression and acute psychotic features. During Study Period II, 1 of 72 patients in the atomoxetine treatment group discontinued due to moderate nausea, which began on the day the patient began atomoxetine administration. It was noted that this patient also started taking the concomitant medication pseudoephedrine/naproxen on the same day. One patient who was assigned to the placebo treatment group discontinued Study LYAX due to an AE prior to taking study drug. During Study Period III, 2 patients discontinued due to somnolence, and 1 patient discontinued due to upper abdominal pain. One patient discontinued due to lethargy the day of randomization to atomoxetine. During Study Period IV, 1 patient discontinued due to anorexia. Table LYAX.14 summarizes the most frequently reported TEAEs that occurred during Study Period II, with $\geq 5\%$ incidence.. Of these TEAEs, the occurrence of nausea (22.2%) and decreased appetite (12.5%) was significantly greater ($p \leq 0.05$) in patients treated with atomoxetine than those of placebo. TEAEs with $\geq 5\%$ incidence for all enrolled patients in Study Periods III/IV are also reported (Table LYAX.15). The most frequently occurring TEAEs were: nausea (22.5%), headache (17.5%), fatigue (15%), decreased appetite (14.2%), abdominal pain–upper (11.7%), weight decrease (11.7%), and unexpected therapeutic drug effect (10.8%).

Table LYAX.14. Summary of Treatment-Emergent Adverse Events with ≥5% Incidence Using MedDRA Preferred Terms
All Enrolled Patients Who Took at Least One Dose of Study Drug
Study Period II

Preferred Term	ATOMOX (N=72)		PLACEBO (N=69)		Total (N=141)		p-Value
	n	(%)	n	(%)	n	(%)	
PATIENTS WITH ≥ 1 TESS	51	(70.8)	49	(71.0)	100	(70.9)	1.00
PATIENTS WITH NO TESS	21	(29.2)	20	(29.0)	41	(29.1)	1.00
Headache	12	(16.7)	7	(10.1)	19	(13.5)	.326
Nausea	16	(22.2)	3	(4.3)	19	(13.5)	.002
Vomiting	9	(12.5)	6	(8.7)	15	(10.6)	.588
Fatigue	9	(12.5)	3	(4.3)	12	(8.5)	.130
Abdominal pain upper	6	(8.3)	5	(7.2)	11	(7.8)	1.00
Dizziness	9	(12.5)	2	(2.9)	11	(7.8)	.056
Decreased appetite	9	(12.5)	0		9	(6.4)	.003
Diarrhoea	1	(1.4)	6	(8.7)	7	(5.0)	.059
Influenza	3	(4.2)	4	(5.8)	7	(5.0)	.715
Pyrexia	2	(2.8)	5	(7.2)	7	(5.0)	.268
Weight decreased	6	(8.3)	1	(1.4)	7	(5.0)	.116
Irritability	4	(5.6)	1	(1.4)	5	(3.5)	.367
Weight increased	1	(1.4)	4	(5.8)	5	(3.5)	.202

Population: Enrolled patients who took at least 1 dose of study drug.

Baseline: Visits 1-4, Endpoint: Visits 5-9

* Frequencies are analyzed using a Fisher's Exact test.

Table LYAX.15. Summary of Treatment-Emergent Adverse Events with ≥5% Incidence Using MedDRA Preferred Terms
All Enrolled Patients Who Took at Least One Dose of Study Drug
Study Period III/IV

Preferred Term	ATOMOX (N=120)	
	n	(%)
PATIENTS WITH ≥ 1 TESS	101	(84.2)
PATIENTS WITH NO TESS	19	(15.8)
Nausea	27	(22.5)
Headache	21	(17.5)
Fatigue	18	(15.0)
Decreased appetite	17	(14.2)
Abdominal pain upper	14	(11.7)
Weight decreased	14	(11.7)
Unexpected therapeutic drug effect	13	(10.8)
Vomiting	9	(7.5)
Dizziness	8	(6.7)
Irritability	8	(6.7)
Somnolence	8	(6.7)
Influenza	6	(5.0)
Insomnia	6	(5.0)
Nasopharyngitis	6	(5.0)
Upper respiratory tract infection	6	(5.0)
Weight increased	6	(5.0)

Population: Enrolled patients who took at least 1 dose of study drug.

Baseline: Visits 1-4, Endpoint: Visits 10-1

Laboratory Data

Laboratory tests, including chemistry, hematology, and urinalysis, were analyzed for all patients enrolled in Study Period II using the mean change from baseline-to-endpoint analysis. Statistically significant ($p < .05$) treatment differences in mean change scores were observed for: monocytes, ALT/SGPT, GGT, BUN, cholesterol, uric acid, creatinine, and platelet count (Table LYAX.16). Table LYAX.17 summarizes the frequency of patients with abnormal laboratory values after baseline in Study Period II. The data indicate that there were no statistically significant abnormal laboratory values reported in the atomoxetine treatment group compared to placebo. Uric acid ($p = .013$) and alkaline phosphatase levels ($p = .004$) were significantly abnormally higher in the placebo treatment group compared to the atomoxetine treatment group.

The mean change from baseline to endpoint for laboratory analytes and the frequency of abnormal laboratory values were recorded for Study Periods III/IV. However, the statistical significance of these data were not evaluated.

Table LYAX.16. Summary of Laboratory (SI) Data
Mean Change from Baseline to Endpoint/Significant
Analytes
All Enrolled Patients Who Took at Least One Dose of Study
Drug
Study Period II

<u>Lab</u> <u>Test</u>	<u>Lab</u> <u>Unit</u>	<u>Therapy</u>	<u>n</u>	<u>Baseline</u>		<u>Change to</u> <u>Endpoint</u>		<u>p-Values</u> <u>Therapy Model</u>	
				<u>Mean</u>	<u>SD</u>	<u>Mean</u>	<u>SD</u>		
MONOS	GI/L	ATOMOX	56	0.414	0.188	-0.032	0.180	.049	FULL1
		PLACEBO	57	0.400	0.146	0.029	0.187		
ALT	U/L	ATOMOX	56	18.286	8.726	-3.268	7.414	<.001	FULL1
		PLACEBO	57	15.947	6.427	1.193	6.986		
GGT	U/L	ATOMOX	56	15.893	8.470	-1.679	4.699	<.001	FULL1
		PLACEBO	57	13.965	4.301	0.895	2.575		
BUN	mmol/L	ATOMOX	57	4.474	1.055	-0.109	1.072	.013	FULL1
		PLACEBO	57	4.195	0.961	0.372	0.998		
UR AC	umol/L	ATOMOX	57	314.281	83.368	-8.912	42.747	.002	FULL1
		PLACEBO	57	293.596	70.420	18.825	42.967		
CHOL	mmol/L	ATOMOX	57	4.215	0.736	-0.146	0.514	.012	FULL1
		PLACEBO	57	4.062	0.832	0.097	0.443		
CREAT	umol/L	ATOMOX	57	58.175	13.306	5.281	11.646	.036	FULL1
		PLACEBO	57	56.421	13.655	0.386	10.248		
PLTCT	GI/L	ATOMOX	56	300.839	76.629	-6.607	36.610	.008	FULL1
		PLACEBO	57	294.421	79.319	13.561	34.076		

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks:
PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA on the ranks using the
mean square for error.

ABBREV: MONOS=monocytes, ALT=ALT/SGPT, GGT=GGT (GGPT/SGGT/YGGT), BUN=urea nitrogen,
UR AC=uric acid, CHOL=cholesterol, CREAT=creatinine, PLTCT=platelet count

Table LYAX.17. Summary of Laboratory (SI) Data
Frequency of Patients with Abnormal Laboratory Values
after Baseline (with TESS Option) All Enrolled Patients Who
Took at Least One Dose of Study Drug
Study Period II

<u>Lab Test</u>	<u>Incidence Group</u>	<u>ATOMOX (1)</u> (Total=72)			<u>PLACEBO(2)</u> (Total=69)			<u>p-Value *</u> <u>Overall</u>
		<u>N</u>	<u>n</u>	<u>(%)</u>	<u>N</u>	<u>n</u>	<u>(%)</u>	
HEMATOCRIT	LOW	51	2	(3.9)	53	4	(7.5)	.678
ERYTH COUNT	LOW	53	2	(3.8)	56	1	(1.8)	.611
EOSINOPHLIS	HIGH	56	1	(1.8)	56	4	(7.1)	.364
MCV	LOW	56	2	(3.6)	48	4	(8.3)	.411
PLT COUNT	HIGH	48	0		53	2	(3.8)	.496
UA-SPC GRAV	LOW	53	2	(3.8)	58	3	(5.2)	1.00
	HIGH	53	5	(9.4)	58	3	(5.2)	.476
CPK	HIGH	55	3	(5.5)	56	6	(10.7)	.489
ALK PHOS	HIGH	52	0		47	7	(14.9)	.004
CALCIUM	HIGH	45	7	(15.6)	47	6	(12.8)	.771
INORG PHOS	HIGH	54	2	(3.7)	53	1	(1.9)	1.00
ALBUMIN	HIGH	47	8	(17.0)	51	5	(9.8)	.376
URIC ACID	HIGH	53	0		55	7	(12.7)	.013
CHOLESTEROL	LOW	52	3	(5.8)	47	2	(4.3)	1.00
	HIGH	53	0		53	3	(5.7)	.243
CREATININE	HIGH	56	4	(7.1)	54	2	(3.7)	.679
BILI, TOTAL	HIGH	56	2	(3.6)	57	2	(3.5)	1.00

Population: Enrolled patients who took at least 1 dose of study drug.

Baseline: Visits 1-4, Endpoint: Visits 5-9

* Frequencies are analyzed using a Fisher's Exact test.

Note: Total = Total number of patients in the treatment group having both baseline and endpoint visits.

N = Total number of at risk patients with the lab test.

n = Total number of at risk patients with the specific lab result (e.g. HIGH).

Abbrev: ERYTH=erythrocyte, MCV=mean cell volume, PLT=platelet, UA SPC GRAV=urinalysis specific gravity, CPK= creatine phosphokinase, ALK PHOS=alkaline phosphatase, INORG PHOS=inorganic phosphate, BILI=bilirubin.

Vitals

The mean change from baseline to endpoint (Table LYAX.18) and the categorical analysis of vital signs (Table LYAX.19), including: height, weight, blood pressure (diastolic and systolic), and temperature indicated that there were no statistically significant differences in the mean changes in the atomoxetine treatment group versus the placebo group, with the exception of weight, in Study Period II. The mean change in weight was statistically significant ($p < .001$) with a mean increase of 2.6 kg in the placebo treatment group and a mean decrease of 0.84 kg in the atomoxetine treatment group.

The mean change from baseline to endpoint for vital signs and a categorical analysis of vital signs were reported for the atomoxetine treatment group in Study Periods III/IV; however, the statistical significance of the results were not analyzed.

**Table LYAX.18. Condensed Summary of Vital Sign Data
Mean Change from Baseline to Endpoint
Study Period II**

Variables Analyzed	Therapy	n	Baseline		Change to Endpoint		p-Values
			Mean	SD	Mean	SD	
DIASTOLIC BP	ATOMOX	71	68.282	8.474	1.507	9.802	.934
	PLACEBO	69	64.377	8.081	1.638	8.798	
SYSTOLIC BP	ATOMOX	71	114.930	10.514	0.113	10.921	.819
	PLACEBO	69	109.348	11.277	0.580	13.082	
HEART RATE	ATOMOX	71	78.592	11.539	6.000	13.897	.096
	PLACEBO	69	76.014	11.861	2.261	12.427	
WEIGHT (KG)	ATOMOX	71	63.307	14.311	-0.839	4.945	<.001
	PLACEBO	68	58.462	12.716	2.579	2.401	
HEIGHT (CM)	ATOMOX	65	164.320	12.271	0.720	1.288	.059
	PLACEBO	63	162.910	9.574	1.187	1.482	
TEMPERATURE (CENTIGRADE)	ATOMOX	71	36.355	0.495	-0.007	0.576	.955
	PLACEBO	69	36.330	0.583	-0.001	0.601	

Population: Enrolled patients who took at least 1 dose of study drug.

Baseline: Visits 1-4, Endpoint: Visits 5-9

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Table LYAX.19. Categorical Changes in Vital Signs and Weight at Endpoint Study Period II

Vital	Incidence	ATOMOX			PLACEBO			Fisher's Exact p-Value
		N	n	(%)	N	n	(%)	
Diastolic Bp	High	68	3	(4.4)	69	1	(1.4)	.366
Pulse	Low	71	1	(1.4)	69	1	(1.4)	1.00
Systolic Bp	High	66	1	(1.5)	67	3	(4.5)	.619
Tempurature	Low	71	1	(1.4)	69	0		1.00
Weight(Kg)	Decrease	71	20	(28.2)	68	2	(2.9)	<.001

*Criteria: Pulse: High: Increase of at least 25 to a value of at least 110; Low: Decrease of at least 20 to a value of at most 65.

Temperature: High: Increase of at least 1.0 to a value of at least 37.8; Low: Decrease of at least 1.3 to a value of at most 35.6.

Weight: Decrease of at least 3.5%

Blood Pressure: High: Increase of at least 5 mm to above 95% percentile.

Patients counted as meeting criteria if criteria was met at endpoint.

Patients were excluded from BP analysis if they have abnormal Blood Pressure at last baseline visit

Baseline: Visit 1-4, Postbaseline: Visit 5-9

Electrocardiograms

Categorical and mean change from baseline-to-endpoint analyses of ECG variables for all enrolled patients were reported for Study Period II. The categorical analysis of ECG heart rate and QTc intervals using the Bazett's formula (QTcB), Fredericia's formula (QTcF), and a data-derived (QTcD) formula, showed no statistically significant differences were observed between treatment groups for any of these variables. The mean change from the baseline analysis showed a statistically significant decrease in: RR interval values ($p < .001$), decrease in QT interval values ($p = .006$), increase in heart rate ($p < .001$), prolongation of QTcB ($p = .045$), and decrease of PR values ($p = .002$) for the mean change in the atomoxetine treatment group compared to the placebo treatment group when corrected using the Bazett formula (Table LYAX.20). There was no statistically significant difference when using data corrections or the Fredericia correction method.

Table LYAX.20. Condensed Summary of ECG Data Mean Change from Baseline to Endpoint—Ranked All Enrolled Patients Who Took at Least One Dose of Study Drug Study Period II

Variables Analyzed	Therapy	n	Baseline		Change to Endpoint		p-Values
			Mean	SD	Mean	SD	
RR	ATOMOX	63	870.606	144.264	-101.184	154.052	<.001
	PLACEBO	58	865.966	129.933	-10.590	111.935	
PR	ATOMOX	63	141.429	18.739	-2.698	16.772	.002
	PLACEBO	58	141.724	20.360	6.552	17.326	
QRS	ATOMOX	63	84.603	7.367	0.635	7.593	.581
	PLACEBO	58	82.759	7.444	1.207	8.182	
QT	ATOMOX	63	374.286	26.379	-17.778	25.109	.006
	PLACEBO	58	372.069	25.735	-4.483	25.899	
QTcB	ATOMOX	63	403.444	23.341	5.429	25.666	.045
	PLACEBO	58	401.776	25.695	-2.517	20.864	
QTcF	ATOMOX	63	393.232	19.237	-2.882	18.925	.809
	PLACEBO	58	391.424	21.967	-3.252	19.402	
QTcD	ATOMOX	63	396.664	20.026	-0.140	20.528	.374
	PLACEBO	58	394.904	22.827	-3.023	19.468	
HR	ATOMOX	63	70.778	11.617	9.159	13.321	<.001
	PLACEBO	58	70.741	10.053	0.983	9.443	

Population: Enrolled patients who took at least 1 dose of study drug.

Baseline: Visits 1-4, Endpoint: Visits 5-9

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Summary ID#5197

Clinical Study Summary: Study B4Z-MC-LYBB

Title of Study: A Phase 3 Open-Label Safety and Efficacy Study of Atomoxetine Hydrochloride in Pediatric Outpatients (6 to 18 Years) with ADHD	
Investigators: This multicenter study included 42 principal investigators.	
Study Centers: This study was conducted at 42 study centers in the United States.	
Length of Study: Approximately 8 months Date first patient enrolled: 20 November 2000 Date last patient completed: 10 July 2001	Phase of Development: 3
Objectives: The primary objective of this study was to demonstrate that atomoxetine (formerly called tomoxetine) is safe and well tolerated when administered acutely (approximately 10 weeks) and when titrated to a dose of 1.8 mg/kg/day. The secondary objectives of this study were: - To assess the open-label efficacy of atomoxetine. - To compare the safety and efficacy of atomoxetine in cytochrome P450 2D6 (CYP2D6) genotypic extensive metabolizer (EM) patients versus poor metabolizer (PM) patients. - To assess the relationship between plasma atomoxetine concentrations and efficacy, and to assess the relationship between plasma atomoxetine concentrations and electrocardiogram (ECG) parameters (including QTc interval).	
Study Design: Study B4Z-MC-LYBB (LYBB) was a Phase 3, multicenter, open-label investigation of the acute safety and efficacy of atomoxetine in up to 1000 outpatients, who were at least 6 years of age but less than 18 years of age when informed consent was obtained, and who met <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</i> (DSM-IV) criteria for Attention-Deficit/Hyperactivity Disorder (ADHD). Study Period II consisted of 11 visits, each with 4- to 14-day intervals, comprising a total therapy period of approximately 10 weeks. Patients who completed the acute treatment period and met inclusion criteria were eligible to enter a long-term, open-label atomoxetine treatment protocol (B4Z-MC-LYAI [LYAI]) that could last up to 3 years.	
Number of Patients: Planned: Up to 1000 Enrolled: 420 Completed Study Period II: 311	
Diagnosis and Main Criteria for Inclusion: Patients met DSM-IV diagnostic criteria for ADHD as assessed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version: Behavioral Disorders Supplement (K-SADS-PL:Behavioral) at Visit 1 and by investigator assessment using DSM-IV criteria at Visit 2 and Visit 3. Each patient's score from the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) was at least 1.0 standard deviation above the age/gender norm for his or her diagnostic subtype at both Visit 2 and Visit 3.	
Test Product, Dose, and Mode of Administration: Atomoxetine: 2.5 mg, 5 mg, 10 mg, 25 mg, 40 mg capsules; dose individually titrated based on body weight starting at a total daily dose that is closest to, but does not exceed, 0.5 mg/kg/day and ending with a maximum dose of 1.8 mg/kg/day, given in divided doses twice daily.	
Duration of Treatment: Approximately 10 weeks.	
Reference Therapy, Dose, and Mode of Administration: None.	
Variables:	

Efficacy: The primary efficacy measure was the ADHDRS-IV-Parent:Inv.

Safety: Adverse events, vital signs, routine laboratory tests, pharmacokinetic blood sampling, and ECGs were recorded. The adverse events were collected through open-ended interview.

Evaluation Methods:

Statistical: Analyses performed included determination of sample size, mean, standard deviation, mean change from baseline to endpoint, 2-sided 95% confidence intervals, Wilcoxon signed-rank test for changes from baseline to endpoint and analysis of variance (ANOVA) for subgroup differences, and nonlinear model (inhibitory Emax model) to predict ADHDRS-IV-Parent:Inv Total Score reduction by peak atomoxetine concentration. Missing data were handled using a last-observation-carried-forward (LOCF) approach.

Summary:

Patient Disposition: There were 420 patients who entered the study, although the data presented only encapsulates the 419 patients who received at least one dose of atomoxetine. Of these 419 patients, 311 patients completed Study Period II. Over the duration of the trial, 6.4% discontinued due to lack of efficacy (patient and doctor perception), 4.8% due to lack of efficacy (patient perception), and 4.3% for adverse events.

Patient Demographics: Table LYBB.1 presents a summary of demographics and other patient characteristics for all entered patients. The majority of enrolled patients were males (75.2%), were Caucasian (79%), and had used stimulants previously (73.6%). Mean and median ages were 11.34 and 11.30 years. Most patients were diagnosed with either the inattentive subtype of ADHD (32.5%), or mixed subtype (64.4%).

Efficacy: As Table LYBB.2 illustrates, mean change from baseline to endpoint on the ADHDRS-IV-Parent:Inv Total score (the primary efficacy variable) was -19.8 ($p < .001$). Improvement occurred in both EM patients and PM patients, although the magnitude of the reduction in ADHDRS-IV-Parent:Inv Total score appeared to be somewhat greater in PM patients than in EM patients (-19.5 for EM patients versus -23.8 for PM patients); a difference that approached, but did not reach, statistical significance ($p = .075$).

The relationship between drug concentration and efficacy response was analyzed through correlation analysis (at Visit 8) and nonlinear modeling (at endpoint) of the change from baseline in ADHDRS-IV-Parent:Inv Total Score and atomoxetine peak concentration. Pearson's correlation coefficient between response and peak concentration was -0.179 ($p\text{-value} = 0.001$), 0.012 ($p\text{-value} = 0.839$) and -0.178 ($p\text{-value} = 0.394$) for all patients, EM patients and PM patients, respectively. These low correlation values coupled with the previously observed efficacy results by dose group suggest that the relationship between peak concentration and efficacy, like the relationship between dose group and efficacy, cannot be explained by a simple linear relationship.

Figure LYBB.1 shows the result of fitting a nonlinear model (inhibitory $E_{\max}$ model) to the observed peak concentration and change from baseline in ADHDRS-IV-Parent:Inv Total Scores data to further explore the relationship between efficacy and peak concentration. The modeling was limited to EM patient data since there was a minimal amount of PM patient data. The resulting fit of this model suggests that the expected maximum improvement from baseline would be -23.5. This suggests an overall maximum benefit of -8.3 over patients with zero peak concentration. However, the interpretation of this result should be taken with caution since there was very limited data on peak concentration levels that were close to zero.

Because the study was not placebo-controlled, no definitive statements concerning efficacy can be made; however, the magnitude of response was consistent with that observed in previous studies generally, and only modestly higher than that observed in placebo-controlled studies.

Safety: Four percent (4.0%) of patients discontinued due to an adverse event. The adverse event profile in this study is similar to that observed in other atomoxetine trials. Events did not increase over time. Table LYBB.3 summarizes the treatment-emergent adverse events that occurred in at least 5% of the patients who took at least 1 dose of study drug, for EM patients, PM patients, and all enrolled patients during Study Period II. Anorexia, usually reported as "decreased appetite" was reported at least once by

11.2% of patients. Comparison of the adverse event profile reported by PM patients (N = 32) relative to that reported by EM patients (N = 387) is limited by the small number of PM patients. Overall the adverse event profile appears to be similar in these two groups.

Change from baseline to endpoint was computed for each laboratory analyte for each patient who took at least 1 dose of study drug and who had a baseline and at least one postbaseline measurement. Laboratory examinations were scheduled at Visit 1, Visit 8, Visit 12, and Visit 14. Table LYBB.4 shows the mean change from baseline to endpoint for all patients, EM patients, and PM patients, as well as within group p-values for these changes. Of the 34 laboratory measurements conducted, changes from baseline for 17 analytes were found to be statistically different from zero for the pool of all patients.

As Table LYBB.5 indicates, statistically significant baseline to endpoint increases or decreases in diastolic blood pressure (+1.4 mm Hg), pulse (+5.7 bpm), weight (-0.3 kg), and height (+1.4 cm) were detected. Changes in vital signs of PM patients may be slightly different than in EM patients, although the comparison is limited by the relatively small number of PM patients. In PM patients, the mean increase in pulse was 7.1 bpm, and weight was decreased by an average of 1.2 kg. Changes in diastolic blood pressure (+4.4 mm Hg) and systolic blood pressure (+1.1 mm Hg) were also slightly higher than observed in the total population. Effects on ECG parameters were consistent with an increased heart rate, and somewhat more pronounced in PM patients.

No evidence for a drug-related QTc prolongation was observed.

Table LYBB.6 summarizes the results of the assessment of the relationship between atomoxetine plasma concentrations with ECG corrected QT intervals. There was a significant correlation between Bazett corrected QT interval and atomoxetine plasma concentration at Visit 8 (peak), Visit 12 (peak), and Visit 12 (trough). The Bazett method over-corrects for heart rate effects, leading to a falsely elevated QTc interval. There were no statistically significant correlations between QTc values using data or Fridericia correction methods and atomoxetine plasma concentrations at any time point.

**Table LYBB.1. Summary of Demographics and Other Patient Characteristics
All Entered Patients
B4Z-MC-LYBB**

Variable	ATOMOX (N=420)	NO DRUG (N=59)	Total (N=479)
Sex: No. (%)			
No. Patients	420	59	479
Female	104 (24.8)	10 (16.9)	114 (23.8)
Male	316 (75.2)	49 (83.1)	365 (76.2)
Origin: No. (%)			
No. Patients	420	59	479
African Descent	34 (8.1)	9 (15.3)	43 (9.0)
Caucasian	332 (79.0)	41 (69.5)	373 (77.9)
East/Southeast A	2 (0.5)	1 (1.7)	3 (0.6)
Hispanic	41 (9.8)	5 (8.5)	46 (9.6)
Other	11 (2.6)	3 (5.1)	14 (2.9)
Age: yrs.			
No. Patients	420	59	479
Mean	11.34	10.55	11.24
Median	11.30	9.68	11.04
Standard Dev.	2.87	3.29	2.93
Minimum	6.02	6.18	6.02
Maximum	17.73	17.35	17.73
Height: cm			
No. Patients	419	47	466
Mean	146.24	139.23	145.53
Median	146.00	134.00	145.00
Standard Dev.	17.13	19.76	17.52
Minimum	112.00	112.00	112.00
Maximum	196.00	182.00	196.00
Unspecified	1	12	13
Weight: kg			
No. Patients	420	47	467
Mean	43.73	36.20	42.97
Median	39.70	29.50	39.10
Standard Dev.	17.83	15.43	17.74
Minimum	20.00	18.80	18.80
Maximum	136.30	68.00	136.30
Unspecified	0	12	12
Family History of ADHD-Mother			
No. Patients	420	59	479
N	306 (72.9)	42 (82.4)	348 (73.9)
U	41 (9.8)	1 (2.0)	42 (8.9)
Y	73 (17.4)	8 (15.7)	81 (17.2)
Unspecified	0	8	8
Family History of ADHD-Father			
No. Patients	420	59	479
N	254 (60.5)	32 (62.7)	286 (60.7)
U	57 (13.6)	7 (13.7)	64 (13.6)
Y	109 (26.0)	12 (23.5)	121 (25.7)
Unspecified	0	8	8
Family History of ADHD-Grandparents			
No. Patients	420	59	479
N	309 (73.6)	37 (72.5)	346 (73.5)
U	76 (18.1)	10 (19.6)	86 (18.3)
Y	35 (8.3)	4 (7.8)	39 (8.3)
Unspecified	0	8	8

(continued)

Table LYBB.1. Summary of Demographics and Other Patient Characteristics
All Entered Patients
B4Z-MC-LYBB (concluded)

Variable	ATOMOX (N=420)	NO DRUG (N=59)	Total (N=479)
Family History of ADHD-Siblings			
No. Patients	420	59	479
N	229 (54.5)	38 (74.5)	267 (56.7)
N/A	30 (7.1)	0	30 (6.4)
U	39 (9.3)	4 (7.8)	43 (9.1)
Y	122 (29.0)	9 (17.6)	131 (27.8)
Unspecified	0	8	8
Prior Stimulant Exposure			
No. Patients	420	59	479
N	111 (26.4)	26 (47.3)	137 (28.8)
Y	309 (73.6)	29 (52.7)	338 (71.2)
Unspecified	0	4	4
DRD4 Allele			
No. Patients	420	59	479
Unspecified	420	59	479
Grade in School			
No. Patients	420	59	479
1	26 (6.2)	10 (18.9)	36 (7.6)
2	36 (8.6)	8 (15.1)	44 (9.3)
3	51 (12.1)	4 (7.5)	55 (11.6)
4	46 (11.0)	8 (15.1)	54 (11.4)
5	49 (11.7)	4 (7.5)	53 (11.2)
6	43 (10.2)	3 (5.7)	46 (9.7)
7	62 (14.8)	2 (3.8)	64 (13.5)
8	35 (8.3)	3 (5.7)	38 (8.0)
9	18 (4.3)	2 (3.8)	20 (4.2)
0	8 (1.9)	2 (3.8)	10 (2.1)
10	30 (7.1)	6 (11.3)	36 (7.6)
11	12 (2.9)	1 (1.9)	13 (2.7)
12	4 (1.0)	0	4 (0.8)
Unspecified	0	6	6

Population: All Entered Patients.
Study Period XX: Specialized Reporting All Visits 1-15
Input data from RMP.SAS.B4ZM.MCLYBBSW
Output stored as RMP.B4Z0.LYBBCTRM.FINAL(DE1C600L)
XDES0001

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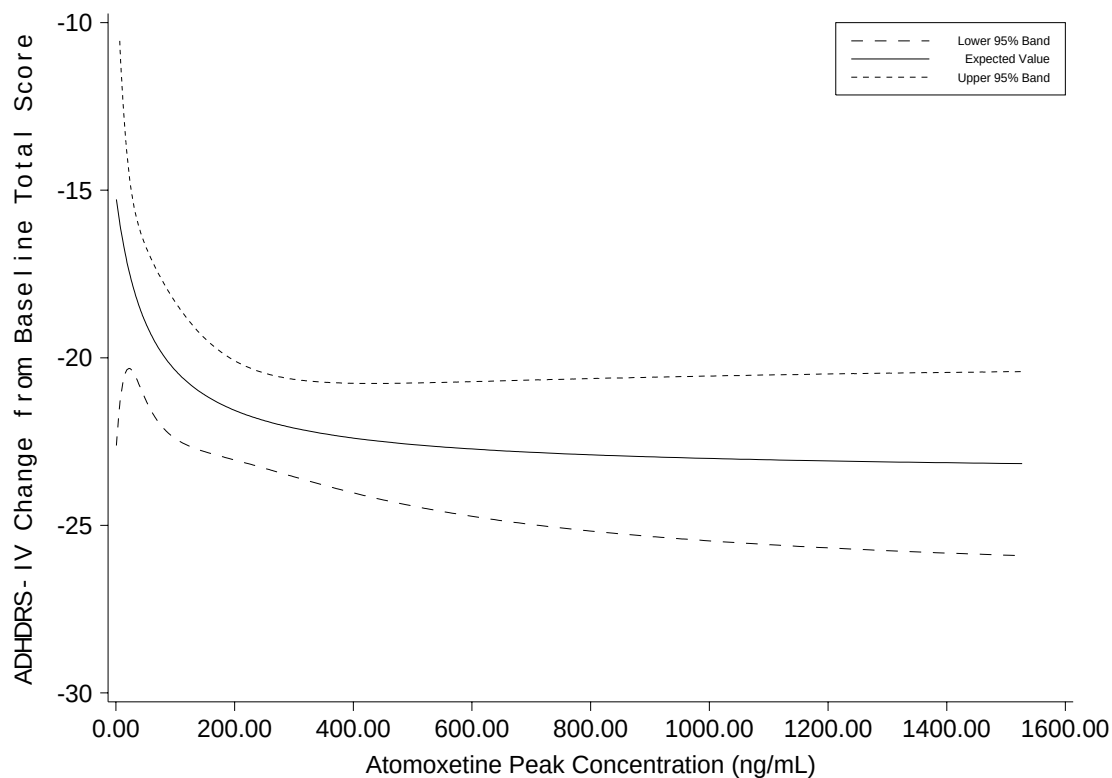
**Table LYBB.2. ADHDRS-IV-Parent:Inv Total Score, T-Score, and Subscale Scores
 Change from Baseline to Endpoint, Study Period II
 B4Z-MC-LYBB**

Treatment	n	Baseline		Endpoint		Change				p-Value ^a
		Mean	SD	Mean	SD	Mean	SD	LCI	UCI	
Total Score Imputed	413	38.8	9.9	19.1	12.6	-19.8	13.0	-21.0	-18.5	<.001
T-Score	413	80.1	11.4	59.1	13.2	-21.0	14.0	-22.3	-19.6	<.001
Inattentive Subscale Score	413	22.0	4.5	11.4	7.0	-10.6	7.3	-11.3	-9.8	<.001
Hyperactive Subscale Score	413	16.8	7.3	7.6	6.8	-9.2	7.0	-9.9	-8.5	<.001

Abbreviations: ATX: atomoxetine; n = number of patients with a baseline and at least one postbaseline measurement;
 SD = standard deviation; Change = endpoint-baseline; C.I. = 95% 2-sided Confidence Interval of Change;
 LCI = Lower bound of 95% C.I.; UCI = Upper bound of 95% C.I.; Baseline: Visit 1-3; Endpoint: Visit 4-14.

^a p-Value is from Wilcoxon signed-rank test

Source data: RMP.B4ZSLYBB.SASPGM(FEFF1)



Source Data: eagle:\programs._g\rmp\b4zs\lybb\LYBB PK vs efficacy nlin plots.sas

Figure LYBB.1. Model-predicted, mean change from baseline to endpoint, ADHDRS-IV-Parent:Inv Total Score and atomoxetine peak concentration for EM patients with confidence bounds, B4Z-MC-LYBB.

**Table LYBB.3. Summary of Treatment Emergent Adverse Events
Incidence ≥5%, (Percent of Patients Reporting)
Study Period II
B4Z-MC-LYBB**

Event	EM Patients (N=387) n (%)	PM Patients (N=32) n (%)	Total (N=419) n (%)	p-value ^a
HEADACHE	106(27.4)	7(21.9)	113(27.0)	.679
RHINITIS	111(28.7)	2(6.3)	113(27.0)	.004
VOMITING	47(12.1)	4(12.5)	51(12.2)	1.000
PHARYNGITIS	46(11.9)	4(12.5)	50(11.9)	.783
ABDOMINAL PAIN	44(11.4)	5(15.6)	49(11.7)	.403
ANOREXIA	44(11.4)	3(9.4)	47(11.2)	1.000
ASTHENIA	43(11.1)	2(6.3)	45(10.7)	.558
NAUSEA	42(10.9)	3(9.4)	45(10.7)	1.000
SOMNOLENCE	40(10.3)	4(12.5)	44(10.5)	.762
COUGH INCREASED	39(10.1)	3(9.4)	42(10.0)	1.000
FEVER	38(9.8)	3(9.4)	41(9.8)	1.000
FLU SYNDROME	34(8.8)	3(9.4)	37(8.8)	.754
PAIN	30(7.8)	2(6.3)	32(7.6)	1.000
INSOMNIA	24(6.2)	4(12.5)	28(6.7)	.255
NERVOUSNESS	25(6.5)	2(6.3)	27(6.4)	1.000
DIZZINESS	24(6.2)	2(6.3)	26(6.2)	1.000
ACCIDENTAL INJURY	19(4.9)	4(12.5)	23(5.5)	.088
DYSPEPSIA	20(5.2)	3(9.4)	23(5.5)	.405
EMOTIONAL LABILITY	21(5.4)	1(3.1)	22(5.3)	1.000
DIARRHEA	19(4.9)	2(6.3)	21(5.0)	.669

^a p-values for comparing PM and EM patients are from Fisher's exact test.
Population: enrolled patients who received at least one dose of atomoxetine.
Program: eagle:/programs_.g/rmp/b4zs/lybb/teae2.sas.

Table LYBB.4. Summary of Baseline to Endpoint Changes in Laboratory Analytes, All Patients and by Genotype Study Period II B4Z-MC-LYBB

ANALYTE (units)	All	p-value ^a	EM	p-value ^a	PM	p-value ^a
AST/SGOT (U/L)	-1.60	<.001	-1.40	<.001	-4.10	<.001
ALT/SGPT (U/L)	-1.86	<.001	-1.79	<.001	-2.79	.007
CPK (U/L)	-2.5	.115	-0.7	.367	-25.3	.020
ALK PHOS (U/L)	-3.8	.074	-2.8	.230	-16.2	.016
GGT (U/L)	+0.12	.941	-0.16	.643	+3.69	.059
BUN (mmol/L)	-0.03	.879	-0.01	.932	-0.22	.387
CALCIUM	+0.004	.350	+0.005	.267	-0.015	.549
PHOSPHORUS (mmol/L)	-0.015	.074	-0.013	.108	-0.041	.390
TOT PROT (gm/L)	+0.1	.802	+0.1	.982	+0.7	.502
ALBUMIN (gm/L)	+0.5	.003	+0.5	.004	+0.4	.576
NF GLUCOSE (mmol/L)	+0.02	.581	+0.02	.693	+0.02	.609
URIC ACID	-6.0	.014	-5.9	.016	-7.6	.586
CHOLESTEROL (mmol/L)	-0.047	.040	-0.051	.030	+0.005	.842
CREATININE (μmole/L)	+2.1	<.001	+2.3	<.001	-0.9	.588
TOT BILI (μmole/L)	0.0	.929	-0.0	.767	+0.3	.587
HCT (count)	+0.010	.001	+0.010	<.001	+0.013	.003
HGB (mmol/L)	-0.025	.318	-0.028	.202	0.009	.409
RBC (trill/L)	-0.041	<.001	-0.043	<.001	-0.021	.888

(continued)

Table LYBB.4. Summary of Baseline to Endpoint Changes in Laboratory Analytes, All Patients and by Genotype Study Period II B4Z-MC-LYBB (concluded)

ANALYTE (units)	All	p-value ^a	EM	p-value ^a	PM	p-value ^a
MCHC (mmol/L Fe)	-0.6	<.001	-0.6	<.001	-0.7	.001
MCH (femtomole Fe)	+0.006	.019	+0.008	.007	-0.013	.313
LEUKOCYTES (bill/L)	-0.06	.128	-0.06	.153	-0.07	.704
BANDS (bill/L)	-0.00	1.00	-0.00	1.00	0.0	n/a
NEUTROPHILS (bill/L)	+0.010	.654	+0.012	.728	-0.021	.681
LYMPHOCYTES (bill/L)	-0.071	.038	-0.077	.024	-0.004	.760
MONOCYTES (bill/L)	+0.004	.836	+0.004	.835	+0.006	.956
EOSINOPHILS (bill/L)	-0.003	.045	-0.001	.129	-0.026	.044
BASOPHILS (bill/L)	+0.007	<.001	+0.008	<.001	+0.004	.340
MCV (femtoliter)	+2.7	<.001	+2.6	<.001	+3.1	<.001
PLATELETS (bill/L)	+4.3	.165	+5.2	.095	-6.4	.403
SODIUM (mmol/L)	+1.0	<.001	+1.0	<.001	+1.1	.034
POTASSIUM (mmol/L)	+0.01	.883	+0.02	.518	-0.14	.025
CHLORIDE (mmol/L)	+0.7	<.001	+0.7	<.001	+0.4	.458
BICARBONATE (mmol/L)	-0.47	.001	-0.46	.002	-0.48	.360
UA-SG	+0.000	.343	+0.001	.160	-0.003	.127

Abbreviations: ALK PHOS = alkaline phosphatase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; HCT = hematocrit; HGB = hemoglobin; MCH = mean cell hemoglobin; MCHC = mean cell hemoglobin concentration; MCV = mean cell volume; NF GLUCOSE = non-fasting glucose; RBC = red blood cells; TOT BILI = total bilirubin; TOT PROT = total protein; UA-SG = urine analysis – specific gravity.

^a Wilcoxon signed-rank test

Data Source: RMP.B4ZO.LYBBCTRM.FINAL(LS30100C),
RMP.B4ZO.LYBBCTRM.FINAL(LS30100O), RMP.B4ZO.LYBBCTRM.FINAL(LS30100P)

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**Table LYBB.5. Summary of Vital Signs Changes Baseline to Endpoint
 Study Period II
 B4Z-MC-LYBB**

Treatment	n	Baseline		Endpoint		Change				p-Value ^a
		Mean	SD	Mean	SD	Mean	SD	LCI	UCI	
Pulse	413	80.6	11.0	86.3	12.2	5.7	11.2	4.6	6.8	<0.001
Height	376	146.5	17.0	147.8	17.0	1.4	3.4	1.0	1.7	<0.001
Weight	413	44.3	17.7	43.9	17.4	-0.3	2.0	-0.5	-0.1	0.003
Temperature	413	36.6	0.5	36.6	0.5	0.0	0.6	-0.0	0.1	0.736
Systolic Blood Pressure	413	106.5	11.2	106.5	10.2	-0.0	9.1	-0.9	0.8	0.736
Diastolic Blood Pressure	413	66.0	7.9	67.4	7.6	1.4	7.8	0.7	2.2	<0.001

Abbreviations: ATX: atomoxetine; n = number of patients with a baseline and at least one postbaseline measurement;
 SD = standard deviation; Change = endpoint-baseline; C.I. = 95% 2-sided Confidence Interval of Change;
 LCI = Lower bound of 95% C.I.; UCI = Upper bound of 95% C.I.; Baseline: Visit 1-3; Endpoint: Visit 4-14.
^a p-Value is from Wilcoxon signed-rank test
 Source data: RMP.B4ZSLYBB.SASPGM(FSAF2AL2)

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Table LYBB.6. Pharmacodynamic Analysis of ECG Measurements
Corrected QT intervals and Plasma Atomoxetine
Study Period II
B4Z-MC-LYBB

Visit	A	B	Sample Time	Sample Size(n)	Correlation Coefficient between A & B	p-value ^a
8	Atomoxetine plasma Concentration	Change of QTcB	Peak	356	.122	.021
		Change of QTcD		356	.036	.498
		Change of QTcF		356	-0.01	.789
12	Atomoxetine plasma Concentration	Change of QTcB	Peak	273	.137	.024
		Change of QTcD		273	.063	.300
		Change of QTcF		273	.015	.811
		Change of QTcB	Trough	270	.141	.020
		Change in QTcD		270	.063	.299
		Change in QTcF		270	.010	.870

Abbreviations: n=number of patients with a baseline measurement for QT interval and at least one plasma concentration measurement; QTcB = QT Interval Bazett Correction; QTcD = QT Interval Data Correction; QTcF = QT Interval Fridericia Correction.

Baseline: Visit 1-3, Endpoint: Peak (Visit 8 or 12), Trough (Visit 12).

^a p-value is the significance probability of the correlation and is calculated based on a test for nonzero Pearson Correlation Coefficient.

Source data: RMP.B4ZSLYBB.SASPGM(FFFPK)

Summary ID# 5285

Clinical Study Summary: Study B4Z-JE-LYBC

A Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Comparison of Fixed-Dose Ranges of Atomoxetine Hydrochloride in Child Outpatients with Attention-Deficit/Hyperactivity Disorder

Date summary approved by Lilly: 02 August 2007

Brief Summary of Results

The primary objective of this study was to investigate the efficacy of atomoxetine treatment in reducing the severity of attention-deficit/hyperactivity disorder (ADHD) symptoms in Japanese pediatric and adolescent outpatients (6-17 years of age) by testing 3 fixed-dose ranges of atomoxetine (1.8 mg/kg/day, 1.2 mg/kg/day, 0.5 mg/kg/day) compared sequentially with placebo.

The main instrument used to assess efficacy was the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Japanese Version (ADHD RS-IV-J) (DuPaul et al. 1998; Yamazaki et al. 2001), an 18-item scale with 1 item for each of the 18 symptoms contained in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*TM (DSM-IV) diagnosis of ADHD (APA 1994). This scale when used by investigators was designated as the ADHD RS-IV-J:I rating scale. The same scale was also used by the patients' teachers to assess symptoms in the classroom setting; this was designated as the ADHD RS-IV-J:School rating scale. The clinician assessment Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity (CGI-AD/HD-S) was used as another measure of efficacy (Guy 1976; NIMH 1985).

The primary efficacy variable used to evaluate atomoxetine treatment was ADHD RS-IV-J:I/School (Sch) total score, a comprehensive assessment in which the primary efficacy measure, the ADHD RS-IV-J:I rating scale, was administered and scored by the investigator in conjunction with teacher scores on the ADHD RS-IV-J:School rating scale. The ADHD RS-IV-J:I total score, ADHD RS-IV-J:School total score and CGI-ADHD-S assessment were used as secondary efficacy variables.

Secondary objectives included comparing the efficacy of each of the above 3-fixed atomoxetine dose ranges with one another and with placebo, comparing the safety of

these 3 dose ranges with that of placebo, and evaluating the plasma concentration of atomoxetine and its main metabolites with respect to dose and patient ability to metabolize atomoxetine based on their CYP2D6 genotype (i.e., EM: Extensive metabolizers, IM: Intermediate metabolizers, PM: Poor metabolizers).

The main results of this study were as follows:

- Atomoxetine 1.8 mg/kg/day was shown to be statistically significant compared with placebo in ameliorating ADHD symptoms in Japanese pediatric ADHD patients (ADHD RS-IV-J:I/Sch total score: $p=0.010$ /one-sided; ADHD RS-IV-J:I total score: $p=0.008$ /one-sided).
- The low 0.5 mg/kg/day dose and intermediate 1.2 mg/kg/day dose were not found to be statistically significant in ameliorating ADHD symptoms compared with placebo.
- A statistically significant linear dose response in efficacy was seen with increasing atomoxetine dose (ADHD RS-IV-J:I/Sch total score: $p=0.008$; ADHD RS-IV-J:I total score: $p=0.007$; ADHD RS-IV-J:School total score: $p=0.026$).
- Measurement of the secondary efficacy variables ADHD RS-IV-J:School total score and CGI-ADHD-S assessment did not show any statistically significant difference between atomoxetine treatment and placebo.
- Analysis of laboratory analytes did not reveal any pattern of abnormalities associated with atomoxetine administration.
- No deaths occurred during this study.
- Two patients discontinued the study due to adverse events.
- One SAE was reported during the course of the study: hospitalization (twice) due to vomiting and headache. This patient recovered and completed the study.
- The most commonly reported treatment-emergent adverse events (TEAEs; $\geq 10\%$) in all atomoxetine treatment groups were nasopharyngitis (15.8% : 29/183), headache (14.2% : 26/183), and decreased appetite (12% : 22/183).
- Two adverse events above the 5% level in patients given atomoxetine were statistically significant: decreased appetite in 12% (22/183 : $p<0.001$) and vomiting in 8.2% (15/183 : $p=0.022$).
- Statistically significant ($p<0.05$) increases in mean diastolic blood pressure and heart rate (pulse) were observed at all atomoxetine doses. A statistically significant dose response ($p<0.001$) was also observed for diastolic blood pressure and heart rate.

- No statistically significant increases in mean QTc interval (Fridericia, Data Driven corrections) were found for any of the atomoxetine treatment groups. All mean increases seen with these two corrections were below 5 msec. Neither the Fridericia nor the Data Driven correction gave any evidence of an atomoxetine linear dose response in QTc mean change.
- Analysis of categorical changes in QTc interval (Fridericia, Data Driven corrections) detected statistically significant trends in QTc prolongation ≥ 30 msec in 15 (8.2%) patients (Fridericia: $p=0.015$) and 16 (8.7%) patients (Driven Driven: $p=0.034$) from the atomoxetine treatment groups. However, there were no prolongation times longer than 450 msec, and none longer than 60 msec. There were no adverse events or study discontinuations related to QTc interval prolongation.
- There were no study discontinuations and no evidence of differences in tolerability among patients with decreased efficiency to metabolize atomoxetine (IM and PM patients with respect to CYP2D6 genotype).

Title of Study: A Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Comparison of Fixed-Dose Ranges of Atomoxetine Hydrochloride in Child Outpatients with Attention-Deficit/Hyperactivity Disorder	
Investigator(s): This multicenter study included 41 principal investigators.	
Study Center(s): This study was conducted at 41 study centers in one country.	
Length of Study: 1 year 7 months Date first patient enrolled: 22 February 2005 Date last patient completed: 29 September 2006	Phase of Development: 2/3
Objectives: Primary objective: To test the efficacy of atomoxetine treatment in reducing the severity of Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms in Japanese children and adolescents who were at least 6 years of age but less than 18 years of age by testing 1.8, 1.2, and 0.5 mg/kg/day doses of atomoxetine compared sequentially with placebo as measured by the ADHD RS-IV-J:I/Sch total score. Secondary objectives: (1) To compare the safety of 3 fixed-dose ranges of atomoxetine with that of placebo. (2) To assess the relationship between atomoxetine dose and both efficacy and safety. (3) To compare the efficacy of each of 3 fixed doses of atomoxetine with one another and with placebo in children who have not had prior treatment with psychostimulants. (4) To evaluate the plasma concentration of atomoxetine, 4-hydroxyatomoxetine, and <i>N</i>-desmethyldatomoxetine with respect to dose and cytochrome P450 2D6 (CYP2D6) metabolic status.	

(5) To evaluate during the course of the study the teacher's assessment as measured by ADHD RS-IV-J:School total score.	
Study Design:	Randomized, double blind, placebo-controlled study (Figure LYBC.1)
Number of Patients:	
Planned:	240 60 per treatment group (4 groups): placebo atomoxetine 0.5 mg/kg/day atomoxetine 1.2 mg/kg/day atomoxetine 1.8 mg/kg/day
Randomized:	245 placebo 62 atomoxetine 0.5 mg/kg/day: 62 atomoxetine 1.2 mg/kg/day: 60 atomoxetine 1.8 mg/kg/day: 61
Completed:	234 placebo: 61 (173: atomoxetine) atomoxetine 0.5 mg/kg/day: 60 atomoxetine 1.2 mg/kg/day: 57 atomoxetine 1.8 mg/kg/day: 56
Diagnosis and Main Criteria for Inclusion:	Japanese male and female patients who were at least 6 but less than 18 years of age and who met the criteria for ADHD found in the <i>Diagnostic and Statistical Manual of Mental Disorders</i> (APA 1994) and in the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version: Behavioral Disorders Supplement (K-SADS-PL: Behavioral) module (Kaufman et al. 1997).
Study Drug, Dose, and Mode of Administration:	Atomoxetine hydrochloride 4 capsule sizes : 2.5 mg, 5 mg, 10 mg, 20 mg Combination of capsules given orally twice a day to provide target daily dosage based on patient body weight.
Reference Therapy, Dose, and Mode of Administration:	Placebo: Identical in appearance and administration to study drug.
Duration of Treatment:	56 days (planned) 48 – 78 days (allowed)
Variables:	
<u>Efficacy:</u>	Primary: ADHD RS-IV-J:I/Sch total score Secondary: ADHD RS-IV-J:I total score ADHD RS-IV-J:School total score CGI-AD/HD-S (clinician assessment)
<u>Safety:</u>	Adverse events, clinical laboratory tests, vital signs, electrocardiograms
<u>Pharmacokinetic:</u>	Concentrations (atomoxetine and its metabolites: 4-hydroxyatomoxetine, and N-desmethyatomoxetine)

Evaluation Methods:

Statistical: The primary efficacy variable was the change from baseline to last observation carried forward (LOCF) endpoint in the ADHD RS-IV-J:I/Sch total score. ADHD RS-IV-J:I/Sch was defined as the ADHD RS-IV-J:I total score assessed in conjunction with the ADHD RS-IV-J:School total score collected at the same time for a specific visit. For the primary efficacy analysis the Williams' test was performed to compare sequentially 1.8 mg/kg/day, 1.2 mg/kg/day, and 0.5 mg/kg/day doses of atomoxetine with placebo in order to determine the minimum effective dose. Statistical significance was $p < 0.025$ (one-sided William's test). Statistical significance in all other tests was two-sided, $p < 0.05$.

Pharmacokinetic: Blood samples taken with a sparse sampling approach were evaluated by population pharmacokinetics to characterize the pharmacokinetics of atomoxetine, 4-hydroxyatomoxetine, and N-desmethylassatomoxetine. Plasma atomoxetine concentrations together with patient characteristics were evaluated using the nonlinear mixed effects modeling program (NONMEM) and graphical analyses. Pharmacokinetics of 4-hydroxyatomoxetine and N-desmethylassatomoxetine were evaluated using graphical methods only.

Results:

Study Design

Study LYBC comprised two study periods (Figure LYBC.1):

- Study Period I: Screening, Medication Washout, and Assessment
- Study Period II: Randomized, Double-Blind Acute Treatment

Patients who met entry criteria completed an initial washout, screening, and assessment period of 12-35 days (Study Period I). This was then followed by approximately 8 weeks of acute treatment (Study Period II). At the end of this period dosages were abruptly discontinued.

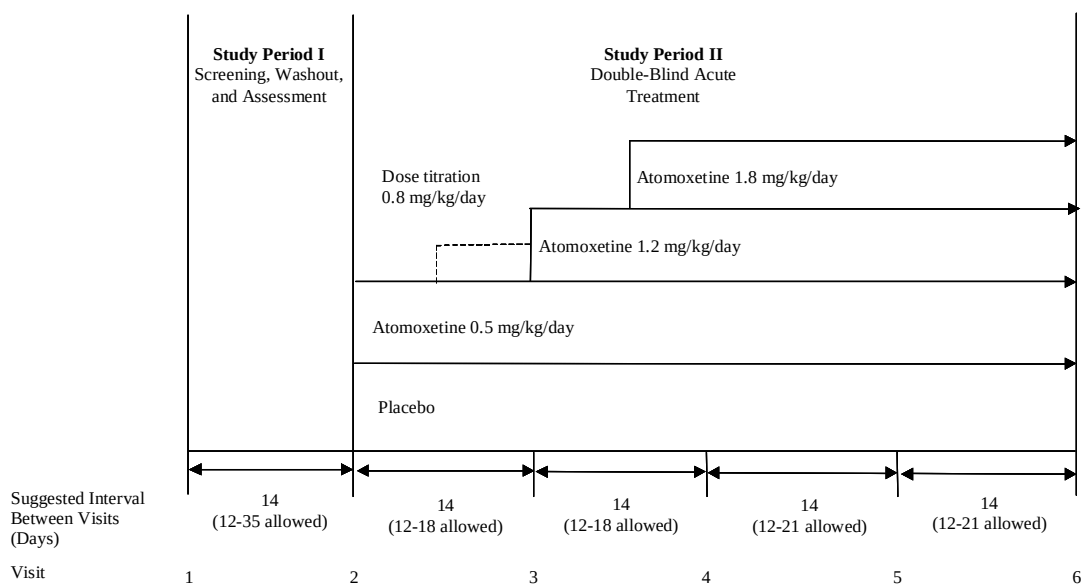


Figure LYBC.1. Study design.

Patient Demographics

Table LYBC.1 shows patient demographics at baseline for the 243 patients in the Full Analysis Set (FAS: see section on Efficacy).

All of the treatment groups were balanced with respect to patient demographics with no major imbalances among treatment groups for any characteristic. Patients ranged from 6 to 17 years of age (mean: 10.53 years). There were 155 (85.6%) males and 26 (14.4%) females in the atomoxetine treatment groups, and of these 181 patients, 100 (55.2%) had prior stimulant use. Two (1.1%) of the patients in the atomoxetine treatment groups were classified as poor metabolizers (PM) with respect to CYP2D6 genotype: 1 patient in the low dose group (atomoxetine 0.5 mg/kg/day) and 1 in the intermediate dose group (atomoxetine 1.2 mg/kg/day). With regards to ADHD subtype, 61.3% (149/243) of the patients were Inattentive, 4.5% (11/243) Hyperactive/Impulsive, and 34.2% (83/243) Mixed.

The severity of disease at baseline for all patients in the Full Analysis Set is summarized in Table LYBC.2. All of the treatment groups were well balanced for each measure of disease severity. No statistically significant difference between groups in mean baseline score was seen for any measure.

In order to better understand the effect of CYP2D6 genotype on the metabolism, efficacy, and safety of atomoxetine, two IM (intermediate metabolizer) patient categories (Category 1, Category 2) based on CYP2D6 allele type were defined as subsets of the EM (extensive metabolizer) patients. The number of EM, IM, and PM patients in each treatment group for the Full Analysis Set is shown in Table LYBC.3 by metabolizer type.

No statistically significant difference was observed between treatment groups with respect to the number of EM / IM / PM patients in each group.

Atomoxetine

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**Table LYBC.1. Patient Demographic Characteristics at Baseline
Full Analysis Set**

		Placebo (N=62)	ATMX 0.5 (N=62)	ATMX 1.2 (N=59)	ATMX 1.8 (N=60)	ATMX all (N=181)	All (N=243)	p-value
Gender	Male	52 (83.9)	52 (83.9)	51 (86.4)	52 (86.7)	155 (85.6)	207 (85.2)	0.953 *
	Female	10 (16.1)	10 (16.1)	8 (13.6)	8 (13.3)	26 (14.4)	36 (14.8)	
Origin	EastAsian	62 (100.0)	62 (100.0)	59 (100.0)	60 (100.0)	181 (100.0)	243 (100.0)	-
Age	No. patients	62	62	59	60	181	243	0.725 **
	Mean	10.76	10.25	10.53	10.58	10.45	10.53	
	SD	2.03	2.57	2.72	2.70	2.65	2.51	
	Min	7.20	6.63	6.50	6.11	6.11	6.11	
	Median	10.59	9.34	9.89	10.87	9.89	10.18	
	Max	15.77	16.21	17.60	17.62	17.62	17.62	
Age:Yrs	6	0 (0.0)	3 (4.8)	2 (3.4)	3 (5.0)	8 (4.4)	8 (3.3)	-
	7	5 (8.1)	9 (14.5)	9 (15.3)	10 (16.7)	28 (15.5)	33 (13.6)	
	8	10 (16.1)	11 (17.7)	8 (13.6)	6 (10.0)	25 (13.8)	35 (14.4)	
	9	8 (12.9)	14 (22.6)	11 (18.6)	5 (8.3)	30 (16.6)	38 (15.6)	
	10	13 (21.0)	3 (4.8)	9 (15.3)	7 (11.7)	19 (10.5)	32 (13.2)	
	11	8 (12.9)	8 (12.9)	3 (5.1)	13 (21.7)	24 (13.3)	32 (13.2)	
	12	8 (12.9)	4 (6.5)	7 (11.9)	6 (10.0)	17 (9.4)	25 (10.3)	
	13	7 (11.3)	2 (3.2)	3 (5.1)	4 (6.7)	9 (5.0)	16 (6.6)	
	14	2 (3.2)	3 (4.8)	3 (5.1)	2 (3.3)	8 (4.4)	10 (4.1)	
	15	1 (1.6)	3 (4.8)	0 (0.0)	1 (1.7)	4 (2.2)	5 (2.1)	
	16	0 (0.0)	2 (3.2)	1 (1.7)	2 (3.3)	5 (2.8)	5 (2.1)	
	17	0 (0.0)	0 (0.0)	3 (5.1)	1 (1.7)	4 (2.2)	4 (1.6)	
CYP2D6	EM	62 (100.0)	61 (98.4)	58 (98.3)	60 (100.0)	179 (98.9)	241 (99.2)	0.616 **
Genotype	PM	0 (0.0)	1 (1.6)	1 (1.7)	0 (0.0)	2 (1.1)	2 (0.8)	

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**Table LYBC.1. Patient Demographic Characteristics at Baseline
Full Analysis Set (Concluded)**

		Placebo (N=62)	ATMX 0.5 (N=62)	ATMX 1.2 (N=59)	ATMX 1.8 (N=60)	ATMX all (N=181)	All (N=243)	p-value
AD/HD Subtype	Inattentive	37 (59.7)	38 (61.3)	35 (59.3)	39 (65.0)	112 (61.9)	149 (61.3)	0.840 **
	Hyp/Imp	1 (1.6)	3 (4.8)	4 (6.8)	3 (5.0)	10 (5.5)	11 (4.5)	
	Mixed	24 (38.7)	21 (33.9)	20 (33.9)	18 (30.0)	59 (32.6)	83 (34.2)	
Prior Stimulant Exposure	Yes	32 (51.6)	34 (54.8)	33 (55.9)	33 (55.0)	100 (55.2)	132 (54.3)	0.966 *
	No	30 (48.4)	28 (45.2)	26 (44.1)	27 (45.0)	81 (44.8)	111 (45.7)	
V1 Height	No.patients	62	62	59	60	181	243	0.822 **
	Mean	139.45	138.00	138.99	140.41	139.12	139.20	
	SD	11.88	14.63	14.63	15.50	14.87	14.15	
	Min	121.40	115.80	114.40	112.70	112.70	112.70	
	Median	137.20	133.35	136.00	139.05	136.50	136.80	
	Max	171.70	169.10	169.40	173.00	173.00	173.00	
V1 Weight	No.patients	62	62	59	60	181	243	0.693 **
	Mean	35.48	34.22	35.58	36.72	35.49	35.49	
	SD	9.73	11.50	11.96	12.51	11.97	11.42	
	Min	22.90	19.80	20.30	18.20	18.20	18.20	
	Median	33.15	29.85	33.10	33.75	32.70	32.70	
	Max	62.00	69.00	68.50	68.30	69.00	69.00	
WISC-III	No.patients	62	61	56	58	175	237	0.939 **
	Mean	100.21	99.34	99.61	100.91	99.95	100.02	
	SD	16.00	12.84	14.97	14.32	13.98	14.50	
	Min	67.00	71.00	67.00	63.00	63.00	63.00	
	Median	100.00	100.00	100.50	100.00	100.00	100.00	
	Max	138.00	122.00	133.00	137.00	137.00	138.00	

*Frequencies are analyzed using Fisher Exact test.

**Means are analyzed using a Type III Sum of Square Analysis of Variance.

Abbreviations: AD/HD = attention deficit/hyperactivity disorder; ATMX = atomoxetine; EM = extensive metabolizer; Hyp/Imp = hyperactive/impulsive; Max = maximum; min = minimum; N = total number of patients; No = number; PM = poor metabolizer; SD = standard deviation; V = visit; WISC-III = Wechsler Intelligence Scale for Children-III; Yrs = years.

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**Table LYBC.2. Severity of Disease at Baseline
Full Analysis Set**

		Placebo (N=62)	ATMX 0.5 (N=62)	ATMX 1.2 (N=59)	ATMX 1.8 (N=60)	ATMX all (N=181)	All (N=243)	p-value*
Baseline	No. Patients	61	62	59	60	181	242	0.798
ADHD RS-IV-J:I/Sch	Mean	32.3	32.3	33.1	31.5	32.3	32.3	
Total score	SD	9.6	8.4	8.9	7.8	8.4	8.7	
	Min	17	16	16	17	16	16	
	Median	31.0	32.0	31.0	30.0	31.0	31.0	
	Max	50	51	52	51	52	52	
Baseline	No. Patients	62	62	59	60	181	243	0.799
ADHD RS-IV-J:I	Mean	32.2	32.3	33.1	31.5	32.3	32.3	
Total score	SD	9.5	8.4	8.9	7.8	8.4	8.7	
	Min	17	16	16	17	16	16	
	Median	31.0	32.0	31.0	30.0	31.0	31.0	
	Max	50	51	52	51	52	52	
Baseline	No. Patients	61	62	59	60	181	242	0.538
ADHD RS-IV-J:School	Mean	20.7	20.3	21.8	18.4	20.1	20.3	
Total score	SD	13.7	12.3	14.2	11.6	12.7	12.9	
	Min	0	0	0	0	0	0	
	Median	19.0	19.0	22.0	19.0	19.0	19.0	
	Max	50	48	54	47	54	54	
Baseline	No. Patients	62	62	59	60	181	243	0.586
CGI-AD/HD-S	Mean	4.8	4.6	4.7	4.6	4.6	4.7	
	SD	0.9	1.0	0.9	0.9	1.0	0.9	
	Min	3	3	3	3	3	3	
	Median	5.0	5.0	5.0	5.0	5.0	5.0	
	Max	6	7	7	7	7	7	

*Means are analyzed using a Type III Sum of Square Analysis of Variance.

Abbreviations: ADHD RS-IV-J:I/Sch = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored/School; ATMX = atomoxetine; CGI-AD/HD-S = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity; Max = maximum; min = minimum; N = total number of patients; No = number; SD = standard deviation.

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**Table LYBC.3. CYP2D6 (EM/IM/PM) at Baseline
Full Analysis Set**

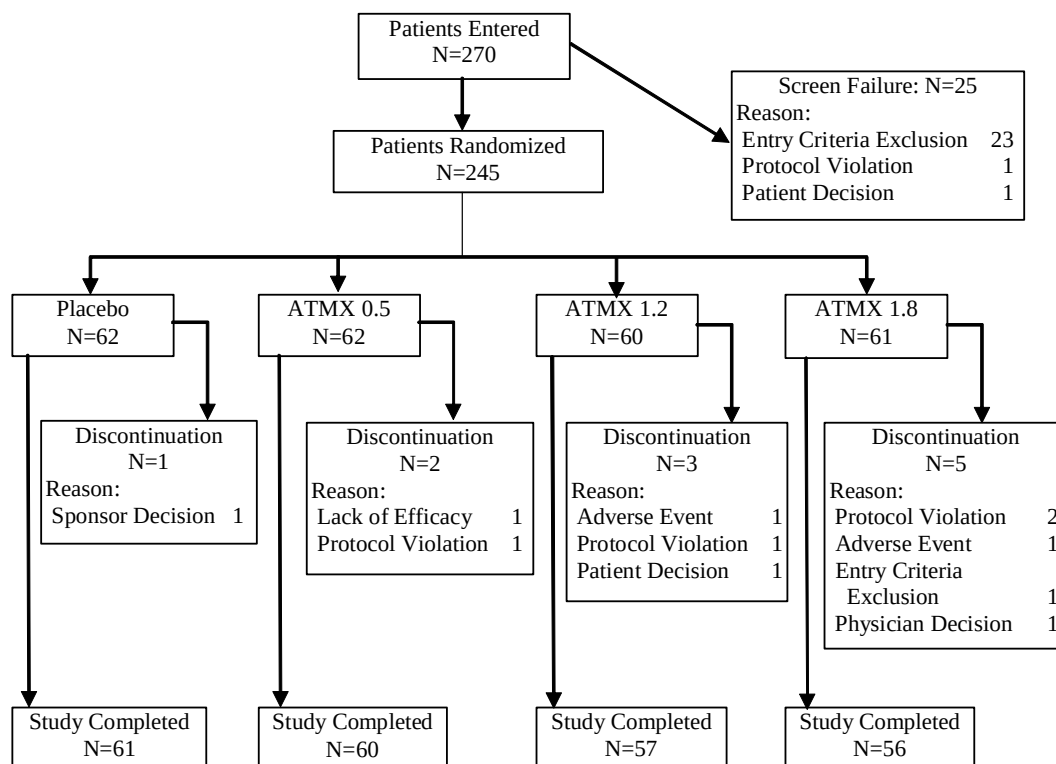
		Placebo (N=62)	ATMX 0.5 (N=62)	ATMX 1.2 (N=59)	ATMX 1.8 (N=60)	ATMX all (N=181)	All (N=243)	p-value
CYP2D6	EM	51 (82.3)	46 (74.2)	44 (74.6)	49 (81.7)	139 (76.8)	190 (78.2)	0.768 *
EM/IM/PM	IM	11 (17.7)	15 (24.2)	14 (23.7)	11 (18.3)	40 (22.1)	51 (21.0)	
Category 1	PM	0 (0.0)	1 (1.6)	1 (1.7)	0 (0.0)	2 (1.1)	2 (0.8)	
CYP2D6	EM	46 (74.2)	42 (67.7)	40 (67.8)	46 (76.7)	128 (70.7)	174 (71.6)	0.782 *
EM/IM/PM	IM	16 (25.8)	19 (30.6)	18 (30.5)	14 (23.3)	51 (28.2)	67 (27.6)	
Category 2	PM	0 (0.0)	1 (1.6)	1 (1.7)	0 (0.0)	2 (1.1)	2 (0.8)	

*Frequencies are analyzed using Fisher Exact test.

Abbreviations: ATMX = atomoxetine; EM = extensive metabolizer; IM = intermediate metabolizer; N = total number of patients; PM = poor metabolizer.

Patient Disposition

An overview of patient disposition is shown in Figure LYBC.2.



Abbreviations: ATMX = atomoxetine; N = total number of patients.

Figure LYBC.2. Patient disposition.

Of the 270 patients who entered the study, 25 failed the initial screening procedures and were discontinued prior to randomization.

Table LYBC.4 shows the percentage of enrolled patients who discontinued from Study Period II for specific reasons. Of the 245 randomized patients, 11 (4.5%) discontinued the study. The single patient who discontinued for lack of efficacy was in the low dose treatment group (atomoxetine 0.5 mg/kg/day). Two patients (0.8%) discontinued the study because of adverse events.

Of the 183 patients in the three atomoxetine treatment groups, 173 (94.5%) completed Study Period II. In the placebo treatment group 61 (98.4%) patients completed Study Period II.

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**Table LYBC.4. Primary Reason for Study Discontinuation
All Randomized Patients**

Reason for Discontinuation	Placebo (N=62)		ATMX 0.5 (N=62)		ATMX 1.2 (N=60)		ATMX 1.8 (N=61)		ATMX all (N=183)		p-value*
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
Patients Completed	61	(98.4)	60	(96.8)	57	(95.0)	56	(91.8)	173	(94.5)	0.314
Adverse event	0	(0.0)	0	(0.0)	1	(1.7)	1	(1.6)	2	(1.1)	0.369
Death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	
Lost to Follow up	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	
Protocol entry exclusion	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.6)	1	(0.5)	0.494
Protocol violation	0	(0.0)	1	(1.6)	1	(1.7)	2	(3.3)	4	(2.2)	0.568
Patient decision/Parent decision	0	(0.0)	0	(0.0)	1	(1.7)	0	(0.0)	1	(0.5)	0.245
Physician decision	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.6)	1	(0.5)	0.494
Sponsor decision	1	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1.000
Lack of efficacy	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	1	(0.5)	1.000

* P-value derived from Fisher Exact test

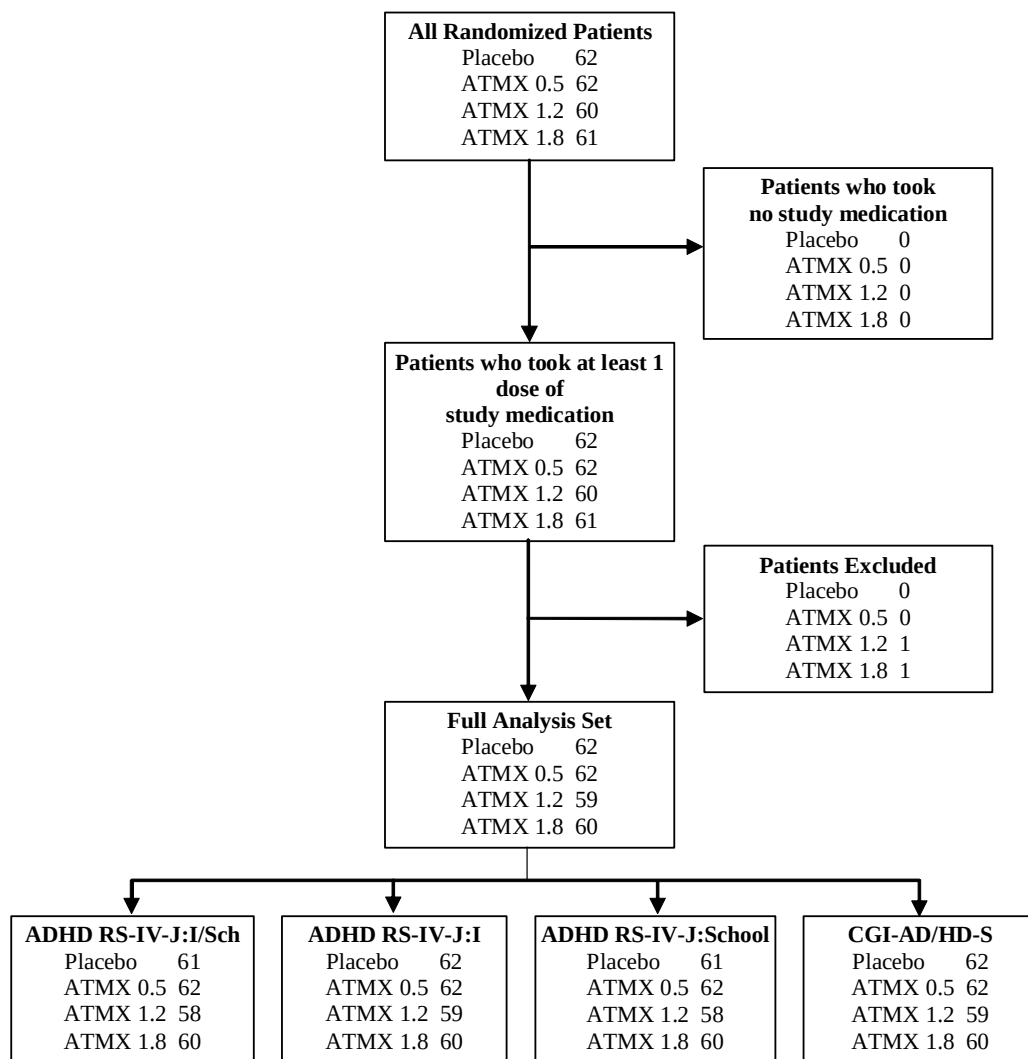
Abbreviations: ATMX = atomoxetine; N = total number of patients.

Efficacy

Datasets analyzed for efficacy are shown in Figure LYBC.3. All efficacy analyses were performed for patients who met the study inclusion criteria, took at least one dose of the study medication, and had a baseline and post-baseline measurement. This set of patients was designated as the Full Analysis Set (FAS).

All randomized patients (245) met the study inclusion criteria, took at least one dose of the study medication (placebo or atomoxetine), and had a baseline and post-baseline measurement. Two of these patients took prohibited drugs prior to the first visit after randomization and were excluded from the efficacy analysis. Thus, 243 patients were included in the efficacy analysis. These patients comprised the Full Analysis Set.

Only ADHD RS-IV-J:I scores that were used to assess patients in conjunction with teacher scores on the ADHD RS-IV-J:School rating scale were included in the primary efficacy analysis. These were designated as ADHD RS-IV-J:I/Sch scores, and only patients with these scores for Visit 2 and at least their final visit (Visit 6, or prior visit LOCF) were included in the ADHD RS-IV-J:I/Sch data set. Two of the 243 patients included in the Full Analysis Set lacked either baseline or post-baseline scores on the ADHD RS-IV-J:School rating scale and were thus excluded from the ADHD RS-IV-J:I/Sch data set. Therefore, 241 patients were included in the primary efficacy analysis (ADHD RS-IV-J:I/Sch data set).



Abbreviations: ADHD RS-IV-J:I/Sch = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored/School; ATMX = atomoxetine; CGI-AD/HD-S = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity.

Figure LYBC.3. Patients included in the efficacy analyses.

Primary Outcome Measure

The primary efficacy variable was the ADHD RS-IV-J:I/Sch total score.

Table LYBC.5 contains the mean baseline, endpoint (LOCF), and change from baseline to endpoint in mean ADHD RS-IV-J:I/Sch total score. Atomoxetine 1.8 mg/kg/day showed a statistically significant overall improvement in mean change of ADHD RS-IV-J:I/Sch total score from baseline to endpoint (-11.6: SD=8.8, p=0.010/one-sided) compared with placebo. There was no statistically significant difference between atomoxetine 1.2 mg/kg/day and placebo. However, decreases from baseline in mean

ADHD RS-IV-J:I/Sch total score did show a statistically significant linear response with increasing atomoxetine dose ($p=0.008$).

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**Table LYBC.5. ADHD RS-IV-J:I/Sch Change from Baseline to LOCF Endpoint
Full Analysis Set**

		Baseline		Endpoint		Change		95%CI**		P-value* Williams	P-value** ANCOVA	
n		Mean	SD	Mean	SD	Mean	SD	Diff**	LCL			UCL
ADHD RS-IV-J:I/Sch : Total score												
Placebo	61	32.3	9.6	24.2	11.4	-8.1	7.1					
ATMX 0.5	62	32.3	8.4	22.7	11.4	-9.6	9.1	-1.5	-4.3	1.3	-	0.280
ATMX 1.2	58	33.3	8.7	22.5	10.3	-10.8	6.8	-2.5	-5.4	0.3	0.037	0.078
ATMX 1.8	60	31.5	7.8	19.8	9.0	-11.6	8.8	-3.7	-6.5	-0.8	0.010	0.011
Dose Response		***		Linear: P = 0.008		Quadratic: P = 0.837						

ADHD RS-IV-J:I/Sch : Inattentive Subscale												
Placebo	61	19.9	3.7	15.2	6.1	-4.7	4.7					
ATMX 0.5	62	19.4	4.1	13.6	6.1	-5.7	5.8	-1.2	-3.0	0.7	-	0.209
ATMX 1.2	58	20.5	4.0	14.1	5.4	-6.3	4.9	-1.4	-3.3	0.4	0.059	0.133
ATMX 1.8	60	20.0	3.8	13.2	5.8	-6.8	5.8	-2.1	-3.9	-0.2	0.019	0.030
Dose Response		***		Linear: P = 0.032		Quadratic: P = 0.676						

ADHD RS-IV-J:I/Sch : Hyperactive/Impulsive Subscale												
Placebo	62	12.3	7.1	8.9	6.7	-3.4	3.3					
ATMX 0.5	62	13.0	6.7	9.1	6.7	-3.9	4.7	-0.4	-1.7	1.0	-	0.599
ATMX 1.2	58	12.9	7.2	8.4	6.3	-4.5	4.0	-1.0	-2.3	0.4	-	0.149
ATMX 1.8	60	11.5	6.0	6.7	4.7	-4.8	4.4	-1.7	-3.0	-0.3	0.033	0.014
Dose Response		***		Linear: P = 0.009		Quadratic: P = 0.731						

N:number of patients who are included in Full Analysis Set.

* P-value(One sided) is derived from Williams test.

** Unadjusted p-value, treatment difference, the confidence interval is derived from pairwise treatment comparison vs Placebo using ANCOVA model.

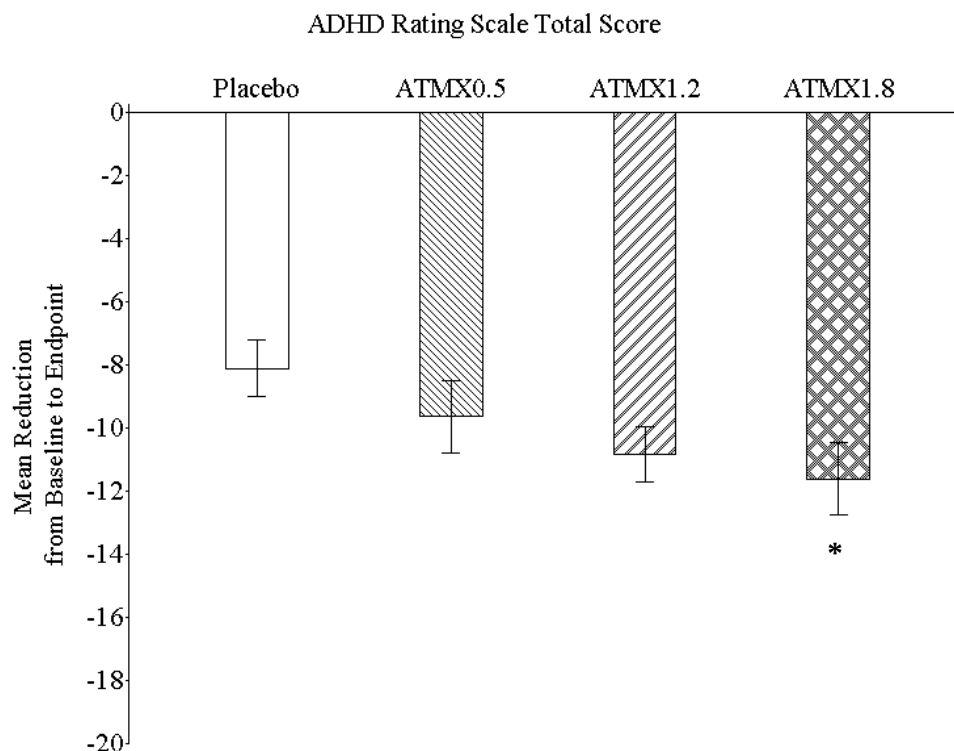
*** Dose Response p-value is derived from then contrasts of the least-square means from ANCOVA model.

ANCOVA model: change = baseline + treatment

Linear Contrast: -3 -1 1 3, Quadratic Contrast: 1 -1 -1 1

Abbreviations: ADHD RS-IV-J:I/Sch = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored/School; ANCOVA = analysis of covariance; ATMX = atomoxetine; CI = confidence interval; Diff = difference; LCL = lower control limit; n = number of patients; SD = standard deviation; UCL = upper control limit.

Figure LYBC.4 shows the mean reduction from baseline to endpoint in ADHD RS-IV-J:I/Sch total score for all treatment groups. The reduction in both the atomoxetine 1.2 mg/kg/day and 1.8 mg/kg/day groups was larger than that of placebo; however only those reductions observed in the 1.8 mg/kg/day group were statistically significant ($p < 0.025$ /one-sided).



Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ATMX = atomoxetine.

* $p < 0.025$.

Figure LYBC.4. Mean reduction from baseline to endpoint in ADHD RS-IV-J:I/Sch Total Scores for all atomoxetine treatment groups in the full analysis set.

Secondary Outcome Measures

The principal secondary efficacy variables were:

- ADHD RS-IV-J:I total score
- ADHD RS-IV-J:School total score
- CGI-AD/HD-S clinician assessment.

In order to better understand the effect of atomoxetine on inattention symptoms compared with hyperactivity-impulsivity symptoms, the following subscale scale scores were also used as secondary efficacy variables:

- ADHD RS-IV-J:I/Sch Inattentive subscale score
- ADHD RS-IV-J:I/Sch Hyperactive/Impulsive subscale score
- ADHD RS-IV-J:I Inattentive subscale score
- ADHD RS-IV-J:I Hyperactive/Impulsive subscale score
- ADHD RS-IV-J:School Inattentive subscale score
- ADHD RS-IV-J:School Hyperactive/Impulsive subscale score

The 18-item ADHD RS-IV-J:I rating scale is designed such that odd-numbered items focus on inattention symptoms and even-numbered items on hyperactivity-impulsive symptoms. Total scores for these specific subsets were used for the above subscale scores.

The following results were obtained for secondary measure outcomes:

- A statistically significant decrease from baseline in mean ADHD RS-IV-J:I/Sch Inattentive subscale score ($p=0.019$ /one-sided) compared with placebo was seen in the atomoxetine 1.8 mg/kg/day group (Table LYBC.5).
- Statistically significant decreases from baseline in both mean ADHD RS-IV-J:I total score ($p=0.008$ /one-sided) and mean ADHD RS-IV-J:I Inattentive subscale score ($p=0.016$ /one-sided) compared with placebo were seen in the atomoxetine 1.8 mg/kg/day group (Table LYBC.6).
- A statistically significant ($p\leq 0.05$) linear dose response with increasing atomoxetine dose was observed for all secondary measure outcomes with the exception of ADHD RS-IV-J:School Hyperactive/Impulsive subscale score and CGI-AD/HD-S clinician assessment (Tables LYBC.5~8).
- No statistically significant differences from baseline were seen in mean ADHD RS-IV-J:School total score, nor were any seen in mean ADHD RS-IV-J:School Inattentive or Hyperactive/Impulsive subscale scores compared with placebo (Table LYBC.7).
- No statistically significant differences were seen in mean CGI-AD/HD-S change from baseline (Table LYBC.8).

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**Table LYBC.6. ADHD RS-IV-J:I Change from Baseline to LOCF Endpoint
Full Analysis Set**

		Baseline		Endpoint		Change		95%CI**		P-value* Williams	P-value** ANCOVA	
n		Mean	SD	Mean	SD	Mean	SD	Diff**	LCL			UCL
ADHD RS-IV-J:I: Total score												
Placebo	62	32.2	9.5	24.2	11.3	-8.0	7.1					
ATMX 0.5	62	32.3	8.4	22.7	11.4	-9.6	9.1	-1.6	-4.4	1.2	-	0.258
ATMX 1.2	59	33.1	8.9	22.1	10.6	-10.9	7.0	-2.8	-5.6	0.1	0.027	0.056
ATMX 1.8	60	31.5	7.8	19.8	9.0	-11.6	8.8	-3.7	-6.6	-0.9	0.008	0.010
Dose Response ***		Linear: P = 0.007				Quadratic: P = 0.756						

ADHD RS-IV-J:I: Inattentive Subscale												
Placebo	62	19.9	3.7	15.3	6.0	-4.6	4.7					
ATMX 0.5	62	19.4	4.1	13.6	6.1	-5.7	5.8	-1.3	-3.1	0.6	-	0.183
ATMX 1.2	59	20.3	4.0	14.0	5.6	-6.4	5.0	-1.6	-3.5	0.3	0.045	0.094
ATMX 1.8	60	20.0	3.8	13.2	5.8	-6.8	5.8	-2.1	-4.0	-0.3	0.016	0.025
Dose Response ***		Linear: P = 0.025				Quadratic: P = 0.593						

ADHD RS-IV-J:I: Hyperactive/Impulsive Subscale												
Placebo	62	12.3	7.1	8.9	6.7	-3.4	3.3					
ATMX 0.5	62	13.0	6.7	9.1	6.7	-3.9	4.7	-0.4	-1.7	1.0	-	0.599
ATMX 1.2	59	12.7	7.3	8.2	6.4	-4.5	4.0	-1.1	-2.4	0.3	-	0.114
ATMX 1.8	60	11.5	6.0	6.7	4.7	-4.8	4.4	-1.7	-3.0	-0.3	0.033	0.014
Dose Response ***		Linear: P = 0.008				Quadratic: P = 0.803						

N:number of patients who are included in Full Analysis Set.

* P-value(One sided) is derived from Williams test.

** Unadjusted p-value, treatment difference, the confidence interval is derived from pairwise treatment comparison vs Placebo using ANCOVA model.

*** Dose Response p-value is derived from then contrasts of the least-square means from ANCOVA model.

ANCOVA model: change = baseline + treatment

Linear Contrast: -3 -1 1 3, Quadratic Contrast: 1 -1 -1 1

Abbreviations: ADHD RS-IV-J:I = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored; ANCOVA = analysis of covariance; ATMX = atomoxetine; CI = confidence interval; Diff = difference; LCL = lower control limit; n = number of patients; SD = standard deviation; UCL = upper control limit.

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**Table LYBC.7. ADHD RS-IV-J:School Change from Baseline to LOCF Endpoint
Full Analysis Set**

		Baseline		Endpoint		Change		95%CI**		P-value*		P-value**
		-----		-----		-----		-----		-----		
	n	Mean	SD	Mean	SD	Mean	SD	Diff**	LCL	UCL	Williams	ANCOVA
ADHD RS-IV-J:School: Total score												
Placebo	61	20.7	13.7	18.6	13.2	-2.2	6.4					
ATMX 0.5	62	20.3	12.3	17.1	12.2	-3.2	7.3	-1.1	-3.5	1.3	-	0.359
ATMX 1.2	58	22.1	14.1	17.7	12.6	-4.4	8.2	-2.0	-4.4	0.5	-	0.119
ATMX 1.8	60	18.4	11.6	14.0	10.8	-4.3	7.5	-2.7	-5.1	-0.2	0.062	0.034
Dose Response ***		Linear: P = 0.026				Quadratic: P = 0.808						

ADHD RS-IV-J:School: Inattentive Subscale												
Placebo	61	12.2	6.9	11.2	7.1	-1.1	4.0					
ATMX 0.5	62	11.7	6.2	10.1	6.5	-1.6	3.9	-0.6	-2.0	0.8	-	0.396
ATMX 1.2	58	12.4	7.0	10.1	6.6	-2.4	4.6	-1.2	-2.7	0.2	-	0.089
ATMX 1.8	60	11.1	6.7	8.6	6.5	-2.5	4.2	-1.6	-3.0	-0.2	0.042	0.026
Dose Response ***		Linear: P = 0.017				Quadratic: P = 0.816						

ADHD RS-IV-J:School: Hyperactive/Impulsive Subscale												
Placebo	62	8.4	7.7	7.3	7.1	-1.1	3.3					
ATMX 0.5	62	8.6	7.2	7.0	6.6	-1.6	4.1	-0.5	-1.8	0.8	-	0.446
ATMX 1.2	58	9.7	8.1	7.6	6.8	-2.1	4.6	-0.7	-2.0	0.6	-	0.322
ATMX 1.8	60	7.3	6.0	5.4	5.5	-1.9	4.1	-1.1	-2.3	0.2	0.145	0.107
Dose Response ***		Linear: P = 0.108				Quadratic: P = 0.922						

N:number of patients who are included in Full Analysis Set.

* P-value(One sided) is derived from Williams test.

** Unadjusted p-value, treatment difference, the confidence interval is derived from pairwise treatment comparison vs Placebo using ANCOVA model.

*** Dose Response p-value is derived from then contrasts of the least-square means from ANCOVA model.

ANCOVA model: change = baseline + treatment

Linear Contrast: -3 -1 1 3, Quadratic Contrast: 1 -1 -1 1

Abbreviations: ADHD RS-IV-J:School = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: School; ANCOVA = analysis of covariance; ATMX = atomoxetine; CI = confidence interval; Diff = difference; LCL = lower control limit; n = number of patients; SD = standard deviation; UCL = upper control limit.

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**Table LYBC.8. CGI-AD/HD-S Change from Baseline to LOCF Endpoint
Full Analysis Set**

		Baseline		Endpoint		Change		95%CI**		P-value*		P-value**
		-----		-----		-----		-----				
n		Mean	SD	Mean	SD	Mean	SD	Diff**	LCL	UCL	Williams	ANCOVA
CGI-AD/HD-S												
Placebo	62	4.8	0.9	4.2	1.1	-0.6	0.8					
ATMX 0.5	62	4.6	1.0	4.0	1.1	-0.6	0.8	-0.1	-0.4	0.2	-	0.562
ATMX 1.2	59	4.7	0.9	4.1	1.1	-0.6	0.8	-0.1	-0.4	0.2	-	0.579
ATMX 1.8	60	4.6	0.9	3.8	0.9	-0.8	1.0	-0.3	-0.6	0.0	0.076	0.047
Dose Response *** Linear: P = 0.060 Quadratic: P = 0.543												

N:number of patients who are included in Full Analysis Set.

* P-value(One sided) is derived from Williams test.

** Unadjusted p-value, treatment difference, the confidence interval is derived from pairwise treatment comparison vs Placebo using ANCOVA model.

*** Dose Response p-value is derived from then contrasts of the least-square means from ANCOVA model.

ANCOVA model: change = baseline + treatment

Linear Contrast: -3 -1 1 3, Quadratic Contrast: 1 -1 -1 1

Abbreviations: ANCOVA = analysis of covariance; ATMX = atomoxetine; CGI-AD/HD-S = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity; CI = confidence interval; Diff = difference; LCL = lower control limit; n = number of patients; SD = standard deviation; UCL = upper control limit.

Safety

Of the 245 patients who entered this study, 183 received at least one dose of atomoxetine. There were no patient deaths. One SAE was reported: hospitalization (twice) due to headache and vomiting. Two patients discontinued the study because of adverse events (affect lability and headache).

Treatment-Emergent Adverse Events

TEAEs were those adverse events that emerged or deteriorated during the study drug administration period. Table LYBC.9 summarizes TEAEs that occurred in at least 5% of patients who took at least one dose of study medication (placebo or atomoxetine).

At least one TEAE was reported for 78.7% (144/183) of the patients given atomoxetine. The most commonly reported events ($\geq 10\%$) in all atomoxetine treatment groups were nasopharyngitis, headache, and decreased appetite. Two adverse events above the 5% level were found to have a statistically significant ($p < 0.05$) relationship to dose: decreased appetite in 12% (22/183 : $p < 0.001$) and vomiting in 8.2% (15/183 : $p = 0.022$) of patients given atomoxetine.

Treatment-Emergent Adverse Drug Reactions (ADRs)

ADRs were those TEAEs indicated by the investigator to be related or possibly related to atomoxetine administration. Table LYBC.10 summarizes ADRs that occurred in at least 5% of patients who took at least one dose of study medication.

At least one ADR was reported for 50.3% (92/183) of the patients given atomoxetine. In these patients the ADR incidence rate was found to have a statistically significant relationship ($p = 0.003$) with increasing atomoxetine dose. The most commonly reported ADRs ($\geq 10\%$) were decreased appetite and headache. Decreased appetite in 11.5% (21/183) of the atomoxetine-treated patients was found to have a statistically significant ($p < 0.001$) dose response.

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**Table LYBC.9. Treatment-Emergent Adverse Events
Experienced By at Least 5% of Patients - MedDRA preferred Term
Patients Who Took at Least 1 Dose of Study Medication**

Event Classification	Placebo	ATMX 0.5	ATMX 1.2	ATMX 1.8	ATMX all	p-value CA Trend Test*
	(N=62) N (%)	(N=62) N (%)	(N=60) N (%)	(N=61) N (%)	(N=183) N (%)	
Patient with ≥ 1 TEAE	43 (69.4)	49 (79.0)	47 (78.3)	48 (78.7)	144 (78.7)	0.284
Patient without TEAE	19 (30.6)	13 (21.0)	13 (21.7)	13 (21.3)	39 (21.3)	
Nasopharyngitis	10 (16.1)	11 (17.7)	7 (11.7)	11 (18.0)	29 (15.8)	0.965
Headache	4 (6.5)	7 (11.3)	10 (16.7)	9 (14.8)	26 (14.2)	0.108
Decreased appetite	2 (3.2)	3 (4.8)	6 (10.0)	13 (21.3)	22 (12.0)	<0.001
Somnolence	4 (6.5)	4 (6.5)	6 (10.0)	8 (13.1)	18 (9.8)	0.142
Nausea	3 (4.8)	4 (6.5)	6 (10.0)	6 (9.8)	16 (8.7)	0.222
Vomiting	0 (0.0)	3 (4.8)	7 (11.7)	5 (8.2)	15 (8.2)	0.022
Abdominal pain	5 (8.1)	5 (8.1)	4 (6.7)	2 (3.3)	11 (6.0)	0.257
Diarrhoea	2 (3.2)	1 (1.6)	6 (10.0)	4 (6.6)	11 (6.0)	0.133

*P-value is derived from Cochran Armitage Trend test.

MedDRA Version 9.1

Abbreviations: ATMX = atomoxetine; N = number of patients; TEAE = treatment-emergent adverse event.

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**Table LYBC.10. Treatment-Emergent Adverse Drug Reactions
Experienced By at Least 5% of Patients - MedDRA preferred Term
Patients Who Took at Least 1 Dose of Study Medication**

Event Classification	Placebo (N=62)	ATMX 0.5 (N=62)	ATMX 1.2 (N=60)	ATMX 1.8 (N=61)	ATMX all (N=183)	p-value CA Trend Test*
	N (%)	N (%)	N (%)	N (%)	N (%)	
Patient with ≥1 ADR	19 (30.6)	25 (40.3)	35 (58.3)	32 (52.5)	92 (50.3)	0.003
Patient without ADR	43 (69.4)	37 (59.7)	25 (41.7)	29 (47.5)	91 (49.7)	
Decreased appetite	2 (3.2)	3 (4.8)	6 (10.0)	12 (19.7)	21 (11.5)	<0.001
Headache	3 (4.8)	5 (8.1)	8 (13.3)	8 (13.1)	21 (11.5)	0.076
Somnolence	3 (4.8)	3 (4.8)	6 (10.0)	8 (13.1)	17 (9.3)	0.051
Nausea	3 (4.8)	4 (6.5)	5 (8.3)	4 (6.6)	13 (7.1)	0.622

*P-value is derived from Cochran Armitage Trend test.

MedDRA Version 9.1

Abbreviations: ADR = adverse drug reaction; ATMX = atomoxetine; N = number of patients.

Serious Adverse Events (SAEs)

One SAE was reported during the course of the study: an 8-year old Japanese male randomized to the atomoxetine 1.8 mg/kg/day group was hospitalized twice due to headache and vomiting. The patient recovered from these events and completed the study.

Study Discontinuations Due to Adverse Events

Two patients discontinued the study because of adverse events: a 10-year-old Japanese male (atomoxetine 1.8 mg/kg/day group; affect lability), and a 14-year-old Japanese female (atomoxetine 1.2 mg/kg/day group; headache).

Clinical Laboratory Values

As determined by the Sponsor, analysis of laboratory analytes did not reveal any pattern of abnormalities associated with atomoxetine administration.

Vital Signs

Mean change from baseline to LOCF endpoint in vital sign measures are shown in Table LYBC.11. There were no study discontinuations related to changes in vital signs.

A statistically significant ($p < 0.05$) increase in mean diastolic blood pressure from baseline to endpoint was observed for all atomoxetine doses. The difference between treatment groups was statistically significant ($p = 0.003$), and the dose-response was found to have a statistically significant ($p < 0.001$) linear component.

A statistically significant linear dose-response ($p = 0.029$) was also observed for mean systolic blood pressure. No statistically significant difference was found between treatment groups.

A statistically significant ($p \leq 0.001$) increase was also observed in mean heart rate (pulse) for all atomoxetine doses. The difference between treatment groups was statistically significant ($p < 0.001$) as was the linearity of the dose response ($p < 0.001$). These results were not unexpected given the pharmacologic action of this drug.

With regards to mean height, a statistically significant dose response was observed with the quadratic contrast from the ANCOVA model ($p = 0.036$). However, there was no statistically significant difference between treatment groups.

Changes in mean weight among treatment groups and the linearity of dose response were both statistically significant ($p < 0.001$). When baseline and endpoint values were compared, statistically significant decreases in weight were seen for both the atomoxetine 1.2 mg/kg/day ($p = 0.002$) and 1.8 mg/kg/day ($p < 0.001$) groups. Dose response was also found to have a statistically significant ($p < 0.001$) linear component.

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Table LYBC.11. Vital Signs
Mean Change from Baseline to LOCF Endpoint
Patients Who Took at Least 1 Dose of Study Medication

			Baseline		Endpoint		Change		p-value	
	Therapy	n	Mean	SD	Mean	SD	Mean	SD	Within*	Between**
Systolic Blood Pressure	Placebo	62	101.63	12.44	102.34	10.94	0.71	13.02	0.669	0.148
	ATMX 0.5	62	103.06	10.27	103.60	11.34	0.53	11.98	0.728	
	ATMX 1.2	60	102.13	10.15	105.70	9.92	3.57	10.16	0.009	
	ATMX 1.8	61	102.20	10.27	105.84	10.02	3.64	12.35	0.025	
	Dose Response*** Linear: P=0.029 Quadratic: P=0.807									
Diastolic Blood Pressure	Placebo	62	57.23	10.22	57.92	8.80	0.69	9.81	0.580	0.003
	ATMX 0.5	62	58.40	9.83	61.21	8.84	2.81	9.81	0.028	
	ATMX 1.2	60	57.73	8.72	61.98	7.52	4.25	9.17	<0.001	
	ATMX 1.8	61	57.93	9.35	63.20	8.79	5.26	10.76	<0.001	
	Dose Response*** Linear: P=<0.001 Quadratic: P=0.388									
Heart Rate(Pulse)	Placebo	62	80.60	11.91	80.97	10.27	0.37	12.10	0.810	<0.001
	ATMX 0.5	62	81.08	12.34	86.10	10.75	5.02	11.55	0.001	
	ATMX 1.2	60	81.43	12.34	89.97	13.98	8.53	16.59	<0.001	
	ATMX 1.8	61	84.00	13.18	92.07	14.60	8.07	13.09	<0.001	
	Dose Response*** Linear: P=<0.001 Quadratic: P=0.181									
Height	Placebo	61	139.65	11.87	140.84	11.92	1.19	0.69	<0.001	0.062
	ATMX 0.5	62	138.00	14.63	138.88	14.47	0.89	0.72	<0.001	
	ATMX 1.2	60	139.39	14.83	140.11	14.92	0.72	1.32	<0.001	
	ATMX 1.8	61	140.13	15.53	141.07	15.66	0.93	0.98	<0.001	
	Dose Response*** Linear: P=0.092 Quadratic: P=0.036									

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Table LYBC.11. Vital Signs
Mean Change from Baseline to LOCF Endpoint
Patients Who Took at Least 1 Dose of Study Medication (Concluded)

			Baseline		Endpoint		Change		p-value	
	Therapy	n	Mean	SD	Mean	SD	Mean	SD	Within*	Between**
Weight	Placebo	62	35.68	9.69	36.59	9.83	0.91	0.97	<0.001	<0.001
	ATMX 0.5	62	34.62	11.56	34.66	11.66	0.05	0.94	0.705	
	ATMX 1.2	60	36.16	12.00	35.62	11.85	-0.53	1.26	0.002	
	ATMX 1.8	61	36.77	12.35	35.99	11.80	-0.78	1.32	<0.001	
		Dose Response***								
		Linear:		P=<0.001		Quadratic:		P=0.026		

N: number of patients who took at least one dose of study medication

* Within p-value is derived from paired t-test.

** Between p-value is derived from ANCOVA.

*** Dose Response p-value is derived from the contrasts of the least-square means from ANCOVA model.

ANCOVA model: change = baseline + treatment

Linear Contrast -3 -1 1 3

Quadratic Contrast 1 -1 -1 1

Abbreviations: ATMX = atomoxetine; n = number of patients; SD = standard deviation.

Table LYBC.12 summarizes the categorical analysis results of changes in blood pressure (systolic and diastolic), heart rate (pulse), and weight for atomoxetine- and placebo-treated patients. For each criterion the percentage of patients meeting the criteria in a treatment-emergent manner (at any Study Period II visit) was computed for each treatment group.

With the exception of systolic and diastolic blood pressure, all trends were statistically significant ($p < 0.05$). Increased heart rate (pulse) was not unexpected due to atomoxetine's noradrenergic mechanism of action.

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Table LYBC.12. Summary of Vital Signs Data
Analysis of Categorical Changes in Blood Pressure, Heart Rate(Pulse) and Weight
Patients Who Took at Least 1 Dose of Study Medication

Criteria.	Placebo (N=62)			ATMX 0.5 (N=62)			ATMX 1.2 (N=60)			ATMX 1.8 (N=61)			ATMX all (N=183)			p-value CA Trend Test*
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	
A	61	3	4.9	60	6	10.0	60	10	16.7	59	11	18.6	179	27	15.1	0.012
B	62	6	9.7	62	10	16.1	60	21	35.0	61	13	21.3	183	44	24.0	0.019
C	61	2	3.3	60	2	3.3	60	5	8.3	59	7	11.9	179	14	7.8	0.030
D	62	0	0.0	62	4	6.5	60	16	26.7	61	20	32.8	183	40	21.9	<0.001
E	62	0	0.0	62	1	1.6	60	0	0.0	61	0	0.0	183	1	0.5	0.755
F	62	4	6.5	62	5	8.1	60	5	8.3	59	6	10.2	181	16	8.8	0.493

Criteria:

A: Maximum heart rate (Pulse) Visits 3-6 of ≥ 110 bpm

B: Change to Maximum Heart rate (Pulse) of ≥ 25 bpm

C: A and B

D: Weight Loss from baseline to endpoint of $\geq 3.5\%$

E: Sitting Max. Systolic BP of $\geq$ Hypertension Assessment Criteria

F: Sitting Max. Diastolic BP of $\geq$ Hypertension Assessment Criteria

*p-value is derived from Cochran Armitage Trend test.

Abbreviations: ATMX = atomoxetine; N = number of patients; n = number of patients meeting the criteria; TEAE = treatment-emergent adverse event.

Electrocardiograms

Summaries of the mean change from baseline to LOCF endpoint in electrocardiogram (ECG) intervals and heart rate are shown in Table LYBC.13.

Mean increases in heart rate were observed for all atomoxetine treatment groups compared with placebo. These leveled off at atomoxetine 1.2 mg/kg/day, but all increases were statistically significant ($p < 0.05$). Differences between treatment groups were also statistically significant ($p < 0.001$).

Relative to placebo, all doses of atomoxetine were also associated with mean decreases in QT interval. On the other hand, the Bazett correction for QT interval, showed a statistically significant ($p < 0.05$) prolongation of the mean QTc interval for each atomoxetine treatment group.

However, for drugs associated with increased heart rate, the Bazett correction is known to over-correct for heart rate effects. In this case the Fridericia or Data Driven correction is more appropriate. Analyses of the ECG results using the Fridericia correction showed a mean decrease in QT interval for the atomoxetine 1.2 mg/kg/day and 1.8 mg/kg/day groups. A 2.07 msec prolongation was still seen in the atomoxetine 0.5 mg/kg/day group, but this was less than half of that seen with the Bazett correction. Data driven correction resulted in mean increases of QTc interval for all atomoxetine treatment groups, but none of the observed increases were found to be statistically significant, either with the Data Driven or Fridericia correction. All mean increases seen with either of these two QT interval corrections were below 5 msec. Also, unlike the Bazett correction, neither the Fridericia nor the Data Driven correction gave any evidence of a statistically significant linear dose response.

Table LYBC.14 summarizes categorical changes in QTc intervals using Food and Drug Administration (FDA) criteria. Even though statistically significant trends were observed for criterion D (increase from baseline ≥ 30 msec) for both the Fridericia ($p = 0.015$) and Data Driven ($p = 0.034$) corrected QTc intervals, no cases were reported for a QTc interval > 450 msec (criteria A, B, C), nor were any cases reported for a QTc increase from baseline ≥ 60 msec (criteria E). The number of patients in the atomoxetine treatment groups with QTc prolongation between 30 msec and 60 msec seen with both correction methods were: Fridericia (8.2% : 15/183), Data Driven (8.7% : 16/183).

No serious adverse events due to QTc interval prolongation were reported during the study.

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Table LYBC.13. Electrocardiograms
Mean Change from Baseline to LOCF Endpoint
Patients Who Took at Least 1 Dose of Study Medication

			Baseline		Endpoint		Change		p-value	
	Therapy	n	Mean	SD	Mean	SD	Mean	SD	Within*	Between**
Heart Rate	Placebo	62	73.60	11.16	72.56	10.34	-1.03	10.65	0.448	<0.001
	ATMX 0.5	62	77.82	13.53	81.47	13.16	3.65	11.97	0.020	
	ATMX 1.2	60	75.08	11.10	87.02	13.14	11.93	13.13	<0.001	
	ATMX 1.8	61	74.95	11.58	86.25	14.61	11.30	11.79	<0.001	
	Dose Response*** Linear: P=<0.001 Quadratic: P=0.011									
RR Interval	Placebo	62	833.26	123.47	841.78	108.29	8.52	112.20	0.552	<0.001
	ATMX 0.5	62	793.00	132.62	754.66	116.34	-38.35	110.93	0.008	
	ATMX 1.2	60	816.97	125.11	705.97	112.63	-111.00	129.66	<0.001	
	ATMX 1.8	61	819.98	131.04	715.46	122.09	-104.52	118.99	<0.001	
	Dose Response*** Linear: P=<0.001 Quadratic: P=0.003									
PR Interval	Placebo	62	144.98	26.28	146.82	22.13	1.84	19.29	0.456	0.822
	ATMX 0.5	62	146.95	17.86	146.85	20.46	-0.10	14.98	0.960	
	ATMX 1.2	60	147.30	19.96	146.23	19.64	-1.07	15.28	0.591	
	ATMX 1.8	61	141.10	15.23	142.16	14.34	1.07	12.74	0.516	
	Dose Response*** Linear: P=0.375 Quadratic: P=0.732									

Atomoxetine

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Table LYBC.13. Electrocardiograms
Mean Change from Baseline to LOCF Endpoint
Patients Who Took at Least 1 Dose of Study Medication (Continued)

			Baseline		Endpoint		Change		p-value	
	Therapy	n	Mean	SD	Mean	SD	Mean	SD	Within*	Between**
QRS Interval	Placebo	62	87.37	8.91	87.05	8.64	-0.32	4.53	0.577	0.472
	ATMX 0.5	62	86.47	7.43	87.00	8.01	0.53	4.79	0.385	
	ATMX 1.2	60	86.02	6.85	87.22	6.22	1.20	4.98	0.067	
	ATMX 1.8	61	86.84	9.02	87.79	7.82	0.95	6.07	0.226	
	Dose Response*** Linear: P=0.142 Quadratic: P=0.574									
QT Interval	Placebo	62	370.39	25.22	371.53	24.60	1.15	20.63	0.664	<0.001
	ATMX 0.5	62	359.05	26.46	355.10	23.23	-3.95	19.65	0.118	
	ATMX 1.2	60	365.28	26.85	346.75	23.10	-18.53	23.74	<0.001	
	ATMX 1.8	61	365.02	23.52	348.54	25.66	-16.48	23.51	<0.001	
	Dose Response*** Linear: P=<0.001 Quadratic: P=0.017									
Corrected QT Interval (Bazett)	Placebo	62	407.47	18.68	406.29	16.97	-1.18	18.93	0.626	0.010
	ATMX 0.5	62	405.29	21.71	410.94	21.96	5.65	20.00	0.030	
	ATMX 1.2	60	406.07	20.56	415.02	21.15	8.95	22.47	0.003	
	ATMX 1.8	61	405.44	21.07	414.33	18.90	8.89	20.32	0.001	
Dose Response*** Linear: P=0.002 Quadratic: P=0.173										

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Table LYBC.13. Electrocardiograms
Mean Change from Baseline to LOCF Endpoint
Patients Who Took at Least 1 Dose of Study Medication (Concluded)

		Baseline			Endpoint		Change		p-value	
	Therapy	n	Mean	SD	Mean	SD	Mean	SD	Within*	Between**
Corrected QT Interval (Fridericia)	Placebo	62	394.46	16.38	394.08	15.88	-0.38	14.83	0.841	0.786
	ATMX 0.5	62	389.07	18.00	391.14	17.35	2.07	14.78	0.275	
	ATMX 1.2	60	391.63	18.48	390.50	16.83	-1.13	17.16	0.613	
	ATMX 1.8	61	391.13	16.66	390.80	15.58	-0.33	16.79	0.878	
	Dose Response***									
	Linear:			P=0.401		Quadratic:		P=0.851		
Corrected QT Interval (Data Driven)	Placebo	62	398.80	16.53	398.13	15.71	-0.67	15.75	0.737	0.868
	ATMX 0.5	62	394.54	18.52	397.73	18.27	3.19	15.99	0.122	
	ATMX 1.2	60	396.39	18.62	398.58	17.70	2.19	18.31	0.359	
	ATMX 1.8	61	395.86	17.54	398.60	15.81	2.74	17.34	0.221	
	Dose Response***									
	Linear:			P=0.482		Quadratic:		P=0.693		

N: number of patients who took at least one dose of study medication

* Within p-value is derived from paired t-test.

** Between p-value is derived from ANCOVA.

*** Dose Response p-value is derived from the contrasts of the least-square means from ANCOVA model.

ANCOVA model: change = baseline + treatment

Linear Contrast -3 -1 1 3

Quadratic Contrast 1 -1 -1 1

Abbreviations: ATMX = atomoxetine; n = number of patients; SD = standard deviation.

Atomoxetine

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Table LYBC.14. Summary of ECG Data
Analysis of Categorical Changes in QTc Using FDA Criteria
Patients Who Took at Least 1 Dose of Study Medication

		Placebo (N=62)			ATMX 0.5 (N=62)			ATMX 1.2 (N=60)			ATMX 1.8 (N=61)			ATMX all (N=183)			p-value CA Trend Test*
Criteria		N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	
Corrected	A	62	0	0.0	62	0	0.0	59	0	0.0	61	0	0.0	182	0	0.0	0.015
QT Interval	B	62	0	0.0	62	0	0.0	60	0	0.0	61	0	0.0	183	0	0.0	
(Fridericia)	C	62	0	0.0	62	0	0.0	60	0	0.0	61	0	0.0	183	0	0.0	
	D	62	2	3.2	62	2	3.2	60	5	8.3	61	8	13.1	183	15	8.2	
	E	62	0	0.0	62	0	0.0	60	0	0.0	61	0	0.0	183	0	0.0	
Corrected	A	62	0	0.0	62	0	0.0	59	0	0.0	61	0	0.0	182	0	0.0	0.034
QT Interval	B	62	0	0.0	62	0	0.0	59	0	0.0	61	0	0.0	182	0	0.0	
(Data Driven)	C	62	0	0.0	62	0	0.0	60	0	0.0	61	0	0.0	183	0	0.0	
	D	62	3	4.8	62	2	3.2	60	6	10.0	61	8	13.1	183	16	8.7	
	E	62	0	0.0	62	0	0.0	60	0	0.0	61	0	0.0	183	0	0.0	

N: Number of patients who did not meet the criterion at baseline

n: Number of patients who met the criterion at postbaseline

* p-value is derived from Cochran Armitage Trend test.

Criteria:

A: QTc interval of > 450 msec

B: QTc interval of > 480 msec

C: QTc interval of > 500 msec

D: QTc interval increases from baseline >= 30 msec

E: QTc interval increases from baseline >= 60 msec

Abbreviations: ATMX = atomoxetine; N = number of patients; n = number of patients meeting the criteria.

Corrected QT intervals (Fridericia, Data Driven) summarized by CYP2D6 metabolic status for EM and PM patients are shown in Table LYBC.15. Analyses of corrected QT intervals (Fridericia, Data Driven) for EM and IM patients (Categories 1, 2) are shown in Tables LYBC.16~17.

No statistically significant trends in mean changes of QTc interval (Fridericia, Data Driven) were observed in either EM or IM (Categories 1, 2) patients with increasing dose, nor was any relationship found between CYP2D6 metabolic status and QTc prolongation when EM and IM patients were compared.

There were no discontinuations due to adverse events, and no evidence of statistically significant differences in atomoxetine tolerability from EM patients among the subgroup of patients with a CYP2D6 genotype consistent with decreased efficiency to metabolize atomoxetine (IM and PM patients).

Atomoxetine

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**Table LYBC.15. Corrected QT interval by Subgroup(CYP2D6 EM/PM)
Mean Change from Baseline to LOCF Endpoint
Patients Who Took at Least 1 Dose of Study Medication**

			Baseline		Endpoint		Change				95%CI**		
CYP2D6				-----	-----	-----	-----	-----					
EM/PM			n	Mean	SD	Mean	SD	Mean	SD	Diff	LCL	UCL	p-value*
Corrected QT Interval (Fridericia)	EM	Placebo	62	394.46	16.38	394.08	15.88	-0.38	14.83				
		ATMX 0.5	61	389.37	18.00	391.26	17.46	1.90	14.84	-0.13	-5.02	4.77	0.959
		ATMX 1.2	59	392.06	18.34	390.73	16.88	-1.33	17.24	-2.08	-7.00	2.84	0.405
		ATMX 1.8	61	391.13	16.66	390.80	15.58	-0.33	16.79	-1.52	-6.41	3.36	0.539

	PM	Placebo	0										
		ATMX 0.5	1	371.03		383.51		12.47					
		ATMX 1.2	1	366.35		377.00		10.65					
		ATMX 1.8	0										

P-value for Subgroup effect: **													0.929
P-value for Subgroup * therapy interaction: **													0.915
Corrected QT Interval (Data Driven)	EM	Placebo	62	398.80	16.53	398.13	15.71	-0.67	15.75				
		ATMX 0.5	61	394.91	18.43	397.85	18.39	2.94	16.00	1.68	-3.46	6.83	0.520
		ATMX 1.2	59	396.85	18.44	398.82	17.75	1.97	18.39	1.68	-3.50	6.85	0.524
		ATMX 1.8	61	395.86	17.54	398.60	15.81	2.74	17.34	1.95	-3.18	7.09	0.454

	PM	Placebo	0										
		ATMX 0.5	1	371.72		390.09		18.36					
		ATMX 1.2	1	369.56		384.26		14.69					
		ATMX 1.8	0										

P-value for Subgroup effect: **													0.883
P-value for Subgroup * therapy interaction: **													0.818

N:number of patients who took at least 1 dose of medication

* P-value is derived from ANCOVA model.

Model: Change = baseline + treatment

** P-value of subgroup effect and subgroup*treatment interaction are derived from ANCOVA model.

Model: Change = baseline + treatment + subgroup + subgroup*treatment interaction

Abbreviations: ATMX = atomoxetine; CI = confidence interval; Diff = difference; EM = extensive metabolizer; LCL = lower control limit; n = number of patients; PM = poor metabolizer; SD = standard deviation; UCL = upper control limit.

Atomoxetine

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**Table LYBC.16. Corrected QT interval by Subgroup(CYP2D6 EM/IM :Category 1)
Mean Change from Baseline to LOCF Endpoint
Patients Who Took at Least 1 Dose of Study Medication**

	CYP2D6 EM/IM ***		n	Baseline		Endpoint		Change		Diff	95%CI**		p-value*
				Mean	SD	Mean	SD	Mean	SD		LCL	UCL	
Corrected QT Interval (Fridericia)	EM	Placebo	51	393.57	16.46	392.84	16.13	-0.73	15.08				
		ATMX 0.5	46	389.81	17.57	392.20	16.87	2.39	14.56	1.41	-4.10	6.92	0.614
		ATMX 1.2	45	393.22	19.48	390.01	17.85	-3.21	17.56	-2.64	-8.16	2.88	0.347
		ATMX 1.8	50	390.58	16.80	392.08	15.94	1.51	16.01	0.88	-4.51	6.26	0.748
	IM	Placebo	11	398.56	16.09	399.82	13.87	1.26	14.20				
		ATMX 0.5	15	388.01	19.83	388.41	19.50	0.40	16.12	-6.43	-17.46	4.59	0.246
		ATMX 1.2	14	388.31	14.00	393.06	13.58	4.75	15.16	-1.93	-13.10	9.24	0.730
		ATMX 1.8	11	393.64	16.60	384.95	12.88	-8.69	18.48	-12.55	-24.15	-0.94	0.035
	P-value for Subgroup effect: **												0.853
	P-value for Subgroup * therapy interaction: **												0.076
Corrected QT Interval (Data Driven)	EM	Placebo	51	397.92	16.55	397.08	16.13	-0.84	16.24				
		ATMX 0.5	46	395.06	18.45	399.01	17.83	3.95	15.57	3.43	-2.36	9.23	0.244
		ATMX 1.2	45	397.62	19.43	397.63	18.82	0.02	18.48	0.71	-5.11	6.53	0.810
		ATMX 1.8	50	395.36	17.52	399.51	16.16	4.15	16.60	3.77	-1.90	9.45	0.191
	IM	Placebo	11	402.87	16.59	402.96	13.16	0.09	13.93				
		ATMX 0.5	15	394.46	19.03	394.29	20.25	-0.16	17.45	-5.12	-16.67	6.44	0.377
		ATMX 1.2	14	394.37	15.17	402.64	13.64	8.27	17.25	3.26	-8.46	14.99	0.578
		ATMX 1.8	11	398.11	18.34	394.47	14.02	-3.64	19.97	-6.48	-18.76	5.79	0.293
	P-value for Subgroup effect: **												0.929
	P-value for Subgroup * therapy interaction: **												0.134

N:number of patients who took at least 1 dose of medication

* P-value is derived from ANCOVA model.

Model: Change = baseline + treatment

** P-value of subgroup effect and subgroup*treatment interaction are derived from ANCOVA model.

Model: Change = baseline + treatment + subgroup + subgroup*treatment interaction

*** PM patients are excluded in the analysis

Abbreviations: ATMX = atomoxetine; CI = confidence interval; Diff = difference; EM = extensive metabolizer; IM = intermediate metabolizer; LCL = lower control limit; n = number of patients; SD = standard deviation; UCL = upper control limit.

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Table LYBC.17. Corrected QT interval by Subgroup(CYP2D6 EM/IM :Category 2)
Mean Change from Baseline to LOCF Endpoint
Patients Who Took at Least 1 Dose of Study Medication

	CYP2D6 EM/IM ***		n	Baseline		Endpoint		Change		Diff	95%CI**		p-value*
				Mean	SD	Mean	SD	Mean	SD		LCL	UCL	
Corrected QT Interval (Fridericia)	EM	Placebo	46	393.99	17.00	392.59	16.82	-1.41	15.46				
		ATMX 0.5	42	389.65	18.02	391.82	17.11	2.17	14.66	1.58	-4.23	7.40	0.592
		ATMX 1.2	41	390.91	14.65	388.27	16.54	-2.64	17.12	-2.65	-8.49	3.19	0.371
		ATMX 1.8	47	390.14	17.13	391.25	15.34	1.12	15.60	0.76	-4.89	6.40	0.792
	IM	Placebo	16	395.80	14.87	398.38	12.23	2.57	12.82				
		ATMX 0.5	19	388.74	18.41	390.04	18.65	1.30	15.63	-4.87	-14.16	4.41	0.298
		ATMX 1.2	18	394.67	25.14	396.35	16.72	1.68	17.62	-1.47	-10.79	7.85	0.753
		ATMX 1.8	14	394.46	15.10	389.27	16.87	-5.19	20.16	-8.45	-18.38	1.48	0.094
	P-value for Subgroup effect: **												0.496
	P-value for Subgroup * therapy interaction: **												0.208
Corrected QT Interval (Data Driven)	EM	Placebo	46	398.41	16.97	396.71	16.66	-1.70	16.39				
		ATMX 0.5	42	394.86	19.01	398.73	18.00	3.87	15.82	3.82	-2.20	9.84	0.212
		ATMX 1.2	41	395.73	15.05	395.73	17.02	0.01	18.25	0.38	-5.67	6.44	0.901
		ATMX 1.8	47	395.05	18.01	398.72	15.20	3.67	15.98	3.71	-2.14	9.57	0.212
	IM	Placebo	16	399.92	15.68	402.20	12.10	2.28	13.79				
		ATMX 0.5	19	395.03	17.58	395.90	19.60	0.87	16.64	-3.94	-14.00	6.11	0.436
		ATMX 1.2	18	399.40	24.84	405.86	17.81	6.46	18.44	3.90	-6.23	14.04	0.444
		ATMX 1.8	14	398.55	16.19	398.18	18.32	-0.37	21.68	-3.36	-14.16	7.44	0.536
	P-value for Subgroup effect: **												0.346
	P-value for Subgroup * therapy interaction: **												0.153

N:number of patients who took at least 1 dose of medication

* P-value is derived from ANCOVA model.

Model: Change = baseline + treatment

** P-value of subgroup effect and subgroup*treatment interaction are derived from ANCOVA model.

Model: Change = baseline + treatment + subgroup + subgroup*treatment interaction

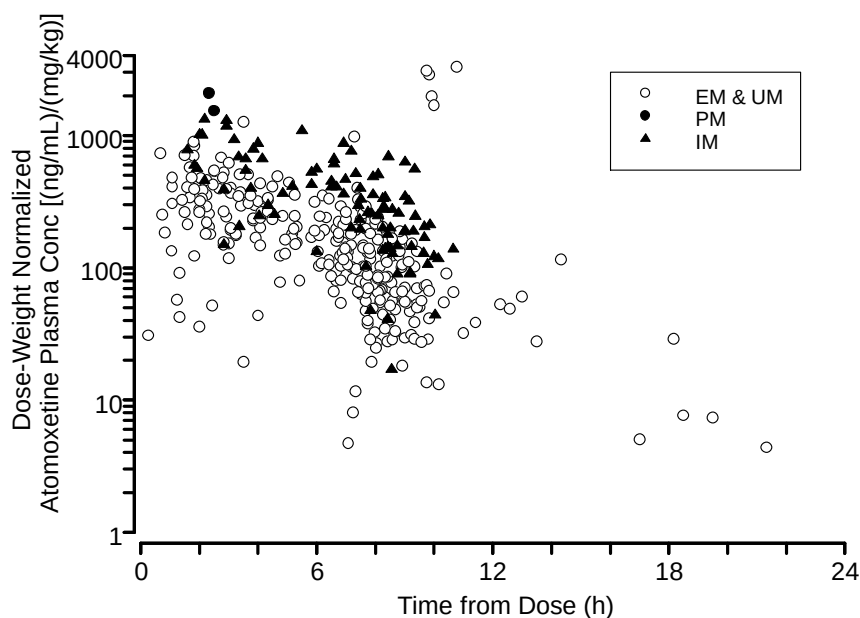
*** PM patients are excluded in the analysis

Abbreviations: ATMX = atomoxetine; CI = confidence interval; Diff = difference; EM = extensive metabolizer; IM = intermediate metabolizer; LCL = lower control limit; n = number of patients; SD = standard deviation; UCL = upper control limit.

Pharmacokinetic Outcomes

Body weight and CYP2D6 EM sub-class (heterozygous EM, homozygous EM or IM) exhibited a statistically significant ($p < 0.001$) effect on atomoxetine clearance. Mean atomoxetine apparent clearance (CL/F) increased with body weight, and was lower in IMs compared with other EMs. No other demographic or patient factors were found to have a statistically significant effect on atomoxetine pharmacokinetics.

The distribution of dose-weight normalized atomoxetine concentrations and individual predicted atomoxetine CL/F overlapped between homozygous EMs, heterozygous EMs, and IMs. Although some IMs exhibited atomoxetine CL/F towards the lower end of the distribution of other EMs, no EM subcategory was uniquely different from the other in terms of atomoxetine PK. In contrast, the decrease in CL/F was statistically significant ($p < 0.001$) in PMs (Figure LYBC.5).



Abbreviations: Conc = concentration; EM = extensive metabolizer; h = hour; IM = intermediate metabolizer; PM = poor metabolizer; UM = ultra-rapid metabolizer.

Figure LYBC.5. Observed dose-weight normalized atomoxetine concentrations stratified by CYP2D6 genotype.

The plot shows a few EM observations from two patients that were atypically high (5 upper open circles at ~10 hours). Initially the genotype data on these patients indicated that they were EMs, however because of their atypically high dose-weight normalized concentrations their respective genotypes were reanalyzed. Results indicated that these two patients actually had genotypes consistent with PMs. The concentration data on these patients was excluded from the Population Pharmacokinetic Analysis.

Two metabolites of atomoxetine, *N*-desmethylatomoxetine and 4-hydroxyatomoxetine, were evaluated graphically. These results are shown in Figure LYBC.6 and, as with the observed concentration evaluations of atomoxetine shown in Figure LYBC.5, include observations from PMs and the two excluded patients.

As shown in the upper panel, the *N*-desmethylatomoxetine dose-weight normalized concentrations showed a large overlap between various genotype subgroups, and as with atomoxetine, some IMs were at the higher end of the distribution of other EMs. Furthermore, PMs exhibited dose-weight normalized concentrations that were higher than other genotypes.

In case of the 4-hydroxyatomoxetine metabolite (lower panel), dose-weight normalized concentrations were much lower than those observed for atomoxetine. There were also no overt differences in dose-weight normalized 4-hydroxyatomoxetine concentrations between the various genotype subgroups.

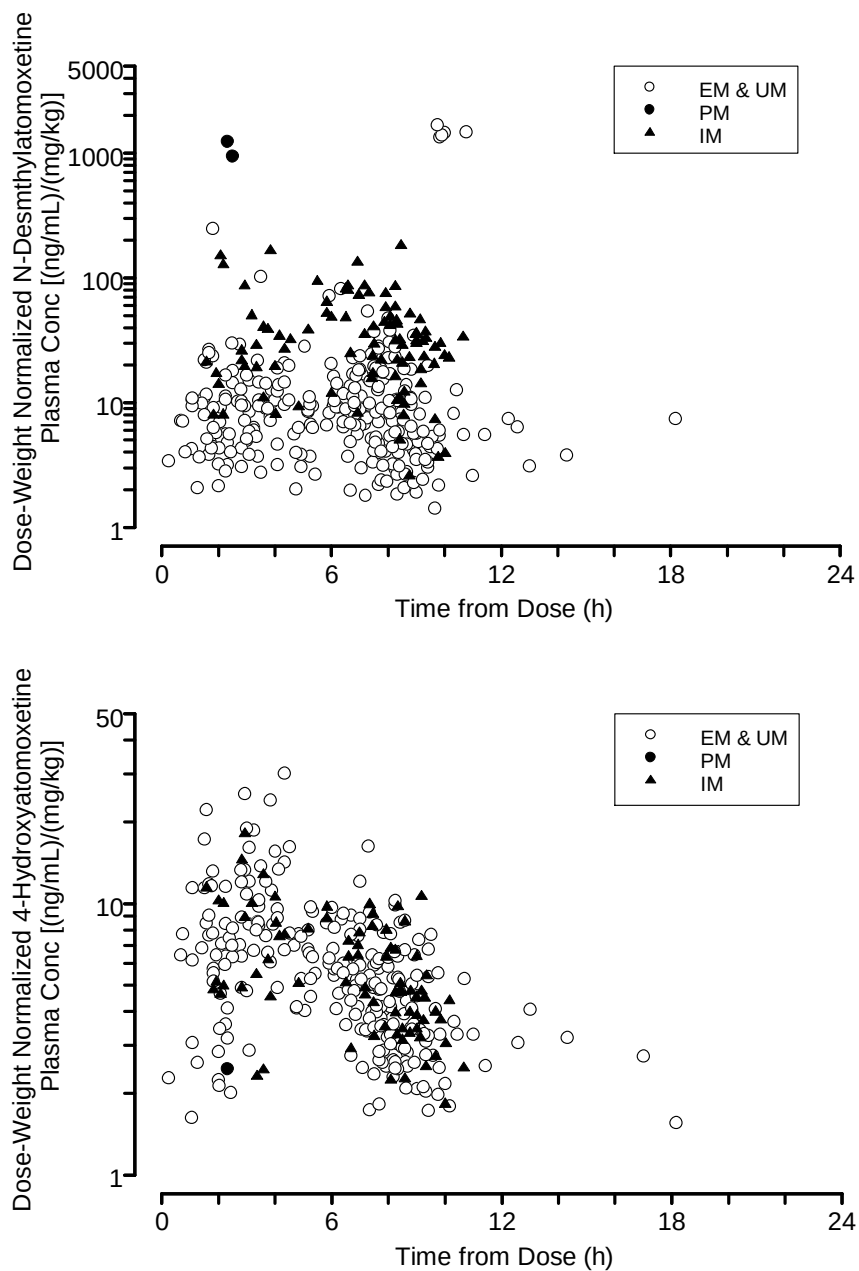


Figure LYBC.6.

Observed dose-weight normalized *N*-desmethylatomoxetine and 4-hydroxyatomoxetine concentrations stratified by CYP2D6 status.

References

- [APA] American Psychiatric Association. 1994. Attention-deficit and disruptive behavior disorders. In: Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association. p.78-85.
- DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. 1998. Reliability and validity. In: ADHD Rating Scale-IV. Checklists, norms, and clinical interpretations. New York, NY: Guilford Press. p. 28-42.
- Guy W. 1976. ECDEU assessment manual for psychopharmacology, revised. Bethesda (MD): U.S. Department of Health, Education, and Welfare.
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. 1997. Schedule for affective disorders and schizophrenia for school-age-children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 36(7):980-988.
- [NIMH] National Institutes of Mental Health. 1985. Psychopharmacology Bulletin 21:839-943.
- Yamazaki K, Kimura T, Koishi S, Asakura A, Ohya A, Hayashida H, et al. 2001. Preparation of the ADHD Rating Scale-IV Japanese Version and its discriminative capability. Normative data of ADHDRS-IV: Japanese Version (Preparation of the diagnostic and treatment guideline for ADHD based on empirical research: research for psychiatric and neurological disorders funded by Ministry of Health and Welfare in 2001).

Summary ID# 5286

Clinical Study Summary: Study B4Z-JE-LYBD

An Open Label, Dose-Titration Safety Study of Atomoxetine Hydrochloride in Outpatient Japanese Children with Attention-Deficit/Hyperactivity Disorder

Date summary approved by Lilly: 27 July 2006

Brief Summary of Results

The primary objective of Study B4Z-JE-LYBD (LYBD) was to assess whether treatment with 1.8 mg/kg/day of LY139603 (hereafter referred to as atomoxetine) would be safe and tolerable in a population of Japanese pediatric attention deficit/hyperactivity disorder (ADHD) patients aged 6 through 18 years. The secondary objectives of the study were to investigate the symptom scores in the attention-deficit/hyperactivity disorder rating scale-IV-parent version (investigator administered and scored, translated and validated in Japanese [ADHDRS-IV-J:I] at baseline) with atomoxetine therapy, and to evaluate the plasma concentration of atomoxetine, 4-hydroxyatomoxetine, and N-desmethylatomoxetine. The results were as follows:

- There were no deaths or serious adverse events (SAEs) in this study. The total rate of discontinuations due to adverse events (AEs) was 8.1%. Two patients (5.4%) discontinued the study due to “headache” and 1 patient (2.7%) discontinued due to “vomiting.”
- Statistically significant mean changes were observed for laboratory values including: hemoglobin ($p=.011$), erythrocyte count ($p=.022$), urinalysis—specific gravity ($p=.038$), aspartate transaminase ($p<.001$), alanine transaminase ($p=.009$), creatine phosphokinase ($p<0.001$), alkaline phosphatase ($p=.003$), thyroxine

(total-T4) ($p=.002$), urea nitrogen ($p=.015$), chloride ($p=.042$), and total protein ($p=.009$).

- An analysis of vital signs showed statistically significant changes in pulse, height, and weight (all $p<.01$).
- Electrocardiogram (ECG) analysis showed statistically significant mean changes for: heart rate ($p<.001$), RR interval ($p<.001$), QRS interval ($p<.001$), QT Bazett correction ($p<.001$), and QT data correction ($p=.026$). Statistically significant mean changes were not observed for QT Fridericia correction.
- Patients showed statistically significant improvements from baseline to endpoint on the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored. For the ADHDRS-IV-J:I Total score, the mean change in last observation carried forward (LOCF) from baseline to endpoint was a reduction of 18.6; for the hyperactivity-impulsivity subscale, the mean change in LOCF from baseline to endpoint was a reduction of 8.1; and for the inattention subscale, the mean change in LOCF from baseline to endpoint was a reduction of 10.5 ($p<.001$ for all three). The Clinical Global Impressions–Attention-Deficit/Hyperactivity Disorder–Severity (CGI-ADHD-S), showed the mean change in LOCF from baseline to endpoint was a reduction of 1.9 ($p<.001$).
- According to the LOCF at endpoint for the percentage-of-responder analyses, 83.3% of patients met the response criterion for ADHDRS-IV-J:I, and 25% met the response criterion for CGI-ADHD-S.

Title of Study: An Open Label, Dose Titration Safety Study of Atomoxetine Hydrochloride in Outpatient Japanese Children with Attention-Deficit/Hyperactivity Disorder	
Investigator(s): This multicenter study included 21 principal investigators.	
Study Center(s): This study was conducted at 19 study centers. (There was 1 principal investigator at each site, but the chief investigators at 2 sites changed during the course of the study; hence, the 21 principal investigators.)	
Length of Study: 7 months Date of first patient enrolled (first patient visit): 07 April 2003 Date of last patient completed: 20 October 2003	Phase of Development: 2
Objectives: The primary objective of this study was to assess whether treatment with 1.8 mg/kg/day of atomoxetine was safe and tolerable in a population of Japanese pediatric ADHD patients aged 6 through 18 years. The secondary objectives of the study were as follows: • To investigate the symptom scores in the ADHDRS-IV-J:I at baseline and with atomoxetine therapy • To evaluate the plasma concentration of atomoxetine, 4-hydroxyatomoxetine, and N-desmethyldatomoxetine.	
Study Design: This was an open-label, forced titration study through increasing doses to a maximum target dose (low dose 0.5 mg/kg/day up to a maximum target dose 1.8 mg/kg/day). The total daily dose for each patient was administered as a divided dose on a twice-daily dosing schedule. The study consisted of 2 study periods, an entry/screening phase (Study Period I, Visit 1 and Visit 2) and an open-label treatment	

phase (Study Period II, Visit 3 through Visit 6 [see Figure LYBD. 1]).
Number of Patients: Planned: 30 Enrolled: 37 Completed: 32
Main Criteria for Inclusion: Eligible participants were male and female Japanese pediatric outpatients, at least 6 years of age and less than 18 years of age at the time of entry, who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition™ (DSM-IV™) and the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children - Present and Lifetime Version: Behavioral Disorders Supplement (K-SADS-PL: Behavioral) module criteria for ADHD.
Study Drug, Dose, and Mode of Administration: Atomoxetine hydrochloride 0.5 mg/kg/day to 1.8 mg/kg/day, given orally, twice daily as a split dose in 2.5, 5, 10, or 20 mg capsules.
Reference Therapy, Dose, and Mode of Administration: No reference therapy was used in this study.
Duration of Treatment: 8 weeks
Variables: <u>Efficacy:</u> ADHDRS-IV-J:I, CGI-ADHD-S <u>Safety:</u> AEs, laboratory tests, vital signs, body weight, height, ECG test <u>Pharmacokinetic:</u> Concentrations (atomoxetine and its metabolites).

Evaluation Methods:

Statistical: In general, all statistical analyses, both efficacy and safety included all patients who met entry criteria, took at least 1 dose of study medication, and had a baseline and postbaseline measurement. This set of patients is referred to as the full analysis set (FAS). If not otherwise stated, all statistical tests were performed using a 2-sided, 0.05 significance level. Dropouts and missing data were accounted for using a LOCF approach, wherein the last value obtained from a patient prior to their early discontinuation of the study is carried forward through the end of the study. However, additional data may have been excluded from the efficacy analysis in the following cases:

- If a patient did not discontinue this study after taking excluded drug(s), the data after that date were excluded from all efficacy analyses.
- If a patient did not discontinue this study after having 2 visits of noncompliance, the data after the second noncompliant visit were excluded from all efficacy analyses.

For both the ADHDRS-IV-J:I Total score and the CGI-ADHD-S score, changes from baseline to endpoint during Study Period II were computed using the LOCF approach and the results were summarized.

Baseline was defined as the last nonmissing measurement obtained on or prior to Visit 2 (end of Study Period I). Endpoint score was defined as the last nonmissing measurement obtained after Visit 2 (end of Study Period I) but on or prior to Visit 6 (end of Study Period II). For each of these efficacy measures, a Wilcoxon signed-rank test was used to assess whether the change was significantly different from zero. Additionally, changes from baseline in the ADHDRS-IV-J:I Total score and CGI-ADHD-S were summarized for each visit from Visit 3 through Visit 6 using only observed data.

In addition to the above, the percentage of patients responding to treatment was calculated. Two methods were used to define treatment response:

- [1] ADHDRS-IV-J:I Total score decrease of $\geq 25\%$ from baseline.
- [2] CGI-ADHD-S score of 1 or 2 at endpoint.

Adverse events (AEs) occurring for the first time after the first dose of the study drug up to the last observation point were analyzed. To contribute to the analysis of AEs, an event must have either occurred for the first time in the study during the treatment period or occurred during the treatment period at a greater severity than during baseline.

Changes from baseline to endpoint scores for laboratory data, vital signs, and ECG intervals were computed. QT corrections were done using several methods. Treatment changes were assessed with paired t-tests or the Wilcoxon signed-rank test. Treatment-emergent out-of-range laboratory values were assessed in a similar fashion as treatment-emergent adverse events (TEAEs). Categorical analyses of changes in ECG intervals and vital signs were also performed and analyzed.

Pharmacokinetic/Pharmacodynamic: A single blood sample for determination of atomoxetine plasma concentration was collected at the final visit for all patients. In addition, blood samples for atomoxetine concentration determination may also have been drawn from patients with an SAE or a clinically significant overdose. If a patient was found to have severe neurologic signs or symptoms at any visit following the initiation of therapy, a blood sample for plasma concentration analysis had to be drawn following the procedures that were required to be completed:

- The date and time of the previous medication dose should have been recorded.
- The exact date and time that a blood sample was drawn should have been recorded on the laboratory test requisition form.

Results:

Study Design

Figure LYBD.1 illustrates the study design for Study LYBD.

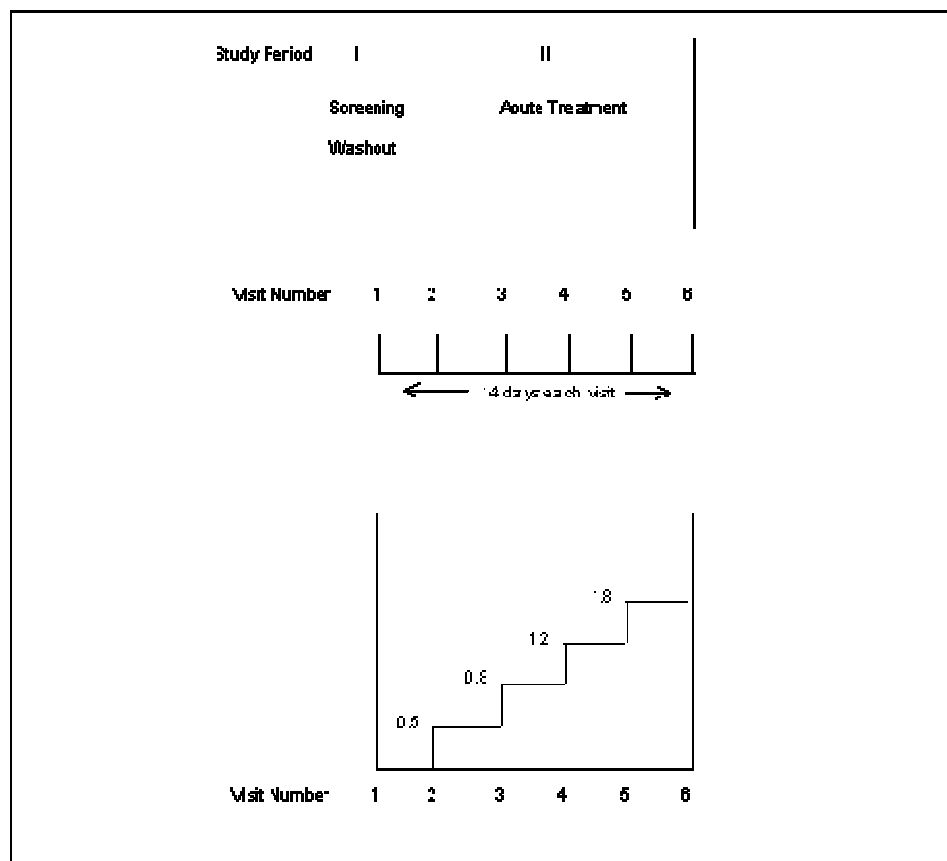


Figure LYBD.1. Study design.

Patient Demographics

Table LYBD.1 summarizes the patient demographics and other baseline characteristics for Study LYBD. Of the 37 enrolled patients, 100% were East/Southeast Asian, 86.5% were male and 13.5% were female. The mean age was 10.19 years (range 6.21 years to 16.82 years). Prior stimulant exposure was noted in 51.4% of the patients. One hundred percent of the patients were determined to be cytochrome P450 2D6 (CYP2D6) extensive metabolizer (EM) patients. (For the pharmacokinetic analysis, 2 patients were classified as ultra-rapid metabolizer (UM) patients; for all other analyses, these UM patients were included in the EM group.) The most common ADHD subtype diagnosis was the predominantly inattentive subtype (62.2%), followed by the combined ADHD subtype (35.1%), and the hyperactive-impulsive subtype (2.7%).

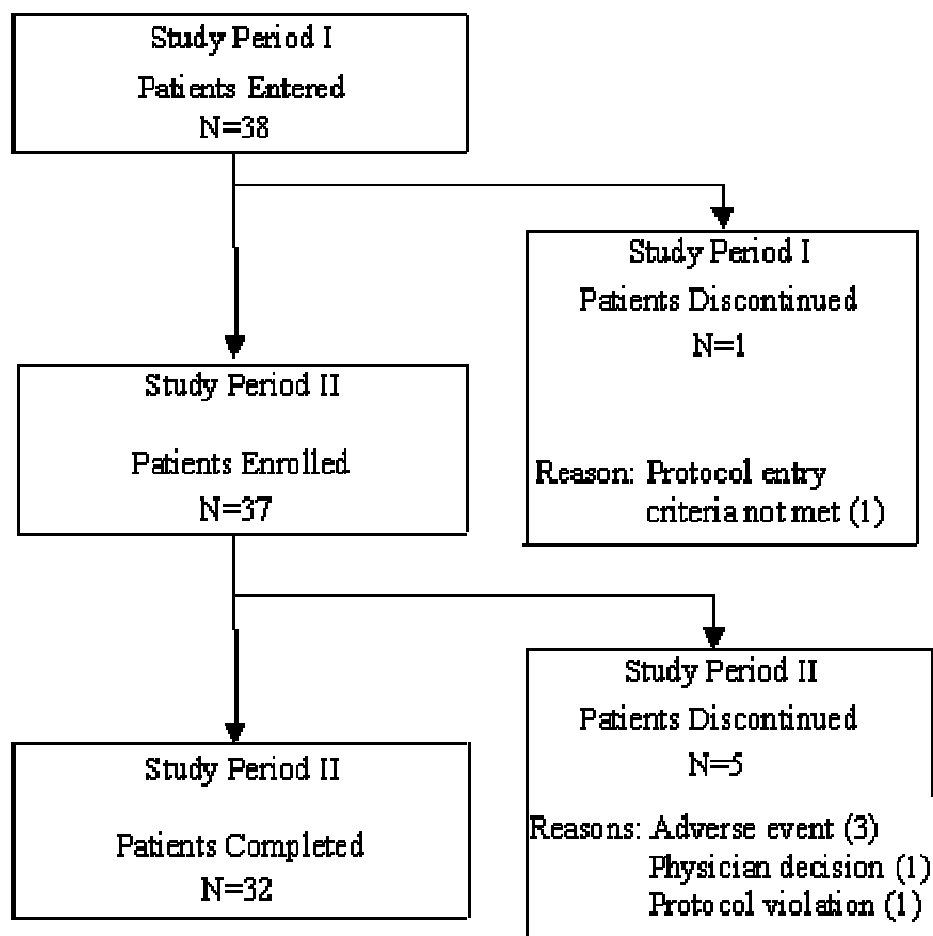
Table LYBD.1. Summary of Demographics and Other Patient Characteristics

Variable	Atomoxetine (N=37)	Variable	Atomoxetine (N=37)
Sex: No. (%)		CYP2D6	
No. Patients	37	No. Patients	37
Female	5 (13.5)	EXTN	37 (100)
Male	32 (86.5)		
Origin: No. (%)		DSM-IV ADHD Subtype	
No. Patients	37	No. Patients	37
East/Southeast A	37 (100)	HYP/IMP	1 (2.7)
		INATTV	23 (62.2)
		MIXED	13 (35.1)
Age: yrs.		Prior Stimulant Exposure	
No. Patients	37	No. Patients	37
Mean	10.19	N	18 (48.6)
Median	10.21	Y	19 (51.4)
Standard Dev.	2.78		
Minimum	6.21	WISC full scale IQ	
Maximum	16.82	No. Patients	35
Height: cm		Mean	98.00
No. Patients	37	Median	96.00
Mean	138.64	Standard Dev.	15.29
Median	135.50	Minimum	72.00
Standard Dev.	16.18	Maximum	137.00
Minimum	112.00		
Maximum	167.80		
Weight: kg			
No. Patients	37		
Mean	36.21		
Median	31.50		
Standard Dev.	14.10		
Minimum	18.40		
Maximum	74.60		

Population: Full Analysis Set
Initial Visit ONLY

Patient Disposition

This study consisted of 2 study periods: an entry/screening phase (Study Period I, Visit 1 and Visit 2) and an open-label treatment phase (Study Period II, Visit 3 through Visit 6). Figure LYBD.2 shows the patient disposition.



Abbreviations: N = number.

Figure LYBD.2. Patient disposition.

Thirty-eight patients entered the study and 1 patient discontinued prior to receiving atomoxetine because the patient did not meet protocol criteria. Of the 37 patients who were enrolled in the study, 5 patients discontinued during Study Period II. Three patients discontinued due to AEs, 1 due to physician decision, and 1 due to a protocol violation. The AEs leading to discontinuation were headache (2 patients) and vomiting (1 patient). The physician decision for discontinuation was due to the inability to determine safety and efficacy information from a patient's mother, and the protocol violation leading to discontinuation was due to patient noncompliance. Thirty-two patients completed the study.

Primary Endpoint – Safety

The primary objective of this study is to assess whether treatment with 1.8 mg/kg/day of atomoxetine will be safe and tolerable in a population of Japanese pediatric ADHD patients aged 6 through 18 years. The safety evaluation included an analysis of AE data,

and contains the analyses of changes in laboratory measurements, vital sign measurements, and ECG data. Treatment-emergent adverse events (TEAEs) and treatment-emergent abnormal laboratory values were assessed.

Adverse Events

No deaths or SAEs were reported during the study. In this study, 33 patients (89.2%) given atomoxetine reported at least 1 TEAE. The most commonly reported AEs ($\geq 10\%$) were: abdominal pain, constipation, diarrhea, nasopharyngitis, decrease in weight, decrease in appetite, anorexia, headache, and somnolence. Table LYBD.2 summarizes the TEAEs of $\geq 5\%$. The rate of discontinuations due to AEs was 8.1%. Two patients (5.4%) discontinued the study due to “headache” and 1 patient (2.7%) discontinued due to “vomiting.”

Table LYBD.2. Summary of Treatment-Emergent Adverse Events with $\geq 5\%$ Incidence - Full Analysis Set

Preferred Term	n (N = 37)	%
Tachycardia	2	5.4
Nausea	2	5.4
Vomiting	2	5.4
Pyrexia	2	5.4
Arthralgia	2	5.4
Insomnia	2	5.4
Cough	2	5.4
Rash	2	5.4
Stomatitis	3	8.1
Malaise	3	8.1
Pharyngitis	3	8.1
Upper respiratory tract inflammation	3	8.1
Diarrhoea	4	10.8
Constipation	5	13.5
Nasopharyngitis	5	13.5
Weight decreased	5	13.5
Somnolence	5	13.5
Anorexia	6	16.2
Abdominal pain	7	18.9
Decreased appetite	8	21.6
Headache	8	21.6
Patients with one or more TESS	33	89.2
Patients with NO TESS	4	10.8

Population: Full Analysis Set

Baseline: Visits 1-2, Endpoint: Visits 3 - 6

TESS: Treatment Emergent Signs and Symptoms

Laboratory Values

Table LYBD.3 summarizes mean changes from baseline to endpoint for each laboratory analyte. Statistically significant mean changes were observed for laboratory values including: hemoglobin ($p=.011$), erythrocyte count ($p=.022$), urinalysis—specific gravity ($p=.038$), aspartate transaminase ($p<.001$), alanine transaminase ($p=.009$), creatine phosphokinase ($p<.001$), alkaline phosphatase ($p=.003$), thyroxine (total-T4) ($p=.002$), urea nitrogen ($p=.015$), chloride ($p=.042$), and total protein ($p=.009$).

Table LYBD.4 shows the percentage of patients with treatment-emergent abnormally high or low analyte values. For a given analyte value to be considered treatment-

emergent abnormally high, it must occur after treatment with atomoxetine has started and the corresponding analyte value should not have been high at baseline. Likewise, low values seen after dosing will only be counted if the corresponding value at baseline was not low.

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Table LYBD.3. Summary of Laboratory Data (CN)
Mean Change from Baseline to Endpoint by Analyte -
Full Analysis Set

Lab Test	Lab Unit	N	Baseline		Change		p-value	
			Mean	SD	Mean	SD	increased	decreased
HEMATOCRIT	%	36	40.578	2.625	0.578	2.234	0.138	----
HEMOGLOBIN	g/dl	36	13.519	0.910	0.289	0.660	0.011	----
ERYTHROCYTE COUNT	E4/mm3	36	474.389	30.586	10.333	24.333	0.022	----
LEUKOCYTE COUNT	CELLS/UL	36	6881.11	2302.40	-477.50	1834.53	----	0.254
NEUTROPHILS	%	36	45.611	8.865	0.028	11.572	0.835	----
LYMPHOCYTES	%	36	43.167	8.178	0.472	10.405	0.748	----
MONOCYTES	%	36	6.222	1.869	-0.500	2.535	----	0.267
EOSINOPHILS	%	36	4.306	3.846	-0.056	2.888	----	0.813
BASOPHILS	%	36	0.694	0.786	0.028	1.108	0.890	----
MEAN CELL VOLUME (MCV)	fL	36	85.667	3.726	-0.583	1.918	----	0.072
PLATELET COUNT	E4/mm3	36	29.008	5.586	0.792	4.783	0.482	----
UA-SPECIFIC GRAVITY	NO UNITS	36	1.024	0.008	0.003	0.008	0.038	----
AST/SGOT	U/L	36	27.500	7.640	-2.444	4.669	----	<0.001
ALT/SGPT	U/L	36	20.778	17.833	-3.889	10.482	----	0.009
CREATINE PHOSPHOKINASE	U/L	36	175.250	92.878	-32.333	60.631	----	<0.001
ALKALINE PHOSPHATASE	U/L	36	837.556	273.598	-55.972	132.162	----	0.003
GGT (GGPT/SGGT/YGGT)	U/L	36	17.000	10.094	-0.972	4.306	----	0.294
THYROXINE, TOTAL-T4	ug/dl	36	7.933	1.587	0.611	1.091	0.002	----
THYROID STIM. HORMONE	uIU/ml	36	1.792	0.880	-0.164	0.595	----	0.127
UREA NITROGEN	mg/dl	36	14.900	3.950	-1.311	3.558	----	0.015
CREATININE	mg/dl	36	0.642	0.118	0.000	0.086	----	----
CALCIUM	mg/dl	36	9.603	0.392	0.108	0.442	0.189	----
INORGANIC PHOSPHORUS	mg/dl	36	4.850	0.584	0.008	0.541	0.916	----
SODIUM	mEq/L	36	140.111	1.410	-0.028	1.812	----	0.890
POTASSIUM	mEq/L	36	4.186	0.297	-0.056	0.397	----	0.426
CHLORIDE	mEq/L	36	102.694	1.546	-0.694	2.136	----	0.042
TOTAL PROTEIN	g/dl	36	7.081	0.304	0.183	0.389	0.009	----
ALBUMIN	g/dl	36	4.414	0.295	0.047	0.226	0.239	----
GLUCOSE, FASTING	mg/dl	36	84.944	12.574	-1.750	17.087	----	0.465
URIC ACID	mg/dl	36	4.536	1.333	-0.106	0.684	----	0.132
CHOLESTEROL	mg/dl	36	169.444	32.575	-1.361	17.383	----	0.636
BILIRUBIN, TOTAL	mg/dl	36	0.506	0.370	0.014	0.188	0.432	----

Abbreviations: N = number of patients with a baseline and at least one post baseline measurement.
SD = standard deviation, p Value is from Wilcoxon signed rank test
Change = endpoint - baseline, Baseline: Visit 1-2, Endpoint: Visit 3-6

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**Table LYBD.4. Summary of Laboratory (CN) Data
Frequency of Patients with Abnormal Laboratory Values with Treatment-Emergent Adverse Event (TEAE) Option - Full Analysis Set**

Lab Test	Incidence Group	ATOMOXETINE (Total=37)			Lab Test	Incidence Group	ATOMOXETINE (Total=37)		
		N	n	(%)			N	n	(%)
HEMATOCRIT	HIGH	36	5	(13.9)	UA-WBC	ABNORMAL	34	3	(8.8)
HEMOGLOBIN	HIGH	36	5	(13.9)	UA-PROTEIN	ABNORMAL	36	1	(2.8)
ERYTHROCYTE COUNT	HIGH	36	1	(2.8)	AST/SGOT	HIGH	32	1	(3.1)
LEUKOCYTE COUNT	LOW	34	1	(2.9)	ALT/SGPT	HIGH	31	4	(12.9)
NEUTROPHILS	LOW	19	7	(36.8)	UREA NITROGEN	HIGH	32	1	(3.1)
	HIGH	29	3	(10.3)	INORGANIC PHOSPHORUS	HIGH	33	1	(3.0)
LYMPHOCYTES	LOW	33	4	(12.1)	CHLORIDE	LOW	36	3	(8.3)
	HIGH	22	7	(31.8)	TOTAL PROTEIN	HIGH	36	2	(5.6)
MONOCYTES	LOW	34	4	(11.8)	URIC ACID	LOW	34	1	(2.9)
	HIGH	31	1	(3.2)	BILIRUBIN, TOTAL	HIGH	34	1	(2.9)
EOSINOPHILS	LOW	26	3	(11.5)	CREATININE	HIGH	36	1	(2.8)
	HIGH	24	2	(8.3)	GLUCOSE, FASTING	LOW	34	1	(2.9)
MEAN CELL VOLUME	LOW	36	2	(5.6)		HIGH	32	4	(12.5)
UA-SPECIFIC GRAVITY	HIGH	26	7	(26.9)					

Population: Full Analysis Set

Baseline: Visits 1-2, Endpoint: Visits 3 - 6

Total = Total number of patients in the treatment group having both baseline and endpoint visits.

N = Total number of at risk patients with the lab test.

n = Total number of at risk patients with the specific lab result (e.g. HIGH).

Vital Signs

Vital signs were examined to determine if treatment with atomoxetine was associated with changes in heart rate (pulse) or blood pressure. The following analyses were performed:

- analyses of mean change from baseline to endpoint
- categorical analyses of change in each variable.

Table LYBD.5 summarizes the mean change from baseline to endpoint in vital sign measures. There were statistically significant changes in pulse, height, and weight (all $p < .001$). Table LYBD.6 summarizes the categorical changes in heart rate (pulse) and weight for atomoxetine-treated patients, and Table LYBD.7 summarizes the categorical changes in blood pressure for atomoxetine-treated patients. The criteria for the analysis of blood pressure were obtained from the Guidelines for the Management of Hypertension (Japan Society of Hypertension 2000). Five patients (13.5%) exhibited high diastolic blood pressure, and 1 patient (2.70%) exhibited high systolic pressure.

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**Table LYBD.5. Summary of Vital Sign Data
Change from Baseline to Endpoint -
Full Analysis Set**

Treatment		n	Baseline			Endpoint			Change					p-Value*
			Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	LCI	UCI	
ATMX														
Pulse		37	81.9	80.0	12.2	92.3	90.0	14.5	10.4	12.0	14.1	5.8	14.9	<0.001
Height		37	138.6	135.5	16.2	139.8	136.7	16.2	1.2	1.0	0.8	0.9	1.5	<0.001
Weight		37	36.6	33.5	14.3	35.5	30.3	14.1	-1.1	-1.0	1.1	-1.5	-0.8	<0.001
Systolic Blood Pressure		37	103.7	104.0	12.9	102.3	103.0	9.4	-1.4	-1.0	14.5	-6.0	3.3	0.790
Diastolic Blood Pressure		37	57.9	58.0	8.9	59.7	60.0	8.6	1.8	2.0	11.8	-2.0	5.6	0.354

Abbreviations: ATMX: atomoxetine; n = number of patients with a baseline and at least one post baseline measurement;
SD = standard deviation; Change = endpoint-baseline; C.I. = 95% 2-sided Confidence Interval of Change;
LCI = Lower bound of 95% C.I.; UCI = Upper bound of 95% C.I.; Baseline: Visit 1-2; Endpoint: Visit 3-6.
* p-Value is from Wilcoxon signed-rank test

Table LYBD.6. Summary of Vital Sign Data
Categorical Changes in Heart Rate (Pulse) and Weight - Full Analysis Set

Atomoxetine N=37		
Criteria	n	(%)
A.	9	24.3%
B.	11	29.7%
C.	6	16.2%
D.	15	40.5%

A=Maximum heart rate(visits 3-6) of ≥ 110 bpm.

B=Change to maximum heart rate of ≥ 25 bpm.

C=A and B.

D=Weight loss from baseline to endpoint of 3.5%.

N=number of randomized patients with at least one dose of study drug.

Patients with a baseline heart rate of ≥ 100 bpm are excluded from analyses A and C.

Table LYBD.7. Summary of Vital Sign Data
Categorical Changes in Blood Pressure - Full Analysis Set

Test	Incidence group	N	n	ATOMOX (N=37) (%)
Sitting Avg. Systolic BP (mmHg)	HIGH	37	1	(2.70)
Sitting Avg. Systolic BP (mmHg)	NORMAL	37	36	(97.30)
Sitting Avg. Diastolic BP (mmHg)	HIGH	37	5	(13.51)
Sitting Avg. Diastolic BP (mmHg)	NORMAL	37	32	(86.49)

Population: Enrolled patients who took at least 1 dose of study drug.

Hypertension assessment criteria: The Guideline for the Management of Hypertension
(The Japanese Society of Hypertension)

Baseline: Visits 1-2(LOCF), Endpoint: Visits 3 - 6

N = Number of patients Normal at Baseline.

n = Number of patients in the Incidence Group Post Baseline.

Electrocardiograms (ECGs)

Table LYBD.8 summarizes the mean change for ECG intervals and heart rate from baseline to endpoint. For QT correction, Bazett's formula, Fridericia's formula, and a data-driven approach were used. Because Bazett's formula overcorrects for heart rate effects (thereby erroneously suggesting a prolongation of the QTc interval in the setting of a chronotropic drug, such as atomoxetine), Fridericia's formula or the data-driven approach would be more appropriate to assess the QT prolongation by atomoxetine treatment. Electrocardiogram (ECG) analysis showed statistically significant mean

changes for heart rate ($p < .001$), RR interval ($p < .001$), QRS interval ($p < .001$), QT Bazett correction ($p < .001$), and QT data correction ($p = .026$). Statistically significant mean changes were not observed for QT Fridericia correction. For this study, ECGs were single, clinical ECGs and were not collect at specific times of day.

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Table LYBD.8. Summary of Changes from Baseline to Endpoint for ECG and Heart Rate

Treatment		Baseline			Endpoint			Change					p-Value*
ATMX	n	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	LCI	UCI	
Heart Rate	37	74.0	75.0	10.4	88.1	86.0	14.1	14.1	13.0	13.5	9.8	18.4	<0.001
RR Interval	37	827.1	800.0	123.5	696.7	697.7	104.2	-130	-124	130.1	-172	-88.5	<0.001
QRS Interval	37	80.4	80.0	7.5	82.9	84.0	7.5	2.5	3.0	4.4	1.1	3.9	<0.001
QT BAZETT CORRECTION	37	395.3	395.0	17.1	409.6	411.0	18.7	14.3	16.0	20.6	7.7	21.0	<0.001
QT Data CORRECTION	37	386.1	383.7	15.9	392.6	391.9	16.8	6.6	8.2	17.5	0.9	12.2	0.026
QT FRIDERICIA CORRECTION	37	381.7	380.3	16.0	384.5	382.6	17.0	2.7	4.5	17.0	-2.7	8.2	0.294

Abbreviations: ATMX: atomoxetine; n = number of patients with a baseline and at least one post baseline measurement;
SD = standard deviation; Change = endpoint-baseline; C.I. = 95% 2-sided Confidence Interval of Change;
LCI = Lower bound of 95% C.I.; UCI = Upper bound of 95% C.I.; Baseline: Visit 1-2; Endpoint: Visit 3-6.
* p-Value is from Wilcoxon signed-rank test

Secondary Endpoints – Efficacy and Pharmacokinetics

Secondary endpoints included an analysis of the symptom scores in the ADHDRS-IV-J:I at baseline and with atomoxetine therapy and an evaluation of the plasma concentration of atomoxetine, 4-hydroxyatomoxetine, and N-desmethylatomoxetine.

Efficacy

The summary of the efficacy analyses is divided into 2 sections:

- Analyses of the ADHDRS-IV-J:I Total score:

The primary analysis of the ADHDRS-IV-J:I Total score consisted of a Wilcoxon signed-rank test of changes from baseline to endpoint score. Change was computed using a last visit carried forward approach.

Additionally, ADHDRS-IV-J:I subscales for Inattention and Hyperactivity-Impulsivity were analyzed in the same manner as the ADHDRS-IV-J:I Total score.
- Analyses of the CGI-ADHD-S: The CGI-ADHD-S was analyzed in the same manner as the ADHDRS-IV-J:I.

Additionally, patients were categorized as responders using multiple definitions specified in the protocol:

- patients with a $\geq 25\%$ decrease from baseline to endpoint in the ADHDRS-IV-J:I Total score
- patients with an endpoint CGI-ADHD-S score of at most 2.

Table LYBD.9 gives the results of change from baseline to endpoint for the ADHDRS-IV-J:I (Total score, hyperactivity-impulsivity subscale, and inattention subscale). For the ADHDRS-IV-J:I Total score, the mean change in LOCF from baseline to endpoint was a reduction of 18.6; for the inattention subscale, the mean change in LOCF from baseline to endpoint was a reduction of 10.5; and for the hyperactivity-impulsivity subscale, the mean change in LOCF was a reduction of 8.1 from baseline to endpoint. All 3 of these changes are statistically significant ($p < 0.001$).

Table LYBD.10 summarizes the analysis of the changes from baseline to endpoint in CGI-ADHD-S. The mean change in LOCF from baseline to endpoint was a reduction of 1.9, a statistically significant ($p < .001$) change.

Table LYBD.11 contains the results of the percentage-of-responder analyses. According to the LOCF at endpoint, 83.3% of the patients met the response criterion for ADHDRS-IV-J:I and 25% of the patients met the response criterion for CGI-ADHD-S.

Table LYBD.12 contains the analyses of scores obtained from the ADHDRS-IV-J:I performed separately for patients falling into each of the ADHD subtypes (hyperactive-impulsive, inattentive, and mixed). The changes from baseline to endpoint for the

inattentive and combined ADHD subtypes were statistically significant ($p < .001$). For the inattentive subgroup, the mean change from baseline to endpoint was a reduction of 18.0; for the combined subgroup, the mean change from baseline to endpoint was a reduction of 19.2.

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**Table LYBD.9. ADHDRS-IV-J:I Total Score
Change from Baseline to Endpoint**

Visit	n	Baseline		Endpoint		Change		p-value*	p-value**
		Mean	SD	Mean	SD	Mean	SD		
3	36	35.00	9.45	28.0	9.6	-7.0	6.69	<.001	<.001
4	35	34.60	9.28	22.5	10.6	-12.1	9.97	<.001	<.001
5	35	34.60	9.28	18.0	11.3	-16.6	11.81	<.001	<.001
6	33	34.36	9.07	14.5	9.4	-19.8	11.94	<.001	<.001
LOCF at Endpoint	36	35.00	9.45	16.4	12.2	-18.6	12.32	<.001	<.001

INATTENTIVE									
LOCF at Endpoint	36	20.78	3.79	10.3	6.7	-10.5	6.58	<.001	
HYPERACTIVE/IMPULSIVE									
LOCF at Endpoint	36	14.22	7.00	6.1	6.4	-8.1	6.57	<.001	

*p-value based on Wilcoxon signed rank test from analysis of changes from baseline for the LOCF Change from baseline to endpoint (visit 6).

**p-value based on a paired t-test from analysis of change from baseline.

Population: Full Analysis Set

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Table LYBD.10. CGI-ADHD-S
Change from Baseline to Endpoint

Visit	n	Baseline		Endpoint		Change		p-value*	p-value**
		Mean	SD	Mean	SD	Mean	SD		
3	36	5.06	0.79	4.6	0.8	-0.5	0.65	<.001	<.001
4	35	5.03	0.79	4.0	1.0	-1.0	1.18	<.001	<.001
5	35	5.03	0.79	3.5	1.1	-1.5	1.34	<.001	<.001
6	34	5.03	0.80	3.1	1.1	-1.9	1.30	<.001	<.001
LOCF at Endpoint	36	5.06	0.79	3.2	1.1	-1.9	1.31	<.001	<.001

*p-value based on Wilcoxon signed rank test from analysis of change from baseline to endpoint (visit 6).

**p-value based on a paired t-test from analysis of change from baseline to endpoint.

Population: Full Analysis Set

Table LYBD.11. Percentage of Responders

Visit	ADHDRS-J:I Response*			CGI-ADHD-S Response**		
	N	n	%	N	n	%
3	36	14	38.9%	36	0	0.00%
4	35	20	57.1%	35	2	5.71%
5	35	26	74.3%	35	4	11.4%
6	33	29	87.9%	34	9	26.5%
LOCF at Endpoint	36	30	83.3%	36	9	25.0%

* Responder is defined as having 25% or greater decrease from baseline to endpoint in the ADHDRS-J:I total score.

** Responder is defined as having an endpoint score of 1 or 2 on the CGI-ADHD-Severity score.

All patients with a baseline and at least one post baseline measurement who also took at least one dose of study medication were included.

Atomoxetine

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**Table LYBD.12. ADHDRS-IV-J:I Total Score
Change from Baseline to Endpoint by Subtype**

Subtype:	n	Baseline		Endpoint		Change		p-value*	p-value**
		Mean	SD	Mean	SD	Mean	SD		
Hyperactive/Impulsive	1	26.00	.	1.0	.	-25.0	.		
Inattentive	22	30.77	7.43	12.7	8.2	-18.0	11.13	<.001	<.001
Mixed	13	42.85	7.60	23.7	14.6	-19.2	14.89	<.001	<.001

*p-value based on Wilcoxon signed rank test from analysis of changes from baseline for the LOCF Change from baseline to endpoint (visit 6).

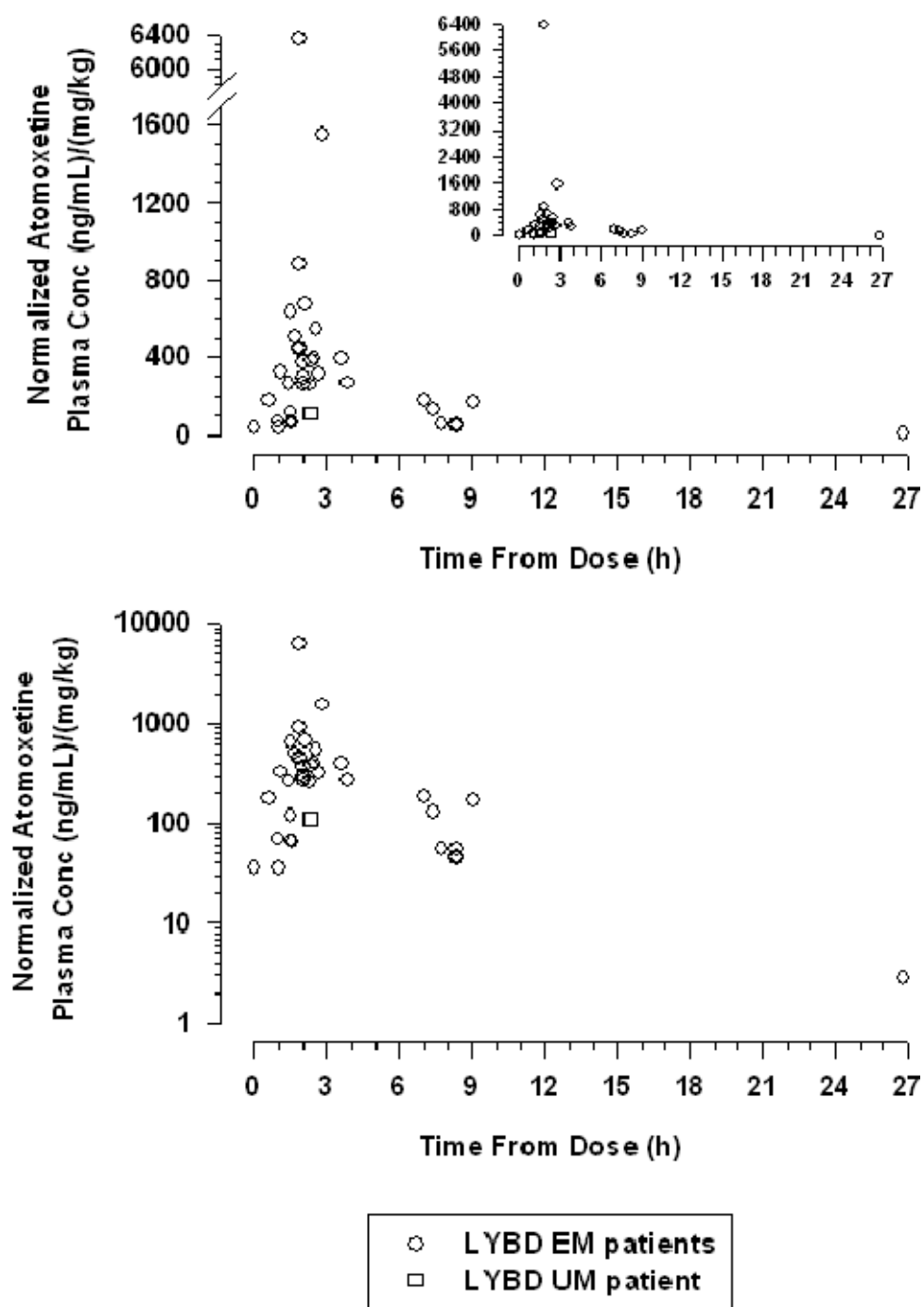
**p-value based on a paired t-test from analysis of change from baseline.

Population: Full Analysis Set

Pharmacokinetic Analysis

A blood sample was drawn from 36 of the 37 patients receiving atomoxetine for measurement of atomoxetine, 4-hydroxyatomoxetine, and *N*-desmethyatomoxetine in plasma. One patient had an additional sample drawn at Visit 5 (after approximately 6 weeks of treatment) when it was thought that he would discontinue at Visit 5; however, he continued in the study and had a sample drawn at Visit 6 as well. Thus, 37 concentration results were available from 36 patients. Of the 37 results, 36 were quantifiable for atomoxetine, 34 for 4-hydroxyatomoxetine, and 32 for *N*-desmethyatomoxetine. Of the 36 patients with a plasma sample, 34 were CYP2D6 EM patients. Two patients were classified as UMs. No CYP2D6 poor metabolizer patients were identified.

Concentration results are shown in Figure LYBD.3, Figure LYBD.4, and Figure LYBD.5 below. For comparison purposes, concentrations were normalized for most recent dose (mg/kg). Concentrations are shown on both Cartesian and semilog scales as shown in Figure LYBD.3 and Figure LYBD.5.



Upper plot is shown with and without (inset) break in y-axis.

Figure LYBD.3.

Dose-weight normalized atomoxetine plasma concentrations versus time in Japanese EM and UM children on Cartesian (upper panel) and semilog (lower panel) scales, B4Z-JE-LYBD.

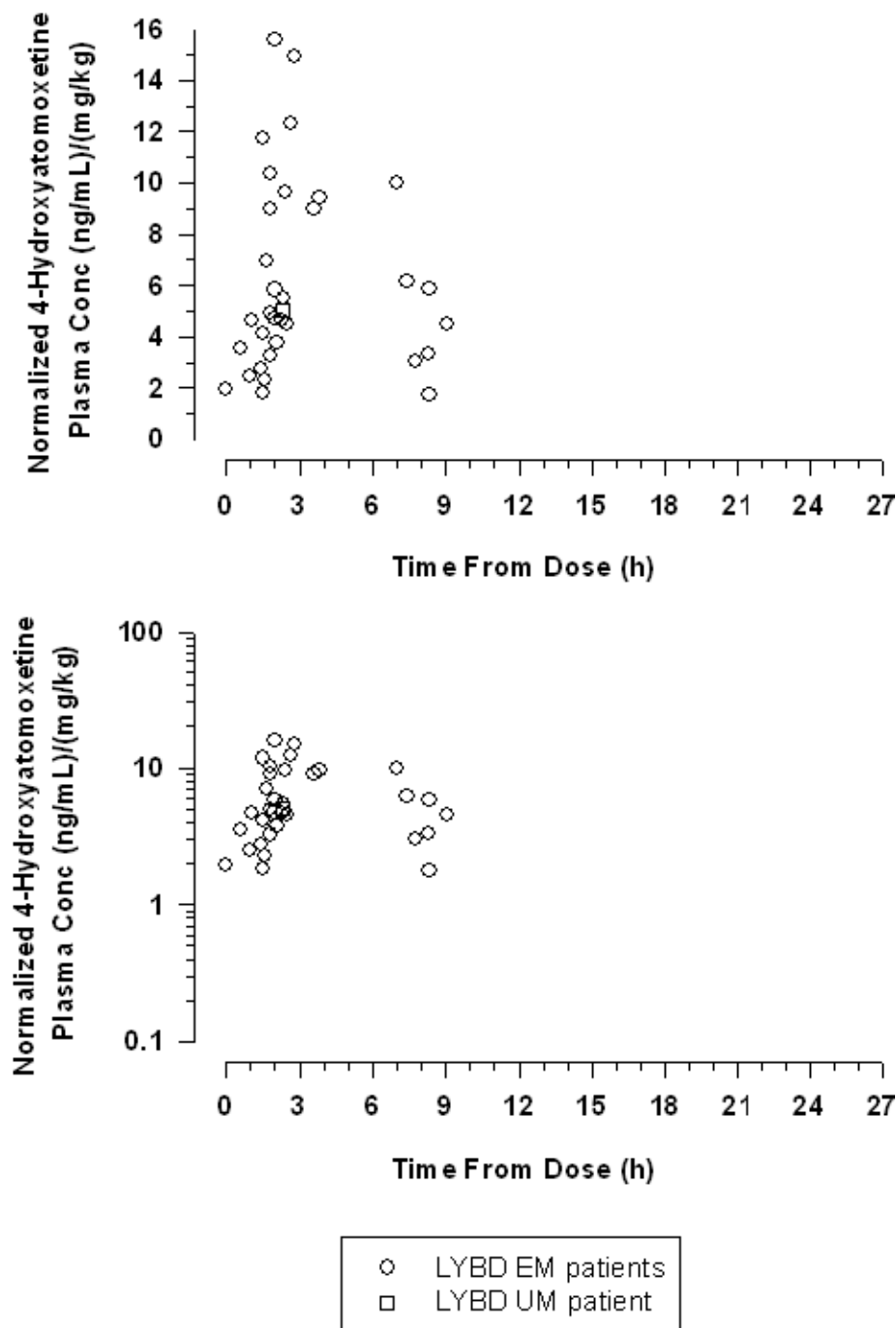


Figure LYBD.4.

Dose-weight normalized 4-hydroxyatomoxetine plasma concentrations versus time in Japanese EM and UM children on Cartesian (upper panel) and semilog (lower panel) scales, B4Z-JE-LYBD.

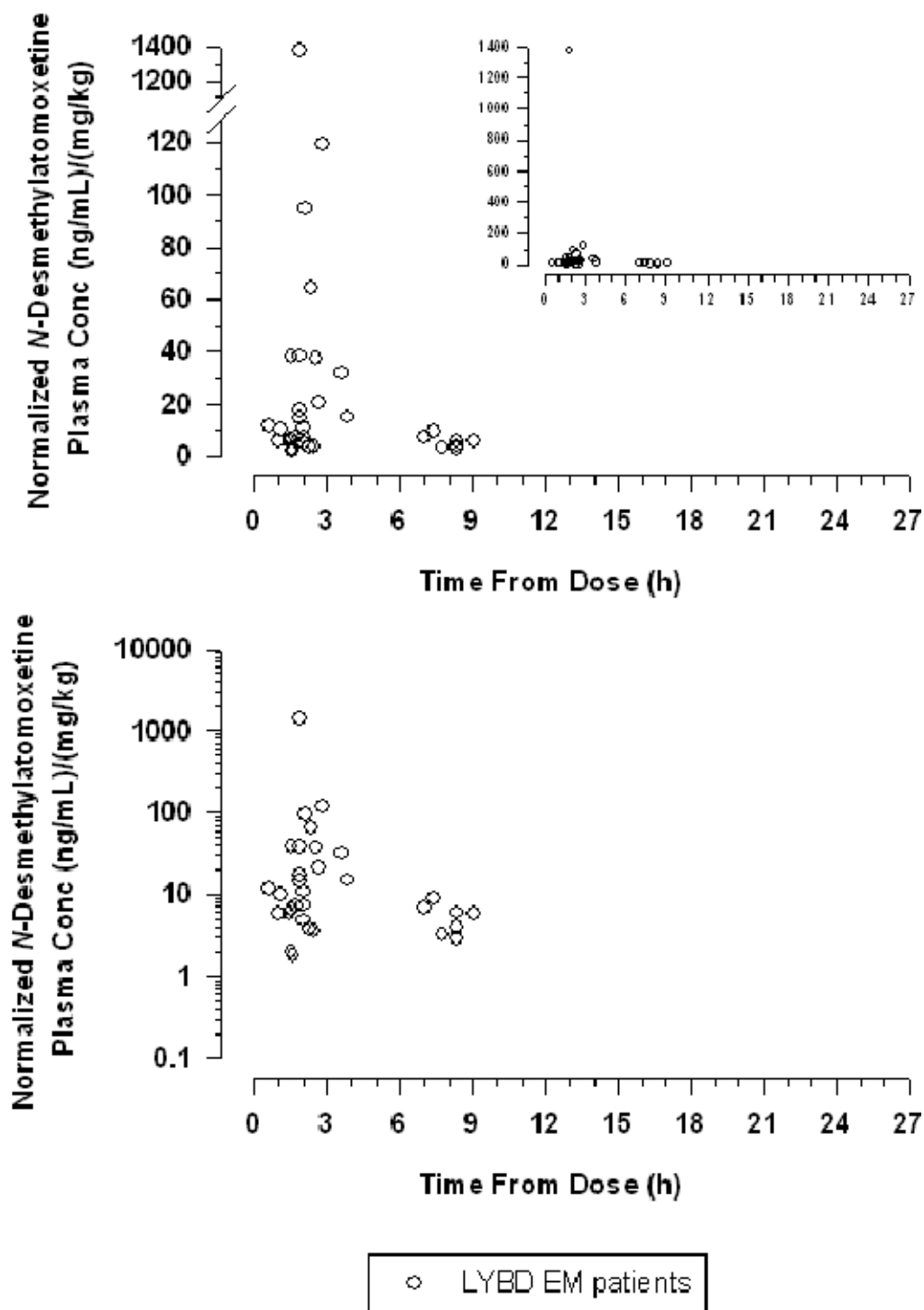


Figure LYBD.5.

Dose-weight normalized N-desmethyatomoxetine plasma concentrations versus time in Japanese EM children on Cartesian (upper panel) and semilog (lower panel) scales, B4Z-JE-LYBD.

Summary ID#5670

Clinical Study Summary: Study B4Z-US-LYBG

Title of Study: A Randomized, Double-Blind, Placebo-Controlled Trial of Once Daily Atomoxetine Hydrochloride to Evaluate Efficacy in the Treatment of Attention-Deficit/Hyperactivity Disorder in Children Ages 6 through 12 with an Assessment of Evening Behavior	
Investigators: This multicenter study included 12 principal investigators.	
Study Centers: This study was conducted at 12 study centers in the United States.	
Length of Double-Blind Study: 4 months Date of first patient enrolled: 14 March 2002 Date of last patient completed: 19 July 2002 Length of Open-Label Extension: 9 months Date first patient entered open-label extension: 06 May 2002 Date last patient completed open-label extension: 11 April 2003	Phase of Development: 3/3b
Objectives: <u>Double-Blind Study:</u> The primary objective of this study was to test the hypothesis that acute treatment for approximately 8 weeks with atomoxetine (titrated to a maximum dose of 1.8 mg/kg/day and given once a day in the morning) provides superior efficacy compared with placebo in children with Attention-Deficit/Hyperactivity Disorder (ADHD) diagnosed using the <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</i> (DSM-IV) criteria. Efficacy was measured by comparing the differences in the treatment at the end of 8 weeks using the Attention Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv), the primary efficacy measure. The secondary objectives of the study were as follows (grouping only applies to sequential testing for labeling purposes): <u>Group 1:</u> • To test the hypothesis that atomoxetine provides superior efficacy on evening behaviors compared with placebo in children with ADHD. Efficacy was measured using the evening subscore of the Daily Parent Ratings of Evening and Morning Behavior-Revised (DPREMB-Revised). • To test the hypothesis that atomoxetine provides superior efficacy on morning behaviors compared with placebo in children with ADHD. Efficacy was measured using the Morning subscore of the DPREMB-Revised. • To compare the change in parent/patient-reported outcomes (quality of life) between atomoxetine and placebo in children with ADHD as assessed by the Child Health Questionnaire: Parent Form 50 (CHQ-PF50). <u>Group 2:</u> • To evaluate onset-of-action of atomoxetine by collecting daily ratings of ADHD symptoms in the home setting as measured by the total score of the DPREMB-Revised. • To compare the change in ADHD symptoms between atomoxetine and placebo treatment in children with ADHD as measured by the General Impressions Scale: Child and Parent (GIS-CP), the Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S), the Brown Attention-Deficit Disorder Scales: Parent Form (Brown ADD Scales: Parent), and the Conners' Global Index-Parent Evening.	

- To compare the change in the parent-reported behavior subscores of the ADHD Symptom Checklist-4-Behavior (ADHD-SC4) between atomoxetine and placebo treatment in children with ADHD. For label inclusion purposes, these secondary objectives were analyzed according to a two-step “Gatekeeping strategy” as follows: Step 1: If the primary analysis achieved statistical significance at the .05 level, then proceed to test each hypothesis in secondary objectives Group 1 in the order indicated above. If the primary analysis did not achieve statistical significance, then no further testing of the secondary objectives was performed. Step 2: If each hypothesis in Group 1 was rejected, then the hypotheses for Group 2 were tested at a .05 significance level. Open-Label Extension: The objectives for the open-label extension portion of Study LYBG were: - To assess the efficacy of long-term treatment with atomoxetine in treating ADHD symptoms as measured by the ADHDRS-IV-Parent: Inv Scale, CGI-ADHD-S, the Conners’ Global Index-Parent Evening, Brown ADD Scales: Parent, Life Participation Scale (LPS), and the General Impressions Scale: Child and Parent (GIS-CP). - To assess the change in parent/subject-reported outcomes (quality of life) based on CHQ-PF50. - To assess the change in the parent-reported behavior subscores of the ADHD-SC4. - To assess the safety and tolerability of long-term treatment with atomoxetine for up to 1 year.
Study Design: Study B4Z-US-LYBG (LYBG) was a randomized, multicenter, double-blind, placebo-controlled trial. Children who met DSM-IV and Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version: Behavioral Disorders Supplement (K-SADS-PL:Behavioral) module criteria for ADHD, and scored at least 1.5 standard deviations above the age/gender norm for their ADHD diagnostic subtype on the ADHDRS-IV Parent:Inv were randomized to receive either atomoxetine hydrochloride (hereafter referred to as atomoxetine) or placebo in a double-blinded fashion for a treatment period of about 8 weeks, with optional subsequent treatment with open-label atomoxetine for 6 months. During the double-blind, placebo-controlled treatment phase, there were approximately 14 days between Visit 1 and Visit 2, approximately 7 days between Visit 2 and Visit 3, approximately 21 days between Visit 3 and Visit 4, and approximately 28 days until the final visit (Visit 5). Parents completed a daily questionnaire evaluating their child’s behavior at home over the course of the day(DPREMB-Revised) beginning 5 days prior to Visit 2 and continuing for approximately 4 weeks (to Visit 4).
Number of Patients: Planned: 106 active drug, 53 placebo Randomized: 133 active drug, 64 placebo Completed: 107 active drug, 47 placebo Enrolled in open-label period: 153 Completed open-label period: 81
Diagnosis and Main Criteria for Inclusion: Patients were at least 6 years of age and no more than 12 years of age prior to Visit 2. Patients met DSM-IV diagnostic criteria for ADHD. The diagnosis of ADHD was confirmed during the screening visit by administration of the K-SADS-PL:Behavioral. All patients scored at least 1.5 standard deviations above the age/gender norm for their ADHD diagnostic subtype on the ADHDRS-IV-Parent:Inv at Visit 1 and at Visit 2. (Note: Children who met criteria for the combined subtype scored at least 1.5 standard deviations above the age/gender norm for the total score.) Additionally, all patients were free of any medication used to treat ADHD for at least a period equal to a washout of 5 half-lives of the active compound (or active metabolite) prior to Visit 2 and at least 5 days prior to Visit 2.
Test Product, Dose, and Mode of Administration: Atomoxetine: 0.8 mg/kg/day to 1.8 mg/kg/day, given once daily; atomoxetine capsules, 2.5 mg, 5, mg, 10 mg, 20 mg, 25 mg, and 40 mg dose.
Duration of Treatment:

<u>Double-Blind Study:</u> Approximately 8 weeks. <u>Open-Label Extension:</u> Approximately 9 months.
Reference Therapy, Dose, and Mode of Administration: <u>Double-Blind Study:</u> Placebo, given once daily. <u>Open-Label Extension:</u> None.
Variables: <u>Efficacy:</u> Treatment differences on the following measures: ADHDRS-IV-Parent:Inv, LPS for ADHD, DPREMB-Revised, CGIP-E, GIS-CP, ADHD-SC4, Brown ADD Scales:Parent, and CGI-ADHD-S. <u>Safety:</u> Treatment-emergent adverse events, vital signs, height and weight, laboratory analytes, and electrocardiograms (ECGs). <u>Health Outcomes:</u> Physical and psychosocial well being using the CHQ-PF50.
Statistical Methods: <u>Double-Blind Study:</u> Continuous efficacy measures collected at multiple timepoints were analyzed using an MMRM analysis with terms for therapy, visit, investigator, cytochrome P450 2D6 (CYP2D6) metabolic status, therapy by visit interaction, and baseline by visit interaction. Other continuous efficacy measures were analyzed using analysis of covariance (ANCOVA) to test for a treatment difference in the mean change from baseline to last-observation-carried-forward (LOCF) endpoint. These efficacy analyses included terms for baseline score, therapy, and investigator. Continuous safety measures were analyzed using analysis of variance (ANOVA) to test for treatment difference in the mean change from baseline to LOCF endpoint. These analyses generally included terms for therapy and investigator. Categorical data were tabulated and frequencies were compared across treatment groups using Fisher's exact test. <u>Open-Label Extension:</u> Baseline for all analyses was Visit 5, the end of the acute period. The ADHDRS, CGI-ADHD-S, and CGIP-E were the only scales collected at each postbaseline visit. These variables were analyzed using a restricted maximum likelihood (REML)-based mixed effects model, repeated measures technique. The model included the fixed categorical effects of investigator, visit, CYP2D6 metabolism status and the continuous, fixed covariate of baseline (Visit 5). A t-test was used to test whether the least squares change from baseline was significantly different from zero at each visit. Changes from baseline to LOCF endpoint for the other efficacy scales and safety measures were compared to zero change using the Wilcoxon signed-rank test. Frequency of clinical response (defined as a decrease from baseline of 25% on ADHDRS total score), clinical remission (defined as an endpoint CGI-ADHD-S score of 1 or 2), reasons for discontinuation, demographics, and treatment-emergent adverse events were tabulated and percentages computed. All patients with a baseline and at least one postbaseline measure were included in the analysis of efficacy and health outcome measures, and all patients who took at least one dose of study drug were included in the analysis of safety measures.
Summary: <u>Patient Disposition:</u> Of the 260 patients who entered the study, 63 patients were not assigned to treatment (randomized). At the beginning of Visit 3, 64 patients were randomized to placebo and 133 patients were randomized to atomoxetine. Of the 197 patients randomized, 154 (78.2%) completed Study Period II. <u>Patient Demographics:</u> Table LYBG.1 summarizes demographic characteristics for all randomized patients. Of the 197 randomized patients, 70.6% were male; 72.6% were Caucasian; 48.2% had no prior stimulant exposure, and 8.2% were determined to be cytochrome P450 2D6 (CYP2D6) poor metabolizer (PM) patients. The mean age was 9.48 years (range of 6.07 years to 12.88 years). Similar to the population at randomization, the patients in the open-label extension period were primarily Caucasian (75.2%), male (69.3%), and of combined ADHD subtype (68.6%). The average patient age was 9.37 years (standard deviation = 1.83). The open-label extension period was closed out by the sponsor, so the majority of patients (81 of 153, 53%) discontinued due to sponsor decision. The other reasons for discontinuation were adverse event (7.2%), lost to follow-up (14.4%), lack of efficacy (11.1%), patient conflict (8.5%), protocol violation (5.2%), and physician decision (.7%). The average exposure to

atomoxetine was approximately 260 days.

Efficacy: Regardless of the analysis method (MMRM or LOCF change using an ANCOVA model), atomoxetine-treated patients showed statistically significantly greater improvement in baseline to endpoint mean scores for the primary efficacy variable (the ADHDRS-IV-Parent:Inv Total score) compared with placebo-treated patients. As Table LYBG.2 illustrates, the repeated measures analysis of the primary efficacy variable at Visit 5 showed a mean score of 25.79 for atomoxetine-treated patients versus a mean score of 35.63 for placebo-treated patients, making a mean treatment difference of -9.84 ($p<.001$). In this study, efficacy was evident on the primary efficacy measure as early as 1 week after the start of atomoxetine treatment and continued at each visit until endpoint. There was no difference in efficacy based on gender, median age, or ADHD subtype.

This study was designed to have adequate statistical power to detect a treatment effect using the ADHDRS-IV-Parent:Inv, but was not specifically powered to detect differences in the secondary efficacy measures. Nevertheless, statistically significant differences in mean change from baseline to endpoint were observed for most secondary efficacy measures. The secondary efficacy measures were: the evening, morning, and total scores on the DPREMB-Revised; the Psychosocial Summary subscore of the CHQ-PF50; the evening, morning, and total scores on the GIS-CP; the Conners' Global Index-Parent Evening scale; the ADHD-SC4; the Brown ADD Scales: Parent; and the CGI-ADHD-S.

For the evening subscore of the DPREMB-Revised, there was a significant treatment difference ($p<.001$), as Table LYBG.3 illustrates. Additionally, the atomoxetine treatment group had a statistically significantly greater mean decrease in the DPREMB-Revised:Evening subscore compared with the placebo treatment group at all postbaseline visits. Table LYBG.4 displays the results for the morning subscore of the DPREMB-Revised. There was a significant treatment difference on the morning subscore ($p=.018$) and the atomoxetine treatment group had a statistically significantly greater mean decrease compared with the placebo treatment group at Week 2 and Week 3 of the study. As Table LYBG.5 shows, the atomoxetine treatment group had statistically significantly ($p<.05$) greater mean improvement scores on the DPREMB-Revised total scores compared with the placebo treatment group on Days 1, 2, 3, 6, and 7, and trended toward statistically significantly greater mean improvement scores on Day 4 and Day 5 ($p=.075$, $p=.052$, respectively). Table LYBG.6 summarizes the LOCF change from baseline to endpoint in the morning behavior score, evening behavior score, and total score of the DPREMB-Revised. For this analysis, the average score over the last week collected for a particular patient serves as his/her endpoint value. The atomoxetine treatment group had statistically significantly greater mean decrease in the DPREMB-Revised evening behavior and total scores compared with the placebo treatment group ($p=.001$ and $p=.002$, respectively). With regard to the morning behavior score, a greater numerical mean decrease in score was seen with atomoxetine treatment compared to placebo, but this difference failed to reach statistical significance ($p=.066$).

The baseline and mean change from baseline to LOCF results for the Psychosocial Summary subscore of the CHQ-PF50 are summarized in Table LYBG.7. The independent effects in the ANCOVA model were investigator, treatment, and baseline score. The atomoxetine treatment group had statistically significantly greater mean improvement scores compared with the placebo treatment group ($p=.003$).

Table LYBG.8 summarizes the baseline and mean change from baseline to LOCF results for the General Impressions Scale-Parent (GIS-P) total score on the improvement in daily behavior. The independent effects in the ANCOVA model were investigator, treatment, and baseline score. The atomoxetine treatment group had statistically significantly greater mean improvement scores compared with the placebo treatment group ($p<.001$). Table LYBG.9 summarizes the LOCF change from baseline to endpoint in the GIS-P morning and evening scores. The atomoxetine treatment group showed statistically significantly greater improvement compared with the placebo treatment group on the GIS-P morning score ($p<.001$) and the GIS-P evening score ($p=.001$) subscales. Table LYBG.10 summarizes the baseline and mean change from baseline to LOCF results for the General Impressions Scale-Child (GIS-C) daily score on the improvement in daily behavior. A greater numerical mean decrease in score was seen with atomoxetine

treatment compared to placebo, but this difference was not statistically significant. Table LYBG.11 summarizes the LOCF change from baseline to endpoint in the GIS-C morning and evening scores. A greater numerical mean decrease in score was seen with atomoxetine treatment compared to placebo on both the GIS-C morning and evening scores; these differences were not statistically significant, although there was a trend towards significance for evening behaviors ($p=.076$).

Table LYBG.12 contains the results from the repeated measures analysis of the Conners' Global Index-Parent Evening total score. The atomoxetine treatment group had statistically significantly greater mean improvement in the Conners' Global Index-Parent Evening total score compared with the placebo treatment group at all postbaseline visits. Table LYBG.13 summarizes the LOCF change from baseline to endpoint in the total score and the scores of the Restless-Impulsive and Emotional Liability subscales of the Conners' Global Index-Parent Evening scale. The atomoxetine treatment group showed statistically significantly greater improvement compared with the placebo treatment group on the Total score ($p<.001$) and on the Restless-Impulsive subscales ($p<.001$). Both treatment groups showed mean baseline to endpoint improvement on the Emotional Liability subscale score, but this difference was not statistically significant.

On the ADHD-SC4 Behavior Oppositional Defiant subscore, a greater numerical mean improvement in score was seen with atomoxetine treatment compared to placebo, but this difference was not statistically significant. A greater improvement in mean score was seen with atomoxetine treatment compared to placebo on the ADHD-SC4 Behavior Peer Conflict scale, but this difference was not statistically significant. Both treatment groups showed mean baseline to endpoint improvement on the ADHD-SC4 Behavior Stimulant Side Effect subscale score, but this difference was not statistically significant.

Table LYBG.14 summarizes the baseline and mean change from baseline to LOCF results for the Brown ADD Scales: Parent total score. The atomoxetine treatment group had statistically significantly greater mean improvement compared with the placebo treatment group ($p=.009$) in total score. Both treatment groups showed mean baseline to endpoint improvement. Table LYBG.15 summarizes LOCF change from baseline to endpoint analysis on the cluster scores for the Brown ADD Scales: Parent for the aspects of executive functioning: Activation, Focus, Effort, Emotion, Memory, Action, and sum of the first 5 scores. Both treatment groups showed mean baseline to endpoint improvement on each subscale. The atomoxetine treatment group had statistically significantly greater mean improvement compared with the placebo treatment group on all subscales except for the Emotion subscale. A greater numerical mean improvement in score was seen with atomoxetine treatment compared to placebo on the Emotion subscale, but this difference was not statistically significant.

Table LYBG.16 summarizes the LOCF change from baseline to endpoint in the CGI-ADHD-S rating scale. This scale represents a 1-item score of the investigator's clinical assessment of a patient's ADHD severity. The atomoxetine treatment group had statistically significantly greater mean decrease in CGI-ADHD-S scores compared with the placebo treatment group ($p<.001$). Baseline mean scores for both therapies (5.04 for atomoxetine group, 5.03 for placebo group) indicated "markedly ill" disease status. At endpoint, the mean score in the atomoxetine treatment group was 3.46, indicating severity had lessened to between "mildly ill" to "moderately ill," while the endpoint mean in the placebo treatment group was 4.32, indicating a severity of "moderately ill" to "markedly ill."

The acute portion of this study used dose titration based on clinical response. The final mean dose of 1.27 mg/kg/day in this part of the trial is consistent with the final mean doses of 1.35 mg/kg/day and 1.33 mg/kg/day in two previous atomoxetine once-daily trials and with the final total daily dose observed in other atomoxetine studies that have employed dose titration based on clinical response. It is also consistent with the results of the dose finding study, which demonstrated that a dose of approximately 1.2 mg/kg/day is associated with maximal response for most patients.

Similar to the acute results, patients treated with atomoxetine in the open-label extension of LYBG showed significant improvement on the primary outcome measure, the ADHDRS total score ($p<.001$). The average improvement was 9.58 points from baseline; patients demonstrated improvement at the first

postbaseline visit and this improvement increased in magnitude over time (test for Visit term, $p < .001$). Those patients with data at Visit 13 had a least squares mean improvement of 13.42 from baseline. The clinical importance of this change is reflected in the decrease in ADHDRS total t-scores of 10.5. At endpoint, the patients had an ADHDRS total t-score of 58.1, less than 1 standard deviation above scores age and gender norms for non-ADHD children. Endpoint t-scores for the hyperactive-impulsive and inattention subscores were similar. Half of the patients met remission criteria and 85.5% of patients were responders to atomoxetine.

There was a significant improvement from baseline for the CGI-ADHD-S that increased in magnitude over time (test for Visit term, $p < .001$). Baseline to endpoint change in the CGI-ADHD-S was also significant ($p < .001$). Patients had a significant improvement from baseline on the Conners' Global Index-Parent Evening scale of 3 to 4 points at each postbaseline visit; this improvement did not vary significantly over time (test for Visit term, $p = .135$). In the analyses of scales collected only at baseline and endpoint, patients treated with atomoxetine showed significant improvements from baseline ($p < .001$) for the Brown Total score (change = -19.4, standard deviation = 33.68) and cluster scores, LPS Total score (change = 9.14, standard deviation = 17.87), ADHD-SC4 subscores (changes ranged from -1.55 to 1.86), and the GIS-P (Daily, AM, and PM, changes from -.65 to -.74). The only scale that did not show significant change from baseline was the GIS-C; the three items from this scale did not show separation from placebo during the acute portion of the trial. The reported changes noted were mean changes from baseline.

Safety: There were no deaths or serious adverse events (SAEs) reported in the acute portion of this study. Six patients (4.5%) assigned to the atomoxetine treatment group discontinued due to an adverse event. Three patients reported syncope, 1 patient reported aggression, and 1 patient reported fatigue. Additionally, 1 patient (1.6%) assigned to the placebo treatment group discontinued from the study due to nausea.

Table LYBG.17 summarizes treatment-emergent adverse events by system organ class and preferred term. This summary only includes treatment-emergent adverse events that were reported in $\geq 5\%$ of randomized patients who had taken at least 1 dose of study medication. The most frequently reported adverse events were in the following system organ classes: gastrointestinal, nervous system, and metabolism and nutrition. Using the MedDRA preferred term (PT) as event descriptor, a statistically significantly greater percentage of atomoxetine-treated patients compared with placebo-treated patients reported appetite decreased (17.6% versus 6.3%; $p = .045$), somnolence (14.5% versus 1.6%; $p = .005$), and fatigue (9.9% versus 1.6%; $p = .039$).

Statistically significant ($p < .05$) treatment differences in mean change scores were observed in the atomoxetine treatment group compared with the placebo treatment group for alkaline phosphatase (-0.4 versus 18.2), inorganic phosphorus (-0.036 versus 0.055), total protein (1.1 versus -1.4), and albumin (0.8 versus -0.9). No statistically significant differences between treatment groups were observed in the incidence of abnormal laboratory values.

There was a statistically significant ($p < .001$) difference between atomoxetine and placebo for weight change. The data showed a baseline to endpoint mean decrease (0.7 kg) in weight for atomoxetine and a mean increase (0.74 kg) in weight in the placebo treatment group. Additionally, there was a statistically significant ($p = .001$) difference between atomoxetine and placebo for supine systolic pulse. The data showed a baseline to endpoint mean decrease (0.77 mm Hg) in supine systolic pulse for the placebo treatment group and a mean increase (5.99 mm Hg) in supine systolic pulse in the atomoxetine treatment group. These differences between treatment groups are consistent with findings in previous atomoxetine studies.

Statistically significant differences between atomoxetine and placebo were found for heart rate, the PR interval, and the RR interval. Relative to placebo, atomoxetine was associated with a mean decrease of the PR interval (-2.64 for atomoxetine-treated patients versus +1.86 for placebo-treated patients; $p = .036$) and the RR interval (-59.84 for atomoxetine-treated patients versus -24.20 for placebo-treated patients; $p = .052$), and a mean increase in heart rate (+6.80 for atomoxetine-treated patients versus +1.42 for placebo-

treated patients; $p=.009$). The decrease in RR interval would be expected with an elevation of heart rate. There were no statistically significant differences in QTc changes between the atomoxetine and placebo treatment groups. There was no evidence of QTc prolongation.

In the open-label extension portion of the study, there were no deaths and one SAE in this study. A single serious adverse event of abscessed tooth was reported in an 8.6-year-old female. The event of abscessed tooth was unrelated to treatment with atomoxetine in the opinion of the investigator. Eleven patients (7.2%) discontinued the open-label period due to an adverse event. The majority of patients (79.7%) reported at least one treatment-emergent adverse event during the open-label period. Headache (20.9%) was the most frequently reported treatment emergent adverse event, followed by nausea (15.7%), somnolence (15.7%), appetite decreased (15.0%), abdominal pain (14.4%), vomiting (13.7%), and fatigue (9.2%).

There were statistically significant decreases from baseline in alkaline phosphatase, AST/SGOT, creatine phosphokinase, hematocrit, inorganic phosphorus, and mean cell volume. Laboratory analytes with statistically significant increases from baseline were bicarbonate, chloride, leukocyte count, monocytes, neutrophils, and platelet count. Even though there were statistically significant change scores, they were small relative to baseline.

Supine pulse increased 2.13 bpm from baseline ($p=.023$) while orthostatic pulse decreased 1.36 bpm from baseline ($p=.041$). Weight and height significantly increased from baseline (.93 kg and 2.23 cm, $p<.001$ for each). There were no other significant changes from baseline in vital signs. There were no significant changes from baseline in ECG intervals and ECG heart rate increased by 1.81 bpm ($p=.062$). All changes reported are mean changes from baseline.

Health Outcomes: Table LYBG.18 summarizes change from baseline to endpoint on the 12 subscales of the CHQ-PF50. The atomoxetine treatment group scores separated from the placebo treatment group scores on the Behavior, Family Activities, and Parent Impact-Time subscales. In the Role Emotional/Behavior subscale, the atomoxetine treatment group approached statistical significance ($p=.052$).

During the extension, five of the CHQ subscales (Behavior, Family Activities, Parent Emotional Impact, Self-Esteem, and Psychosocial Summary) showed significant improvement from baseline ($p<.001$) with the greatest improvement observed in the Family Activities and Self-Esteem scores.

**Table LYBG.1 Patient Demographics and Other Characteristics
Comparison of Treatment Groups at Baseline
All Randomized Patients**

Variable	ATOMOX (N=133)	Placebo (N=64)	Total (N=197)	p-Value
Sex: No. (%)				
No. Patients	133	64	197	1.00*
Female	39 (29.3)	19 (29.7)	58 (29.4)	
Male	94 (70.7)	45 (70.3)	139 (70.6)	
Origin: No. (%)				
No. Patients	133	64	197	.814*
African Descent	18 (13.5)	7 (10.9)	25 (12.7)	
Caucasian	96 (72.2)	47 (73.4)	143 (72.6)	
East/Southeast A	1 (0.8)	0	1 (0.5)	
Hispanic	14 (10.5)	6 (9.4)	20 (10.2)	
Other	4 (3.0)	4 (6.3)	8 (4.1)	
Age: yrs				
No. Patients	133	64	197	.738**
Mean	9.51	9.41	9.48	
Median	9.49	9.71	9.55	
Standard Dev.	1.84	1.78	1.82	
Minimum	6.07	6.22	6.07	
Maximum	12.88	12.82	12.88	
Height (cm) at Visit 1				
No. Patients	132	64	196	.469**
Mean	135.34	134.01	134.91	
Median	134.50	133.75	134.00	
Standard Dev.	12.31	11.53	12.05	
Minimum	110.00	108.00	108.00	
Maximum	168.00	164.00	168.00	
Unspecified	1	0	1	
Weight (kg) at Visit 1				
No. Patients	133	64	197	.338**
Mean	35.50	33.89	34.98	
Median	32.70	31.95	32.20	
Standard Dev.	11.12	10.91	11.05	
Minimum	20.00	20.00	20.00	
Maximum	64.70	60.80	64.70	
CYP2D6 Status				
No. Patients	133	64	197	.781*
EXTN	123 (92.5)	57 (90.5)	180 (91.8)	
SLOW	10 (7.5)	6 (9.5)	16 (8.2)	
Unspecified	0	1	1	
ADHD Subtype				
No. Patients	133	64	197	.915*
HYP/IMP	5 (3.8)	2 (3.1)	7 (3.6)	
INATTV	35 (26.3)	19 (29.7)	54 (27.4)	
MIXED	93 (69.9)	43 (67.2)	136 (69.0)	
Previous Stimulant Exposure				
No. Patients	133	64	197	.545*
No	62 (46.6)	33 (51.6)	95 (48.2)	
Yes	71 (53.4)	31 (48.4)	102 (51.8)	
Drug taken majority of time with food				
No. Patients	133	64	197	
Unspecified	133	64	197	

(continued)

**Table LYBG.1. Patient Demographics and Other Characteristics
Comparison of Treatment Groups at Baseline
All Randomized Patients (concluded)**

Variable	ATOMOX (N=133)	Placebo (N=64)	Total (N=197)	p-Value
At Least 1 Dose of Study Drug				
No. Patients	133	64	197	1.00*
No	1 (0.8)	0	1 (0.5)	
Yes	131 (99.2)	63 (100)	194 (99.5)	
Unspecified	1	1	2	
Family History of ADHD - Mother				
No. Patients	133	64	197	.949*
Yes	17 (12.8)	8 (12.5)	25 (12.7)	
No	111 (83.5)	53 (82.8)	164 (83.2)	
Unknown	5 (3.8)	3 (4.7)	8 (4.1)	
Family History of ADHD - Father				
No. Patients	133	64	197	.464*
Yes	22 (16.5)	15 (23.4)	37 (18.8)	
No	100 (75.2)	43 (67.2)	143 (72.6)	
Unknown	11 (8.3)	6 (9.4)	17 (8.6)	
Family History of ADHD - Grandparents				
No. Patients	133	64	197	.957*
Yes	7 (5.3)	4 (6.3)	11 (5.6)	
No	108 (81.2)	51 (79.7)	159 (80.7)	
Unknown	18 (13.5)	9 (14.1)	27 (13.7)	
Family History of ADHD - Siblings				
No. Patients	133	64	197	.524*
Yes	33 (24.8)	20 (31.3)	53 (26.9)	
No	84 (63.2)	36 (56.3)	120 (60.9)	
Unknown	8 (6.0)	2 (3.1)	10 (5.1)	
N/A	8 (6.0)	6 (9.4)	14 (7.1)	

Program: RMP.B4ZSLYBG.SASPGM(SDEMA02P)

Input data from RMP.SAS.B4ZM.L.USLYBGSW

* Frequencies are analyzed using a Fishers-Exact test.

** Means are analyzed using a Type III Sum of Squares analysis of variance
(ANOVA): PROC GLM model=treatment.

XDES0001

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Table LYBG.2. ADHDRS-IV-Parent: Inv Total Score
Repeated Measures Least-Squares Means
Study Period II

VISIT	ATOMOXETINE			PLACEBO			TREATMENT DIFFERENCE		
	LS MEAN	SE	P-VAL A	LS MEAN	SE	P-VAL A	LS MEAN	SE	P-VAL B
3	30.66	1.56	<.001	36.67	1.79	<.001	-6.01	1.70	<.001
4	27.54	1.70	<.001	33.97	2.10	<.001	-6.43	2.11	.003
5	25.79	1.73	<.001	35.63	2.16	<.001	-9.84	2.19	<.001
95% CONFIDENCE INTERVAL ON CHANGE FROM BASELINE TO VISIT 5									
(-10.81 , -2.28) (-19.79, -12.99)									
SUMMARY OF MODEL PARAMETERS			F-VALUE	P-VALUE C					
BASELINE			28.94	<.001					
TREATMENT			19.97	<.001					
VISIT			0.01	.988					
INVESTIGATOR			2.32	.011					
CYP2D6			0.03	.857					
TREATMENT*VISIT			2.25	.109					
BASELINE*VISIT			0.30	.745					
RESULTS BASED ON A MIXED MODEL WITH VISIT, BASELINE, TREATMENT, CYP2D6GEN,INVESTIGATOR, TREATMENT BY VISIT INTERACTION AND BASELINE BY VISIT INTERACTION USING AN UNSTRUCTURED COVARIANCE MATRIX TO MODEL CORRELATIONS WITHIN PATIENT ACROSS VISITS.									
A) P-VALUES ARE FROM TESTS FOR A NONZERO LEAST SQUARES MEAN AT THE GIVEN VISIT.									
B) P-VALUES ARE FROM TESTS FOR A TREATMENT DIFFERENCE IN LEAST SQUARES MEANS AT THE GIVEN VISIT.									
C) P-VALUES ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE.									
PROGRAM: \\EAGLE\EAGLE.GRP\PROGRAMS._G\RMP\B4ZS\LYBG\FINAL1(SEFMA01P)									
OUTPUT : \\TIGER\TIGER.GRP\ATOMOX_STAT\LYBG\FINAL1(SEFMA01P)									

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Table LYBG.3. DPREMB-Revised:Evening Subscale
Repeated Measures Least-Squares Means
Study Period II

WEEK	ATOMOXETINE			PLACEBO			TREATMENT DIFFERENCE		
	LS MEAN	SE	P-VAL A	LS MEAN	SE	P-VAL A	LS MEAN	SE	P-VAL B
1	6.86	0.42	<.001	8.91	0.49	<.001	-2.05	0.47	<.001
2	6.65	0.43	<.001	8.29	0.50	<.001	-1.64	0.50	.001
3	6.09	0.44	<.001	7.82	0.54	<.001	-1.73	0.54	.002
4	5.59	0.48	<.001	7.18	0.63	<.001	-1.59	0.65	.017
95% CONFIDENCE INTERVAL ON CHANGE FROM BASELINE TO WEEK 4									
(-5.49 , -3.01) (-6.78 , -4.88)									
SUMMARY OF MODEL PARAMETERS				F-VALUE	P-VALUE C				
BASELINE				167.01	<.001				
TREATMENT				15.67	<.001				
WEEK				1.25	.295				
INVESTIGATOR				1.86	.048				
CYP2D6				1.17	.281				
TREATMENT*WEEK				0.30	.825				
BASELINE*WEEK				0.74	.529				
RESULTS BASED ON A MIXED MODEL WITH VISIT, BASELINE, TREATMENT, CYP2D6GEN,INVESTIGATOR, TREATMENT BY VISIT INTERACTION AND BASELINE BY VISIT INTERACTION USING AN UNSTRUCTURED COVARIANCE MATRIX TO MODEL CORRELATIONS WITHIN PATIENT ACROSS WEEKS.									
A) P-VALUES ARE FROM TESTS FOR A NONZERO LEAST SQUARES MEAN AT THE GIVEN WEEK.									
B) P-VALUES ARE FROM TESTS FOR A TREATMENT DIFFERENCE IN LEAST SQUARES MEANS AT THE GIVEN WEEK.									
C) P-VALUES ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE.									
PROGRAM: \\EAGLE\EAGLE.GRP\PROGRAMS._G\RMP\B4ZS\LYBG\FINAL1(SEFMA09P)									
OUTPUT : \\TIGER\TIGER.GRP\ATOMOX_STAT\LYBG\FINAL1(SEFMA09P)									

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Table LYBG.4. DPREMB-Revised:Morning Subscale
Repeated Measures Least-Squares Means
Study Period II

WEEK	ATOMOXETINE			PLACEBO			TREATMENT DIFFERENCE		
	LS MEAN	SE	P-VAL A	LS MEAN	SE	P-VAL A	LS MEAN	SE	P-VAL B
1	2.75	0.17	<.001	3.09	0.20	<.001	-0.34	0.19	.070
2	2.50	0.18	<.001	3.04	0.21	<.001	-0.54	0.21	.011
3	2.37	0.19	<.001	2.96	0.23	<.001	-0.59	0.24	.015
4	2.25	0.20	<.001	2.57	0.27	<.001	-0.32	0.28	.263
95% CONFIDENCE INTERVAL ON CHANGE FROM BASELINE TO WEEK 4									
(-1.81 , -0.75) (-2.00 , -1.20)									
SUMMARY OF MODEL PARAMETERS				F-VALUE	P-VALUE C				
BASELINE				179.67	<.001				
TREATMENT				5.75	.018				
WEEK				0.13	.942				
INVESTIGATOR				1.65	.089				
CYP2D6				0.04	.840				
TREATMENT*WEEK				0.79	.503				
BASELINE*WEEK				0.71	.550				
RESULTS BASED ON A MIXED MODEL WITH VISIT, BASELINE, TREATMENT, CYP2D6GEN, INVESTIGATOR, TREATMENT BY VISIT INTERACTION AND BASELINE BY VISIT INTERACTION USING AN UNSTRUCTURED COVARIANCE MATRIX TO MODEL CORRELATIONS WITHIN PATIENT ACROSS WEEKS.									
A) P-VALUES ARE FROM TESTS FOR A NONZERO LEAST SQUARES MEAN AT THE GIVEN WEEK.									
B) P-VALUES ARE FROM TESTS FOR A TREATMENT DIFFERENCE IN LEAST SQUARES MEANS AT THE GIVEN WEEK.									
C) P-VALUES ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE.									
PROGRAM: \\EAGLE\EAGLE.GRP\PROGRAMS._G\RMP\B4ZS\LYBG\FINAL1(SEFMA08P)									
OUTPUT : \\TIGER\TIGER.GRP\ATOMOX_STAT\LYBG\FINAL1(SEFMA08P)									

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Table LYBG.5. DPREMB-Revised Total Score
Repeated Measures Least-Squares Means for First Week Posttreatment
Study Period II

DAY	ATOMOXETINE			PLACEBO			TREATMENT DIFFERENCE		
	LS MEAN	SE	P-VAL A	LS MEAN	SE	P-VAL A	LS MEAN	SE	P-VAL B
1	11.15	0.84	<.001	14.79	1.03	<.001	-3.64	1.07	<.001
2	9.95	0.84	<.001	12.95	1.02	<.001	-3.00	1.06	.005
3	10.50	0.86	<.001	13.24	1.06	<.001	-2.74	1.11	.015
4	9.58	0.84	<.001	11.52	1.04	<.001	-1.94	1.08	.075
5	9.29	0.86	<.001	11.52	1.09	<.001	-2.23	1.14	.052
6	10.18	0.84	<.001	12.34	1.04	<.001	-2.17	1.08	.046
7	9.76	0.87	<.001	13.08	1.10	<.001	-3.32	1.16	.005
95% CONFIDENCE INTERVAL ON CHANGE FROM BASELINE TO DAY 7									
(-5.28 , -0.93) (-8.14 , -4.71)									
SUMMARY OF MODEL PARAMETERS				F-VALUE	P-VALUE C				
BASELINE				107.97	<.001				
TREATMENT				12.32	<.001				
DAY				0.65	.686				
INVESTIGATOR				1.36	.196				
CYP2D6				2.37	.125				
TREATMENT*DAY				0.48	.822				
BASELINE*DAY				0.58	.749				

RESULTS BASED ON A MIXED MODEL WITH VISIT, BASELINE, TREATMENT, CYP2D6GEN, INVESTIGATOR, TREATMENT BY VISIT INTERACTION AND BASELINE BY VISIT INTERACTION USING AN UNSTRUCTURED COVARIANCE MATRIX TO MODEL CORRELATIONS WITHIN PATIENT ACROSS DAYS IN THE FIRST WEEK.
 A) P-VALUES ARE FROM TESTS FOR A NONZERO LEAST SQUARES MEAN AT THE GIVEN DAY.
 B) P-VALUES ARE FROM TESTS FOR A TREATMENT DIFFERENCE IN LEAST SQUARES MEANS AT THE GIVEN DAY.
 C) P-VALUES ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE.

PROGRAM: \\EAGLE\EAGLE.GRP\PROGRAMS_G\RMP\B4ZS\LYBG\FINAL1(SEFMA07P)
 OUTPUT : \\TIGER\TIGER.GRP\ATOMOX_STAT\LYBG\FINAL1(SEFMA07P)

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**Table LYBG.6. Daily Parent Rating Scale of Evening and Morning Behavior-Revised (DPREMB-Revised) Total and Subscores
 Change from Baseline to Endpoint
 Study Period II**

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		MEAN	SD	MEAN	SD	MEAN	SD		
MORNING BEHAVIOR SCORE									
TMX	126	4.00	2.08	2.43	1.97	-1.58	1.67	<.001	.066
PLA	59	3.52	1.89	2.57	1.66	-0.95	1.64	<.001	----
95% CONFIDENCE INTERVAL:						(-0.0, 0.88)			
EVENING BEHAVIOR SCORE									
TMX	126	11.68	4.79	6.41	4.43	-5.27	4.03	<.001	.001
PLA	59	10.76	4.46	7.69	4.72	-3.07	3.92	<.001	----
95% CONFIDENCE INTERVAL:						(0.72, 2.89)			
TOTAL BEHAVIOR SCORE									
TMX	126	16.89	7.25	9.46	6.71	-7.43	5.75	<.001	.002
PLA	59	15.38	6.55	11.02	6.64	-4.36	5.60	<.001	----
95% CONFIDENCE INTERVAL:						(0.90, 4.03)			

A) P-VALUE IS FROM WILCOXON SIGNED-RANK TEST.

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH INVESTIGATOR, TREATMENT, BASELINE AS COVARIATE

PROGRAM: \\EAGLE\EAGLE.GRP\PROGRAMS._G\RMP\B4ZS\LYBG\FINAL1(SEFLA13P)

OUTPUT : \\TIGER\TIGER.GRP\ATOMOX_STAT\LYBG\FINAL1(SEFLA13P)

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Table LYBG.7. **Child Health Questionnaire-Parent-Completed Full Length (CHQ-PF50)**
Psychosocial Subscore
Change from Baseline to Endpoint
Study Period II

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		MEAN	SD	MEAN	SD	MEAN	SD		
PSYCHOSOCIAL SUMMARY SCORE									
TMX	115	31.37	9.75	40.90	11.33	9.52	11.01	<.001	.003
PLA	53	33.09	9.96	37.13	12.33	4.04	9.07	.001	----
95% CONFIDENCE INTERVAL: (-7.95, -1.60)									

A) P-VALUE IS FROM WILCOXON SIGNED-RANK TEST.

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH INVESTIGATOR, TREATMENT, BASELINE AS COVARIATE

PROGRAM: \\EAGLE\EAGLE.GRP\PROGRAMS._G\RMP\B4ZS\LYBG\FINAL1(SEFLA25P)

OUTPUT : \\TIGER\TIGER.GRP\ATOMOX_STAT\LYBG\FINAL1(SEFLA25P)

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Table LYBG.8. **General Impressions Scale: Parent (GIS-P)**
Daily Score
Change from Baseline to Endpoint
Study Period II

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE A	P-VALUE B
		-----		-----		-----			
		MEAN	SD	MEAN	SD	MEAN	SD		
IMPROVEMENT IN DAILY BEHAVIOR									
TMX	127	4.31	1.10	3.04	1.29	-1.28	1.58	<.001	<.001
PLA	60	4.55	1.02	3.90	1.20	-0.65	1.30	<.001	----
95% CONFIDENCE INTERVAL:						(0.43 , 1.20)			

A) P-VALUE IS FROM WILCOXON SIGNED-RANK TEST.

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH INVESTIGATOR, TREATMENT, BASELINE AS COVARIATE

PROGRAM: \\EAGLE\EAGLE.GRP\PROGRAMS._G\RMP\B4ZS\LYBG\FINAL1(SEFLA18P)

OUTPUT : \\TIGER\TIGER.GRP\ATOMOX_STAT\LYBG\FINAL1(SEFLA18P)

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Table LYBG.9. General Impressions Scale: Parent (GIS-P)
Morning and Evening Scores
Change from Baseline to Endpoint
Study Period II

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE A	P-VALUE B
		MEAN	SD	MEAN	SD	MEAN	SD		
IMPROVEMENT IN MORNING BEHAVIOR									
TMX	127	4.17	0.99	3.00	1.21	-1.17	1.43	<.001	<.001
PLA	60	4.27	0.82	3.87	1.08	-0.40	1.36	.023	----
95% CONFIDENCE INTERVAL:						(0.48 , 1.20)			
IMPROVEMENT IN EVENING BEHAVIOR									
TMX	127	4.36	1.04	3.17	1.22	-1.20	1.35	<.001	.001
PLA	60	4.48	1.00	3.82	1.16	-0.67	1.34	<.001	----
95% CONFIDENCE INTERVAL:						(0.25 , 0.98)			

A) P-VALUE IS FROM WILCOXON SIGNED-RANK TEST.

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH INVESTIGATOR, TREATMENT, BASELINE AS COVARIATE

PROGRAM: \\EAGLE\EAGLE.GRP\PROGRAMS._G\RMP\B4ZS\LYBG\FINAL1(SEFLA19P)

OUTPUT : \\TIGER\TIGER.GRP\ATOMOX_STAT\LYBG\FINAL1(SEFLA19P)

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Table LYBG.10. **General Impressions Scale: Child (GIS-C)**
Daily Score
Change from Baseline to Endpoint
Study Period II

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE A	P-VALUE B
		-----		-----		-----			
		MEAN	SD	MEAN	SD	MEAN	SD		
IMPROVEMENT IN DAILY BEHAVIOR									
TMX	127	3.68	1.49	3.04	1.59	-0.64	2.04	<.001	.711
PLA	60	3.68	1.51	3.18	1.74	-0.50	1.78	.003	----
95% CONFIDENCE INTERVAL: (-0.40 , 0.59)									

A) P-VALUE IS FROM WILCOXON SIGNED-RANK TEST.

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH INVESTIGATOR, TREATMENT, BASELINE AS COVARIATE

PROGRAM: \\EAGLE\EAGLE.GRP\PROGRAMS._G\RMP\B4ZS\LYBG\FINAL1(SEFLA16P)

OUTPUT : \\TIGER\TIGER.GRP\ATOMOX_STAT\LYBG\FINAL1(SEFLA16P)

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Table LYBG.11. General Impressions Scale: Child (GIS-C)
Morning and Evening Scores
Change from Baseline to Endpoint
Study Period II

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE A	P-VALUE B
		MEAN	SD	MEAN	SD	MEAN	SD		
IMPROVEMENT IN MORNING BEHAVIOR									
TMX	127	3.66	1.47	2.68	1.54	-0.98	2.12	<.001	.307
PLA	60	3.00	1.25	2.93	1.56	-0.07	1.85	.525	----
95% CONFIDENCE INTERVAL: (-0.24 , 0.75)									
IMPROVEMENT IN EVENING BEHAVIOR									
TMX	127	3.78	1.69	2.72	1.62	-1.06	2.25	<.001	.076
PLA	60	3.43	1.52	3.10	1.60	-0.33	1.74	.179	----
95% CONFIDENCE INTERVAL: (-0.05 , 0.93)									

A) P-VALUE IS FROM WILCOXON SIGNED-RANK TEST.

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH INVESTIGATOR, TREATMENT, BASELINE AS COVARIATE

PROGRAM: \\EAGLE\EAGLE.GRP\PROGRAMS._G\RMP\B4ZS\LYBG\FINAL1(SEFLA17P)

OUTPUT : \\TIGER\TIGER.GRP\ATOMOX_STAT\LYBG\FINAL1(SEFLA17P)

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Table LYBG.12. Conners' Global Index-Parent Evening Total Score
Repeated Measures Least-Squares Means
Study Period II

VISIT	ATOMOXETINE			PLACEBO			TREATMENT DIFFERENCE		
	LS MEAN	SE	P-VAL A	LS MEAN	SE	P-VAL A	LS MEAN	SE	P-VAL B
3	15.17	0.81	<.001	18.29	0.97	<.001	-3.12	0.96	.001
4	14.34	0.82	<.001	16.70	1.01	<.001	-2.36	1.00	.019
5	14.23	0.84	<.001	17.89	1.05	<.001	-3.66	1.04	<.001
95% CONFIDENCE INTERVAL ON CHANGE FROM BASELINE TO VISIT 5									
(-4.28 , -0.15) (-7.52 , -4.23)									
SUMMARY OF MODEL PARAMETERS				F-VALUE	P-VALUE C				
BASELINE				87.65	<.001				
TREATMENT				15.14	<.001				
VISIT				2.68	.070				
INVESTIGATOR				2.10	.023				
CYP2D6				1.26	.264				
TREATMENT*VISIT				0.92	.399				
BASELINE*VISIT				1.37	.255				
RESULTS BASED ON A MIXED MODEL WITH VISIT, BASELINE, TREATMENT, CYP2D6GEN,INVESTIGATOR, TREATMENT BY VISIT INTERACTION AND BASELINE BY VISIT INTERACTION USING FIRST-ORDER AUTOREGRESSIVE COVARIANCE MATRIX TO MODEL CORRELATIONS WITHIN PATIENT ACROSS VISITS.									
A) P-VALUES ARE FROM TESTS FOR A NONZERO LEAST SQUARES MEAN AT THE GIVEN VISIT.									
B) P-VALUES ARE FROM TESTS FOR A TREATMENT DIFFERENCE IN LEAST SQUARES MEANS AT THE GIVEN VISIT.									
C) P-VALUES ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE.									
PROGRAM: \\EAGLE\EAGLE.GRP\PROGRAMS._G\RMP\B4ZS\LYBG\FINAL1(SEFMA12P)									
OUTPUT : \\TIGER\TIGER.GRP\ATOMOX_STAT\LYBG\FINAL1(SEFMA12P)									

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Table LYBG.13. Conners' Global Index-Parent Evening Subscores
Change from Baseline to Endpoint
Study Period II

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE A	P-VALUE B
		-----		-----		-----			
		MEAN	SD	MEAN	SD	MEAN	SD		
TOTAL SCORE									
TMX	127	20.12	6.05	13.30	7.26	-6.82	6.76	<.001	<.001
PLA	60	20.08	5.46	16.85	7.25	-3.23	6.90	<.001	----
95% CONFIDENCE INTERVAL:						(1.76 , 5.65)			
RESTLESS/IMPULSIVE SUBSCALE									
TMX	127	15.79	4.19	10.12	5.59	-5.67	5.28	<.001	<.001
PLA	60	15.45	4.06	13.50	5.34	-1.95	5.15	.003	----
95% CONFIDENCE INTERVAL:						(2.12 , 5.17)			
EMOTIONAL LIABILITY SUBSCALE									
TMX	127	4.33	2.58	3.18	2.46	-1.15	2.42	<.001	.852
PLA	60	4.63	2.36	3.35	2.71	-1.28	2.42	<.001	----
95% CONFIDENCE INTERVAL:						(-0.59, 0.71)			

A) P-VALUE IS FROM WILCOXON SIGNED-RANK TEST.

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH INVESTIGATOR, TREATMENT, BASELINE AS COVARIATE

PROGRAM: \\EAGLE\EAGLE.GRP\PROGRAMS._G\RMP\B4ZS\LYBG\FINAL1(SEFLA15P)

OUTPUT : \\TIGER\TIGER.GRP\ATOMOX_STAT\LYBG\FINAL1(SEFLA15P)

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Table LYBG.14. Brown ADD Scales®:Parent Total Score
Change from Baseline to Endpoint
Study Period II

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE A	P-VALUE B
		MEAN	SD	MEAN	SD	MEAN	SD		
TOTAL SCORE									
TMX	126	111.05	23.88	78.66	36.49	-32.39	33.48	<.001	.009
PLA	59	111.02	19.83	91.69	31.57	-19.32	31.04	<.001	----
95% CONFIDENCE INTERVAL: (3.29 , 22.90)									

A) P-VALUE IS FROM WILCOXON SIGNED-RANK TEST.

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT AND BASELINE AS COVARIATE

PROGRAM: \\EAGLE\EAGLE.GRP\PROGRAMS._G\RMP\B4ZS\LYBG\FINAL1(SEFLA22P)

OUTPUT : \\TIGER\TIGER.GRP\ATOMOX_STAT\LYBG\FINAL1(SEFLA22P)

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Table LYBG.15. Brown ADD Scales®:Parent Cluster Scores
Change from Baseline to Endpoint
Study Period II

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE A	P-VALUE B
		MEAN	SD	MEAN	SD	MEAN	SD		
FOCUS RAW SCORE									
TMX	127	20.28	3.81	13.62	6.68	-6.66	6.34	<.001	.002
PLA	60	19.90	3.60	16.48	5.95	-3.42	6.10	<.001	----
		95% CONFIDENCE INTERVAL: (1.19 , 4.96)							
ACTIVATION RAW SCORE									
TMX	127	18.28	4.38	12.80	6.31	-5.48	5.91	<.001	.018
PLA	60	18.00	3.93	14.63	5.36	-3.37	5.04	<.001	----
		95% CONFIDENCE INTERVAL: (0.35 , 3.66)							
EFFORT RAW SCORE									
TMX	127	20.58	4.98	14.86	7.22	-5.72	6.70	<.001	.003
PLA	59	20.75	4.26	17.95	6.45	-2.80	6.29	.003	----
		95% CONFIDENCE INTERVAL: (1.03 , 4.97)							
EMOTION RAW SCORE									
TMX	126	17.14	6.12	12.64	6.96	-4.50	6.11	<.001	.367
PLA	60	17.30	5.95	13.45	6.54	-3.85	6.34	<.001	----
		95% CONFIDENCE INTERVAL: (-0.94, 2.54)							
MEMORY RAW SCORE									
TMX	127	12.97	3.79	9.14	4.67	-3.83	4.67	<.001	.017
PLA	59	13.12	3.31	10.76	4.74	-2.36	4.61	<.001	----
		95% CONFIDENCE INTERVAL: (0.28 , 2.88)							
ACTION RAW SCORE									
TMX	127	21.78	5.47	15.41	7.65	-6.37	6.87	<.001	.005
PLA	59	22.15	5.04	18.61	7.04	-3.54	6.62	<.001	----
		95% CONFIDENCE INTERVAL: (0.90 , 4.94)							
SUM OF RAW SCORES 1-5									
TMX	126	89.27	19.81	63.21	29.66	-26.06	27.29	<.001	.012
PLA	59	88.86	16.98	73.08	26.26	-15.78	25.27	<.001	----
		95% CONFIDENCE INTERVAL: (2.23 , 18.17)							

A) P-VALUE IS FROM WILCOXON SIGNED-RANK TEST.

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT AND BASELINE AS COVARIATE
 PROGRAM: \\EAGLE\EAGLE.GRP\PROGRAMS_G\RMP\B4ZS\LYBG\FINAL1(SEFLA23P)
 OUTPUT : \\TIGER\TIGER.GRP\ATOMOX_STAT\LYBG\FINAL1(SEFLA23P)

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Table LYBG.16. Clinical Global Impression of ADHD Severity (CGI-ADHD-S)
Change from Baseline to Endpoint
Study Period II

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE A	P-VALUE B
		MEAN	SD	MEAN	SD	MEAN	SD		
CGI--ADHD SEVERITY									
TMX	126	5.04	0.81	3.46	1.34	-1.58	1.38	<.001	<.001
PLA	60	5.03	0.78	4.32	1.03	-0.72	1.09	<.001	----
95% CONFIDENCE INTERVAL:						(0.49 , 1.23)			

A) P-VALUE IS FROM WILCOXON SIGNED-RANK TEST.

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT AND BASELINE AS COVARIATE

PROGRAM: \\EAGLE\EAGLE.GRP\PROGRAMS._G\RMP\B4ZS\LYBG\FINAL1(SEFLA24P)

OUTPUT : \\TIGER\TIGER.GRP\ATOMOX_STAT\LYBG\FINAL1(SEFLA24P)

**Table LYBG.17. Summary of Treatment-Emergent Adverse Events
by System Organ Class Using MedDRA
Preferred Terms in at Least 5% of Patients
All Randomized Patients
Study Period II**

System Organ Class: Overall				
Preferred Term	ATOMOX (N=131) n (%)	Placebo (N=63) n (%)	Total (N=194) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	92 (70.2)	28 (44.4)	120 (61.9)	.001
PATIENTS WITH NO TESS	39 (29.8)	35 (55.6)	74 (38.1)	.001
System Organ Class: Ear and labyrinth disorders				
Preferred Term	ATOMOX (N=131) n (%)	Placebo (N=63) n (%)	Total (N=194) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	0	1 (1.6)	1 (0.5)	.325
PATIENTS WITH NO TESS	131 (100)	62 (98.4)	193 (99.5)	.325
System Organ Class: Eye disorders				
Preferred Term	ATOMOX (N=131) n (%)	Placebo (N=63) n (%)	Total (N=194) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	3 (2.3)	2 (3.2)	5 (2.6)	.660
PATIENTS WITH NO TESS	128 (97.7)	61 (96.8)	189 (97.4)	.660
System Organ Class: Gastrointestinal disorders				
Preferred Term	ATOMOX (N=131) n (%)	Placebo (N=63) n (%)	Total (N=194) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	45 (34.4)	10 (15.9)	55 (28.4)	.010
PATIENTS WITH NO TESS	86 (65.6)	53 (84.1)	139 (71.6)	.010
Abdominal pain upper	20 (15.3)	4 (6.3)	24 (12.4)	.103
Nausea	15 (11.5)	5 (7.9)	20 (10.3)	.615
Dyspepsia	8 (6.1)	1 (1.6)	9 (4.6)	.276
Vomiting NOS	8 (6.1)	1 (1.6)	9 (4.6)	.276
Diarrhoea NOS	2 (1.5)	4 (6.3)	6 (3.1)	.089
System Organ Class: General disorders and administration site conditions				
Preferred Term	ATOMOX (N=131) n (%)	Placebo (N=63) n (%)	Total (N=194) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	19 (14.5)	4 (6.3)	23 (11.9)	.153
PATIENTS WITH NO TESS	112 (85.5)	59 (93.7)	171 (88.1)	.153
Fatigue	13 (9.9)	1 (1.6)	14 (7.2)	.039
System Organ Class: Immune system disorders				
Preferred Term	ATOMOX (N=131) n (%)	Placebo (N=63) n (%)	Total (N=194) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	1 (0.8)	1 (1.6)	2 (1.0)	.545
PATIENTS WITH NO TESS	130 (99.2)	62 (98.4)	192 (99.0)	.545

(continued)

**Table LYBG.17. Summary of Treatment-Emergent Adverse Events
by System Organ Class Using MedDRA
Preferred Terms in at Least 5% of Patients
All Randomized Patients
Study Period II (continued)**

System Organ Class: Infections and infestations				
Preferred Term	ATOMOX (N=131) n (%)	Placebo (N=63) n (%)	Total (N=194) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	19 (14.5)	4 (6.3)	23 (11.9)	.153
PATIENTS WITH NO TESS	112 (85.5)	59 (93.7)	171 (88.1)	.153
System Organ Class: Injury, poisoning and procedural complications				
Preferred Term	ATOMOX (N=131) n (%)	Placebo (N=63) n (%)	Total (N=194) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	3 (2.3)	0	3 (1.5)	.552
PATIENTS WITH NO TESS	128 (97.7)	63 (100)	191 (98.5)	.552
System Organ Class: Investigations				
Preferred Term	ATOMOX (N=131) n (%)	Placebo (N=63) n (%)	Total (N=194) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	4 (3.1)	0	4 (2.1)	.306
PATIENTS WITH NO TESS	127 (96.9)	63 (100)	190 (97.9)	.306
System Organ Class: Metabolism and nutrition disorders				
Preferred Term	ATOMOX (N=131) n (%)	Placebo (N=63) n (%)	Total (N=194) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	25 (19.1)	4 (6.3)	29 (14.9)	.019
PATIENTS WITH NO TESS	106 (80.9)	59 (93.7)	165 (85.1)	.019
Appetite decreased NOS	23 (17.6)	4 (6.3)	27 (13.9)	.045
System Organ Class: Musculoskeletal and connective tissue disorders				
Preferred Term	ATOMOX (N=131) n (%)	Placebo (N=63) n (%)	Total (N=194) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	4 (3.1)	1 (1.6)	5 (2.6)	1.00
PATIENTS WITH NO TESS	127 (96.9)	62 (98.4)	189 (97.4)	1.00
System Organ Class: Nervous system disorders				
Preferred Term	ATOMOX (N=131) n (%)	Placebo (N=63) n (%)	Total (N=194) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	36 (27.5)	10 (15.9)	46 (23.7)	.104
PATIENTS WITH NO TESS	95 (72.5)	53 (84.1)	148 (76.3)	.104
Somnolence	19 (14.5)	1 (1.6)	20 (10.3)	.005
Headache NOS	9 (6.9)	9 (14.3)	18 (9.3)	.115
System Organ Class: Psychiatric disorders				
Preferred Term	ATOMOX (N=131) n (%)	Placebo (N=63) n (%)	Total (N=194) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	22 (16.8)	2 (3.2)	24 (12.4)	.005
PATIENTS WITH NO TESS	109 (83.2)	61 (96.8)	170 (87.6)	.005

(continued)

**Table LYBG.17. Summary of Treatment-Emergent Adverse Events
by System Organ Class Using MedDRA
Preferred Terms in at Least 5% of Patients
All Randomized Patients
Study Period II (concluded)**

System Organ Class: Renal and urinary disorders				
	ATOMOX (N=131)	Placebo (N=63)	Total (N=194)	p-Value*
Preferred Term	n (%)	n (%)	n (%)	
PATIENTS WITH >= 1 TESS	0	1 (1.6)	1 (0.5)	.325
PATIENTS WITH NO TESS	131 (100)	62 (98.4)	193 (99.5)	.325
System Organ Class: Respiratory, thoracic and mediastinal disorders				
	ATOMOX (N=131)	Placebo (N=63)	Total (N=194)	p-Value*
Preferred Term	n (%)	n (%)	n (%)	
PATIENTS WITH >= 1 TESS	8 (6.1)	7 (11.1)	15 (7.7)	.255
PATIENTS WITH NO TESS	123 (93.9)	56 (88.9)	179 (92.3)	.255
System Organ Class: Skin and subcutaneous tissue disorders				
	ATOMOX (N=131)	Placebo (N=63)	Total (N=194)	p-Value*
Preferred Term	n (%)	n (%)	n (%)	
PATIENTS WITH >= 1 TESS	12 (9.2)	2 (3.2)	14 (7.2)	.234
PATIENTS WITH NO TESS	119 (90.8)	61 (96.8)	180 (92.8)	.234

Events are Preferred Terms

Baseline: Visits 1-2, Endpoint: Visits 3-5

Program: RMP.B4ZSLYBG.SASPGM(STESA01P)

Input data from RMP.SAS.B4ZM.L.USLYBGSW

* Frequencies are analyzed using a Fisher's Exact test.

XAES0002 MEDDRA VERSION: 5.0

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Approved: 11 November 2004

**Table LYBG.18. Child Health Questionnaire-Parent-Completed Full Length (CHQ-PF50)
 Mental Health Subscale Scores
 Change from Baseline to Endpoint
 Study Period II**

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE A	P-VALUE B
		MEAN	SD	MEAN	SD	MEAN	SD		
BODYILY PAIN									
TMX	116	86.81	17.22	80.43	20.19	-6.38	22.82	.006	.425
PLA	54	83.33	20.92	81.85	23.48	-1.48	25.51	.771	----
		95% CONFIDENCE INTERVAL: (-4.02, 9.47)							
BEHAVIOR									
TMX	116	40.78	18.87	56.94	19.27	16.16	20.17	<.001	.017
PLA	54	43.13	17.91	51.35	19.67	8.22	16.59	<.001	----
		95% CONFIDENCE INTERVAL: (-12.3, -1.22)							
FAMILY ACTIVITIES									
TMX	116	45.69	25.57	62.41	25.43	16.72	24.60	<.001	.005
PLA	54	49.70	26.15	54.30	29.27	4.59	23.28	.061	----
		95% CONFIDENCE INTERVAL: (-17.8, -3.21)							
GENERAL HEALTH									
TMX	116	75.27	15.69	76.90	14.11	1.63	13.60	.293	.748
PLA	54	78.24	15.86	79.39	16.77	1.15	11.71	.435	----
		95% CONFIDENCE INTERVAL: (-3.19, 4.44)							
MENTAL HEALTH									
TMX	116	66.03	16.49	73.15	16.00	7.11	15.52	<.001	.497
PLA	54	67.96	15.62	72.59	17.80	4.63	16.48	.060	----
		95% CONFIDENCE INTERVAL: (-6.07, 2.96)							
PARENT EMOTIONAL									
TMX	116	43.57	17.82	56.42	24.18	12.85	23.67	<.001	.293
PLA	53	44.64	17.90	53.17	21.54	8.53	19.64	.002	----
		95% CONFIDENCE INTERVAL: (-10.6, 3.23)							

(continued)

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Approved: 11 November 2004

**Table LYBG.18. Child Health Questionnaire-Parent-Completed Full Length (CHQ-PF50)
 Mental Health Subscale Scores
 Change from Baseline to Endpoint
 Study Period II (concluded)**

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE A	P-VALUE B
		MEAN	SD	MEAN	SD	MEAN	SD		
PHYSICAL FUNCTION									
TMX	116	95.79	12.09	96.47	12.23	0.68	13.52	.637	.875
PLA	54	97.06	9.91	96.78	14.82	-0.28	16.83	.547	----
		95% CONFIDENCE INTERVAL:				(-3.74, 4.39)			
PHYSICAL SUMMARY									
TMX	115	55.03	8.47	53.69	7.89	-1.34	8.98	.017	.348
PLA	53	55.79	6.69	55.04	9.81	-0.75	8.21	.884	----
		95% CONFIDENCE INTERVAL:				(-1.34, 3.78)			
PARENT TIME IMPACT									
TMX	116	62.65	23.97	76.25	24.67	13.60	27.36	<.001	.016
PLA	54	66.33	23.74	68.50	26.94	2.17	23.29	.294	----
		95% CONFIDENCE INTERVAL:				(-17.0, -1.74)			
ROLE EMOTIONAL/BEHAVIOR									
TMX	116	60.62	36.21	79.95	29.22	19.33	34.44	<.001	.052
PLA	54	64.02	31.15	71.72	32.27	7.70	33.38	.116	----
		95% CONFIDENCE INTERVAL:				(-17.4, 0.07)			
ROLE PHYSICAL									
TMX	115	89.91	23.48	91.96	20.50	2.04	26.79	.371	.622
PLA	54	95.33	17.33	94.41	20.27	-0.93	11.58	.688	----
		95% CONFIDENCE INTERVAL:				(-4.60, 7.67)			
SELF ESTEEM									
TMX	116	61.45	20.36	69.53	19.97	8.09	22.60	<.001	.131
PLA	54	67.31	20.94	67.80	21.99	0.48	16.57	.450	----

A) P-VALUE IS FROM WILCOXON SIGNED-RANK TEST.

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH INVESTIGATOR, TREATMENT, BASELINE AS COVARIATE
 PROGRAM: \\EAGLE\EAGLE.GRP\PROGRAMS._G\RMP\B4ZS\LYBG\FINAL1(SEFLA26P)
 OUTPUT : \\TIGER\TIGER.GRP\ATOMOX_STAT\LYBG\FINAL1(SEFLA26P)

Summary ID# 5671

Clinical Study Summary: Study B4Z-US-LYBH

Placebo-Controlled Study of the Effects of Atomoxetine Hydrochloride on Bladder Control in Children with Nocturnal Enuresis

Date summary approved by Lilly: 30 November 2006

Brief Summary of Results

This study was a randomized, double-blind, placebo-controlled comparison study of outpatients aged 6 through 14 with nocturnal enuresis with an open-label extension.

Atomoxetine-treated patients reported an increase from 1.51 to 2.98 dry nights per week compared with placebo patients who reported an increase from 1.01 to 1.61 dry nights per week ($p=.01$). Fifteen of the atomoxetine-treated subjects had an increase of at least 2 dry nights per week compared with only 6 of the placebo-treated subjects ($p=.042$). Results of a repeated measures analysis indicated that atomoxetine produced significantly greater efficacy compared with placebo overall and specifically at Visits 5, 6, and 8.

During the discontinuation/no drug period, patients who were previously treated with atomoxetine reported a decrease of 0.8 dry nights per week, while patients who were previously treated with placebo reported a slight increase of .06 nights per week ($p=.01$). Patients who continued into the open-label extension period increased their number of dry nights per week after the re-initiation of treatment and this increase continued over time ($p<.001$).

There were no deaths reported in this study. Of the two reported serious adverse events (SAEs) for this study, one (dehydration) occurred in a placebo-treated patient, the other (asthma not otherwise specified [NOS]) occurred in an atomoxetine-treated patient. There were no significant differences in treatment-emergent adverse events (TEAEs) or reasons for study discontinuation during the acute period between placebo and patients treated with atomoxetine.

Atomoxetine-treated subjects had a statistically significant increase in mean standing pulse and mean supine pulse compared with placebo-treated subjects ($p < .001$ for both measures). Supine pulse increased 8.39 bpm from baseline, while standing pulse increased 11.05 bpm from baseline. There were no significant differences between treatments in blood pressure. During the open-label extension period, subjects had a statistically significant increase in supine pulse. Atomoxetine-treated subjects had a decrease during the acute period in weight of .45 kg compared to an increase of 1.08 kg for placebo ($p < .001$). During the open-label extension period, subjects had significant increases in height and weight (2.64 cm and 1.65 kg, $p < .001$ for each).

Atomoxetine-treated subjects had a statistically significant increase in heart rate and the expected related decreases in PR interval, RR, and QT intervals compared with placebo-treated subjects. None of the subjects had increased corrected QT values. During the open-label extension period, subjects had a significant decrease from baseline in RR interval; they also had a significant increase from baseline in the QRS interval. None of the changes in electrocardiogram (ECG) were considered clinically significant. There were statistically significant change score differences between atomoxetine and placebo for some laboratory values, but they were small relative to baseline.

Title of Study: Placebo-Controlled Study of the Effects of Atomoxetine Hydrochloride on Bladder Control in Children with Nocturnal Enuresis	
Investigator(s): This multicenter study included 7 principal investigators.	
Study Center(s): This study was conducted at 7 study centers in 1 country.	
Length of Study: 8 months Date of first patient enrolled: 03 December 2001 Date of last patient completed: 05 August 2002	Phase of Development: 3b
Objectives: The primary objective of this study was to compare the efficacy of atomoxetine to placebo for treating nocturnal enuresis in a sample of pediatric subjects who met DSM IV criteria for nocturnal enuresis. Efficacy was determined by a comparison of the mean number of dry nights per week using an intent-to-treat analysis of the primary outcome measure, the Dry Night Log-Parent Report (DNL-PR) for atomoxetine-treated and placebo-treated subjects. Secondary objectives: • To compare the safety and tolerability of atomoxetine with placebo in a population who meet DSM-IV criteria for nocturnal enuresis. • To compare the improvement in patient-reported outcomes (quality of life) between atomoxetine and placebo as assessed by the Child Health Questionnaire PF50 (CHQ-PF50). • To assess the safety and tolerability of rapid-dose titration of atomoxetine to the fixed-treatment dose. • To compare the improvement on the Parent Distress Scale (PADS) between atomoxetine- and placebo-treated subjects. • To evaluate, during the open-label extension period, the efficacy of atomoxetine in treating nocturnal enuresis, as determined by a comparison of the mean number of dry nights per week using an intent-to-treat analysis of the primary outcome measure, the Dry Night Log-Parent (DNL-PR) for atomoxetine-treated subjects. • To assess the safety and tolerability of dose titration of atomoxetine to the fixed-treatment dose, assess and track the dosing range of atomoxetine on a BID dosing regimen, and to assess the maintenance of benefits of treatment during the flexible-dosing, open-label extension.	
Study Design: A randomized, double-blind, placebo-controlled comparison study of outpatients aged 6 through 18 years with nocturnal enuresis with an open-label extension.	
Number of Patients: Planned: Approximately 80 pediatric subjects. Randomized: 44 atomoxetine, 43 placebo Completed double-blind period: 35 atomoxetine, 34 placebo	
Diagnosis and Main Criteria for Inclusion: Patients were at least 6 years old but less than 18 years old at Visit 1. Patients met the DSM-IV diagnostic criteria for nocturnal enuresis. The diagnosis of nocturnal enuresis was confirmed during the screening visit by administration of the Voiding History-National Kidney Foundation questionnaire (VH-NKF).	
Test Product, Dose, and Mode of Administration: Atomoxetine 0.5 mg/kg/day, given for three days, 1.0 mg/kg/day for three days and all subsequent days at 1.5 mg/kg/day, all doses were divided and given orally twice a day. Mean final dose for the double-blind treatment period: 1.42 mg/kg.	
Reference Therapy, Dose, and Mode of Administration: Placebo was administered orally BID.	
Duration of Treatment: Twelve weeks double-blind treatment, followed by a 9 to 18 day drug discontinuation period, then a 9 to 18 day period of no study drug, followed by an open-label extension period for up to 15 months.	

Variables:

Efficacy: The primary efficacy measure was the number of dry nights per week with data recorded on the Dry Night Log-Parent Report (DNL-PR). The secondary efficacy measure was the Parent Distress Scale (PADS) which assessed the impact of the child's enuresis on the parent via a 100 mm Visual Analog Scale.

Safety: Safety measures included TEAEs, vital signs, height and weight, laboratory analytes, pregnancy tests at screening, and ECGs.

Health Outcomes: Physical and psychosocial well being was assessed using the Child Health Questionnaire Parent Form 50 (CHQ-PF50).

Evaluation Methods:

Data were analyzed separately for Study Period II (acute double-blind), Study Period III/IV (discontinuation/washout), and Study Period V (open-label extension).

A fixed-effects ANOVA model with terms for treatment and investigator was used to assess whether there was a treatment difference in mean number of dry nights per week, a two-sided significance level of .05 was assumed. Each subject's number of dry nights per week was defined as the product of 7 and the ratio of dry nights to total number of nights recorded during the study period visit window, provided that no more than 30% of the possible nights were missing from that interval.

All postbaseline DNL-PR and PADS scores during the acute period were analyzed using a restricted maximum likelihood (REML) based mixed effects model, repeated measures technique. This analysis included the fixed categorical effects of treatment, investigator, visit, and treatment-by-visit interaction as well as the continuous, fixed covariate of baseline score and a random subject effect. Four different covariance structures were considered to model the within-subject variance: unstructured, heterogeneous toeplitz, heterogeneous autoregressive of order 1, and heterogeneous compound symmetric. The covariance structure that produced the largest Akaike's Information Criteria score was selected for each analysis. These analyses compared atomoxetine and placebo at each postbaseline visit using a contrast from the repeated measures mixed effects model. During the open-label extension period, DNL-PR postbaseline scores were analyzed with a repeated measures model that included only investigator and visit.

Parent Distress Scale and CHQ change from baseline was analyzed during the acute period and drug washout period using a fixed-effects analysis of variance (ANOVA) model with terms for treatment and investigator. For analyses of data during the drug washout period, treatment groups were defined as the treatment to which patients were randomized at Visit 2. Fisher's Exact test was used to test for a treatment difference in incidence of response (increase from baseline to endpoint of 2 or more dry nights per week).

Changes from baseline in labs, vitals, and ECGs were analyzed using a one-way ANOVA model with a term for treatment during the acute period and within group changes (for acute and open-label period) were assessed using Wilcoxon's Signed rank test. Incidence of TEAEs and treatment-emergent abnormal labs were compared across treatments during the acute period using Fisher's Exact test.

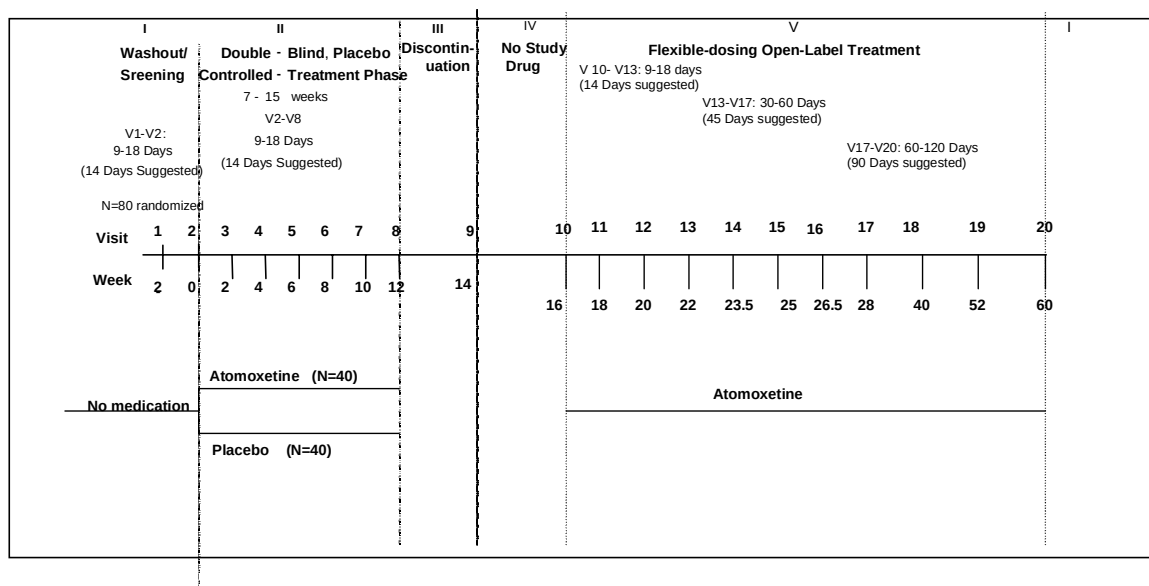


Figure LYBH.1. Study design.

Patient Demographics

There were 95 patients entered in this study of which 8 were not randomized, 44 were randomized to Atomoxetine, and 43 to placebo. The patient population was approximately 26% female and 74% male. The median age of patients in this study was 9.4 years. The majority of the patients (approximately 86%) were Caucasian. See Table LYBH.1 below.

Table LYBH.1. Patient Demographics

Variable	Not Rand (N=8)	ATOMOX (N=44)	Placebo (N=43)	Total (N=95)

Sex: No. (%)				
No. Patients	8	44	43	95
Female	2 (25.0)	11 (25.0)	12 (27.9)	25 (26.3)
Male	6 (75.0)	33 (75.0)	31 (72.1)	70 (73.7)
Origin: No. (%)				
No. Patients	8	44	43	95
African Descent	2 (25.0)	2 (4.5)	1 (2.3)	5 (5.3)
Caucasian	4 (50.0)	38 (86.4)	40 (93.0)	82 (86.3)
Hispanic	2 (25.0)	3 (6.8)	1 (2.3)	6 (6.3)
Other	0	1 (2.3)	1 (2.3)	2 (2.1)
Age: yrs				
No. Patients	8	44	43	95
Mean	9.90	10.22	9.12	9.69
Median	9.38	10.31	9.10	9.40
Standard Dev.	2.35	2.02	1.89	2.04
Minimum	7.44	6.37	6.22	6.22
Maximum	13.81	14.44	13.19	14.44
Height (cm) at Visit 1				
No. Patients	7	44	43	94
Mean	139.36	139.55	135.38	137.63
Median	137.00	138.50	134.00	137.00
Standard Dev.	14.44	12.95	11.90	12.62
Minimum	122.00	119.50	115.00	115.00
Maximum	157.50	163.00	163.00	163.00
Unspecified	1	0	0	1
Weight (kg) at Visit 1				
No. Patients	8	44	43	95
Mean	43.75	38.29	36.18	37.80
Median	39.80	35.25	35.90	35.40
Standard Dev.	20.12	11.30	10.95	12.10
Minimum	22.70	23.20	20.00	20.00
Maximum	78.20	64.90	61.70	78.20
CYP2D6 Status				
No. Patients	8	44	43	95
EXTN	5 (100)	42 (95.5)	41 (95.3)	88 (95.7)
SLOW	0	2 (4.5)	2 (4.7)	4 (4.3)
Unspecified	3	0	0	3

Patient Disposition

Eighteen patients discontinued during the treatment phase (Study Period II); three for adverse events. Three-fourths of the randomized patients (75%) entered the open-label extension period. See Tables LYBH.2 and LYBH.3 below for summary of patient disposition for Study Periods I-V.

Table LYBH.2. Summary Report of Patient Disposition by Visit Study Period I-II

	1	2	3	4	5	6	7	8
	N	N	N	N	N	N	N	N
ADVERSE EVENT	0	0	1	0	0	0	1	1
DEATH	0	0	0	0	0	0	0	0
LACK OF EFFICACY, PATIENT AND PHYSICIAN PERCEPTION	0	0	0	1	0	0	0	0
LACK OF EFFICACY, PATIENT PERCEPTION	0	0	2	0	1	0	0	0
LACK OF EFFICACY, PHYSICIAN PERCEPTION	0	0	0	0	0	0	0	0
LOST TO FOLLOW-UP	1	0	0	0	1	2	1	1
NONCOMPLIANCE	0	0	1	0	1	0	0	0
PATIENT CONFLICT OR OTHER PATIENT DECISION	1	0	1	0	0	0	1	2
PHYSICIAN DECISION	0	0	0	0	0	0	0	0
PROTOCOL COMPLETE	0	0	0	0	0	0	0	0
PROTOCOL VIOLATION	0	0	0	0	0	0	0	0
SATISFACTORY RESPONSE, PATIENT AND PHYSICIAN PERCEPTION	0	0	0	0	0	0	0	0
SATISFACTORY RESPONSE, PATIENT PERCEPTION	0	0	0	0	0	0	0	0
SATISFACTORY RESPONSE, PHYSICIAN PERCEPTION	0	0	0	0	0	0	0	0
SPONSOR DECISION	0	0	0	0	0	0	0	0
STUDY PERIOD I COMPLETED	87	0	0	0	0	0	0	0
STUDY PERIOD II COMPLETED	0	0	0	0	0	0	0	68
NOT RANDOMIZED Entry criteria not met	3	3	0	0	0	0	0	0
TOTAL PATIENTS DISPOSITION AT EACH VISIT	92	3	5	1	3	2	3	72

POPULATION: ALL OF THE PATIENTS ENROLLED IN STUDY PERIODS I-II ARE INCLUDED

Table LYBH.3. Summary Report of Patient Disposition by Visit Study Period III-V

	9	10	11	12	13	14	15	16	17	18
	N	N	N	N	N	N	N	N	N	N
ADVERSE EVENT	0	0	1	0	1	1	0	0	0	0
DEATH	0	0	0	0	0	0	0	0	0	0
LACK OF EFFICACY, PATIENT AND PHYSICIAN PERCEPTION	0	0	1	2	4	5	0	1	1	0
LACK OF EFFICACY, PATIENT PERCEPTION	0	0	0	0	3	2	1	0	0	0
LACK OF EFFICACY, PHYSICIAN PERCEPTION	0	0	0	0	0	0	0	0	0	0
LOST TO FOLLOW-UP	2	0	0	0	0	3	1	1	0	0
NONCOMPLIANCE	0	0	0	0	0	0	2	1	2	1
PATIENT CONFLICT OR OTHER PATIENT DECISION	1	1	2	0	0	0	2	5	2	0
PHYSICIAN DECISION	0	0	0	0	1	0	0	0	0	0
PROTOCOL COMPLETE	0	0	0	0	0	0	0	0	0	0
PROTOCOL VIOLATION	0	0	0	0	0	0	0	0	0	0
SATISFACTORY RESPONSE, PATIENT AND PHYSICIAN PERCEPTION	0	0	0	0	0	0	0	0	0	0
SATISFACTORY RESPONSE, PATIENT PERCEPTION	0	0	0	0	0	0	0	0	0	0
SATISFACTORY RESPONSE, PHYSICIAN PERCEPTION	0	0	0	0	0	0	0	0	0	0
SPONSOR DECISION	0	0	0	0	0	0	0	0	6	10
STUDY PERIOD III COMPLETED	66	0	0	0	0	0	0	0	0	0
STUDY PERIOD IV COMPLETED	0	65	0	0	0	0	0	0	0	0
STUDY PERIOD V COMPLETED	0	0	0	0	0	0	0	0	1	0
TOTAL PATIENTS DISPOSITION AT EACH VISIT	69	66	4	2	9	11	6	8	12	11

POPULATION: ALL OF THE PATIENTS ENROLLED IN STUDY PERIODS III-V ARE INCLUDED

Primary Efficacy Measures

Results of a repeated measures analysis of the DNL-PR of Study Period II, shown in Table LYBH.4a, indicated that atomoxetine produced significantly greater efficacy compared with placebo overall and specifically at Visits 5, 6, and 8. Atomoxetine-treated patients reported an increase from 1.51 to 2.98 dry nights per week compared with placebo patients who reported an increase from 1.01 to 1.61 dry nights per week ($p=.01$) (see Table LYBH.4b).

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**Table LYBH.4a. Dry Night Log-Parent Report: Average Dry Nights Per Week
Repeated Measures Summary Table Study Period II**

Visit	Atomoxetine			Placebo			Treatment Difference		
	LS Mean	SE	p-val a	LS Mean	SE	p-val a	LS Mean	SE	p-val b
3	2.26	0.28	<.001	1.96	0.29	<.001	0.30	0.37	.415
4	2.54	0.30	<.001	1.77	0.31	<.001	0.78	0.39	.053
5	2.90	0.33	<.001	1.94	0.34	<.001	0.96	0.44	.032
6	2.73	0.29	<.001	1.87	0.30	<.001	0.86	0.39	.029
7	2.67	0.32	<.001	2.15	0.32	<.001	0.52	0.42	.224
8	2.83	0.29	<.001	1.69	0.30	<.001	1.14	0.39	.004
95% Confidence Interval on Change from Baseline to Visit 8									
(-0.16, 1.03)				(0.99, 2.16)					
Summary of Model Parameters			F-Value	P-Value c					
Baseline			55.99	<.001					
Treatment			4.98	.029					
Visit			0.99	.430					
Investigator			0.76	.602					
Treatment*Visit			1.69	.149					

Results based on a mixed model with visit, baseline, treatment, investigator, treatment by visit interaction using an unstructured covariance matrix to model correlations within patient across visits.

a) P-values are from tests for a nonzero least squares mean at the given visit.

b) P-values are from tests for a treatment difference in least squares means at the given visit.

c) P-values are from F-tests for a nonzero coefficient estimate.

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**Table LYBH.4b. Dry Night Log-Parent Report: Average Dry Nights per Week
Mean Change From Baseline to Endpoint Study Period II**

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		MEAN	SD	MEAN	SD	MEAN	SD		
AVG DRY NIGHTS PER WEEK									
TMX	42	1.51	1.28	2.98	2.28	1.47	1.60	<.001	.010
PLA	41	1.01	0.95	1.61	1.74	0.60	1.38	.008	----
95% CONFIDENCE INTERVAL: (-1.54, -0.22)									

A) P-VALUE IS FROM WILCOXON SIGNED-RANK TEST.

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT SCORES USING LEAST SQUARES MEANS
FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT AS COVARIATE

TMX = Atomoxetine

Table LYBH.5 shows that 15 of the atomoxetine-treated subjects had an increase of at least 2 dry nights per week compared with only 6 placebo-treated subjects ($p=.042$).

Table LYBH.5. Efficacy Response Rates

Variable	ATOMOX (N=44)	Placebo (N=43)	Total (N=87)	p-Value

Increase of ≥ 2 dry nights per week				
No. Patients	42	41	83	.042*
No	27 (64.3)	35 (85.4)	62 (74.7)	
Yes	15 (35.7)	6 (14.6)	21 (25.3)	

One patient was excluded from this analysis due to Dry Night Log non-compliance

* Frequencies are analyzed using a Fishers-Exact test.

During the discontinuation/no drug period (Study Period III/IV), patients who were previously treated with atomoxetine reported a decrease of 0.8 dry nights per week, while patients who were previously treated with placebo reported an increase of .06 nights per week ($p=.01$) (Table LYBH.6).

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Table LYBH.6. Dry Night Log-Parent Report: Average Dry Nights Per Week Mean Change From Baseline to Endpoint Study Period III/IV

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		MEAN	SD	MEAN	SD	MEAN	SD		
AVG DRY NIGHTS PER WEEK									
TMX	34	3.28	2.51	2.48	2.24	-0.80	1.23	<.001	.010
PLA	33	1.31	1.89	1.37	1.69	0.06	1.09	.790	
95% CONFIDENCE INTERVAL:						(0.20 , 1.37)			

A) P-VALUES ARE FROM THE WILCOXON SIGNED-RANK TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING A FIXED EFFECT ANOVA MODEL WITH TERMS FOR TREATMENT AND INVESTIGATOR

POPULATION: ALL OF THE PATIENTS ENROLLED IN STUDY PERIOD III/IV ARE INCLUDED

Table LYBH.7 shows that the patients who continued into the open-label extension period increased their number of dry nights per week after the reinitiation of treatment and this increase continued over time ($p < .001$).

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**Table LYBH.7. Repeated Measures Summary Table for Dry Night Log
(Average Dry Nights per Week)
Study Period V**

VISIT	LSMEAN	SE	P-VAL (A)	P-VAL (B)
11	0.14	0.77	.852	<.001
12	0.73	0.77	.346	
13	1.56	0.79	.051	
14	1.58	0.80	.051	
15	1.58	0.81	.055	
16	1.24	0.84	.140	
17	1.49	0.84	.079	

RESULTS BASED ON A MIXED MODEL WITH VISIT, BASELINE, CYP2D6GEN, INVESTIGATOR
USING AN UNSTRUCTURED COVARIANCE MATRIX TO MODEL CORRELATIONS WITHIN PATIENT ACROSS VISITS
A) P-VALUES ARE FROM TESTS FOR A NONZERO LEAST SQUARES MEAN AT THE GIVEN VISIT
B) P-VALUE IS FROM F-TEST FOR A NONZERO COEFFICIENT ESTIMATE FOR THE VISIT TERM BASED ON THE MODEL DESCRIBED ABOVE
POPULATION: ALL PATIENTS WHO ENTERED IN THE OPEN LABEL EXTENSION TREATMENT PERIOD ARE INCLUDED

Table LYBH.8 shows that no statistically significant treatment differences in change from baseline were detected on the PADS during the acute period.

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Table LYBH.8. Parent Distress Scale
Mean Change From Baseline to Endpoint
Study Period II

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		-----		-----		-----			
		MEAN	SD	MEAN	SD	MEAN	SD		
PADS SCORE FOR ENURESIS									
TMX	44	50.39	35.24	31.50	29.49	-18.89	29.14	<.001	.313
PLA	41	55.24	28.70	43.27	26.87	-11.98	29.21	.007	----
95% CONFIDENCE INTERVAL:						(-6.29 , 19.36)			

A) P-VALUE IS FROM WILCOXON SIGNED-RANK TEST.

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT AS COVARIATE

Table LYBH.9 shows that there were no statistically significant differences between treatment groups in mean change from baseline in Parent Distress Scale scores during drug discontinuation. Parent Distress Scale scores worsened for both treatment groups during the drug discontinuation; however, there was not a statistically significant difference between the original randomization groups.

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Table LYBH.9. Parent Distress Scale
Mean Change From Baseline To LOCF Endpoint
Study Period III/IV

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		-----		-----		-----			
		MEAN	SD	MEAN	SD	MEAN	SD		
PADS SCORE FOR ENURESIS									
TMX	34	24.62	27.70	29.65	33.02	5.03	20.27	.481	.901
PLA	33	45.52	27.77	51.06	26.63	5.55	23.27	.393	
95% CONFIDENCE INTERVAL:						(-10.53, 11.94)			

A) P-VALUES ARE FROM THE WILCOXON SIGNED-RANK TEST.

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING A FIXED EFFECT ANOVA MODEL WITH TERMS FOR TREATMENT AND INVESTIGATOR

POPULATION: ALL OF THE PATIENTS ENROLLED IN STUDY PERIOD III/IV ARE INCLUDED

TMX = Atomoxetine

Safety

There were no deaths reported in this study. Of the two reported SAEs for this study (see Table LYBH.10), one (dehydration) occurred in a placebo-treated patient. The other (asthma NOS) occurred in an atomoxetine-treated patient.

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Table LYBH.10. Listing of Patients who died or had SAEs

Inv	Pat	Therapy Group	Days from Start of Therapy	Event Resolved?	Event Duration (days)	Preferred Term Name
4	J	Placebo	49	Yes	2	Dehydration
7	P	ATOMOX	129	Yes	2	Asthma NOS

Visits 1-8

There were no statistically significant differences in TEAEs (Table LYBH.11) or reasons for study discontinuation (LYBH.12) during the acute period between placebo-treated and atomoxetine-treated patients. Table LYBH.13 gives a summary of TEAEs during the open-label extension period.

**Table LYBH.11. Summary of Treatment-Emergent Adverse Events that Occurred in ≥5% of Patients
All Randomized Patients with ≥1 Dose of Study Drug**

Preferred Term	ATOMOX (N=44)		Placebo (N=43)		Total (N=87)		p-Value*
	n	(%)	n	(%)	n	(%)	
PATIENTS WITH ≥ 1 TESS	29	(65.9)	25	(58.1)	54	(62.1)	.512
PATIENTS WITH NO TESS	15	(34.1)	18	(41.9)	33	(37.9)	.512
Headache NOS	9	(20.5)	4	(9.3)	13	(14.9)	.229
Nausea	4	(9.1)	3	(7.0)	7	(8.0)	1.00
Appetite decreased NOS	3	(6.8)	2	(4.7)	5	(5.7)	1.00
Gastroenteritis viral NOS	3	(6.8)	1	(2.3)	4	(4.6)	.616
Gastroenteritis NOS	3	(6.8)	1	(2.3)	4	(4.6)	.616
Heart rate increased	3	(6.8)	0		3	(3.4)	.241
Insomnia	3	(6.8)	0		3	(3.4)	.241
Irritability	3	(6.8)	1	(2.3)	4	(4.6)	.616
Pyrexia	3	(6.8)	2	(4.7)	5	(5.7)	1.00
Vomiting NOS	3	(6.8)	3	(7.0)	6	(6.9)	1.00
Abdominal pain upper	1	(2.3)	3	(7.0)	4	(4.6)	.360
Diarrhoea NOS	1	(2.3)	3	(7.0)	4	(4.6)	.360
Nasopharyngitis	0		3	(7.0)	3	(3.4)	.116
Upper respiratory tract infection NOS	0		4	(9.3)	4	(4.6)	.055

Baseline: Visits 1-2, Endpoint: Visits 3-8
Frequencies are analyzed using a Fisher's Exact test.

Table LYBH.12. Reasons for Discontinuation

Reason for Discontinuation	ATOMOX (N=44)		Placebo (N=43)		p-Value*
	n	(%)	n	(%)	
Study Period II Completed	35	(79.5)	34	(79.1)	1.00
Adverse Event	2	(4.5)	1	(2.3)	1.00
Lack of efficacy, patient perception	2	(4.5)	1	(2.3)	1.00
Lack of efficacy, pat and MD perception	0		1	(2.3)	.494
Unable to contact pat(lost to follow-up)	3	(6.8)	2	(4.7)	1.00
Personal conflict or other pat decision	1	(2.3)	3	(7.0)	.360
Noncompliance	1	(2.3)	1	(2.3)	1.00

Study Period II: Visits 3-8

Table LYBH.13. Summary Report of Treatment-Emergent Adverse Events; Open-Label Extension Period: B4Z-US-LYBH

TESS: BY DESCENDING FREQUENCY	N	N	%
PATIENT >= 1 TESS	65	49	75.4%
Upper respiratory tract infection NOS	65	8	12.3%
Nasopharyngitis	65	7	10.8%
Nausea	65	7	10.8%
Vomiting NOS	65	7	10.8%
Headache	65	6	9.2%
Abdominal pain upper	65	4	6.2%
Pyrexia	65	4	6.2%
Appetite decreased NOS	65	3	4.6%
Cough	65	3	4.6%
Ear infection NOS	65	3	4.6%
Gastroenteritis viral NOS	65	3	4.6%
Influenza like illness	65	3	4.6%
TESS: BY DESCENDING FREQUENCY	N	N	%
Micturition urgency	65	3	4.6%
Pharyngitis streptococcal	65	3	4.6%
Pharyngolaryngeal pain	65	3	4.6%
Rash NOS	65	3	4.6%
Sinusitis NOS	65	3	4.6%
Unexpected therapeutic drug effect	65	3	4.6%
Upper respiratory tract infection viral NOS	65	3	4.6%
Aggression	65	2	3.1%
Asthma NOS	65	2	3.1%
Contusion	65	2	3.1%
Dizziness	65	2	3.1%
Heart rate increased	65	2	3.1%

(continued)

Table LYBH.13. Summary Report of Treatment-Emergent Adverse Events; Open-Label Extension Period: B4Z-US-LYBH (continued)

Influenza	65	2	3.1%
Nasal congestion	65	2	3.1%
Pain in extremity	65	2	3.1%
Pollakiuria	65	2	3.1%
Post procedural pain	65	2	3.1%
Toothache	65	2	3.1%
Abdominal pain NOS	65	1	1.5%
Accidental overdose	65	1	1.5%
Anorexia	65	1	1.5%
Anxiety	65	1	1.5%
Appetite increased NOS	65	1	1.5%
Arthralgia	65	1	1.5%
Attention deficit/hyperactivity disorder	65	1	1.5%
TESS: BY DESCENDING FREQUENCY			
Back pain	65	1	1.5%
Cerebellar syndrome	65	1	1.5%
Chest pain	65	1	1.5%
Conjunctivitis	65	1	1.5%
Constipation	65	1	1.5%
Dehydration	65	1	1.5%
Disturbance in attention	65	1	1.5%
Dysuria	65	1	1.5%
Ear piercing	65	1	1.5%
Epistaxis	65	1	1.5%
Excoriation	65	1	1.5%
Fatigue	65	1	1.5%
Feeling cold	65	1	1.5%

(continued)

Table LYBH.13. Summary Report of Treatment-Emergent Adverse Events; Open-Label Extension Period: B4Z-US-LYBH (concluded)

Insomnia	65	1	1.5%
Intention tremor	65	1	1.5%
Irritability	65	1	1.5%
Mood swings	65	1	1.5%
Mouth injury	65	1	1.5%
Multiple allergies	65	1	1.5%
Oral pain	65	1	1.5%
Orthodontic procedure	65	1	1.5%
Otitis media NOS	65	1	1.5%
Pain exacerbated	65	1	1.5%
Pain in jaw	65	1	1.5%
Pruritus	65	1	1.5%
Psychomotor hyperactivity	65	1	1.5%
TESS: BY DESCENDING FREQUENCY	N	N	%
Rash erythematous	65	1	1.5%
Rash generalised	65	1	1.5%
Rash macular	65	1	1.5%
Rhinorrhoea	65	1	1.5%
Scab	65	1	1.5%
Sinus headache	65	1	1.5%
Social avoidant behaviour	65	1	1.5%
Somnolence	65	1	1.5%
Sweating increased	65	1	1.5%
Tearfulness	65	1	1.5%
Ventricular hypertrophy	65	1	1.5%
Weight increased	65	1	1.5%

POPULATION: ALL OF PATIENTS WHO ENROLLED IN THE OPEN LABEL EXTENSION PERIOD AND
 TOOK AT LEAST ONE DOSE OF STUDY DRUG ARE INCLUDED

Table LYBH.14 shows that atomoxetine-treated subjects had a statistically significant increase in heart rate and the expected related decreases in PR interval, RR, and QT intervals compared with placebo-treated subjects during the acute period.

Table LYBH.14 **Summary of Change from Baseline to Endpoint for ECG Parameters**
All Randomized Patients with ≥ 1 Dose of Study Drug

Variables Analyzed	Therapy	n	-----Baseline-----		Change to -----Endpoint-----		p-Values
			Mean	SD	Mean	SD	
HR	ATOMOX	44	74.98	10.87	8.11	12.30	.001
	Placebo	41	78.90	13.43	-0.12	13.27	(.822)
PR	ATOMOX	44	131.55	15.30	-4.82	10.91	.007
	Placebo	41	137.22	16.68	1.17	9.62	(.296)
QRS	ATOMOX	44	82.59	9.18	1.45	5.81	.782
	Placebo	41	80.59	8.29	1.12	5.14	(.327)
QT	ATOMOX	44	372.14	22.64	-14.14	22.13	.007
	Placebo	41	361.61	27.91	-0.88	26.53	(.445)
QTCD	ATOMOX	44	403.72	11.19	0.38	11.01	.990
	Placebo	41	399.26	13.12	0.52	10.66	(.022)
QTCF	ATOMOX	44	398.89	11.16	-1.92	10.88	.356
	Placebo	41	393.45	14.02	0.35	11.71	(.022)
QTCR	ATOMOX	44	402.01	11.07	-0.44	10.84	.730
	Placebo	41	397.20	13.33	0.46	10.90	(.019)
RR	ATOMOX	44	817.00	119.99	-78.67	114.93	.004
	Placebo	41	781.36	127.77	-8.73	124.61	(.865)

Protocol B4Z-US-LYBH Final Report
Atomoxetine vs Placebo on Bladder Control in Children with Nocturnal Enuresis

Research Project Code: B4Z

Baseline: Visits 1-2, Endpoint: Visits 3-8

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDUC1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Note: Each investigator has at least one patient in each treatment group.

Legend of Variable Abbreviations:

Abbrev.	Description
HR	ECG Heart Rate
PR	PR Interval
QRS	QRS Interval
QT	QT Interval
QTCD	QTC Data-based Correction
QTCF	QTC Fridericia Correction
QTCR	QTC RR Correction
RR	RR Interval

None of the subjects had increased corrected QT values (Table LYBH.15).

Atomoxetine hydrochloride

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Table LYBH.15. Incidence of Potentially Clinically Significant Changes in ECG - Study Period II

		PLA			TMX			Fisher's Exact PVALUE
		N	n	%	N	n	%	P-value
Heart Rate	High	36	0	0.0%	44	6	13.6%	.030
	Low	39	1	2.6%	38	0	0.0%	1.00
QTCD(Data Corrected)	High	41	0	0.0%	44	0	0.0%	n/a
QTCF(Fridericia)	High	41	0	0.0%	44	0	0.0%	n/a

Heart rate - High: Increase of at least 20 to a value of at least 100

- Low: Decrease of at least 15 to a value of at most 60

QTCF(Fridericia) - High: Increase of at least 30 to a value of at least 435

QTCD(Data Corrected) - High: Increase of at least 30 to a value of at least 440

Patients counted as meeting criteria if criteria was met at any postbaseline visit

Population: Enrolled patients who took at least one dose of study drug

Population: Patient should only be in N if they do not meet criteria at baseline

Table LYBH.16 shows that during the open-label extension period, subjects had a statistically significant decrease from baseline in RR interval; they also had a statistically significant increase from baseline in the QRS interval. Table LYBH.17 gives a summary of the change from baseline lab values. Table LYBH.18 lists the mean change from baseline to last-observation carried forward (LOCF) Endpoint for laboratory tests. Table LYBH.19 gives a summary of frequency of patients with treatment-emergent abnormal lab values.

Atomoxetine hydrochloride

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Table LYBH.16. Mean Change from Baseline to LOCF Endpoint For ECGs: Open Label Extension Period

MEASUREMENT	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)
		MEAN	SD	MEAN	SD	MEAN	SD	
ECG HEART RATE	60	80.18	10.83	83.08	11.58	2.90	11.36	.053
ECG RR INTERVAL	60	762.56	108.81	735.94	101.95	-26.62	105.20	.047
ECG PR INTERVAL	60	135.10	17.18	133.60	15.32	-1.50	11.09	.414
ECG QRS INTERVAL	60	82.63	9.30	83.63	9.69	1.00	3.60	.045
ECG QT INTERVAL	60	361.93	24.07	356.93	22.33	-5.00	25.15	.200
FRIDERICIA QTC INTERVAL	60	396.82	13.70	396.07	14.13	-0.75	13.53	.844
DATABASE CORRECTED QTC INTERVAL	60	403.16	13.32	403.23	14.32	0.06	12.63	.512

A) P-VALUES ARE FROM THE WILCOXON SIGNED-RANK TEST

POPULATION: ALL OF PATIENTS WHO ENROLLED IN THE OPEN LABEL EXTENSION PERIOD AND
TOOK AT LEAST ONE DOSE OF STUDY DRUG ARE INCLUDED

Table LYBH.17. Summary of Change from Baseline to Endpoint for Laboratory Analytes
All Randomized Patients with ≥1 Dose of Study Drug

Lab Test	Lab Unit	Therapy	n	-----Baseline-----		Change to -----Endpoint-----		p-Values
				Mean	SD	Mean	SD	
HCT	l	ATOMOX	43	0.3684	0.0249	0.0160	0.0238	.205
		Placebo	40	0.3688	0.0238	0.0083	0.0289	(.004)
HGB	mm1/L-Fe	ATOMOX	43	8.082	0.513	0.085	0.429	.837
		Placebo	40	8.020	0.520	0.070	0.460	(.008)
RBC	TI/L	ATOMOX	43	4.619	0.331	0.002	0.269	.597
		Placebo	40	4.663	0.334	-0.030	0.276	(.016)
WBC	GI/L	ATOMOX	43	6.67	1.63	0.21	1.60	.927
		Placebo	40	7.01	1.88	0.27	1.71	(.779)
BANDS	GI/L	ATOMOX	43	0.000	0.000	0.000	0.000	.267
		Placebo	40	0.001	0.008	-0.001	0.008	(.520)
POLYS	GI/L	ATOMOX	43	3.580	1.180	0.355	1.230	.564
		Placebo	40	3.711	1.456	0.237	1.643	(.869)
LYMPHS	GI/L	ATOMOX	43	2.441	0.681	-0.100	0.649	.373
		Placebo	40	2.671	0.863	-0.005	0.744	(.375)
MONOS	GI/L	ATOMOX	43	0.405	0.107	-0.034	0.131	.006
		Placebo	40	0.392	0.145	0.044	0.121	(.664)
EOSN	GI/L	ATOMOX	43	0.203	0.139	-0.026	0.112	.316
		Placebo	40	0.186	0.125	-0.002	0.126	(.498)
BASO	GI/L	ATOMOX	43	0.044	0.022	0.006	0.023	.184
		Placebo	40	0.047	0.024	-0.002	0.024	(.802)
MCV	fL	ATOMOX	43	80.0	4.3	3.4	3.0	.036
		Placebo	40	79.4	4.0	2.1	2.9	(.885)
PLTCT	GI/L	ATOMOX	43	311.0	62.7	1.3	52.6	.116
		Placebo	40	314.9	62.2	-16.1	44.9	(.293)

(continued)

Table LYBH.17. Summary of Change from Baseline to Endpoint for Laboratory Analytes
All Randomized Patients with ≥ 1 Dose of Study Drug
(continued)

Lab Test	Lab Unit	Therapy	n	-----Baseline-----		Change to -----Endpoint-----		p-Values
				Mean	SD	Mean	SD	
U-SPGR	NO UNITS	ATOMOX	44	1.0255	0.0061	0.0010	0.0095	.958
		Placebo	40	1.0253	0.0073	0.0005	0.0098	(.177)
AST	U/L	ATOMOX	43	27.0	5.9	-1.1	6.2	.514
		Placebo	39	30.7	13.1	-2.4	10.9	(.623)
ALT	U/L	ATOMOX	44	18.1	6.0	-1.1	8.1	.131
		Placebo	40	24.3	24.1	-5.6	21.9	(.018)
CPK	U/L	ATOMOX	44	110.1	39.4	14.4	68.2	.816
		Placebo	40	112.9	40.6	12.0	33.5	(.678)
ALKPH	U/L	ATOMOX	44	240.2	65.4	-8.0	41.0	.515
		Placebo	40	245.0	48.7	-2.8	29.3	(.804)
GGT	U/L	ATOMOX	44	12.0	3.5	-0.3	3.1	.916
		Placebo	40	12.9	3.7	-0.4	2.8	(.784)
BUN	mmol/L	ATOMOX	44	4.90	1.25	-0.17	1.12	.022
		Placebo	40	5.20	1.03	0.43	1.32	(.674)
CALC	mmol/L	ATOMOX	44	2.445	0.073	0.015	0.103	.150
		Placebo	40	2.475	0.102	-0.013	0.095	(.216)
PHOS	mmol/L	ATOMOX	44	1.648	0.162	-0.030	0.212	.161
		Placebo	40	1.626	0.144	0.027	0.135	(.571)
SODIUM	mmol/L	ATOMOX	44	141.7	1.6	-0.4	2.2	.579
		Placebo	40	141.5	1.7	-0.1	2.2	(.317)
POTAS	mmol/L	ATOMOX	44	4.29	0.32	-0.05	0.42	.943
		Placebo	40	4.33	0.46	-0.03	0.38	(.924)
CHLOR	mmol/L	ATOMOX	44	104.3	1.7	-0.8	2.5	.050
		Placebo	40	104.0	1.5	0.1	1.7	(.189)
TPROT	g/L	ATOMOX	44	72.1	3.7	-0.3	4.5	.581
		Placebo	40	72.0	4.4	-0.7	3.5	(.462)
ALBUM	g/L	ATOMOX	44	43.0	2.4	0.5	3.2	.150
		Placebo	40	43.7	2.5	-0.4	2.9	(.092)
NFGLU	mmol/L	ATOMOX	44	5.03	0.66	0.15	0.86	.362
		Placebo	40	5.12	0.85	-0.02	1.00	(.909)
UR AC	umol/L	ATOMOX	44	219.7	49.1	-3.1	39.9	.055
		Placebo	40	228.8	48.3	14.1	42.9	(.386)
CHOL	mmol/L	ATOMOX	44	4.170	0.643	-0.031	0.640	.860
		Placebo	40	4.213	0.726	0.005	0.367	(.183)

(continued)

Table LYBH.17. Summary of Change from Baseline to Endpoint for Laboratory Analytes
All Randomized Patients with ≥ 1 Dose of Study Drug (concluded)

Lab Test	Lab Unit	Therapy	n	-----Baseline-----		Change to -----Endpoint-----		p-Values
				Mean	SD	Mean	SD	
BICARB	mmol/L	ATOMOX	44	22.98	1.91	0.38	2.06	.506
		Placebo	40	22.74	2.17	0.07	2.35	(.836)
CREAT	umol/L	ATOMOX	44	45.8	8.6	2.2	8.3	.851
		Placebo	40	45.5	7.6	2.2	9.5	(.020)
T.BILI	umol/L	ATOMOX	38	6.6	3.1	0.7	2.9	.437
		Placebo	33	5.3	2.0	0.2	2.0	(.563)

Baseline: Visits 1-2, Endpoint: Visits 3-8

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDUCL - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=investigator and treatment for the overall p-Value and model=investigator, treatment, and interaction for the interaction p-Value. Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Note: Each investigator has at least one patient in each treatment group.

Legend of Lab Test Code Abbreviations:

Abbrev.	Description
HCT	HEMATOCRIT
HGB	HEMOGLOBIN
RBC	ERYTHROCYTE COUNT
WBC	LEUKOCYTE COUNT
BANDS	BANDS
POLYS	NEUTROPHILS, SEGMENTED
LYMPHS	LYMPHOCYTES
MONOS	MONOCYTES
EOSN	EOSINOPHILS
BASO	BASOPHILS
MCV	MEAN CELL VOLUME (MCV)
PLTCT	PLATELET COUNT
U-SPGR	UA-SPECIFIC GRAVITY
AST	AST/SGOT
ALT	ALT/SGPT
CPK	CREATINE PHOSPHOKINASE
ALKPH	ALKALINE PHOSPHATASE
GGT	GGT (GGPT/SGGT/YGGT)
BUN	UREA NITROGEN
CALC	CALCIUM
PHOS	INORGANIC PHOSPHORUS
SODIUM	SODIUM
POTAS	POTASSIUM
CHLOR	CHLORIDE
TPROT	TOTAL PROTEIN
ALBUM	ALBUMIN
NFGLU	GLUCOSE, NON-FASTING
UR AC	URIC ACID
CHOL	CHOLESTEROL
BICARB	BICARBONATE, HCO ₃
CREAT	CREATININE
T.BILI	BILIRUBIN, TOTAL

Table LYBH.18. **Mean Change From Baseline to LOCF Endpoint for Laboratory Tests**
Open-Label Extension Period: B4Z-US-LYBH

	BASELINE			CHANGE		WITHIN GROUP
	N	MEAN	STD	MEAN	STD	P-VALUE
ALBUMIN	56	42.45	2.33	1.20	3.15	.005
ALKALINE PHOSPHATASE	57	231.98	59.16	14.67	45.15	.040
ALT/SGPT	56	20.86	17.04	-2.13	18.22	.065
AST/SGOT	56	29.09	11.11	-2.02	10.06	.010
BANDS	55	0.00	0.00	0.00	0.00	N/A
BASOPHILS	55	0.05	0.02	0.00	0.02	.750
BICARBONATE, HCO3	56	22.68	2.13	-0.02	2.36	.971
BILIRUBIN, TOTAL	43	6.36	2.67	0.08	1.94	.821
CALCIUM	57	2.45	0.08	0.02	0.09	.033
CHLORIDE	57	104.37	2.01	1.21	2.54	<.001
CHOLESTEROL	57	4.03	0.65	0.05	0.41	.412
CREATINE PHOSPHOKINASE	56	122.14	47.17	-9.23	46.29	.059
CREATININE	57	49.78	10.38	-1.86	8.14	.058
EOSINOPHILS	55	0.19	0.20	-0.00	0.10	.690
ERYTHROCYTE COUNT	55	4.55	0.36	0.19	0.25	<.001
GGT (GGPT/SGGT/YGGT)	57	12.09	3.12	0.93	3.99	.064
GLUCOSE, NON-FASTING	56	4.89	0.81	0.15	1.27	.325
HEMATOCRIT	55	0.38	0.03	0.02	0.03	<.001
HEMOGLOBIN	55	7.98	0.57	0.31	0.48	<.001
INORGANIC PHOSPHORUS	57	1.65	0.15	-0.05	0.23	.149
LEUKOCYTE COUNT	55	6.86	1.83	-0.17	1.99	.453
LYMPHOCYTES	55	2.53	0.71	-0.00	0.60	.970
MEAN CELL VOLUME (MCV)	55	82.95	5.46	0.84	3.89	.142
MONOCYTES	55	0.39	0.14	0.01	0.15	.757
NEUTROPHILS, SEGMENTED	55	3.70	1.40	-0.18	1.66	.300

(continued)

POPULATION: ALL OF PATIENTS WHO ENROLLED IN THE OPEN LABEL EXTENSION PERIOD AND
 TOOK AT LEAST ONE DOSE OF STUDY DRUG ARE INCLUDED

Table LYBH.18. Mean Change From Baseline to LOCF Endpoint for Laboratory Tests
Open-Label Extension Period: B4Z-US-LYBH (concluded)

	BASELINE			CHANGE		WITHIN GROUP
	N	MEAN	STD	MEAN	STD	P-VALUE
PLATELET COUNT	55	308.00	73.57	-0.31	64.01	.817
POTASSIUM	57	4.27	0.39	-0.01	0.38	.930
SODIUM	57	141.96	1.65	-0.68	2.15	.022
TOTAL PROTEIN	57	70.54	4.15	1.32	3.62	.009
UA-SPECIFIC GRAVITY	56	1.03	0.01	0.00	0.01	.572
UREA NITROGEN	57	5.26	1.13	-0.36	1.30	.056
URIC ACID	57	246.48	52.66	-13.98	39.14	.012

POPULATION: ALL OF PATIENTS WHO ENROLLED IN THE OPEN LABEL EXTENSION PERIOD AND TOOK AT LEAST ONE DOSE OF STUDY DRUG ARE INCLUDED

Table LYBH.19 presents a summary of frequency of patients with treatment-emergent abnormal lab values.

Table LYBH.19. Summary of Frequency of Patients with Treatment-Emergent Abnormal Lab Values
All Randomized Patients with ≥1 Dose of Study Drug

	ATOMOX (1)			Placebo (2)			- p-Value *
Incidence	(Total=44)			(Total=43)			
Group	N	n	(%)	N	n	(%)	Overall

Lab Test: HEMATOCRIT							

LOW	36	4	(11.1)	35	3	(8.6)	1.00
HIGH	43	0		40	1	(2.5)	.482
Lab Test: HEMOGLOBIN							

LOW	42	0		37	0		
HIGH	43	0		40	0		
Lab Test: ERYTHROCYTE COUNT							

LOW	43	0		40	0		
HIGH	43	0		40	0		
Lab Test: LEUKOCYTE COUNT							

LOW	41	0		38	0		
HIGH	43	0		40	0		

(continued)

Table LYBH.19. Summary of Frequency of Patients with Treatment-Emergent Abnormal Lab Values
All Randomized Patients with ≥ 1 Dose of Study Drug
(continued)

	ATOMOX (1)			Placebo (2)			- p-Value *	-
Incidence	(Total=44)			(Total=43)				
Group	N	n	(%)	N	n	(%)	Overall	

Lab Test: BANDS								

LOW	43	0		40	0			
HIGH	43	0		40	0			
Lab Test: NEUTROPHILS, SEGMENTED								

LOW	43	0		39	0			
HIGH	43	0		39	2	(5.1)	.223	
Lab Test: LYMPHOCYTES								

LOW	42	0		39	2	(5.1)	.229	
HIGH	43	0		40	0			
Lab Test: MONOCYTES								

LOW	43	0		39	0			
HIGH	43	0		40	0			
Lab Test: EOSINOPHILS								

LOW	43	0		40	0			
HIGH	40	0		37	1	(2.7)	.481	
Lab Test: BASOPHILS								

LOW	43	0		40	0			
HIGH	43	0		40	0			
Lab Test: MEAN CELL VOLUME (MCV)								

LOW	37	1	(2.7)	30	0		1.00	
HIGH	43	0		40	0			
Lab Test: PLATELET COUNT								

LOW	43	0		40	0			
HIGH	36	3	(8.3)	36	1	(2.8)	.614	
Lab Test: UA-SPECIFIC GRAVITY								

LOW	43	2	(4.7)	37	3	(8.1)	.658	
HIGH	43	6	(14.0)	35	3	(8.6)	.504	
Lab Test: AST/SGOT								

LOW	43	0		39	0			
HIGH	42	1	(2.4)	34	0		1.00	

(continued)

Table LYBH.19. **Summary of Frequency of Patients with Treatment-Emergent Abnormal Lab Values**
All Randomized Patients with ≥ 1 Dose of Study Drug
(continued)

	ATOMOX (1)			Placebo(2)			- p-Value *	-
Incidence	(Total=44)			(Total=43)				
Group	N	n	(%)	N	n	(%)	Overall	

Lab Test: ALT/SGPT								

LOW	44	1	(2.3)	40	0		1.00	
HIGH	44	1	(2.3)	36	1	(2.8)	1.00	
Lab Test: CREATINE PHOSPHOKINASE								

LOW	44	0		40	0			
HIGH	44	1	(2.3)	38	0		1.00	
Lab Test: ALKALINE PHOSPHATASE								

LOW	44	1	(2.3)	40	0		1.00	
HIGH	41	0		37	1	(2.7)	.474	
Lab Test: GGT (GGPT/SGGT/YGGT)								

LOW	44	0		40	0			
HIGH	44	0		40	0			
Lab Test: UREA NITROGEN								

LOW	44	0		40	0			
HIGH	44	0		40	0			
Lab Test: CALCIUM								

LOW	44	0		40	0			
HIGH	39	2	(5.1)	32	1	(3.1)	1.00	

(continued)

Table LYBH.19. Summary of Frequency of Patients with Treatment-Emergent Abnormal Lab Values
All Randomized Patients with ≥ 1 Dose of Study Drug
(continued)

	ATOMOX (1)			Placebo (2)			- p-Value * -
Incidence	(Total=44)			(Total=43)			
Group	N	n	(%)	N	n	(%)	Overall

Lab Test: INORGANIC PHOSPHORUS							

LOW	44	0		40	0		
HIGH	43	1	(2.3)	39	2	(5.1)	.602
Lab Test: SODIUM							

LOW	44	0		40	0		
HIGH	43	0		40	0		
Lab Test: POTASSIUM							

LOW	44	0		40	0		
HIGH	44	0		38	0		
Lab Test: CHLORIDE							

LOW	44	0		40	0		
HIGH	43	0		40	0		
Lab Test: TOTAL PROTEIN							

LOW	44	0		40	0		
HIGH	43	0		40	0		
Lab Test: ALBUMIN							

LOW	44	0		40	0		
HIGH	39	3	(7.7)	36	2	(5.6)	1.00
Lab Test: GLUCOSE, NON-FASTING							

LOW	43	1	(2.3)	40	0		1.00
HIGH	44	0		40	0		
Lab Test: URIC ACID							

LOW	44	1	(2.3)	39	0		1.00
HIGH	44	0		40	2	(5.0)	.224

(continued)

Table LYBH.19. **Summary of Frequency of Patients with Treatment-Emergent Abnormal Lab Values**
All Randomized Patients with ≥ 1 Dose of Study Drug (concluded)

Incidence Group	ATOMOX (1) (Total=44)			Placebo (2) (Total=43)			- p-Value * -
	N	n	(%)	N	n	(%)	Overall

Lab Test: CHOLESTEROL							

LOW	40	2	(5.0)	36	2	(5.6)	1.00
HIGH	39	3	(7.7)	33	3	(9.1)	1.00
Lab Test: BICARBONATE, HCO ₃							

LOW	44	0		40	0		
HIGH	44	0		40	0		
Lab Test: CREATININE							

LOW	44	0		40	1	(2.5)	.476
HIGH	41	0		39	6	(15.4)	.011
Lab Test: BILIRUBIN, TOTAL							

LOW	44	0		40	0		
HIGH	44	1	(2.3)	40	0		1.00

Baseline: Visits 1-2, Endpoint: Visits 3-8

* Frequencies are analyzed using a Fisher's Exact test.

Note: Total = Total number of patients in the treatment group having both baseline and endpoint visits.

N = Total number of at risk patients with the lab test.

n = Total number of at risk patients with the specific lab result (e.g. HIGH).

Atomoxetine-treated subjects had a statistically significant increase in mean standing pulse and mean supine pulse compared with placebo-treated subjects ($p < .001$). Supine pulse increased 8.39 bpm from baseline, while standing pulse increased 11.05 bpm from baseline. There were no statistically significant differences between treatments in blood pressure. Atomoxetine-treated subjects had an acute decrease in weight of .45 kg compared to an increase of 1.08 kg for placebo ($p < .001$) (see Table LYBH.20).

Table LYBH.20. Summary of Change from Baseline to Endpoint for Vital Signs All Randomized Patients with ≥ 1 Dose of Study Drug

Variables Analyzed	Therapy	n	-----Baseline-----		Change to -----Endpoint-----		p-Values Therapy (Int*1)
			Mean	SD	Mean	SD	
WEIGHTKG	ATOMOX	44	38.59	11.64	-0.45	1.94	<.001
	Placebo	41	36.69	11.29	1.08	1.88	(.382)
HEIGHTCM	ATOMOX	44	139.61	12.87	1.10	2.44	.544
	Placebo	41	136.01	12.03	0.87	1.51	(.437)
SYSBPST	ATOMOX	44	104.59	9.49	1.95	8.35	.505
	Placebo	41	103.07	10.24	0.83	9.00	(.723)
SYSBPSU	ATOMOX	44	106.30	8.64	-0.05	8.11	.739
	Placebo	41	103.88	10.42	0.73	9.68	(.792)
DIABPST	ATOMOX	44	66.66	8.14	2.14	8.48	.088
	Placebo	41	66.00	10.31	-1.12	8.32	(.100)
DIABPSU	ATOMOX	44	63.05	7.94	1.84	9.63	.656
	Placebo	41	61.27	8.45	1.00	8.73	(.842)
PULSEST	ATOMOX	44	82.52	12.08	11.05	13.33	<.001
	Placebo	41	86.05	11.32	0.66	11.64	(.999)
PULSESU	ATOMOX	44	75.16	9.45	8.39	12.27	<.001
	Placebo	41	79.80	10.38	-1.22	9.88	(.893)

Baseline: Visits 1-2, Endpoint: Visits 3-8

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDUC1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM
 model=investigator and treatment for the overall p-Value and
 model=investigator, treatment, and interaction for the interaction p-Value.
 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Note: Each investigator has at least one patient in each treatment group.

Legend of Variable Abbreviations:

DIABPST Diastolic BP - Standing
 DIABPSU Diastolic BP - Supine
 HEIGHTCM Height
 PULSEST Pulse - Standing
 PULSESU Pulse - Supine
 SYSBPST Systolic BP - Standing
 SYSBPSU Systolic BP - Supine
 WEIGHTKG Weight

As shown in Table LYBH.21, during the open-label extension period, subjects had a statistically significant increase in supine pulse, as well as statistically significant increases in height and weight (2.64 cm and 1.65 kg, $p < .001$ for each).

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**Table LYBH.21. Mean Change from Baseline to LOCF Endpoint for Vitals:
Open Label Extension Period**

MEASUREMENT	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)
		MEAN	SD	MEAN	SD	MEAN	SD	
SUPINE SBP	61	104.54	9.30	105.25	11.16	0.70	11.16	.700
STANDING SBP	61	102.70	10.66	104.85	11.23	2.15	10.15	.070
SUPINE DBP	61	60.85	8.06	63.02	10.10	2.16	10.32	.134
STANDING DBP	61	63.66	9.61	65.59	10.31	1.93	10.30	.111
SUPINE PULSE	61	81.07	11.80	85.11	11.75	4.05	11.58	.014
STANDING PULSE	61	88.23	12.62	92.54	15.26	4.31	15.28	.058
ORTHOSTATIC SBP	61	1.84	7.73	0.39	6.21	-1.44	8.66	.165
ORTHOSTATIC DBP	61	-2.80	7.54	-2.57	5.66	0.23	9.43	.855
ORTHOSTATIC PULSE	61	7.16	7.13	7.43	10.29	0.26	9.96	.841
WEIGHT (KG)	61	38.05	11.92	39.71	13.66	1.65	3.28	<.001
HEIGHT (CM)	61	138.58	12.68	141.22	13.58	2.64	2.63	<.001

A) P-VALUES ARE FROM THE WILCOXON SIGNED-RANK TEST
POPULATION: ALL OF PATIENTS WHO ENROLLED IN OPEN LABEL EXTENSION PERIOD AND
TOOK AT LEAST ONE DOSE OF STUDY DRUG ARE INCLUDED

Health Outcomes

Table LYBH.22a indicates that the only statistically significant difference on the CHQ-PF50 was a statistically significant decrease in “family activities” for atomoxetine compared with placebo. Table LYBH.22b shows the CHQ-PF50 scores mean change from baseline to LOCF endpoint. Table LYBH.23 gives a summary of final, maximum, and modal dose for all randomized patients that took at least one dose of study drug.

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Table LYBH.22a. Child Health Questionnaire Parent Form 50 -- Cluster Subscore
Mean Change From Baseline To Endpoint Study Period II

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE A	P-VALUE B
		MEAN	SD	MEAN	SD	MEAN	SD		
BODYILY PAIN									
TMX	39	87.44	14.46	86.67	19.65	-0.77	18.97	.911	.314
PLA	37	89.73	16.91	85.68	18.49	-4.05	20.47	.318	----
		95% CONFIDENCE INTERVAL: (-13.60,4.44)							
BEHAVIOR									
TMX	39	76.46	17.89	77.33	17.07	0.87	14.20	.713	.468
PLA	37	65.08	23.59	68.30	21.67	3.22	14.92	.114	----
		95% CONFIDENCE INTERVAL: (-4.34 ,9.33)							
FAMILY ACTIVITIES									
TMX	39	88.64	15.68	84.15	18.11	-4.49	13.94	.136	.024
PLA	37	71.43	27.54	74.46	28.92	3.03	13.80	.135	----
		95% CONFIDENCE INTERVAL: (1.04 ,14.25)							
GENERAL HEALTH									
TMX	39	82.74	11.95	84.21	10.29	1.46	12.22	.447	.191
PLA	37	80.62	16.22	78.57	15.43	-2.05	12.24	.320	----
		95% CONFIDENCE INTERVAL: (-9.61 ,1.95)							
MENTAL HEALTH									
TMX	39	82.44	11.80	80.26	12.14	-2.18	11.17	.333	.692
PLA	37	75.81	16.31	74.73	18.03	-1.08	10.94	.542	----
		95% CONFIDENCE INTERVAL: (-4.17 ,6.24)							
PARENT EMOTIONAL									
TMX	39	80.87	19.60	79.90	22.61	-0.97	25.15	.855	.527
PLA	37	69.78	25.80	73.11	28.11	3.32	20.26	.154	----
		95% CONFIDENCE INTERVAL: (-7.34 ,14.19)							

(continued)

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**Table LYBH.22a. Child Health Questionnaire Parent Form 50: Cluster Subscore
Mean Change From Baseline To Endpoint Study Period II
(continued)**

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE A	P-VALUE B
		MEAN	SD	MEAN	SD	MEAN	SD		
PHYSICAL FUNCTION									
TMX	40	99.43	2.83	97.15	7.58	-2.28	8.30	.117	.873
PLA	37	99.03	3.00	97.19	7.07	-1.84	6.74	.141	----
		95% CONFIDENCE INTERVAL:				(-3.26 ,3.83)			
PHYSICAL SUMMARY									
TMX	39	56.28	2.84	55.44	6.43	-0.85	6.11	.940	.424
PLA	37	56.54	4.25	55.00	6.13	-1.54	4.99	.039	----
		95% CONFIDENCE INTERVAL:				(-3.58 ,1.52)			
PARENT TIME IMPACT									
TMX	39	92.36	13.82	91.26	17.75	-1.10	18.22	.834	.381
PLA	37	79.84	22.89	82.89	24.79	3.05	18.59	.239	----
		95% CONFIDENCE INTERVAL:				(-4.91 ,12.68)			
PSYCHOSOCIAL SUMMARY SCORE									
TMX	39	51.87	9.35	51.87	8.79	0.00	7.53	.888	.630
PLA	37	44.51	14.30	45.57	14.69	1.05	9.42	.230	----
		95% CONFIDENCE INTERVAL:				(-3.08 ,5.06)			
ROLE EMOTIONAL/BEHAVIOR									
TMX	40	93.73	15.06	96.00	12.86	2.28	13.07	.227	.662
PLA	37	81.16	30.29	81.11	29.92	-0.05	25.43	.952	----
		95% CONFIDENCE INTERVAL:				(-11.60,7.42)			
ROLE PHYSICAL									
TMX	39	99.56	2.72	97.41	11.90	-2.15	12.30	.500	.977
PLA	37	97.27	11.54	95.41	11.08	-1.86	11.79	.219	----
		95% CONFIDENCE INTERVAL:				(-5.63 ,5.47)			

(continued)

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**Table LYBH.22a. Child Health Questionnaire Parent Form 50 -- Cluster Subscore
Mean Change From Baseline To Endpoint Study Period II
(concluded)**

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE A	P-VALUE B
		MEAN	SD	MEAN	SD	MEAN	SD		
SELF ESTEEM									
TMX	39	83.44	15.00	82.97	15.28	-0.46	11.15	.833	.795
PLA	37	76.62	19.60	75.51	23.20	-1.11	19.96	.802	----
95% CONFIDENCE INTERVAL: (-8.47 ,6.51)									

A) P-VALUE IS FROM WILCOXON SIGNED-RANK TEST.

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH INVESTIGATOR, TREATMENT AS COVARIATE

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**Table LYBH.22b. Child Health Questionnaire Parent Form 50: Cluster Subscores
Mean Change from Baseline to LOCF Endpoint Study Period III/IV**

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		MEAN	SD	MEAN	SD	MEAN	SD		
BEHAVIOR									
TMX	33	79.30	16.63	78.79	17.02	-0.52	11.18	.796	.668
PLA	33	67.03	21.86	65.73	24.05	-1.30	12.48	.961	
		95% CONFIDENCE INTERVAL:				(-7.32, 4.72)			
BODILY PAIN									
TMX	33	90.00	15.81	87.88	15.36	-2.12	16.91	.482	.644
PLA	33	85.76	19.37	84.55	18.04	-1.21	20.88	.827	
		95% CONFIDENCE INTERVAL:				(-7.53, 12.09)			
FAMILY ACTIVITIES									
TMX	33	86.85	16.42	85.79	15.90	-1.06	11.60	.387	.947
PLA	33	73.18	29.30	72.15	27.86	-1.03	11.54	.686	
		95% CONFIDENCE INTERVAL:				(-5.67, 6.06)			
GENERAL HEALTH									
TMX	33	85.79	8.75	85.76	10.00	-0.03	7.34	.824	.125
PLA	33	78.58	15.64	75.06	14.38	-3.52	11.43	.085	
		95% CONFIDENCE INTERVAL:				(-8.63, 1.08)			
MENTAL HEALTH									
TMX	33	82.58	10.01	83.94	12.67	1.36	10.48	.703	.272
PLA	33	74.39	17.84	73.48	18.43	-0.91	10.42	.821	
		95% CONFIDENCE INTERVAL:				(-8.00, 2.30)			
PARENT EMOTIONAL									
TMX	33	85.09	18.27	84.61	17.19	-0.48	15.53	.695	.764
PLA	33	73.70	27.44	72.27	25.06	-1.42	14.85	.484	
		95% CONFIDENCE INTERVAL:				(-8.91, 6.58)			

(continued)

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Table LYBH.22b. Child Health Questionnaire Parent Form 50: Cluster Subscores
Mean Change from Baseline to LOCF Endpoint Study Period III/IV
(concluded)

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		MEAN	SD	MEAN	SD	MEAN	SD		
PHYSICAL FUNCTIONING									
TMX	33	98.79	4.90	99.12	3.24	0.33	6.06	.938	.817
PLA	33	96.85	7.43	96.85	7.85	0.00	7.48	1.000	
95% CONFIDENCE INTERVAL: (-4.00, 3.17)									
PHYSICAL SUMMARY SCORE									
TMX	33	56.67	4.26	56.64	3.23	-0.03	4.33	.350	.530
PLA	33	54.94	6.48	54.00	5.60	-0.94	4.78	.295	
95% CONFIDENCE INTERVAL: (-3.12, 1.63)									
PARENT TIME IMPACT									
TMX	33	94.15	15.65	92.06	15.56	-2.09	8.64	.109	.836
PLA	33	83.88	23.56	80.42	22.76	-3.45	11.44	.125	
95% CONFIDENCE INTERVAL: (-5.58, 4.53)									
ROLE EMOTIONAL/BEHAVIOR									
TMX	33	97.91	8.23	95.21	16.31	-2.70	10.33	.250	.295
PLA	33	81.85	27.70	81.94	27.07	0.09	21.91	.660	
95% CONFIDENCE INTERVAL: (-4.06, 13.13)									
ROLE PHYSICAL									
TMX	33	98.97	5.92	98.97	5.92	0.00	8.50	1.000	.592
PLA	33	94.85	11.63	93.33	17.35	-1.52	12.17	.656	
95% CONFIDENCE INTERVAL: (-6.96, 4.01)									
SELF ESTEEM									
TMX	33	84.79	13.46	81.39	20.22	-3.39	15.92	.340	.557
PLA	33	76.39	21.40	75.06	21.80	-1.33	13.31	.625	
95% CONFIDENCE INTERVAL: (-5.39, 9.90)									
PSYCHOSOCIAL SUMMARY SCORE									
TMX	33	53.52	7.59	52.67	9.09	-0.85	5.41	.685	.916
PLA	33	45.70	14.21	44.97	14.44	-0.73	6.90	.784	
95% CONFIDENCE INTERVAL: (-3.00, 3.33)									

A) P-VALUES ARE FROM THE WILCOXON SIGNED-RANK TEST.

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING A FIXED EFFECT ANOVA MODEL WITH TERMS FOR TREATMENT AND INVESTIGATOR

POPULATION: ALL OF THE PATIENTS ENROLLED IN STUDY PERIOD III/IV ARE INCLUDED

**Table LYBH.23. Summary of Final, Maximum, and Modal Dose
All Randomized Patients with ≥ 1 Dose of Study Drug**

Variable	ATOMOX (N=44)

Final Prescribed Daily Dose (mg)	
No. Patients	44
Mean	53.86
Median	60.00
Standard Dev.	16.28
Minimum	15.00
Maximum	90.00
Final Prescribed Daily Dose (mg/kg)	
No. Patients	44
Mean	1.42
Median	1.43
Standard Dev.	0.21
Minimum	0.45
Maximum	1.73
Maximum Prescribed Daily Dose (mg)	
No. Patients	44
Mean	54.20
Median	60.00
Standard Dev.	16.88
Minimum	15.00
Maximum	90.00

Visits 3-8

Summary ID# 5831

Clinical Study Summary: Study B4Z-MC-LYBI

A Randomized, Double-Blind Comparison of Atomoxetine Hydrochloride, Extended-Release Methylphenidate Hydrochloride (Concerta), and Placebo in Pediatric Outpatients with DSM-IV Attention- Deficit/Hyperactivity Disorder

Date summary approved by Lilly: 06 April 2006

Brief Summary of Results

This study was designed to investigate the comparability of atomoxetine and methylphenidate. It incorporated an approximately 6-week acute treatment period, and to avoid biasing the results toward atomoxetine excluded subjects previously demonstrated to be unresponsive to (or intolerant of) an adequate trial of methylphenidate or amphetamine.

The key results of the study are as follows:

- Atomoxetine did not demonstrate noninferiority to Concerta® (methylphenidate hydrochloride, McNeil). There was a higher percentage of responders to methylphenidate. Both atomoxetine and methylphenidate demonstrated significant symptom improvement compared with placebo.
- In prior stimulant users, methylphenidate demonstrated significant symptom improvement compared with placebo.
- In stimulant-naïve patients, there was no statistical difference between atomoxetine and methylphenidate, and both active treatments were statistically superior to placebo.
- When patients receiving acute treatment with methylphenidate were switched to acute treatment with atomoxetine, 45% of the patients who were nonresponders to methylphenidate became responders to atomoxetine, while 76% of patients who were responders to methylphenidate also responded to atomoxetine.
- In patients who met the definition of atomoxetine nonresponders, no statistically significant symptom improvement was observed in patients receiving higher dose atomoxetine (up to 3.0 mg/kg/day) compared with patients continuing at previous doses.
- In patients who met the definition of atomoxetine responders, lower-dose atomoxetine (up to 0.5 mg/kg/day) was not statistically different than previous-dose atomoxetine, and few patients in either dose group relapsed (3 patients in each group).
- Tolerability was similar for atomoxetine and methylphenidate, with differential effects for somnolence (atomoxetine) and insomnia (methylphenidate).
- Discontinuations due to adverse events were low.

Title of Study: A Randomized, Double-Blind Comparison of Atomoxetine Hydrochloride, Extended-Release Methylphenidate Hydrochloride (Concerta), and Placebo in Pediatric Outpatients with DSM-IV Attention-Deficit/Hyperactivity Disorder	
Investigator(s): This multicenter study included 21 principal investigators.	
Study Center(s): This study was conducted at 20 study centers in one country. Note: The principal investigator at one investigative site transitioned the study to a new principal investigator.	
Length of Study: Approximately 14 months Date first patient enrolled: 02 August 2002 Date last patient completed: 30 September 2003	Phase of Development: 3
Study Design and Objectives: This study was designed to investigate the comparability of atomoxetine and methylphenidate. It incorporated an approximately 6-week acute treatment period, and, to avoid biasing the results toward atomoxetine, excluded subjects previously demonstrated to be unresponsive to (or intolerant of) an adequate trial of methylphenidate or amphetamine. This study comprised 4 study periods (Study Period I was screening, Study Period IV was open-label) and included 3 different randomizations: an initial randomization of all subjects to acute treatment, a randomization of only subjects who responded to acute atomoxetine treatment, and a randomization of subjects who did not respond to acute atomoxetine treatment. Each subject was randomized at most twice. For each of the randomizations, the corresponding treatment periods were treated as separate studies of the efficacy of atomoxetine. Each of these separate studies was aimed at answering a different clinical question based on a unique population, and, therefore, has a separate primary objective along with a corresponding primary efficacy analysis. The significance of each primary objective was independent of whether significance was seen with any of the other primary objectives. Study Period II Primary Objective (Assessment 1): The primary objective of the acute treatment period was to test the hypothesis that atomoxetine is noninferior to methylphenidate in improving Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms following an approximately 6-week period of double-blind treatment, as assessed by a comparison of response rates derived from the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv). Secondary Objectives: Secondary objectives of the acute treatment period of the study were as follows: - to compare the efficacy of atomoxetine, methylphenidate, and placebo on evening and early morning ADHD symptoms, as measured by change in ratings on the Daily Parent Ratings of Evening and Morning Behavior-Revised (DPREMB-Revised) - to compare the tolerability of atomoxetine and methylphenidate, as assessed by treatment-emergent adverse events (TEAEs) - to compare the effects of atomoxetine and methylphenidate on the emergence of new tics, as assessed by the Yale Global Tic Severity Scale (YGTSS) - to compare the effects of atomoxetine and methylphenidate on affective flexibility, as measured by the Assessment of Affective Range (AAR) - to assess the comparability of the efficacy of atomoxetine and methylphenidate on the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) - to compare atomoxetine, methylphenidate, and placebo on other secondary measures, including measures of health outcomes.	

Study Period III:

Primary Objective (for Responders to Acute Treatment with Atomoxetine): The primary objective of the double-blind continuation period in the group of subjects who met blinded response criteria after acute treatment (Study Period II) with atomoxetine was to confirm the hypothesis that continued treatment with atomoxetine at the final acute-phase dose was superior to continued treatment with atomoxetine at a lower dose, as assessed by a comparison between the groups in their time to relapse. Relapse was defined by prespecified blinded criteria.

Primary Objective (for Nonresponders to Acute Treatment with Atomoxetine): The primary objective of the double-blind continuation period in the group of subjects who failed to meet blinded response criteria after a period of acute treatment (Study Period II) with atomoxetine was to test the hypothesis that continued treatment with atomoxetine at an increased dose (maximum approximately 3.0 mg/kg/day) was superior to continued treatment with atomoxetine at previously established efficacious doses, as assessed by the ADHDRS-IV-Parent:Inv.

Secondary Objective (for Subjects Randomized to Methylphenidate in Study Period II):

The secondary objective of the double-blind continuation phase of the study was to assess the efficacy of atomoxetine among those subjects assigned to methylphenidate in Study Period II who were nonresponders or partial responders (defined by prespecified blinded criteria) at the end of Study Period II. Summaries of descriptive statistics, and comparisons of responses to atomoxetine among acute-phase methylphenidate responders and nonresponders, were also planned.

Study Design: A randomized, double-blind, comparison of atomoxetine, extended-release methylphenidate, and placebo. During Study Period II, all patients were randomized to acute double-blind treatment with atomoxetine, methylphenidate, or placebo. Following acute treatment, patients entered randomized, double-blind, continuation therapy with atomoxetine for approximately 8 months.

Number of Patients:

Planned: 518 patients (222 patients per treatment group for atomoxetine and methylphenidate; 74 patients in the placebo treatment group)

Study Period II (N=516 Randomized Patients)

Randomized: 222 Atomoxetine; 220 Methylphenidate; 74 Placebo.

Completed: 186 Atomoxetine; 180 Methylphenidate*; 57 Placebo*.

* The 180 methylphenidate and 57 placebo Study Period II completers were switched to acute treatment with atomoxetine for approximately 8 weeks before completers were rerandomized in Study Period III.

Study Period III (N=351 Randomized Patients)

Atomoxetine Responders (229)

Randomized: 116 Previous-Dose Atomoxetine; 113 Lower-Dose Atomoxetine.

Completed: 83 Previous-Dose Atomoxetine; 73 Lower-Dose Atomoxetine.

Atomoxetine Nonresponders (122)

Randomized: 62 Previous-Dose Atomoxetine; 60 Higher-Dose Atomoxetine.

Completed: 32 Previous-Dose Atomoxetine; 28 Higher-Dose Atomoxetine.

Diagnosis and Main Criteria for Inclusion: Patients were males or females aged at least 6 years and not more than 16 years at Visit 1. For inclusion, patients had to meet *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*® (DSM-IV) criteria for ADHD (any subtype), as determined by a physician investigator's clinical assessment and confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL) structured interview. In addition, patients had to have a severity rating at least 1.5 standard deviations above their age and gender norms on the ADHDRS-IV-Parent:Inv and a Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity (CGI-ADHD-S) score ≥ 4 at both Visit 1 and Visit 2.

Test Product, Dose, and Mode of Administration:

Study Period II: Atomoxetine, at target doses of 0.8, 1.2, or 1.8 mg/kg/day, given orally twice a day in 2.5-, 5-, 10-, 20-, 25-, and 40-mg capsules.

Study Period III: Atomoxetine, at doses ranging from 0.5 mg/kg/day up to a maximum dose of 3.0 mg/kg/day, given orally twice a day in 2.5-, 5-, 10-, 20-, 25-, and 40-mg capsules. The exact dose was based on the patient's weight.

Reference Therapy, Dose, and Mode of Administration: Methylphenidate, 18, 36, or 54 mg/day, given orally once a day using the prolonged-release version of Concerta in 18-mg capsules (OROS®).

Reference Therapy: The study employed a double-dummy design; both atomoxetine-matched placebo capsules and Concerta-matched placebo capsules were supplied.

Duration of Treatment:

Study Period II: Approximately 6 weeks, plus an additional 8 weeks of atomoxetine treatment for patients who were initially randomized to methylphenidate or placebo.

Study Period III: Approximately 8 months.

Variables:

Efficacy: Variables included the 18-item Total score of the ADHDRS-IV-Parent:Inv and its subscale scores (Inattention and Hyperactivity-Impulsivity), and scores on the following secondary measures: CGI-ADHD-S; DPREMB-Revised; YGTSS; AAR; CPRS-R:S; Children's Depression Rating Scale-Revised (CDRS-R); Pediatric Anxiety Rating Scale (PARS); Social Skills Rating System-Parent (SSRS-P); Life Participation Scale (LPS); and Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Improvement (CGI-ADHD-I). Health outcomes were evaluated using the Child Health Questionnaire (CHQ).

Safety: Adverse events (AEs), vital signs, laboratory tests, and electrocardiograms (ECGs).

Methods:

Statistical: A 2-sided, 95% lower confidence interval (CI) was used in the test of noninferiority between atomoxetine and methylphenidate for the primary analysis of response rates. Repeated measures analysis was used to compare scores and subscale scores on the primary and secondary efficacy variables. The repeated measures analysis was based on the restricted maximum likelihood method assuming an unstructured covariance matrix. A Satterthwaite approximation was used for the denominator degrees of freedom in the t-test. Scores and subscale scores were also summarized by calculating change from baseline to last-observation-carried-forward (LOCF) endpoint. The CGI-ADHD-I was summarized using analysis of variance (ANOVA); all other efficacy variables were analyzed using analysis of covariance (ANCOVA) models with prespecified independent effects. Time-to-relapse curves were analyzed using Kaplan-Meier estimated survival curves, and comparisons were made using the log-rank test. Descriptive statistics summarized patient characteristics, AEs, and other safety data. Fisher's exact test was used for treatment comparisons in categorical data. A 2-sided, 0.05 significance level was used for all statistical tests, unless otherwise specified.

Figure LYBI.1 shows the design for Study LYBI, including an illustration of when efficacy assessments occurred. For ease of reference, these assessments were numbered 1 through 4.

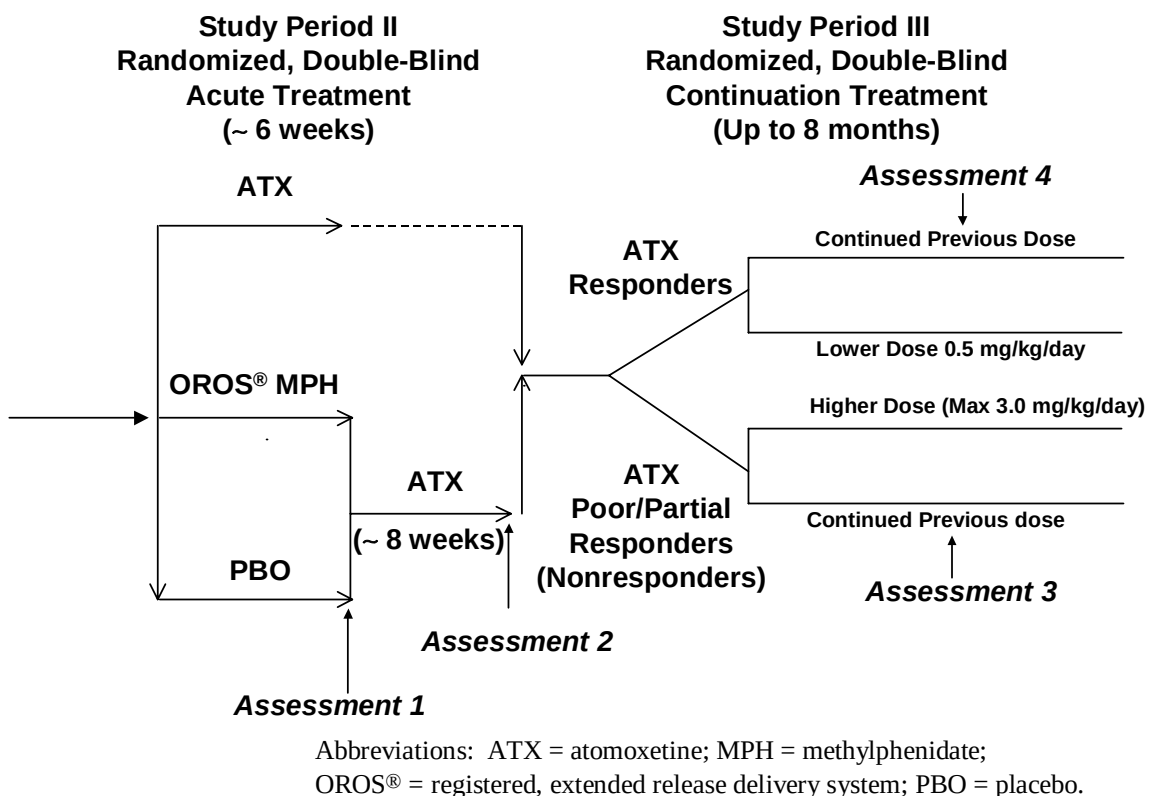


Figure LYBI.1. Illustration of study assessments.

Results:

Patient Demographics

Study Period II: Randomized, Double-Blind, Acute Treatment (Assessment 1)

Table LYBI.1 summarizes baseline demographics and other characteristics for all patients who were randomized to treatment with atomoxetine, methylphenidate, or placebo in Study Period II. There were no statistically significant differences observed among treatment groups at baseline. The majority of patients (60.1%) reported prior stimulant exposure (61.7% atomoxetine, 59.5% methylphenidate, and 56.8% placebo). The most common ADHD subtype, regardless of treatment assignment, was the Combined (Mixed) type. Baseline ADHD severity for all randomized patients using the CGI-ADHD-S scale was not statistically significantly different.

Table LYBI.1. Patient Characteristics
Comparison of Treatment Groups at Baseline
Randomized Patients
Study Period II

Variable	ATOMOX (N=222)	METHYL (N=220)	PLACEBO (N=74)	Total (N=516)	p-Value
Sex: No. (%)					
No. Patients	222	220	74	516	.288*
Female	50 (22.5)	64 (29.1)	19 (25.7)	133 (25.8)	
Male	172 (77.5)	156 (70.9)	55 (74.3)	383 (74.2)	
Origin: No. (%)					
No. Patients	222	220	74	516	.218*
African Descent	34 (15.3)	33 (15.0)	17 (23.0)	84 (16.3)	
Caucasian	132 (59.5)	145 (65.9)	40 (54.1)	317 (61.4)	
East/Southeast A	0	1 (0.5)	0	1 (0.2)	
Hispanic	39 (17.6)	28 (12.7)	8 (10.8)	75 (14.5)	
Other	17 (7.7)	13 (5.9)	9 (12.2)	39 (7.6)	
Age: yrs.					
No. Patients	222	220	74	516	.896**
Mean	10.30	10.24	10.13	10.25	
Median	10.23	9.93	9.53	10.09	
Standard Dev.	2.22	2.48	2.65	2.40	
Minimum	6.05	6.04	6.10	6.04	
Maximum	15.78	16.94	15.88	16.94	
CYP2D6					
No. Patients	222	220	74	516	.302*
EXTN	207 (93.2)	211 (96.3)	71 (95.9)	489 (95.0)	
SLOW	15 (6.8)	8 (3.7)	3 (4.1)	26 (5.0)	
Unspecified	0	1	0	1	
Height: cm					
No. Patients	222	219	74	515	.928**
Mean	139.66	139.63	138.96	139.55	
Median	139.00	137.00	137.00	137.50	
Standard Dev.	13.72	15.01	14.06	14.30	
Minimum	114.00	108.50	114.00	108.50	
Maximum	175.00	183.00	170.00	183.00	
Unspecified	0	1	0	1	
Weight: kg					
No. Patients	221	220	74	515	.737**
Mean	37.35	37.32	36.29	37.18	
Median	36.00	35.00	34.55	35.40	
Standard Dev.	10.72	11.21	10.46	10.88	
Minimum	22.00	21.50	22.00	21.50	
Maximum	60.00	59.90	59.90	60.00	
Unspecified	1	0	0	1	
DSM-IV ADHD Subtype					
No. Patients	222	220	74	516	.247*
HYP/IMP	7 (3.2)	3 (1.4)	1 (1.4)	11 (2.1)	
INATTV	53 (23.9)	71 (32.3)	22 (29.7)	146 (28.3)	
MIXED	162 (73.0)	146 (66.4)	51 (68.9)	359 (69.6)	

(continues)

**Table LYBI.1. Patient Characteristics
Comparison of Treatment Groups at Baseline
Randomized Patients
Study Period II (Concluded)**

Variable	ATOMOX (N=222)	METHYL (N=220)	PLACEBO (N=74)	Total (N=516)	p-Value
Family History-ADHD-Mother					
No. Patients	222	220	74	516	.270*
N	156 (70.9)	154 (70.0)	60 (81.1)	370 (72.0)	
U	19 (8.6)	22 (10.0)	7 (9.5)	48 (9.3)	
Y	45 (20.5)	44 (20.0)	7 (9.5)	96 (18.7)	
Unspecified	2	0	0	2	
Family History-ADHD-Father					
No. Patients	222	220	74	516	.867*
N	139 (63.2)	136 (61.8)	43 (58.1)	318 (61.9)	
U	28 (12.7)	34 (15.5)	11 (14.9)	73 (14.2)	
Y	53 (24.1)	50 (22.7)	20 (27.0)	123 (23.9)	
Unspecified	2	0	0	2	
Family History-ADHD-Grandparents					
No. Patients	222	220	74	516	.530*
N	164 (74.5)	161 (73.2)	61 (82.4)	386 (75.1)	
U	37 (16.8)	38 (17.3)	10 (13.5)	85 (16.5)	
Y	19 (8.6)	21 (9.5)	3 (4.1)	43 (8.4)	
Unspecified	2	0	0	2	
Family History-ADHD-Siblings					
No. Patients	222	220	74	516	.582*
N	135 (61.4)	123 (55.9)	38 (51.4)	296 (57.6)	
N/A	12 (5.5)	9 (4.1)	6 (8.1)	27 (5.3)	
U	13 (5.9)	18 (8.2)	6 (8.1)	37 (7.2)	
Y	60 (27.3)	70 (31.8)	24 (32.4)	154 (30.0)	
Unspecified	2	0	0	2	
Prior Stimulant Exposure					
No. Patients	222	220	74	516	.736*
N	85 (38.3)	89 (40.5)	32 (43.2)	206 (39.9)	
Y	137 (61.7)	131 (59.5)	42 (56.8)	310 (60.1)	
Grade in School					
No. Patients	222	220	74	516	.458*
0	2 (0.9)	2 (0.9)	0	4 (0.8)	
1	14 (6.3)	21 (9.5)	13 (17.6)	48 (9.3)	
10	3 (1.4)	3 (1.4)	1 (1.4)	7 (1.4)	
11	0	1 (0.5)	0	1 (0.2)	
2	26 (11.7)	26 (11.8)	7 (9.5)	59 (11.4)	
3	30 (13.5)	32 (14.5)	13 (17.6)	75 (14.5)	
4	35 (15.8)	35 (15.9)	8 (10.8)	78 (15.1)	
5	34 (15.3)	22 (10.0)	3 (4.1)	59 (11.4)	
6	32 (14.4)	28 (12.7)	10 (13.5)	70 (13.6)	
7	23 (10.4)	25 (11.4)	9 (12.2)	57 (11.0)	
8	19 (8.6)	16 (7.3)	6 (8.1)	41 (7.9)	
9	4 (1.8)	9 (4.1)	4 (5.4)	17 (3.3)	

Abbreviations: A = Asian; ADHD = Attention-Deficit/Hyperactivity Disorder; ATOMOX = atomoxetine; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; Dev. = deviation; EXTN = extensive metabolizer; HYP/IMP = hyperactivity/impulsivity; INATTN = inattentive; METHYL = methylphenidate; N = total number of patients; N/A = not applicable; N = No or number; U = unknown; Y = yes; yrs = years.

Population: All Enrolled Patients.

Study Period I: Visits 1 through 2.

NOTE: Pooled Investigator Used in Analysis

* Frequencies are analyzed using a Chi-Square test.

** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=investigator and treatment.

Study Period II: Patient Characteristics for the Subgroup of Patients Randomized to Methylphenidate and Switched to Atomoxetine During Randomized, Double-Blind, Continuation Treatment (Assessment 2)

A total of 220 patients were randomized to acute, double-blind treatment with methylphenidate, and 180 of these patients completed Study Period II and were switched to treatment with atomoxetine during Study Period III. Of the 180 patients switched to atomoxetine, 178 patients had an ADHDRS-IV-Parent:Inv endpoint score and were included in Assessment 2. Table LYBI.2 summarizes patient characteristics by response status to methylphenidate for these 178 patients.

**Table LYBI.2. Patient Characteristics
Organized by Response to Methylphenidate
Methylphenidate Patients* Switched to Atomoxetine**

Characteristic	Methylphenidate Nonresponders N=70	Methylphenidate Responders N=108
Sex (M/F)	55/15	71/37
Mean age in years (SD)	10.6 (2.5)	10.3 (2.5)
ADHD Diagnostic Subtype n(%)		
Hyperactive/Impulsive	0	1 (0.93)
Inattentive	25 (35.71)	38 (35.19)
Combined	45 (64.29)	69 (63.89)
Comorbid Diagnosis n (%)		
Oppositional Defiant Disorder	30 (42.9)	35 (32.4)
Prior Stimulant Exposure n (%)		
No	18 (25.71)	50 (46.30)
Yes	52 (74.29)	58 (53.70)

Abbreviations: ADHD = Attention-Deficit/Hyperactivity Disorder; F = female; M = male; N= total number of patients; n = number of patients with specific characteristic; SD = standard deviation.

* ADHDRS-IV-Parent:Inv endpoints were missing for 2 patients.

Study Period III: Patient Characteristics for Atomoxetine Nonresponders and Atomoxetine Responders During Randomized, Double-Blind, Continuation Treatment (Assessments 3 and 4)

Table LYBI.3 summarizes treatment comparisons for baseline demographics and other characteristics for patients who were rerandomized to treatment during the double-blind, continuation treatment period. The groups were comparable in terms of sex, age, ADHD subtype, and prior-stimulant-use status at baseline.

Table LYBI.3. Patient Characteristics Comparisons of Treatment Groups at Baseline All Randomized Patients Study Period III

Characteristics	Assessment 3 Atomoxetine Nonresponders N=122			Assessment 4 Atomoxetine Responders N=229		
	Previous Dose n=62	Higher Dose (max. 3.0 mg/kg/day) n=60	p-Value	Previous Dose n=116	Lower Dose (0.5 mg/kg/day) n=113	p-Value
Sex (M/F)	49/13	51/9	.482	84/32	79/34	.771
Mean age in years (SD)	9.9 (2.3)	10.1 (2.5)	.628	10.6 (2.6)	10.5 (2.3)	.725
ADHD Subtype n (%)			.244			.100
Hyperactive/Impulsive	3 (4.84)	3 (5.00)		3 (2.59)	0	
Inattentive	9 (14.52)	16 (26.67)		41 (35.34)	32 (28.32)	
Combined	50 (80.65)	41 (68.33)		72 (62.07)	81 (71.68)	
Prior Stimulant Exposure n (%)			1.000			.501
No	21 (33.87)	21 (35.00)		43 (37.07)	47 (41.59)	
Yes	41 (66.13)	39 (65.00)		73 (62.93)	66 (58.414)	

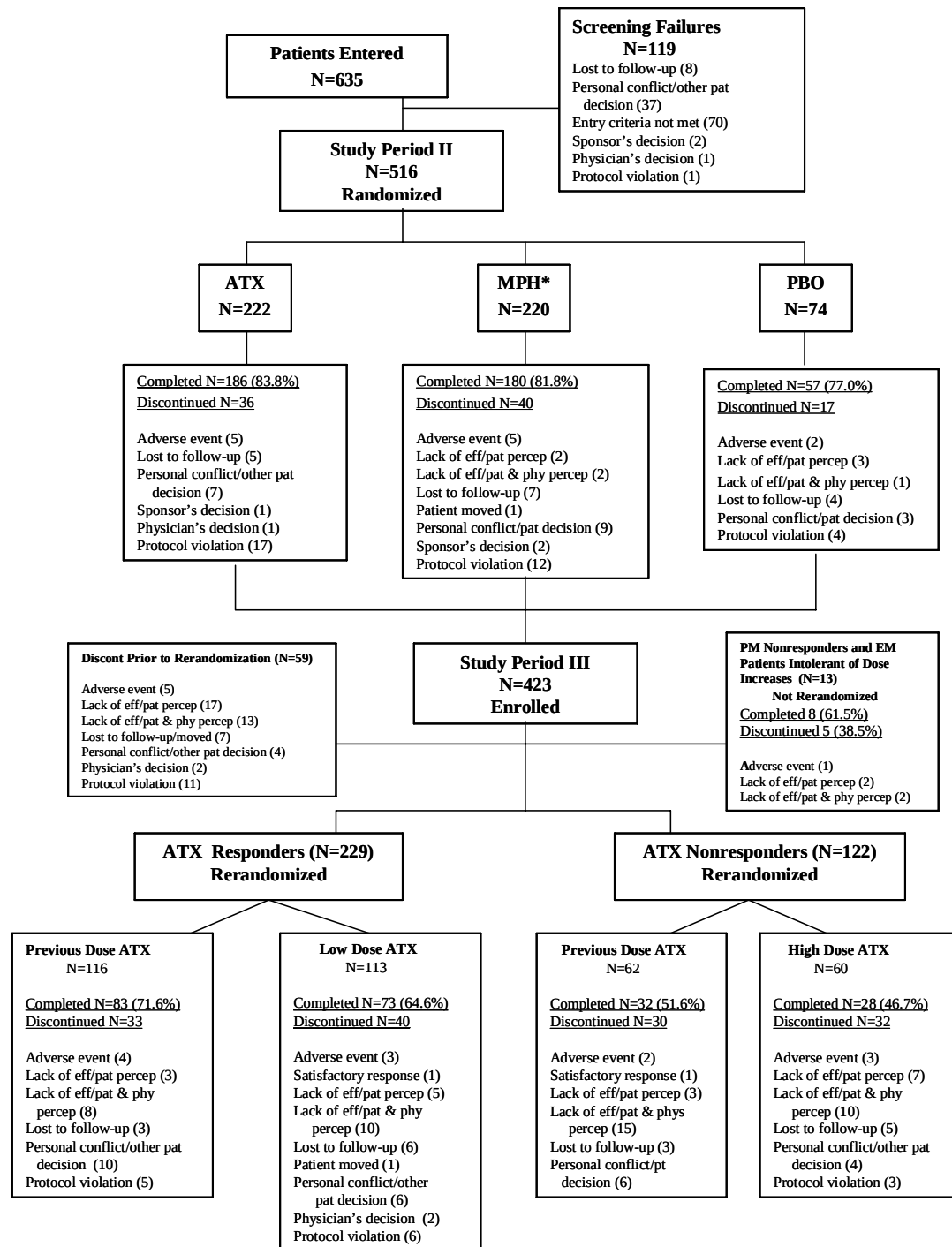
Abbreviations: ADHD = Attention-Deficit/Hyperactivity Disorder; F = female; M = male;
max = maximum; N = total number of patients; n = number of patients with specific characteristics;
SD = standard deviation.

* p-values generated from Fisher's exact tests for comparisons of sex and prior stimulant exposure, from a chi-square test for comparisons of ADHD subtype, and from a two-sample t-test for comparisons of mean age.

Patient Disposition

Figure LYBI.2 presents a summary of patient disposition. Of the 635 patients who entered into the study, 516 were randomly assigned to approximately 6 weeks of double-blind treatment with atomoxetine, methylphenidate, or placebo in Study Period II. Completion rates were compared, and there were no statistically significant differences among treatment groups. During the acute treatment period, protocol violations were the most common reasons for study discontinuation in the atomoxetine and methylphenidate treatment groups, while perceived lack of efficacy, lost to follow-up, and protocol violations were the most common reasons for discontinuation in the placebo treatment group. The 180 methylphenidate patients who completed Study Period II were switched to acute treatment with atomoxetine for approximately 8 weeks before being assigned to treatment in Study Period III (Figure LYBI.3). The 57 placebo patients were also switched to atomoxetine therapy.

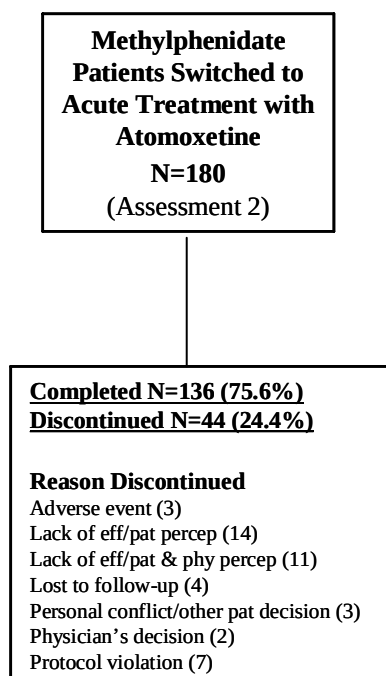
A total of 423 patients continued into the double-blind atomoxetine continuation treatment period (Study Period III). Thirteen patients were not rerandomized during Study Period III, because they either had the CYP2D6 poor metabolizer (PM) genotype or were extensive metabolizer (EM) patients unable to tolerate a dose increase.



Abbreviations: ATX = atomoxetine; Discont = discontinued; eff = efficacy; EM = extensive metabolizer; MPH = methylphenidate; N = number of patients; pat = patient; percep = perception; phy = physician; PBO = placebo; PM = poor metabolizer.

* Figure LYBI.3 illustrates disposition for the 180 MPH-treated patients who completed Study Period II before being switched to acute treatment with atomoxetine (Assessment 2).

Figure 2. Patient disposition.



Abbreviations: eff = efficacy; N = number of patients; pat = patient; percep = perception; phy = physician.

Figure LYBI.3. Disposition for methylphenidate-treated patients switched to atomoxetine for approximately 8 weeks (Assessment 2).

Primary Efficacy Analyses

Study Period II: Randomized, Double-Blind, Acute Treatment Results of the Primary Efficacy Analysis (Assessment 1)

The primary efficacy analysis tested the noninferiority of atomoxetine versus methylphenidate by comparing response rates. The blinded definition of response was at least a 40% improvement in ADHD symptoms, as measured by the ADHDRS-IV-Parent:Inv Total score at endpoint.

Table LYBI.4 summarizes the results of the primary analysis. The primary analysis did not yield statistical evidence of noninferiority since the lower end of the confidence interval (-21.2) was less than the predefined noninferiority limit of -15.0.

**Table LYBI.4. Percentage of Patients Classified as Responders
ADHDRS-IV-Parent:Inv Total Score
Atomoxetine versus Methylphenidate
Randomized Patients, Study Period II**

Therapy	No. Randomized	No. Responded	%	95% CI (LCI, UCI) ATX% - MPH%
Atomoxetine	213	95	44.6	(-21.2, -2.3)
Methylphenidate	211	119	56.4	

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator-Administered and Scored; ATX = atomoxetine; CI = confidence interval; LCI = lower confidence interval; MPH = methylphenidate; No. = number; UCI = upper confidence interval.

* To be classified as a responder, a patient had to have at least a 40% reduction from baseline in ADHDRS-IV-Parent:Inv Total score.

Response rates for both active treatments also were compared with placebo. No adjustments were made for multiple comparisons because these comparisons were conducted primarily for the purpose of validating the study. Table LYBI.5 contains these comparisons for all patients randomized to treatment in Study Period II, and by prior stimulant status. Both active treatments (atomoxetine and methylphenidate) were superior to placebo ($p=.003$ and $p<.001$, respectively), and methylphenidate was superior to atomoxetine ($p=.016$). Results of these comparisons by prior stimulant status are discussed below.

Secondary Efficacy Analysis Using the Primary Efficacy Measure

Secondary and subgroup analyses using the primary efficacy measure were specified in the protocol. The analyses are presented as follows:

- percentage of patients classified as responders by prior stimulant use status
- mean change from baseline to LOCF endpoint and subgroup analysis by prior stimulant use status
- repeated measures analysis using the ADHDRS-IV-Parent:Inv Total and Subscale scores
- subgroup analysis by CYP2D6 genotype.

Percentage of Patients Classified as Responders by Prior Stimulant Use Status

Table LYBI.5 summarizes response rates for all patients classified as responders, and by stimulant status (prior stimulant users and stimulant-naïve patients). In the prior-stimulant-users subgroup, statistically significant differences were observed in the comparisons between methylphenidate and atomoxetine ($p=.026$) and between

methylphenidate and placebo ($p=.001$). Atomoxetine was not statistically significantly different from placebo ($p=.090$) in this subgroup.

In stimulant-naïve patients, the difference between methylphenidate and atomoxetine was not statistically significant ($p=.423$). The response rates were higher for both active treatments, but not for placebo (57.0% for atomoxetine, 64.3% for methylphenidate, and 25.0% for placebo), and both active treatments were superior to placebo ($p=.004$ and $p<.001$, respectively).

**Table LYBI.5. Percentages of Patients Classified as Responders
ADHDRS-IV-Parent:Inv Total Score
Randomized Patients
Study Period II**

	ATX		MPH		PBO		ATX vs MPH	MPH vs PBO	ATX vs PBO
	n/N	%	n/N	%	n/N	%	p-value	p-value	p-value
All Patients	95/213	44.6	119/211	56.4	16/68	23.5	.016	<.001	.003
Prior Stimulant Users	50/134	37.3	65/127	51.2	9/40	22.5	.026	.002	.090
Stimulant-Naïve Patients	45/79	57.0	54/84	64.3	7/28	25.0	.423	<.001	.004

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator-Administered and Scored; ATX = atomoxetine; MPH = methylphenidate; N = total number of patients; n = total number of responders per treatment group; PBO = placebo; vs = versus.

* p-values are based on the Fisher's exact test.

Patients known to respond poorly to stimulants and patients who did not tolerate stimulants were excluded from enrollment in the study, with no similar exclusion possible for atomoxetine tolerance. Other groups of patients with comorbidities (for example, motor tic or Tourette's) that are often seen in the clinical treatment of ADHD also were excluded from the study.

This study was not powered to assess differences in stimulant-naïve patients, thus it is not possible to say there are no differences in response between methylphenidate and atomoxetine in this subgroup. These data suggest that if differences in response are present, they are modest, particularly relative to the difference between each of the active treatments and placebo. This observation is reinforced by an examination of treatment effect sizes (differences from placebo) in the stimulant-naïve patients in an analysis of

mean baseline to LOCF endpoint change on the ADHDRS-IV-Parent:Inv, which is presented in Table LYBI.6 below.

**Table LYBI.6. Effect Sizes from the Mean Change from Baseline to LOCF Endpoint Analyses
ADHDRS-IV-Parent:Inv Total Score
Study Period II**

Patient Group	Treatment	Effect Size

All Patients	ATX	0.6
	MPH	0.8
Prior Stimulant Exposed Patients	ATX	0.5
	MPH	0.8
Stimulant Naive Patients	ATX	0.9
	MPH	1.0

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator-Administered and Scored; ATX = atomoxetine; LOCF = last observation carried forward; MPH = methylphenidate.

Effect Size was computed based on ANCOVA model with terms for baseline, treatment, CYP2D6 Status, and investigator
Population: Randomized patients with a baseline and a postbaseline visit.

Mean Change from Baseline to LOCF Endpoint Using the ADHDRS-IV-Parent:Inv Total, Inattention, and Hyperactivity-Impulsivity Subscale Scores for All Randomized Patients and by Prior Stimulant Status

Table LYBI.7 summarizes mean change from baseline to LOCF endpoint in the ADHDRS-IV-Parent:Inv Total score, Inattention Subscale score, and Hyperactivity-Impulsivity Subscale score. Mean change data are included for all patients and by prior stimulant use status (prior stimulant use and stimulant-naïve patients). A statistically significant mean improvement in ADHDRS-IV-Parent:Inv Total score was observed for both atomoxetine and methylphenidate compared with placebo in all groups. Methylphenidate demonstrated statistically significantly greater mean improvement compared with atomoxetine ($p=.015$) in the all-patients group; however, when only stimulant-naïve patients were examined, the difference in improvement was no longer statistically significant ($p=.253$).

Results on the Inattention Subscale mirror those observed on the ADHDRS-IV-Parent:Inv Total score for each patient group. Mean change on the Hyperactivity-Impulsivity Subscale score were not statistically significant in any patient group.

Table LYBI.7. ADHDRS-IV-Parent:Inv Total, Inattention, and Hyperactivity-Impulsivity Subscale Scores
Mean Change from Baseline to LOCF Endpoint
Study Period II

	Atomoxetine			Methylphenidate			Placebo*			ATX vs MPH p-value
	N	Mean Change	SD	N	Mean Change	SD	N	Mean Change	SD	
Total Score										
All Patients	213	-14.4	12.7	211	-16.9	13.1	68	-7.3	11.5	.015
Prior Stimulant Users	134	-12.4	12.2	127	-15.1	13.1	40	-6.2	11.5	.038
Stimulant-Naïve Patients	79	-17.9	13.0	84	-19.7	12.6	28	-9.0	11.6	.253
Inattention Subscale										
All Patients	213	-7.3	7.1	211	-9.0	7.7	68	-4.1	6.9	.006
Prior Stimulant Users	134	-5.9	6.8	127	-7.8	7.8	40	-3.3	6.5	.015
Stimulant-Naïve Patients	79	-9.7	7.1	84	-11.0	7.2	28	-5.2	7.4	.184
Hyperactivity-Impulsivity Subscale										
All Patients	213	-7.1	6.9	211	-7.9	6.8	68	-3.2	5.8	.085
Prior Stimulant Users	134	-6.5	6.6	127	-7.3	6.7	40	-2.8	6.0	.173
Stimulant-Naïve Patients	79	-8.2	7.2	84	-8.7	7.0	28	-3.8	5.5	.418

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator-Administered and Scored; ATX = atomoxetine; LOCF = last observation carried forward; MPH = methylphenidate; N = number of patients; SD = standard deviation; vs = versus.

*Note: All differences for placebo are statistically significant from atomoxetine and from methylphenidate.

Repeated Measures Analysis Using the ADHDRS-IV-Parent:Inv Total and Subscale Scores

Table LYBI.8 summarizes least squares means for each treatment group and the treatment comparisons at each postbaseline visit for the ADHDRS-IV-Parent:Inv Total score, Inattention Subscale score, and the Hyperactivity-Impulsivity Subscale score. Statistically significant mean improvement in ADHDRS-IV-Parent:Inv Total and subscale scores were observed for both atomoxetine and methylphenidate compared with placebo at each postbaseline visit; however, methylphenidate demonstrated statistically significantly greater mean improvement compared with atomoxetine at the final postbaseline visit.

Atomoxetine hydrochloride

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**Table LYBI.8. ADHDRS-IV-Parent:Inv Total Score
Repeated Measures Analysis
All Enrolled Subjects
Study Period II**

Visit (Week)	Treatment	N	LSMean	LSMean Change	SE	Within p-value	Pairwise p-value vs. 3)	vs. 2)
3 (1)	1) Atomoxetine	213	25.90	-14.83	1.13	<.001	<.001	.393
	2) Methylphenidate	211	26.77	-13.96	1.18	<.001	<.001	
	3) Placebo	68	33.40	-7.33	1.57	<.001		
4 (3)	1) Atomoxetine	205	25.14	-15.58	1.18	<.001	<.001	.216
	2) Methylphenidate	193	23.72	-17.01	1.24	<.001	<.001	
	3) Placebo	65	33.17	-7.56	1.69	<.001		
5 (6)	1) Atomoxetine	195	23.58	-17.15	1.21	<.001	<.001	.006
	2) Methylphenidate	188	20.21	-20.51	1.27	<.001	<.001	
	3) Placebo	58	30.82	-9.90	1.78	<.001		

(continues)

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**Table LYBI.8. ADHDRS-IV-Parent:Inv Inattention Subscale Score
Repeated Measures Analysis
All Enrolled Subjects
Study Period II (Continued)**

Visit (Week)	Treatment	N	LSMean	LSMean Change	SE	Within p-value	Pairwise p-value vs. 3)	vs. 2)
3 (1)	1) Atomoxetine	213	14.33	-8.03	0.63	<.001	<.001	.926
	2) Methylphenidate	211	14.39	-7.98	0.66	<.001	<.001	
	3) Placebo	68	17.78	-4.58	0.87	<.001		
4 (3)	1) Atomoxetine	205	13.95	-8.42	0.66	<.001	<.001	.176
	2) Methylphenidate	193	13.06	-9.30	0.69	<.001	<.001	
	3) Placebo	65	17.44	-4.92	0.95	<.001		
5 (6)	1) Atomoxetine	195	13.23	-9.13	0.69	<.001	<.001	.003
	2) Methylphenidate	188	11.17	-11.19	0.72	<.001	<.001	
	3) Placebo	58	16.67	-5.69	1.02	<.001		

(continues)

Atomoxetine hydrochloride

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**Table LYBI.8. ADHDRS-IV-Parent:Inv Hyperactivity/Impusivity Subscale Score
Repeated Measures Analysis
All Enrolled Subjects
Study Period II (Concluded)**

Visit (Week)	Treatment	N	LSMean	LSMean Change	SE	Within p-value	Pairwise p-value vs. 3) vs. 2)	
3 (1)	1) Atomoxetine	213	11.57	-6.79	0.59	<.001	<.001	.147
	2) Methylphenidate	211	12.35	-6.01	0.62	<.001	<.001	
	3) Placebo	68	15.68	-2.69	0.82	.001		
4 (3)	1) Atomoxetine	205	11.18	-7.19	0.61	<.001	<.001	.381
	2) Methylphenidate	193	10.66	-7.71	0.64	<.001	<.001	
	3) Placebo	65	15.75	-2.61	0.87	.003		
5 (6)	1) Atomoxetine	195	10.35	-8.01	0.62	<.001	<.001	.030
	2) Methylphenidate	188	9.02	-9.34	0.65	<.001	<.001	
	3) Placebo	58	14.20	-4.17	0.91	<.001		

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator-Administered and Scored; LSMean = least-squares mean; N = N = number of enrolled subjects with non-missing data at the specified visit; SE = standard error; vs = versus..

95% CI at visit 5: CRT-TMX(-2.53,-0.13);PLA-TMX(2.12,5.58);CRT-PLA(-6.91,-3.44) .

Model Endpoint=trt visit investigator trt*visit baseline baseline*visit cy2d6gen.

Percentage of Patients Classified as Responders by CYP2D6 Genotype

Table LYBI.9.a and Table 9.b contains the response rate comparisons for CYP2D6 EM and PM patients. Note the small number of PM patients in the analysis (atomoxetine [n=14]; methylphenidate [n=7]; placebo [n=3]). The percentage of PM patients who met the definition of response was higher in the atomoxetine group. This observation is preliminary because this study was not statistically powered for subgroup comparisons.

**Table LYBI.9.a. Atomoxetine/Methylphenidate versus Placebo
ADHDRS-IV-Parent:Inv Total Score Response
Reduction from Baseline
All Extensive Metabolizer Patients**

Therapy	N	n	%	95% CI (LCI,UCI) FOR TRT% - PLA%
Atomoxetine	199	84	42.2	(5.1 , 30.1)
Methylphenidate	203	114	56.2	(19.0 , 44.0)
Placebo	65	16	24.6	

**Table LYBI.9.b. Atomoxetine/Methylphenidate versus Placebo
ADHDRS-IV-Parent:Inv Total Score Response
Reduction from Baseline
All Slow Metabolizer Patients**

Therapy	N	n	%	95% CI (LCI,UCI) FOR TRT% - PLA%
Atomoxetine	14	11	78.6	(57.1 , 100.1)
Methylphenidate	7	4	57.1	(20.5 , 93.8)
Placebo	3	0	0.0	

Abbreviations = ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator-Administered and Scored; CI = confidence interval; LCI = lower confidence interval; N = total number of Slow Metabolizer patients; n = number of responders; PLA = placebo; TRT = treatment percentage; UCI = upper confidence interval.

* To be classified as a responder, a patient has to have a reduction from baseline ADHDRS-IV-Parent: Total score of at least 40%

Secondary Efficacy Analyses

The CGI-ADHD-S scale was analyzed using repeated measures analysis analogous to the repeated measures analysis using the ADHDRS-IV-Parent:Inv scale. Mean change from baseline to LOCF endpoint analysis also was conducted for all other efficacy measures, including the CGI-ADHD-S.

Repeated Measures Analysis Using the CGI-ADHD-S

Table LBYBI.10 summarizes least-squares means for each treatment group and the treatment comparisons at each postbaseline visit for the CGI-ADHD-S. Both atomoxetine and methylphenidate demonstrated statistically significant mean improvement in CGI-ADHD-S score compared with placebo, although methylphenidate demonstrated statistically significantly greater mean improvement than atomoxetine at Visit 5.

**Table LYBI.10. CGI-ADHD-S Score
Repeated Measures Analysis
All Enrolled Subjects
Study Period II**

Visit (Week)	Treatment	N	LSMean	LSMean Change	SE	Within p-value	Pairwise p-value vs. 3)	vs. 2)
3 (1)	1) Atomoxetine	213	3.85	-1.14	0.10	<.001	<.001	.951
	2) Methylphenidate	211	3.84	-1.14	0.10	<.001	<.001	
	3) Placebo	68	4.39	-0.59	0.14	<.001		
4 (3)	1) Atomoxetine	205	3.60	-1.39	0.11	<.001	<.001	.497
	2) Methylphenidate	193	3.53	-1.46	0.11	<.001	<.001	
	3) Placebo	65	4.26	-0.72	0.15	<.001		
5 (6)	1) Atomoxetine	195	3.55	-1.43	0.11	<.001	.003	.001
	2) Methylphenidate	188	3.17	-1.81	0.12	<.001	<.001	
	3) Placebo	58	4.06	-0.93	0.17	<.001		

Abbreviations: CGI-ADHD-S = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity; LSMean = least-squares mean; N = number of enrolled subjects with non-missing data at the specified visit; SE = standard error; vs = versus.

95% CI at visit 5: CRT-TMX(-0.61,-0.15);PLA-TMX(0.17,0.84);CRT-PLA(-1.23,-0.55).

Model Endpoint=trt visit investigator trt*visit baseline baseline*visit cy2d6gen.

Mean Change from Baseline to LOCF Endpoint Using the Primary and Secondary Efficacy Measures

Table LYBI.11 and Table LYBI.12 summarize mean change from baseline to LOCF endpoint for the primary efficacy measure (ADHDRS-IV-Parent:Inv) and the CGI-ADHD-S, respectively. Results of the mean change analysis of the ADHDRS-IV-Parent:Inv and CGI-ADHD-S were consistent with the repeated measures analyses for these measures. Both atomoxetine- and methylphenidate-treated patients demonstrated significantly greater improvement than placebo-treated patients. Improvement in the methylphenidate treatment group also was significantly greater than in the atomoxetine treatment group on all but the ADHDRS-IV-Parent:Inv Hyperactivity-Impulsivity Subscale score. The difference was not significant between the two active treatments on this subscale.

Table LYBI.11. ADHDRS-IV-Parent:Inv Score
Change from Baseline to LOCF Endpoint
Study Period II

Variable/ Treatment Group	N	---Baseline---		---Change---		p-val* (vs Placebo)	p-val* (vs Methylphenidate)
		Mean	SD	Mean	SD		

Total Score							
Atomoxetine	213	40.89	8.80	-14.44	12.74	<.001	0.015
Methylphenidate	211	39.96	8.84	-16.90	13.09	<.001	-----
Placebo	68	41.72	8.54	-7.32	11.52	-----	-----
Inattentive Subscale							
Atomoxetine	213	22.34	4.04	-7.31	7.15	<.001	0.006
Methylphenidate	211	22.10	4.16	-9.04	7.71	<.001	-----
Placebo	68	22.79	3.55	-4.10	6.89	-----	-----
Hyperactive/Impulsive Subscale							
Atomoxetine	213	18.55	6.65	-7.13	6.86	<.001	0.085
Methylphenidate	211	17.86	6.70	-7.87	6.83	<.001	-----
Placebo	68	18.93	6.88	-3.22	5.77	-----	-----

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator-Administered and Scored; LOCF = last observation carried forward; N = number of patients; SD = standard deviation; val = value; vs = versus.

* p-value is obtained from ANOVA model with terms for baseline, investigator, treatment, and CYP2D6 metabolism status.

Population: All enrolled patients with at least one baseline and postbaseline measurement.

Table LYBI.12. CGI-ADHD-Severity Score
Change from Baseline to LOCF Endpoint
Study Period II

Therapy	N	---Baseline---		---Change---		p-val* (vs Placebo)	p-val* (vs Methylphenidate)
		Mean	SD	Mean	SD		
Atomoxetine	213	5.0	0.7	-1.2	1.2	0.001	0.004
Methylphenidate	211	4.9	0.8	-1.5	1.3	<.001	-----
Placebo	68	5.1	0.7	-0.7	1.0	-----	-----

Abbreviations: CGI-ADHD-S = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity; LOCF = last observation carried forward; N = number of patients; SD = standard deviation; val = value; vs = versus.

* p-value is obtained from ANOVA model with terms for baseline, pooled investigator, treatment, and CYP2D6 metabolism status.

Population: All enrolled patients with at least one baseline and one postbaseline measurement.

Table LYBI.13 contains mean change from baseline to LOCF endpoint on the CGI-ADHD-I scale. Both active treatment groups demonstrated significant symptom improvement compared with the placebo treatment group. Improvement in the methylphenidate group was statistically greater than the atomoxetine treatment group.

**Table LYBI.13. CGI-ADHD I
Study Period II Endpoint Analysis**

Treatment Group	N	Mean	SD	p-val* (vs Placebo)	p-val* (vs Methylphenidate)
Atomoxetine	213	2.92	1.16	0.002	0.020
Methylphenidate	211	2.65	1.19	<.001	-----
Placebo	68	3.44	1.23	-----	-----

 CGI-ADHD-I = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Improvement; N = number of patients; SD = standard deviation; val = value; vs = versus.

* p-value is obtained from ANOVA model with terms for pooled investigator, CYP2D6 metabolism status and treatment.

Population: All enrolled patients with at least one post-baseline measurement.

The results of the mean change from baseline to LOCF endpoint on the Daily Parent Ratings of Evening and Morning Behavior-Revised (DPREMB-Revised) scale were reviewed. Both atomoxetine- and methylphenidate-treated patients demonstrated significant improvement compared with placebo on Evening Subscale scores (atomoxetine: -0.48 [baseline mean=1.51; endpoint mean=1.04]; methylphenidate: -0.53 [baseline mean=1.49; endpoint mean=.96]; placebo: 0.01 [baseline mean=1.35; endpoint mean=1.37; [p<0.001]]), and atomoxetine demonstrated statistically significant improvement compared with placebo on Morning Subscale scores (atomoxetine: -0.31 [baseline mean=1.20; endpoint mean=.89]; placebo: 0.01 [baseline mean=1.12; endpoint mean=1.13] [p=0.02]).

Patients with motor tics or a diagnosis of Tourette's were excluded from this study. Table LYBI.14 summarizes mean change from baseline to LOCF endpoint on the Yale Global Tic Severity Scale (YGTSS).

Table LYBI.14. YGTSS
Change from Baseline to LOCF Endpoint
Study Period II

Variable/ Treatment Group	N	---Baseline---		---Change---		p-val* (vs Placebo)	p-val* (vs Methylphenidate)
		Mean	SD	Mean	SD		

YGTSS Motor Total							
Atomoxetine	202	0.13	0.91	-0.08	1.08	0.064	0.166
Methylphenidate	196	0.03	0.36	0.16	1.30	0.379	-----
Placebo	64	0.13	0.70	0.17	0.81	-----	-----
YGTSS Phonic Total							
Atomoxetine	202	0.10	0.76	-0.03	1.08	0.658	0.943
Methylphenidate	196	0.03	0.36	0.02	0.21	0.623	-----
Placebo	64	0.00	0.00	0.08	0.62	-----	-----
YGTSS Total Score							
Atomoxetine	202	0.23	1.41	-0.11	1.91	0.127	0.359
Methylphenidate	196	0.05	0.50	0.17	1.32	0.380	-----
Placebo	64	0.13	0.70	0.25	1.35	-----	-----

Abbreviations: LOCF = last observation carried forward; N = number of patients;
SD = standard deviation; val = value, vs = versus; YGTSS = Yale Global Tic Severity
Scale.

* p-value is obtained from ANOVA model with terms for baseline, investigator, treatment,
and CYP2D6 metabolism status.

Population: All enrolled patients with at least one baseline and postbaseline
measurement.

Two secondary measures, the Children's Depression Rating Scale-Revised (CDRS-R) and the Pediatric Anxiety Rating Scale (PARS), examined the presence and severity of depression and anxiety, respectively. Patients with severe anxiety were excluded from this study. Mean scores on the CDRS-R were in the range of borderline depression for all treatment groups at baseline and endpoint.

The mean change from baseline to LOCF endpoint results on the Assessment of Affective Range (AAR; Table LYBI.15) and Social Skills Rating System-Parent (SSRS-P; Table LYBI.16) were reviewed. No change was noted in any of the three treatment groups on the AAR, however there were statistically significant differences in the SSRS-P subscale scores.

Table LYBI.15. AAR-Total Score
Change from Baseline to LOCF Endpoint
Study Period II

Therapy	N	---Baseline---		---Change---		p-val* (vs Placebo)	p-val* (vs Methylphenidate)
		Mean	SD	Mean	SD		
Atomoxetine	198	25.9	3.5	0.4	3.6	0.406	0.377
Methylphenidate	193	26.1	3.4	0.0	3.6	0.150	-----
Placebo	62	26.0	3.8	0.7	3.4	-----	-----

Abbreviations: AAR = Assessment of Affective Range; LOCF = last observation carried forward; N = number of patients; SD = standard deviation; val = value, vs = versus.

* p-value is obtained from ANOVA model with terms for baseline, investigator, treatment, and CYP2D6 metabolism status.

Population: All enrolled patients with at least one baseline and postbaseline measurement.

Table LYBI.16. SSRS-Parent
Change from Baseline to LOCF Endpoint
Study Period II

Variable/ Treatment Group	N	---Baseline---		---Change---		p-val* (vs Placebo)	p-val* (vs Methylphenidate)
		Mean	SD	Mean	SD		

SSRSP Problem Behaviors Standard Score							
Atomoxetine	191	118.66	14.11	-7.26	14.20	0.332	0.028
Methylphenidate	187	117.32	15.30	-9.58	15.07	0.013	-----
Placebo	58	115.02	14.04	-3.59	12.57	-----	-----
SSRSP Social Skill Standard Score							
Atomoxetine	195	81.14	14.34	4.75	12.41	0.553	0.013
Methylphenidate	188	82.01	13.82	7.68	13.62	0.259	-----
Placebo	59	83.42	13.87	4.92	14.14	-----	-----

Abbreviations: LOCF = last observation carried forward; N = number of patients; SD = standard deviation; SSRSP = Social Skills Rating System-Parent; val = value, vs = versus.

* p-value is obtained from ANOVA model with terms for baseline, investigator, treatment, and CYP2D6 metabolism status.

Population: All enrolled patients with at least one baseline and one postbaseline measurement.

Mean change from baseline to LOCF endpoint results on the Conners' Parent Rating Scale Revised: Short Form (CPRS-R:S) were consistent with results on the ADHDRS-IV-Parent:Inv scale in that the methylphenidate treatment group demonstrated statistically significant improvement compared with atomoxetine and placebo treatment groups on the ADHD Index and each subscale score (Table LYBI.17).

Table LYBI.17. CPRS-R: S
Change from Baseline to LOCF Endpoint
Study Period II

Variable/ Treatment Group	N	---Baseline---		---Change---		p-val* (vs Placebo)	p-val* (vs Methylphenidate)
		Mean	SD	Mean	SD		

CPRS ADHD Index							
Atomoxetine	208	27.62	5.90	-7.81	9.23	<.001	0.003
Methylphenidate	195	27.53	5.83	-10.24	9.09	<.001	-----
Placebo	66	27.10	6.51	-2.28	8.43	-----	-----
CPRS Cognitive Problems T-Score							
Atomoxetine	208	74.40	10.34	-9.31	12.44	<.001	0.007
Methylphenidate	196	74.86	10.75	-12.71	13.65	<.001	-----
Placebo	65	73.66	12.79	-2.10	14.22	-----	-----
CPRS Hyperactive T-Score							
Atomoxetine	208	81.67	19.00	-14.08	17.58	<.001	0.009
Methylphenidate	196	81.37	18.16	-17.75	17.43	<.001	-----
Placebo	66	78.81	19.91	-4.33	14.06	-----	-----
CPRS Oppositional T-Score							
Atomoxetine	208	65.54	13.10	-5.12	13.04	0.613	0.003
Methylphenidate	196	66.37	13.61	-8.87	13.36	0.010	-----
Placebo	66	63.74	12.79	-3.23	10.95	-----	-----

Abbreviations: ADHD = Attention-Deficit/Hyperactivity Disorder; CPRS-R:S = Conners' Parent Rating Scale-Revised: Short Form; LOCF = last observation carried forward; N = number of patients; SD = standard deviation; val = value, vs = versus.

* p-value is obtained from ANOVA model with terms for baseline, investigator, treatment, and CYP2D6 metabolism status.
Population: All enrolled patients with at least one baseline and postbaseline measurement.

The mean change results for the Life Participation Scale (LPS; Table LYBI.18) and the Child Health Questionnaire (CHQ; Table LYBI.19) are shown below.

Table LYBI.18. LPS-Life Participation Total
Change from Baseline to LOCF Endpoint
Study Period II

Therapy	N	---Baseline---		--- Change ---		p-val* (vs Placebo)	p-val* (vs Methylphenidate)
		Mean	SD	Mean	SD		
Atomoxetine	200	33.4	9.9	7.0	12.5	0.057	0.021
Methylphenidate	192	34.6	10.7	9.1	14.1	<.001	-----
Placebo	64	35.3	9.7	2.6	11.2	-----	-----

Abbreviations: LOCF = last observation carried forward; LPS = Life Participation Scale; N = number of patients; SD = standard deviation; val = value, vs = versus.

* p-value is obtained from ANOVA model with terms for baseline, investigator, treatment, and CYP2D6 metabolism status.

Table LYBI.19. CHQ Subscale Scores
Change from Baseline to LOCF Endpoint
Study Period II

Variable/ Treatment Group	N	---Baseline---		---Change---		p-val* (vs Placebo)	p-val* (vs Methylphenidate)
		Mean	SD	Mean	SD		

Psychosocial Summary Score							
Atomoxetine	193	34.04	10.52	5.36	11.94	0.034	0.017
Methylphenidate	193	34.46	11.07	7.76	12.65	<.001	-----
Placebo	64	35.95	10.74	1.00	11.99	-----	-----
Mental Health							
Atomoxetine	199	71.26	16.07	3.35	16.14	0.580	0.557
Methylphenidate	195	69.84	17.19	5.19	19.02	0.335	-----
Placebo	65	72.15	18.05	1.72	17.14	-----	-----
Role Emotion/Behavior							
Atomoxetine	199	63.45	33.89	8.78	38.72	0.007	0.018
Methylphenidate	195	64.65	35.17	14.99	38.42	<.001	-----
Placebo	65	65.82	32.03	-5.02	38.52	-----	-----
Self-esteem							
Atomoxetine	199	67.74	18.87	5.58	20.68	0.150	0.295
Methylphenidate	195	67.82	20.26	7.37	22.36	0.030	-----
Placebo	65	71.72	20.18	-0.74	21.33	-----	-----
Parent Impact-Emotional							
Atomoxetine	199	45.49	21.11	6.32	25.05	0.282	0.002
Methylphenidate	195	44.75	18.60	13.12	24.37	0.001	-----
Placebo	65	48.22	19.47	1.09	18.85	-----	-----
Parent Time Impact							
Atomoxetine	200	66.97	20.88	5.81	24.86	0.290	0.063
Methylphenidate	194	65.17	21.89	10.90	26.31	0.018	-----
Placebo	65	66.34	22.13	2.89	23.25	-----	-----
Family Activities							
Atomoxetine	200	50.36	24.28	10.80	22.97	0.042	0.009
Methylphenidate	194	49.92	24.99	16.33	25.10	<.001	-----
Placebo	65	49.02	24.67	4.89	21.73	-----	-----

(continues)

Table LYBI.19. CHQ Subscale Scores
Change from Baseline to LOCF Endpoint
Study Period II (Concluded)

Variable/ Treatment Group	N	---Baseline---		---Change---		p-val*	p-val*
		Mean	SD	Mean	SD	(vs Placebo)	(vs Methylphenidate)
Family Cohesion							
Atomoxetine	198	63.06	24.72	3.99	22.16	0.796	0.664
Methylphenidate	194	62.19	26.49	5.18	22.88	0.961	-----
Placebo	65	66.69	24.64	2.85	20.86	-----	-----
Behavior							
Atomoxetine	201	44.04	19.03	11.26	19.27	0.105	0.016
Methylphenidate	195	46.61	19.06	14.05	19.57	<.001	-----
Placebo	65	47.26	19.24	5.40	19.86	-----	-----
CHQ-PF50 Bodily Pain							
Atomoxetine	200	88.50	15.43	-1.70	19.44	0.482	0.100
Methylphenidate	195	87.08	18.67	-3.95	20.72	0.645	-----
Placebo	65	89.38	17.58	-4.31	20.61	-----	-----
CHQ-PF50 Change in Health Item							
Atomoxetine	198	3.30	0.74	0.04	0.81	0.867	0.975
Methylphenidate	193	3.20	0.61	0.10	0.74	0.884	-----
Placebo	65	3.09	0.49	0.20	0.77	-----	-----
CHQ-PF50 General Health							
Atomoxetine	200	78.19	14.31	-1.00	13.23	0.022	0.183
Methylphenidate	195	77.78	15.28	0.92	13.66	0.173	-----
Placebo	65	74.83	15.15	4.51	10.59	-----	-----
CHQ-PF50 Physical Functioning							
Atomoxetine	200	96.65	13.23	0.51	16.07	0.292	0.203
Methylphenidate	195	97.83	8.87	0.60	9.76	0.052	-----
Placebo	65	96.65	10.41	-0.92	9.72	-----	-----
CHQ-PF50 Physical Summary Score							
Atomoxetine	193	55.71	7.62	-1.01	9.07	0.802	0.968
Methylphenidate	193	55.74	6.51	-1.04	7.25	0.780	-----
Placebo	64	55.16	6.34	-0.97	6.81	-----	-----
CHQ-PF50 Role-Physical							
Atomoxetine	199	92.65	20.03	1.52	22.87	0.163	0.685
Methylphenidate	194	93.31	18.95	1.47	22.50	0.094	-----
Placebo	64	94.20	17.49	-3.63	25.58	-----	-----

Abbreviations: CHQ = Child Health Questionnaire; LOCF = last observation carried forward; LPS = Life Participation Scale; N = number of patients; SD = standard deviation; val = value, vs = versus.

* p-value is obtained from ANOVA model with terms for baseline, investigator, treatment, and CYP2D6 metabolism status.

Population: All enrolled patients with at least one baseline and postbaseline measurement.

Patients Randomized to Methylphenidate in Study Period II and Switched to Atomoxetine in Study Period III (Assessment 2)

In the group of patients randomized to methylphenidate in Study Period II and switched to acute treatment with atomoxetine in Study Period III, the objective was to assess the efficacy of acute treatment with atomoxetine in this patient group. This assessment was performed using descriptive statistics.

Table LYBI.20 summarizes the percentage of patients who responded to atomoxetine once they were switched from methylphenidate. Data are grouped by atomoxetine responder status (responder or nonresponder) for each active treatment. Forty-five percent (45%) of patients who were nonresponders to methylphenidate and who had at least 1 week of exposure to atomoxetine became responders to atomoxetine, while 76% of patients who were responders to methylphenidate and who had at least 1 week of exposure to atomoxetine also responded to atomoxetine.

Table LYBI.20. Percentages of Patients Classified as Atomoxetine Responders or Nonresponders by Their Methylphenidate Response Status Using the ADHDRS-IV-Parent:Inv Total Score Methylphenidate Patients Switched to Atomoxetine Study Period II and III

	ATX Responders n (%)	ATX Nonresponders n (%)
MPH Responders		
All Patients (n=108)	79 (73%)	29 (27%)
≥1 Week of ATX (n=100)	76 (76%)	24 (24%)
MPH Nonresponders		
All Patients (n=70)	30 (43%)	40 (57%)
≥1 Week of ATX (n=64)	29 (45%)	35 (55%)

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored; ATX = atomoxetine; MPH = methylphenidate; n = number of patients.

Study Period III: Randomized, Double-Blind Continuation Treatment

Study Period III tested two separate primary objectives in subgroups of patients. The results are presented by each subgroup: nonresponders to atomoxetine during acute treatment who were rerandomized to previous- or higher-dose (maximum of approximately 3.0 mg/kg/day) atomoxetine, and responders to atomoxetine during acute treatment who were rerandomized to previous- or lower-dose (up to 0.5 mg/kg/day) atomoxetine.

The total sample size for Study LYBI was based on the primary noninferiority analysis (Assessment 1) during Study Period II, and no formal statistical powering was performed for any of the Assessment 3 and 4 comparisons.

Primary Efficacy Results for Nonresponders to Acute Treatment with Atomoxetine (Assessment 3)

In the group of patients who failed to meet the blinded response criteria after acute treatment with atomoxetine (Study Period II), the primary objective was to test the hypothesis that continued treatment with atomoxetine at an increased (higher) dose was superior to continued treatment with atomoxetine at previously established efficacious doses. This hypothesis was tested by repeated measures analysis of the ADHDRS-IV-Parent:Inv Total score.

A total of 122 atomoxetine-treated patients failed to meet the response criteria and were rerandomized to either maintain their current dose of atomoxetine (n=62) or to increase their dose to a maximum of approximately 3.0 mg/kg/day (n=60).

Table LYBI.21 summarizes the repeated measures analysis using the ADHDRS-IV-Parent:Inv Total score. Both dosing groups demonstrated statistically significant decreases in ADHD symptoms from baseline; the difference between dosing groups was not statistically significant.

**Table LYBI.21. ADHDRS-IV-Parent:Inv Total Score
Repeated Measures Analysis
Atomoxetine Nonresponders
Study Period III**

Visit ^d	High Dose			Previous Dose			Treatment Difference		
	LS Mean	SE	p-val ^a	LS Mean	SE	p-val ^a	LS Mean	SE	p-val ^b
1	28.66	1.24	<.001	29.23	1.21	<.001	0.57	1.73	.743
2	26.44	1.29	<.001	28.51	1.24	<.001	2.08	1.79	.247
3	25.18	1.33	<.001	27.06	1.31	<.001	1.88	1.87	.314
4	24.18	1.36	<.001	26.85	1.34	<.001	2.66	1.90	.163
5	23.43	1.40	<.001	24.54	1.37	<.001	1.11	1.97	.572
6	23.44	1.47	<.001	23.94	1.41	<.001	0.50	2.04	.807
7	22.60	1.66	<.001	23.17	1.72	<.001	0.57	2.40	.811
8	20.77	1.72	<.001	22.54	1.72	<.001	1.77	2.44	.467
9	20.19	1.79	<.001	19.72	1.79	<.001	-0.47	2.54	.854
Summary of Model Parameters				F-Value	P-Value c				
Treatment				0.68	.412				
Visit				0.78	.624				
Treatment*Visit				0.39	.926				
Baseline				42.10	<.001				
Baseline*Visit				2.68	.007				

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored; LSMean = least-squares mean; SE = standard error; val = value.

Results based on a mixed model with a term for visit, (treated as a class variable) baseline, treatment, treatment by

visit and baseline by visit interaction using a compound symmetry covariance matrix to model

correlations within patient across visits.

^a P-values are from tests for a nonzero least squares mean at the given visit.

^b P-values are from tests for a treatment difference in least squares means at the given visit.

^c P-values are from F-tests for a nonzero coefficient estimate.

^d Visit number is relative to Study Period III randomization.

Secondary Efficacy Results in Atomoxetine Nonresponders

The results from mean change from baseline (last observation prior to rerandomization) to endpoint analyses using the ADHDRS-IV-Parent:Inv Total score and subscale scores were consistent with the results seen for the repeated measures analysis of these endpoints. Both dosing groups demonstrated significant improvement in ADHD symptoms at endpoint, regardless of dosing arm.

Primary Efficacy Results for Responders to Acute Treatment with Atomoxetine (Assessment 4)

In the group of patients who met the blinded response criteria after acute treatment with atomoxetine (Study Period II), the primary objective was to confirm the hypothesis that continued treatment with atomoxetine at the final acute phase dose was superior to continued treatment with atomoxetine at a lower dose.

A total of 229 patients met the criteria for atomoxetine responders and were rerandomized to either continue at their previous atomoxetine dose (n=116) or to a lower atomoxetine dose (n=113). Relapse was defined as a return in ADHD symptoms (measured by the ADHDRS-IV-Parent:Inv Total score) to 90% or more of baseline values on two consecutive study visits after randomization.

Table LYBI.22 summarizes the percentage of patients in each dosing group that met the definition for relapse. Relapse rates were not statistically significantly different between dosing groups (p=.924; 6 patients total; 3 in each dosing group).

**Table LYBI.22. ADHDRS-IV-Parent:Inv Total Score
Percentage of Patients Relapsing
Atomoxetine Responders
Study Period III**

	Lower Dose ATX N/n (%)	Previous Dose ATX N/n (%)	Log-rank p-Value
Relapsed	113/3 (2.7%)	116/3 (2.6%)	p=.924

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale–IV-Parent Version: Investigator-Administered and Scored; N = total number of patients per dosing group; n = number of patients who relapsed.

Relapse is defined as a return in ADHDRS-IV-Parent:Inv Total score to 90% or more of baseline values on two consecutive study visits postrandomization.

Secondary Efficacy Results in Atomoxetine Responders

Table LYBI.23 summarizes mean change from baseline (last observation prior to rerandomization) to final ADHDRS-IV-Parent:Inv Total score, Inattention Subscale score, and Hyperactivity-Impulsivity Subscale score.

**Table LYBI.23. ADHDRS-IV-Parent:Inv Total and Subscale Scores
Change from Baseline to Endpoint
All Responders in Study Period III**

Variable		Baseline		Change		Within Group	Between Group
Treatment	N	Mean	SD	Mean	SD	p-value ^(b)	p-value ^(a)
TOTAL SCORE							
LOW DOSE	109	14.03	7.21	3.13	10.40	0.017	0.237
PREVIOUS DOSE	115	15.05	7.74	1.09	10.83	0.751	—
95% Confidence Interval for Treatment Difference: (-1.07 , 4.31)							
INATTENTIVE SUBSCORE							
LOW DOSE	109	8.33	4.40	1.59	6.18	0.035	0.307
PREVIOUS DOSE	115	8.43	4.13	0.74	6.13	0.465	—
95% Confidence Interval for Treatment Difference: (-0.74 , 2.34)							
HYP/IMP SUBSCORE							
LOW DOSE	109	5.70	4.43	1.54	5.27	0.015	0.195
PREVIOUS DOSE	115	6.62	4.73	0.35	5.56	0.844	—
95% Confidence Interval for Treatment Difference: (-0.47 , 2.31)							

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored;
HYM/IMP = hyperactivity/impulsivity; N = total number of patients per dosing group;
SD = standard deviation.

(a) P-Value from ANOVA model with terms for baseline value and treatment level.
(b) P-Value obtained from Wilcoxon's Signed-rank Test for mean change from baseline to endpoint.
Baseline Visit: 6, Endpoint Visits: 7-15. Visits adjusted for patients randomized at Visit 9 by subtracting 3 from visit number prior to analysis.

Safety: Study Period II

Adverse Events (AEs)

There were no patient deaths. Five patients reported at least one SAE during Study Period II: 4 in patients randomized to atomoxetine and 1 in a patient randomized to methylphenidate. Three patients reported SAEs that were thought to be unrelated to study drug (abnormal behaviour [methylphenidate]), (gastroenteritis, otitis media, and pharyngitis [atomoxetine]), and (chest pain [atomoxetine]) and 2 were thought unlikely but possibly related to study drug (gastroenteritis viral [atomoxetine]) and (lethargy [atomoxetine]). None of these patients discontinued treatment because of the SAE.

Table LYBI.24 summarizes patient discontinuations due to AEs during acute, double-blind treatment. Twelve patients discontinued because of an AE (atomoxetine [n=5], methylphenidate [n=5], placebo [n=2]); overall the discontinuation rate of 2.3% patients who took at least 1 dose of study drug. Treatment-group differences in the incidence of

discontinuations due to AEs were not statistically significant. All 12 events may have been temporally related to study drug.

**Table LYBI.24. Summary of Discontinuations Due to Adverse Events
Randomized Patients
Study Period II**

Preferred Term	ATOMOX (N=221) n (%)	METHYL (N=220) n (%)	PLACEBO (N=74) n (%)	Total (N=515) n (%)	p-Value*
PATIENTS DISCONTINUED	5 (2.3)	5 (2.3)	2 (2.7)	12 (2.3)	1.00
Nausea	1 (0.5)	0	1 (1.4)	2 (0.4)	.267
Abdominal pain upper	1 (0.5)	0	0	1 (0.2)	
Anorexia	0	1 (0.5)	0	1 (0.2)	
Bruxism	0	1 (0.5)	0	1 (0.2)	
Depressed mood	0	1 (0.5)	0	1 (0.2)	
Feeling abnormal	1 (0.5)	0	0	1 (0.2)	
Insomnia	0	1 (0.5)	0	1 (0.2)	
Irritability	1 (0.5)	0	0	1 (0.2)	
Pruritus	0	1 (0.5)	0	1 (0.2)	
Rash pruritic	0	0	1 (1.4)	1 (0.2)	
Trichotillomania	1 (0.5)	0	0	1 (0.2)	

Abbreviations: ATMOX = atomoxetine; METHYL = methylphenidate; N = total number of patients; n = number of patients discontinued due to specific AE.

Population: Enrolled patients who took at least 1 dose of study drug.
Visits 2-5

* Frequencies are analyzed using a Fisher's Exact test.

A treatment-emergent adverse event (TEAE) was defined as an event that first occurred or worsened after randomization.

Table LYBI.25 summarizes TEAEs by MedDRA preferred terms in order of decreasing frequency for events reported in at least 5% of randomized patients who took at least 1 dose of study drug. This table also includes the rates for the placebo-treated group and overall p-value across all three treatment groups. During acute treatment, the most commonly reported TEAEs for atomoxetine- and methylphenidate-treated patients were headache, appetite decreased NOS (not otherwise specified), and abdominal pain upper.

**Table LYBI.25. Summary of Treatment-Emergent Adverse Events
with $\geq 5\%$ Incidence
Using MedDRA Preferred Terms
Randomized Patients
Study Period II**

Preferred Term	ATOMOX (N=221) n (%)	METHYL (N=219) n (%)	PLACEBO (N=74) n (%)	Total (N=514) n (%)	p-Value*
PATIENTS WITH ≥ 1 TESS	149 (67.4)	146 (66.7)	40 (54.1)	335 (65.2)	.100
PATIENTS WITH NO TESS	72 (32.6)	73 (33.3)	34 (45.9)	179 (34.8)	.100
Headache	39 (17.6)	25 (11.4)	7 (9.5)	71 (13.8)	.096
Appetite decreased NOS	31 (14.0)	37 (16.9)	2 (2.7)	70 (13.6)	.003
Abdominal pain upper	24 (10.9)	22 (10.0)	4 (5.4)	50 (9.7)	.423
Irritability	14 (6.3)	13 (5.9)	1 (1.4)	28 (5.4)	.247
Nausea	9 (4.1)	13 (5.9)	6 (8.1)	28 (5.4)	.354
Insomnia	9 (4.1)	17 (7.8)	1 (1.4)	27 (5.3)	.070
Vomiting NOS	15 (6.8)	8 (3.7)	4 (5.4)	27 (5.3)	.330
Somnolence	14 (6.3)	4 (1.8)	3 (4.1)	21 (4.1)	.046
Cough	7 (3.2)	8 (3.7)	4 (5.4)	19 (3.7)	.659
Fatigue	12 (5.4)	5 (2.3)	1 (1.4)	18 (3.5)	.137
Initial insomnia	6 (2.7)	12 (5.5)	0	18 (3.5)	.062

Abbreviations: ATMOX = atomoxetine; METHYL = methylphenidate; N = total number of patients; n = number of patients who reported specific TEAE; TESS = treatment-emergent signs and symptoms.

Population: Enrolled patients who took at least 1 dose of study drug.

Baseline: Visits 1-2, Endpoint: Visits 3-5

* Frequencies are analyzed using a Fisher's Exact test.

Table LYBI.26 presents statistical comparisons between atomoxetine and methylphenidate for each of the TEAEs that occurred in at least 5% of patients. A significantly greater percentage of atomoxetine-treated patients reported somnolence ($p=.028$), while a significantly greater percentage of methylphenidate-treated patients reported insomnia ($p=.026$).

**Table LYBI.26. Treatment-Emergent Adverse Events with Greater than 5% Frequency
Methylphenidate versus Atomoxetine
Study Period II**

Event	Atomoxetine N=221 n (%)	Methylphenidate N=219 n (%)	p-values Fisher's Exact Test
Headache	39 (17.6)	25 (11.4)	.078
Appetite decreased NOS	31 (14.0)	37 (16.9)	.431
Abdominal pain upper	24 (10.9)	22 (10.0)	.876
Combined Insomnia ^a	15 (6.8)	29 (13.2)	.026
Vomiting NOS	15 (6.8)	8 (3.7)	.198
Irritability	14 (6.3)	13 (5.9)	1.000
Somnolence	14 (6.3)	4 (1.8)	.028
Fatigue	12 (5.4)	5 (2.3)	.136
Nausea	9 (4.1)	13 (5.9)	.391

Abbreviations: N = total number of patients; n = number of patients who reported specific TEAE; NOS = not otherwise specified.

Population: Enrolled patients who took at least one dose of either atomoxetine or methylphenidate.

^a This term includes the combined total of insomnia events (initial, middle, and late).

Clinical Laboratory Evaluation

Routine chemistry, hematology, and urinalysis tests were collected from each patient at intervals specified in the study schedule. Specimens were prepared at the study site. Laboratory values are reported in Systeme Internationale (SI) units. The assessment of laboratory data includes an analysis of change from baseline to endpoint measurements and an analysis of the percentages of patients with treatment-emergent out-of-range measurements.

Change from Baseline to Endpoint in Laboratory Values

Change from baseline to endpoint was computed for each analyte, and treatment-group differences were assessed using ANOVA with investigator and treatment as independent effects in the model. The rank of the observation was the dependent variable due to anticipated non-normality.

Table LYBI.27 summarizes the mean change by treatment group during Study Period II. Statistically significant treatment differences in mean change scores across all three treatments were observed for monocytes, eosinophils, alkaline phosphatase, gamma-glutamyltransferase, and albumin.

Table LYBI.27. Summary of Laboratory Data
Mean Change from Baseline to Endpoint by Analyte
Study Period II

Lab Test	Lab Unit	Therapy	-----Baseline-----		Change to -----Endpoint-----		- p-Values -	
			n	Mean	SD	Mean	SD	Therapy Model
MONOS	GI/L	ATOMOX	194	0.406	0.131	-0.020	0.134	.001 RDUC1
		METHYL	187	0.394	0.139	-0.033	0.138	
		PLACEBO	60	0.383	0.238	0.022	0.256	
EOSN	GI/L	ATOMOX	194	0.207	0.174	0.005	0.137	.019 RDUC1
		METHYL	187	0.233	0.275	-0.019	0.232	
		PLACEBO	60	0.225	0.216	0.020	0.164	
ALKPH	U/L	ATOMOX	195	258.462	71.081	-7.862	36.862	<.001 RDUC1
		METHYL	186	256.828	80.094	-16.742	35.759	
		PLACEBO	61	273.148	75.307	8.410	30.234	
GGT	U/L	ATOMOX	195	13.318	3.599	-0.338	2.777	.040 RDUC1
		METHYL	186	13.403	4.375	-0.570	2.634	
		PLACEBO	61	14.164	6.056	0.328	2.315	
ALBUM	g/L	ATOMOX	193	45.409	2.652	0.073	3.001	.027 RDUC1
		METHYL	186	44.989	2.861	0.720	3.024	
		PLACEBO	61	44.984	2.384	-0.557	3.274	

Abbreviations: ALBUM = ALBUMIN; ALKPH = ALKALINE PHOSPHATASE; EOSN = EOSINOPHILS;
GGT = GGT (GGT/SGGT/YGGT), Lab = laboratory; MONOS = MONOCYTES, n = number of patients;
SD = standard deviation.

Population: Enrolled patients who took at least 1 dose of study drug.

Baseline: Visits 1-2, Endpoint: Visits 3-5

NOTE: Pooled Investigator Used in Analysis

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDUC1 - Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks:
PROC GLM model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA on the ranks using the
mean square for error.
Note: Each investigator has at least one patient in each treatment group.

Percentages of Patients with Treatment-Emergent Out-of-Range Laboratory Values

Central lab reference ranges were used in this study to define out-of-range laboratory values. These ranges are adjusted for age, race, and sex. Table LYBI.28 summarizes treatment differences in percentages of patients with laboratory values that were normal at baseline, but found to be above or below the normal range at any time after randomization. Statistically significant differences were observed in creatine phosphokinase (methylphenidate and placebo), alkaline phosphatase (placebo), and cholesterol (methylphenidate and placebo). Four patients were excluded because of missing baseline values.

Atomoxetine hydrochloride

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Table LYBI.28. **Summary of Laboratory (SI) Data**
Frequency of Patients with Abnormal Lab Values after Baseline (w/TESS Option)

							----- p-Value * -----		
Incidence Group	ATOMOX (1) (Total=221)			METHYL (2) (Total=219)			PLACEBO (3) (Total=74)		
	N	n	(%)	N	n	(%)	N	n	(%)

Lab Test: CREATINE PHOSPHOKINASE									

LOW	193	0		186	0		61	0	
HIGH	189	0		174	7	(4.0)	55	2	(3.6)
							.008		
								.005	
									.050
Lab Test: ALKALINE PHOSPHATASE									

LOW	195	0		185	0		61	0	
HIGH	167	3	(1.8)	157	2	(1.3)	48	4	(8.3)
							.032		
								1.00	
									.046
-- p-Value * --									
Incidence									
Group (2)VS.(3)									

Lab Test: CREATINE PHOSPHOKINASE									

LOW									
HIGH 1.00									
Lab Test: ALKALINE PHOSPHATASE									

LOW									
HIGH .028									

(continues)

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**Table LYBI.28. Summary of Laboratory (SI) Data
Frequency of Patients with Abnormal Lab Values after Baseline (w/TESS Option)
(Concluded)**

Incidence Group	ATOMOX (1) (Total=221)			METHYL (2) (Total=219)			PLACEBO(3) (Total=74)			----- p-Value * -----		
	N	n	(%)	N	n	(%)	N	n	(%)	Overall	(1) VS. (2)	(1) VS. (3)

Lab Test: CHOLESTEROL												

LOW	184	5	(2.7)	171	15	(8.8)	55	6	(10.9)	.014	.019	.020
HIGH	172	9	(5.2)	176	6	(3.4)	58	0		.194	.440	.116
Lab Test: CHOLESTEROL												

LOW										.602		
HIGH										.341		

Abbreviations: ATMOX = atomoxetine; Lab = laboratory; METHYL = methylphenidate; N = total number of patients; n = number of patients with reported abnormal lab value; TESS = treatment-emergent signs and symptoms.

Population: Enrolled patients who took at least 1 dose of study drug.

Baseline: Visits 1-2, Endpoint: Visits 3-5

* Frequencies are analyzed using a Fisher's Exact test.

Note: Total = Total number of patients in the treatment group having both baseline and endpoint visits.

N = Total number of at risk patients with the lab test.

n = Total number of at risk patients with the specific lab result (e.g. HIGH).

Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital signs and weight were obtained at every visit. Physical exams, height measurements, and ECGs were obtained at baseline and at the end of Study Period II.

Mean change from baseline to endpoint in vital signs and ECG data were computed. Treatment differences were assessed using ANOVA with investigator and treatment as independent effects in the models. The observed data were the dependent variables. Categorical analyses of change in vital signs and ECG intervals were also computed.

Vital Signs

Mean Change from Baseline to Endpoint in Vital Signs

Table LYBI.29 summarizes treatment comparisons in mean change from baseline to endpoint for Study Period II. Statistically significant changes were observed for diastolic blood pressure, pulse, and temperature. Placebo-treated patients gained an average of 1.10 kg, while methylphenidate-treated patients lost an average of 0.93 kg, and atomoxetine-treated patients lost an average of 0.62 kg. Each of the treatment comparisons of change in weight was statistically significant.

**Table LYBI.29. Summary of Vital Signs and Weight
Mean Change from Baseline to Endpoint
Atomoxetine versus Methylphenidate, Atomoxetine versus
Placebo,
and Methylphenidate versus Placebo
Study Period II**

Variable analyzed: Diastolic BP Average (DIASAVG)

No.	Therapy	n	Baseline			Change		
			Mean	Median	SD	Mean	Median	SD
1)	ATOMOX	213	63.242	63.000	7.534	3.803	4.000	7.962
2)	METHYL	211	61.967	62.000	8.301	3.135	3.500	8.439
3)	PLACEBO	68	63.794	63.000	8.309	0.368	0.000	7.777

Variable analyzed: Diastolic BP Average (DIASAVG)

----- p-Values -----						
Pairwise*3						
No.	Therapy	Within	Inter-	Overall*2	vs. (2)	vs. (3)
		Group*1	action*2			
1)	ATOMOX	<.001	.434	.011	.393	.003
2)	METHYL	<.001				.017
3)	PLACEBO	.686				

Variable analyzed: Heart Rate Average (PULSAVG)

No.	Therapy	n	Baseline			Change		
			Mean	Median	SD	Mean	Median	SD
1)	ATOMOX	213	81.869	82.000	11.021	6.378	6.000	10.877
2)	METHYL	211	82.173	82.000	11.177	3.024	3.000	11.761
3)	PLACEBO	68	82.125	80.000	12.881	0.397	0.000	11.965

Variable analyzed: Heart Rate Average (PULSAVG)

----- p-Values -----						
Pairwise*3						
No.	Therapy	Within	Inter-	Overall*2	vs. (2)	vs. (3)
		Group*1	action*2			
1)	ATOMOX	<.001	.033	<.001	.002	<.001
2)	METHYL	<.001				.118
3)	PLACEBO	.601				

Variable analyzed: Weight in KG (WEIGHT)

No.	Therapy	n	Baseline			Change		
			Mean	Median	SD	Mean	Median	SD
1)	ATOMOX	213	37.616	36.100	10.781	-0.617	-0.500	1.374
2)	METHYL	211	38.011	36.200	11.531	-0.930	-0.900	1.293
3)	PLACEBO	68	37.059	36.100	10.423	1.100	0.900	1.342

(continues)

Table LYBI.29. Summary of Vital Signs and Weight Mean Change from Baseline to Endpoint Atomoxetine versus Methylphenidate, Atomoxetine versus Placebo, and Methylphenidate versus Placebo Study Period II (Concluded)

Variable analyzed: Weight in KG (WEIGHT)

		----- p-Values -----				
		Pairwise*3				

No.	Therapy	Within Group*1	Inter-action*2	Overall*2	vs. (2)	vs. (3)

1)	ATOMOX	<.001	.077	<.001	.015	<.001
2)	METHYL	<.001				<.001
3)	PLACEBO	<.001				

Variable analyzed: Temperature in Centigrade (TEMP)

			Baseline			Change		
No.	Therapy	n	Mean	Median	SD	Mean	Median	SD
1)	ATOMOX	213	36.479	36.600	0.539	-0.059	0.000	0.570
2)	METHYL	211	36.395	36.400	0.508	0.079	0.100	0.569
3)	PLACEBO	68	36.441	36.400	0.636	0.126	0.100	0.659

Variable analyzed: Temperature in Centigrade (TEMP)

		----- p-Values -----				
		Pairwise*3				

No.	Therapy	Within Group*1	Inter-action*2	Overall*2	vs. (2)	vs. (3)

1)	ATOMOX	.171	.125	.016	.017	.020
2)	METHYL	.026				.514
3)	PLACEBO	.065				

Abbreviations: ATMOX = atomoxetine; METHYL = methylphenidate; N = total number of patients; n = number of patients; SD = standard deviation; Temp = temperature; vs = versus.

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon Signed Rank procedure.

*2 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=investigator and treatment for the overall

p-Value and model=investigator, treatment, and interaction for the interaction p-Value.

*3 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Note: Each investigator has at least one patient in each treatment group.

Population: Enrolled patients who took at least 1 dose of study drug.

Baseline: Visits 1-2, Endpoint: Visits 3-5

Categorical Analysis of Changes in Vital Signs

Table LYBI.30 summarizes the comparison of categorical changes in blood pressure, heart rate, temperature, and weight for each pair of treatment groups. For each criterion (for example, maximum heart rate of at least 110 bpm), the percentage of patients meeting the criteria in a treatment-emergent manner at any Study Period II visit was

computed for each treatment group. Patients meeting the criteria at baseline were excluded from the analysis. The criteria for the analysis of blood pressure were obtained from the 95th percentiles from standards of the National Heart, Lung, and Blood Institute (National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents 1996).

Statistically significantly more methylphenidate-treated patients than atomoxetine-treated patients experienced weight loss, while placebo-treated patients had statistically significantly less weight loss than either active drug. There were no other significant differences among treatment groups.

Atomoxetine hydrochloride

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**Table LYBI.30. Summary of Vital Signs and Weight
Categorical Changes in Heart Rate (Pulse), Blood Pressure and Weight
Randomized Patients
Study Period II**

Abnormal Vitals		Atomoxetine			Methylphenidate			Placebo			Fisher's Exact	
		N	n	%	N	n	%	N	n	%	p-Value	
Vital	Direction*										ATX vs MPH	ATX vs PBO
Diastolic Blood Pressure	High	211	6	2.8%	209	8	3.8%	67	1	1.5%	.600	1.00
Pulse	High	213	4	1.9%	211	3	1.4%	68	0	0.0%	1.00	.575
	Low	213	0	0.0%	211	0	0.0%	68	1	1.5%	n/a	.242
Systolic Blood Pressure	High	208	8	3.8%	209	10	4.8%	65	1	1.5%	.810	.691
Temperature (°C)	High	213	0	0.0%	211	1	0.5%	68	0	0.0%	.498	n/a
	Low	213	2	0.9%	211	3	1.4%	68	0	0.0%	.685	1.00
Weight (kg)	Decrease	213	68	31.9%	211	90	42.7%	68	1	1.5%	.027	<.001

Abbreviations: ATX = atomoxetine; MPH = methylphenidate; N = total number of patients; n = number of patients with categorical change; PBO = placebo.

*Criteria: Pulse - High: Increase of at least 25 to a value of at least 110

- Low: Decrease of at least 20 to a value of at most 65

Temperature - High: Increase of at least 1.0 to a value of at least 37.8

- Low: Decrease of at least 1.3 to a value of at most 35.6

Weight - Decrease of at least 3.5%

Blood Pressure - High: Increase of at least 5 mm to above 95% percentile

Patients counted as meeting criteria if criteria was met at endpoint.

Population: Study period two randomized patients

Patients were excluded from BP analysis if they have abnormal Blood Pressure at last baseline visit

Electrocardiograms (ECGs)

Mean Change from Baseline to Endpoint in ECG Data

Table LYBL.31 summarizes treatment group comparisons in mean change from baseline to endpoint for heart rate and ECG intervals (RR, PR, QRS, QT, and QT corrected using Bazett's, Fridericia's, and Data-corrected methods). Statistically significant differences between atomoxetine-treated patients and placebo-treated patients were found for heart rate, QT interval, and the RR interval. Statistically significant differences between atomoxetine-treated patients and methylphenidate-treated patients were found for heart rate, PR interval, and the RR interval.

**Table LYBI.31. Electrocardiogram Intervals and Heart Rate
Mean Change from Baseline to Endpoint
Randomized Patients, Study Period II**

Variable	Therapy	N	Baseline		Change to Endpoint		p-Values		
			Mean	SD	Mean	SD	Within Group*1	vs PBO*2	vs MPH*2
RR Interval	ATX	199	803.2	121.6	-66.7	123.9	<.001	.001	.003
	MPH	194	791.3	121.4	-32.3	119.3	<.001	.145	
	PBO	64	794.3	127.3	-7.9	94.2	.666		
PR Interval	ATX	198	137.2	19.2	-2.4	14.1	.012	.115	.013
	MPH	194	136.6	18.1	1.1	16.9	.519	.868	
	PBO	64	135.9	16.1	0.8	12.9	.776		
QRS Interval	ATX	199	78.5	7.5	-0.3	7.5	.626	.818	.404
	MPH	194	78.6	7.3	0.5	7.5	.340	.723	
	PBO	64	79.2	6.7	0.0	8.2	.992		
QT Interval	ATX	199	358.7	26.0	-10.4	23.7	<.001	.003	.090
	MPH	194	357.5	25.6	-6.3	25.6	<.001	.077	
	PBO	64	358.4	25.9	0.0	21.7	.929		
QTcB	ATX	199	402.1	21.8	5.7	23.8	<.001	.207	.076
	MPH	194	403.6	20.5	1.7	24.5	.299	.987	
	PBO	64	404.3	22.7	1.9	20.1	.763		
QTcF	ATX	199	386.8	19.1	-0.1	18.6	.801	.686	.539
	MPH	194	387.4	18.0	-1.2	20.7	.421	.405	
	PBO	64	388.1	19.3	1.2	17.6	.774		
QTcD	ATX	199	391.9	19.4	1.8	19.8	.184	.826	.281
	MPH	194	392.8	18.3	-0.3	21.5	.921	.592	
	PBO	64	393.5	19.9	1.4	18.1	.790		
Heart Rate	ATX	199	76.5	12.1	7.0	13.3	<.001	<.001	.007
	MPH	194	77.6	11.9	3.7	12.3	<.001	.100	
	PBO	64	77.4	11.7	0.8	9.8	.669		

Abbreviations: ATX=atomoxetine; MPH=methylphenidate; N = number of patients; PBO=placebo;

QTcB = Bazett-corrected QT interval; QTcD = data-corrected QT interval; QTcF = Fridericia-corrected QT interval; SD = standard deviation; vs = versus.

Baseline: Visit 1 and Visit 2, Endpoint: Visit 3 through Visit 5.

*1 The significance of a location shift from zero of the change from baseline within a treatment group is tested by the Wilcoxon signed-rank test.

*2 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

Population: Enrolled patients who took at least 1 dose of study drug.

Categorical Analysis of Changes in QTc Intervals and Heart Rate

Analysis of categorical changes in QTc intervals and heart rate were performed for patients in each treatment group who met the Committee for Proprietary Medicinal Products (CPMP) guideline (1997) criteria for changes at maximum postbaseline measures in corrected QTc interval and heart rate following baseline. For each criterion, the percentage of patients meeting the criteria in a treatment-emergent manner (at any Study Period II visit) was computed for each treatment group. Patients meeting the criteria at baseline were excluded from the analysis. There were no statistically significant differences between the active treatment groups.

Safety Study Period III

Adverse Events (AEs)

There were no patient deaths in this study. Three patients reported SAEs during Study Period III: (asthma [atomoxetine]); (aggression [atomoxetine]); (headache, accidental overdose [atomoxetine]). All of the SAEs were thought unlikely, but possibly, related to study drug.

Atomoxetine Nonresponders

Table LYBI.32 summarizes patient discontinuations due to AEs for patients who did not meet the definition of response during double-blind, continuation treatment. A total of 5 atomoxetine nonresponders were discontinued because of an AE. The table presents data for only 4 of these patients because the 5th patient entered the study with occasional headaches that were listed as a secondary condition. Although the patient discontinued at Visit 8 for the AE of headache, because this condition was listed as a secondary condition at study entry, it was not treatment-emergent. Treatment differences were not statistically significant for the 4 patients (Table LYBI.32). All 5 events may have been temporally related to study drug. Overall, the discontinuation rate due to AEs was 5 (4.1%) out of the 122 patients who took study drug.

**Table LYBI.32. Summary of Discontinuations Due to Adverse Events
Comparison of Dose Groups
Atomoxetine Nonresponders
Study Period III**

Preferred Term	Previous (N=62) n (%)	Higher (N=60 ^a) n (%)	Total (N=122) n (%)	p-Value*
PATIENTS DISCONTINUED	2 (3.2)	2 (3.3)	4 (3.3)	1.00
Affect lability	1 (1.6)	0	1 (0.8)	
Dysphoria	1 (1.6)	0	1 (0.8)	
Headache	0	1 (1.7)	1 (0.8)	
Tic	0	1 (1.7)	1 (0.8)	

^a Note one patient is not included in the higher-dose group in the table. This patient discontinued due to an AE (headache), which was present and recorded as a secondary condition at study entry.

Population: Enrolled patients who took at least 1 dose of study drug.

SP III: Visits 6-15

Therapy: NREM=Non-Responder EXTN Metabolizer, PRV=ATX Previous Dose, HI=Up to ATX 3.0 mg/kg

* Frequencies are analyzed using Fisher's exact test.

Atomoxetine Responders

Table LYBI.33 summarizes patient discontinuations due to AEs for patients who met the definition for response during double-blind, continuation treatment. Seven patients discontinued because of an AE. Treatment differences were not statistically significant between dosing groups. All 7 events may have been temporally related to study drug. Overall, the discontinuation rate due to AEs was 7 out of 229 (3.1%) patients who took at least 1 dose of study drug..

**Table LYBI.33. Summary of Discontinuations Due to Adverse Events
Comparison of Dose Groups
Atomoxetine Responders
Study Period III**

Preferred Term	RESP_PRV (N=116) n (%)	RESP_LOW (N=113) n (%)	Total (N=229) n (%)	p-Value*
PATIENTS DISCONTINUED	4 (3.4)	3 (2.7)	7 (3.1)	1.00
Fatigue	0	2 (1.8)	2 (0.9)	.242
Aggression	1 (0.9)	0	1 (0.4)	
Depression	1 (0.9)	0	1 (0.4)	
Dyskinesia	1 (0.9)	0	1 (0.4)	
Heart rate increased	0	1 (0.9)	1 (0.4)	
Somnolence	1 (0.9)	0	1 (0.4)	

Abbreviations: PRV = previous; RESP = responder; N = total number of atomoxetine responders per dose group; n = number of atomoxetine responders per dose group reporting specific AE.

Population: Enrolled patients who took at least 1 dose of study drug.

SP III: Visits 6-15

Therapy: RESP=Responder, PRV=ATX Previous Dose, LOW=ATX 0.5 mg/kg

* Frequencies are analyzed using a Fisher's exact test.

Atomoxetine Nonresponders

Table LYBI.34 summarizes TEAEs by MedDRA preferred terms in order of decreasing frequency for events reported in nonresponders who took at least 1 dose of study medication. During longer-term treatment, there were no significant differences between dosing groups.

**Table LYBI.34. Summary of Treatment-Emergent Adverse Events
Ordered by Decreasing Frequency
Using MedDRA Preferred Terms
Atomoxetine Nonresponders
Study Period III**

	NREM PRV (N=62)		NREM HI (N=59)		Total (N=121)		p-Value*
Preferred Term	n	(%)	n	(%)	n	(%)	

PATIENTS WITH >= 1 TESS	50	(80.6)	48	(81.4)	98	(81.0)	1.00
PATIENTS WITH NO TESS	12	(19.4)	11	(18.6)	23	(19.0)	1.00
Decreased appetite	10	(16.1)	13	(22.0)	23	(19.0)	.489
Headache	12	(19.4)	11	(18.6)	23	(19.0)	1.00
Pyrexia	11	(17.7)	9	(15.3)	20	(16.5)	.809
Nasopharyngitis	9	(14.5)	10	(16.9)	19	(15.7)	.805
Abdominal pain upper	8	(12.9)	6	(10.2)	14	(11.6)	.778
Fatigue	8	(12.9)	5	(8.5)	13	(10.7)	.560
Cough	8	(12.9)	4	(6.8)	12	(9.9)	.364
Insomnia	4	(6.5)	4	(6.8)	8	(6.6)	1.00
Mood swings	3	(4.8)	5	(8.5)	8	(6.6)	.484
Vomiting	2	(3.2)	6	(10.2)	8	(6.6)	.157
Irritability	3	(4.8)	3	(5.1)	6	(5.0)	1.00
Unexpected therapeutic drug effect	5	(8.1)	1	(1.7)	6	(5.0)	.208
Nasal congestion	5	(8.1)	0		5	(4.1)	.058
Pharyngitis streptococcal	3	(4.8)	2	(3.4)	5	(4.1)	1.00
Pharyngolaryngeal pain	3	(4.8)	2	(3.4)	5	(4.1)	1.00
Sinusitis	1	(1.6)	4	(6.8)	5	(4.1)	.200
Affect lability	3	(4.8)	1	(1.7)	4	(3.3)	.619
Aggression	3	(4.8)	1	(1.7)	4	(3.3)	.619
Anger	2	(3.2)	2	(3.4)	4	(3.3)	1.00
Constipation	2	(3.2)	2	(3.4)	4	(3.3)	1.00
Contusion	1	(1.6)	3	(5.1)	4	(3.3)	.356
Dizziness	2	(3.2)	2	(3.4)	4	(3.3)	1.00
Dyspepsia	1	(1.6)	3	(5.1)	4	(3.3)	.356
Ear infection	3	(4.8)	1	(1.7)	4	(3.3)	.619
Gastroenteritis viral	2	(3.2)	2	(3.4)	4	(3.3)	1.00
Influenza	3	(4.8)	1	(1.7)	4	(3.3)	.619
Nightmare	2	(3.2)	2	(3.4)	4	(3.3)	1.00
Skin laceration	3	(4.8)	1	(1.7)	4	(3.3)	.619
Somnolence	0		4	(6.8)	4	(3.3)	.054
Crying	3	(4.8)	0		3	(2.5)	.244
Emotional disorder	2	(3.2)	1	(1.7)	3	(2.5)	1.00
Flushing	1	(1.6)	2	(3.4)	3	(2.5)	.613
Hypersomnia	2	(3.2)	1	(1.7)	3	(2.5)	1.00
Increased appetite	1	(1.6)	2	(3.4)	3	(2.5)	.613
Multiple allergies	3	(4.8)	0		3	(2.5)	.244
Nausea	1	(1.6)	2	(3.4)	3	(2.5)	.613
Upper respiratory tract infection	2	(3.2)	1	(1.7)	3	(2.5)	1.00
Viral infection	3	(4.8)	0		3	(2.5)	.244
Weight decreased	2	(3.2)	1	(1.7)	3	(2.5)	1.00
Asthma	1	(1.6)	1	(1.7)	2	(1.7)	1.00
Bronchitis	2	(3.2)	0		2	(1.7)	.496
Cerumen impaction	0		2	(3.4)	2	(1.7)	.236
Hyperhidrosis	1	(1.6)	1	(1.7)	2	(1.7)	1.00
Neck pain	1	(1.6)	1	(1.7)	2	(1.7)	1.00
Otitis media	1	(1.6)	1	(1.7)	2	(1.7)	1.00
Rash	2	(3.2)	0		2	(1.7)	.496
Rhinorrhoea	0		2	(3.4)	2	(1.7)	.236
Seasonal allergy	2	(3.2)	0		2	(1.7)	.496
Sleep disorder	1	(1.6)	1	(1.7)	2	(1.7)	1.00
Tearfulness	1	(1.6)	1	(1.7)	2	(1.7)	1.00
Tooth extraction	2	(3.2)	0		2	(1.7)	.496
Abdominal pain	0		1	(1.7)	1	(0.8)	
Abnormal behaviour	1	(1.6)	0		1	(0.8)	
Acne	0		1	(1.7)	1	(0.8)	
Agitation	0		1	(1.7)	1	(0.8)	

(continues)

**Table LYBI.34. Summary of Treatment-Emergent Adverse Events
Ordered by Decreasing Frequency
Using MedDRA Preferred Terms
Atomoxetine Nonresponders
Study Period III (Continued)**

Preferred Term	NREM_PRV (N=62)		NREM_HI (N=59)		Total (N=121)		p-Value*
	n	(%)	n	(%)	n	(%)	
Allergy to animal	0		1	(1.7)	1	(0.8)	
Anorexia	1	(1.6)	0		1	(0.8)	
Anxiety	0		1	(1.7)	1	(0.8)	
Blepharospasm	0		1	(1.7)	1	(0.8)	
Blood bilirubin increased	0		1	(1.7)	1	(0.8)	
Depressed mood	1	(1.6)	0		1	(0.8)	
Depression	1	(1.6)	0		1	(0.8)	
Diarrhoea	0		1	(1.7)	1	(0.8)	
Dry mouth	0		1	(1.7)	1	(0.8)	
Dry throat	1	(1.6)	0		1	(0.8)	
Dysmenorrhoea	1	(1.6)	0		1	(0.8)	
Dysphagia	0		1	(1.7)	1	(0.8)	
Dysphoria	1	(1.6)	0		1	(0.8)	
Educational problem	0		1	(1.7)	1	(0.8)	
Endodontic procedure	1	(1.6)	0		1	(0.8)	
Excoriation	0		1	(1.7)	1	(0.8)	
Eye injury	0		1	(1.7)	1	(0.8)	
Eye swelling	0		1	(1.7)	1	(0.8)	
Feeling jittery	0		1	(1.7)	1	(0.8)	
Foot fracture	1	(1.6)	0		1	(0.8)	
Gastroenteritis	1	(1.6)	0		1	(0.8)	
Growing pains	1	(1.6)	0		1	(0.8)	
Herpes simplex	1	(1.6)	0		1	(0.8)	
Human bite	0		1	(1.7)	1	(0.8)	
Hypoglycaemia	0		1	(1.7)	1	(0.8)	
Illusion	1	(1.6)	0		1	(0.8)	
Infectious mononucleosis	1	(1.6)	0		1	(0.8)	
Ingrowing nail	1	(1.6)	0		1	(0.8)	
Initial insomnia	1	(1.6)	0		1	(0.8)	
Joint sprain	0		1	(1.7)	1	(0.8)	
Laceration	1	(1.6)	0		1	(0.8)	
Learning disorder	0		1	(1.7)	1	(0.8)	
Lethargy	0		1	(1.7)	1	(0.8)	
Limb injury	1	(1.6)	0		1	(0.8)	
Logorrhoea	1	(1.6)	0		1	(0.8)	
Loose stools	0		1	(1.7)	1	(0.8)	
Muscle cramp	1	(1.6)	0		1	(0.8)	
Musculoskeletal stiffness	0		1	(1.7)	1	(0.8)	
Nervousness	0		1	(1.7)	1	(0.8)	
Oral pain	1	(1.6)	0		1	(0.8)	
Pain in extremity	1	(1.6)	0		1	(0.8)	
Pallor	0		1	(1.7)	1	(0.8)	
Palpitations	0		1	(1.7)	1	(0.8)	
Panic attack	1	(1.6)	0		1	(0.8)	
Paronychia	0		1	(1.7)	1	(0.8)	
Pharyngitis	1	(1.6)	0		1	(0.8)	
Psoriasis	0		1	(1.7)	1	(0.8)	
Psychomotor hyperactivity	0		1	(1.7)	1	(0.8)	
Respiratory tract infection	0		1	(1.7)	1	(0.8)	
Restlessness	1	(1.6)	0		1	(0.8)	
Sedation	1	(1.6)	0		1	(0.8)	
Sinus headache	1	(1.6)	0		1	(0.8)	
Skin papilloma	0		1	(1.7)	1	(0.8)	

(continues)

**Table LYBI.34. Summary of Treatment-Emergent Adverse Events
Ordered by Decreasing Frequency
Using MedDRA Preferred Terms
Atomoxetine Nonresponders
Study Period III (Concluded)**

Preferred Term	NREM_PRV (N=62)		NREM_HI (N=59)		Total (N=121)		p-Value*
	n	(%)	n	(%)	n	(%)	
Sneezing	0		1	(1.7)	1	(0.8)	
Streptococcal infection	1	(1.6)	0		1	(0.8)	
Tension headache	1	(1.6)	0		1	(0.8)	
Thermal burn	1	(1.6)	0		1	(0.8)	
Tic	0		1	(1.7)	1	(0.8)	
Tinea infection	1	(1.6)	0		1	(0.8)	
Toothache	1	(1.6)	0		1	(0.8)	
Tremor	1	(1.6)	0		1	(0.8)	
Urinary tract infection	0		1	(1.7)	1	(0.8)	
Varicella	1	(1.6)	0		1	(0.8)	
Viral upper respiratory tract infection	0		1	(1.7)	1	(0.8)	
Wound infection	0		1	(1.7)	1	(0.8)	
Wrist fracture	1	(1.6)	0		1	(0.8)	

Abbreviations: HI = higher dose; NREM = Non-Responder; PRV = previous; N = total number of atomoxetine nonresponders per dose group; n = number of atomoxetine nonresponders per dose group reporting specific AE.

Population: Enrolled patients who took at least 1 dose of study drug.

Baseline: Last Visit prior to ATX, Endpoint: ATX Visits after SP III Randomization

Therapy: NREM=Non-Responder EXTN Metabolizer, PRV=ATX Previous Dose, HI=Up to ATX 3.0 mg/kg

* Frequencies are analyzed using a Fisher's Exact test.

Atomoxetine Responders

Table LYBI.35 summarizes TEAEs by MedDRA preferred terms in order of decreasing frequency for events reported in responders who took at least 1 dose of study medication.

**Table LYBI.35. Summary of Treatment-Emergent Adverse Events
Greater than 2% of Total Frequency
Ordered by Decreasing Frequency
Using MedDRA Preferred Terms
Atomoxetine Responders
Study Period III**

Preferred Term	RESP_PRV (N=116) n (%)	RESP_LOW (N=112) n (%)	Total (N=228) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	98 (84.5)	85 (75.9)	183 (80.3)	.134
PATIENTS WITH NO TESS	18 (15.5)	27 (24.1)	45 (19.7)	.134
Headache	24 (20.7)	18 (16.1)	42 (18.4)	.397
Decreased appetite	17 (14.7)	15 (13.4)	32 (14.0)	.850
Nasopharyngitis	16 (13.8)	13 (11.6)	29 (12.7)	.693
Abdominal pain upper	14 (12.1)	8 (7.1)	22 (9.6)	.264
Irritability	12 (10.3)	9 (8.0)	21 (9.2)	.649
Pharyngolaryngeal pain	12 (10.3)	9 (8.0)	21 (9.2)	.649
Pyrexia	12 (10.3)	9 (8.0)	21 (9.2)	.649
Cough	6 (5.2)	10 (8.9)	16 (7.0)	.308
Somnolence	6 (5.2)	9 (8.0)	15 (6.6)	.432
Upper respiratory tract infection	9 (7.8)	6 (5.4)	15 (6.6)	.596
Fatigue	6 (5.2)	7 (6.3)	13 (5.7)	.781
Influenza	6 (5.2)	7 (6.3)	13 (5.7)	.781
Vomiting	9 (7.8)	4 (3.6)	13 (5.7)	.254
Mood swings	9 (7.8)	2 (1.8)	11 (4.8)	.060
Nasal congestion	7 (6.0)	3 (2.7)	10 (4.4)	.334
Pharyngitis streptococcal	6 (5.2)	4 (3.6)	10 (4.4)	.749
Nausea	6 (5.2)	3 (2.7)	9 (3.9)	.500
Weight decreased	3 (2.6)	4 (3.6)	7 (3.1)	.718
Abdominal pain	4 (3.4)	2 (1.8)	6 (2.6)	.684
Dizziness	4 (3.4)	2 (1.8)	6 (2.6)	.684
Insomnia	2 (1.7)	4 (3.6)	6 (2.6)	.440
Affect lability	0	5 (4.5)	5 (2.2)	.027
Diarrhoea	3 (2.6)	2 (1.8)	5 (2.2)	1.00
Ear pain	2 (1.7)	3 (2.7)	5 (2.2)	.679
Sinusitis	4 (3.4)	1 (0.9)	5 (2.2)	.370

Abbreviations: N = total number of atomoxetine responders per dose group; n = number of atomoxetine responders per dose group reporting specific AE; PRV = previous; RESP = Responder;.

Population: Enrolled patients who took at least 1 dose of study drug.

Baseline: Last Visit prior to ATX, Endpoint: ATX Visits after SP III Randomization

Therapy: RESP=Responder, PRV=ATX Previous Dose, LOW=ATX 0.5 mg/kg

* Frequencies are analyzed using a Fisher's Exact test.

Clinical Laboratory Evaluation

According to the Study Schedule, chemistry, hematology, and urinalysis tests were to be performed at the final visit (Visit 15) of the study. The assessment of laboratory data includes an analysis of change from baseline to endpoint measurements and an analysis of the percentages of patients with treatment-emergent out-of-range measurements. For these analyses, baseline is defined as the last visit prior to receiving atomoxetine in Study Period III.

Change from Baseline to Endpoint in Laboratory Values

Atomoxetine Nonresponders

There were no statistically significant treatment differences in mean change scores on any of the analytes tested for atomoxetine nonresponders.

Atomoxetine Responders

A statistically significant treatment difference in mean change occurred in the following analytes: hematocrit, mean cell volume, alkaline phosphokinase, uric acid, and creatinine (Table LYBI.36).

**Table LYBI.36. Summary of Laboratory Data
Mean Change from Baseline to Endpoint by Analyte
Atomoxetine Responders
Study Period III**

Lab Test	Lab Unit	Therapy	n	-----Baseline-----		Change to -----Endpoint-----		p-Values
				Mean	SD	Mean	SD	
HCT	1	RESP_PRV	85	0.401	0.032	0.011	0.024	.018
		RESP_LOW	89	0.404	0.029	0.002	0.026	
MCV	fL	RESP_PRV	85	84.706	4.682	1.459	2.680	<.001
		RESP_LOW	89	85.461	4.253	-0.090	3.132	
ALKPH	U/L	RESP_PRV	89	259.461	81.441	-28.708	59.971	<.001
		RESP_LOW	90	268.822	80.472	-2.711	58.019	
UR AC	umol/L	RESP_PRV	89	239.933	70.614	14.876	55.562	.039
		RESP_LOW	90	243.144	63.668	-0.256	41.703	
CREAT	umol/L	RESP_PRV	89	49.551	12.601	0.416	10.600	.003
		RESP_LOW	90	48.611	10.361	-2.978	9.270	

Note: Models:

Abbreviations: ALKPH = ALKALINE PHOSPHATASE; CREAT = CREATININE; HCT = HEMATOCRIT;
Lab = laboratory; MCV = MEAN CELL VOLUME, n = number of patients; PRV = previous;
RESP = responder; SD = standard deviation; UR AC = URIC ACID,.

RDUCL - Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks:
PROC GLM model=investigator and treatment for the overall p-Value and
model=investigator, treatment, and interaction for the interaction p-Value.
Least-squares mean option in PROC GLM from the ANOVA on the ranks using the
mean square for error.

Note: Each investigator has at least one patient in each treatment group.

Percentages of Patients with Treatment-Emergent Out-of-Range Laboratory Values

Atomoxetine Nonresponders

The incidence of abnormal values was low, and no statistically significant differences were observed between dosing groups in the percentages of nonresponders with laboratory values that were normal at baseline but found to be above or below the normal range at any time after randomization.

Atomoxetine Responders

The incidence of abnormal values was low, and no statistically significant differences were observed between dosing groups in the percentages of responders with laboratory values that were normal at baseline but found to be above or below the normal range at any time after randomization.

Vital Signs

Mean Change from Baseline to Endpoint in Vital Signs

Atomoxetine Nonresponders

No statistically significant changes were observed between dosing groups (previous dose and higher dose) in comparisons of mean change from baseline to endpoint in vital signs for atomoxetine nonresponders.

Atomoxetine Responders

Table LYBI.37 summarizes treatment comparisons in mean change from baseline to endpoint in vital signs for atomoxetine responders. Statistically significant differences between responder dosing groups were observed for heart rate and weight during Study Period III. Patients in the lower-dose group had a slightly higher average weight gain compared with patients in the previous-dose group (1.70 kg).

**Table LYBI.37. Summary of Vital Signs and Weight
Mean Change from Baseline to Endpoint
Atomoxetine Responders
Study Period III**

Variable	Therapy	N	Baseline		Change to Endpoint		p-Values	
			Mean	SD	Mean	SD	Within Group	vs Lower Dose
Dias BP (mm Hg)	Previous Dose	115	63.2	8.6	3.7	8.8	<.001	.362
	Lower Dose	110	63.5	8.7	2.5	7.9	<.001	
Sys BP (mm Hg)	Previous Dose	115	102.4	10.0	4.4	11.1	<.001	.191
	Lower Dose	110	103.2	10.2	2.4	10.0	.031	
Heart rate (bpm)	Previous Dose	115	80.5	11.2	9.0	12.5	<.001	.013
	Lower Dose	110	81.6	13.4	5.2	13.9	<.001	
Weight (kg)	Previous Dose	115	40.0	11.2	0.6	3.1	.030	<.001
	Lower Dose	110	37.0	10.6	2.3	3.0	<.001	
Height (cm)	Previous Dose	105	142.0	15.0	3.9	2.5	<.001	.487
	Lower Dose	100	139.5	13.5	4.1	2.0	<.001	
Temperature (°C)	Previous Dose	115	36.4	0.5	-0.01	0.7	.731	.927
	Lower Dose	110	36.5	0.5	0.02	0.6	.675	

Abbreviations: bpm = beats per minute; Dias BP = diastolic blood pressure measured in mm Hg;

N = number of patients; SD = standard deviation; Sys BP = systolic blood pressure measures in mm Hg.

Baseline: last visit prior to atomoxetine. Endpoint: atomoxetine visits after SP III randomization.

Categorical Analysis of Changes in Vital Signs

Atomoxetine Nonresponders

Categorical changes in blood pressure, heart rate, temperature, and weight at the end of Study Period III for all randomized nonresponders showed no differences between dosing groups in this analysis.

Atomoxetine Responders

Table LYBI.38 summarizes categorical changes in blood pressure, heart rate, temperature, and weight at the end of Study Period III for all randomized responders. The proportion of patients who experienced at least a 3.5% decrease in weight was significantly higher for the previous-dose group compared to the lower-dose group. There were no other statistically significant differences between dosing groups.

Atomoxetine hydrochloride

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**Table LYBI.38. Categorical Changes in Heart Rate (Pulse), Blood Pressure and Weight
Atomoxetine Responders
Study Period III**

Abnormal Vitals		LOW Dose			Previous Dose			Fisher's Exact
		N	n	%	N	n	%	P-value
Vital	Direction*							
Diastolic Blood Pressure	High	108	4	3.7%	113	6	5.3%	.749
Pulse	High	113	4	3.5%	116	5	4.3%	1.00
	Low	113	1	0.9%	116	0	0.0%	.493
Systolic Blood Pressure	High	108	6	5.6%	111	8	7.2%	.784
Temperature (C)	High	113	0	0.0%	116	0	0.0%	n/a
	Low	113	2	1.8%	116	1	0.9%	.618
Weight (kg)	Decrease	113	5	4.4%	116	30	25.9%	<.001

*Criteria: Pulse - High: Increase of at least 25 to a value of at least 110

- Low: Decrease of at least 20 to a value of at most 65

Temperature - High: Increase of at least 1.0 to a value of at least 37.8

- Low: Decrease of at least 1.3 to a value of at most 35.6

Weight - Decrease of at least 3.5%

Blood Pressure - High: Increase of at least 5 mm to above 95% percentile

Patients counted as meeting criteria if criteria was met at endpoint.

Population: Study period three, randomized responders.

Patients were excluded from BP analysis if they have abnormal Blood Pressure at last baseline visit

Electrocardiograms (ECGs)

Mean change from baseline to endpoint and changes in ECG intervals and heart rate were analyzed for all randomized responders and nonresponders.

Mean Change from Baseline to Endpoint in ECG Data

Atomoxetine Nonresponders

Table LYBI.39 summarizes mean change from baseline to endpoint in ECG intervals and heart rate for Study Period III randomized nonresponders. A statistically significant difference was found for the RR interval.

**Table LYBI.39. Mean Change from Baseline in ECG Intervals
Atomoxetine Nonresponders
Study Period III**

Variable	Therapy	N	Baseline		Change to Endpoint		p-Value	
			Mean	SD	Mean	SD	Within Group	PRV vs HI
RR Interval	Previous Dose	47	827.7	133.9	-118.3	122.4	<.001	.036
	Lower Dose	46	781.2	101.7	-64.8	112.6	<.001	
PR Interval	Previous Dose	47	134.7	18.7	-0.2	13.1	.984	.315
	Lower Dose	46	133.7	15.0	-2.8	12.4	.135	
QRS Interval	Previous Dose	47	77.7	6.3	2.6	7.4	.019	.086
	Lower Dose	46	78.9	7.1	0.0	8.2	1.0	
QT Interval	Previous Dose	47	363.6	28.5	-21.7	25.0	<.001	.051
	Lower Dose	46	355.7	24.4	-12.0	22.0	<.001	
QTc B	Previous Dose	47	401.4	22.1	6.2	27.5	.205	.794
	Lower Dose	46	403.6	20.1	4.6	25.3	.320	
QTc F	Previous Dose	47	388.2	20.3	-4.0	22.5	.162	.582
	Lower Dose	46	386.8	18.2	-1.5	19.7	.617	
QTc D	Previous Dose	47	392.6	20.4	-0.7	23.7	.639	.807
	Lower Dose	46	392.4	18.4	0.5	21.1	.919	
Heart Rate	Previous Dose	47	74.2	10.9	12.2	12.6	<.001	.083
	Lower Dose	46	78.1	10.5	7.4	12.6	<.001	

Abbreviations: ECG = electrocardiogram; HI = higher dose; N = number; PRV = previous dose; QTcB = Bazett-corrected QT interval; QTcD = data-corrected QT interval; QTcF = Fridericia-corrected QT interval, SD = standard deviation.

Baseline: last visit prior to atomoxetine. Endpoint: atomoxetine visits after SP III randomization.

Atomoxetine Responders

Table LYBI.40 summarizes mean change from baseline to endpoint in ECG intervals and heart rate for Study Period III randomized responders. Statistically significant differences between dosing groups were observed for heart rate and the RR interval.

**Table LYBI.40. Mean Change from Baseline in ECG Intervals
Atomoxetine Responders
Study Period III**

Variable	Therapy	N	Baseline		Change to Endpoint		p-Values	
			Mean	SD	Mean	SD	Within Group	PRV vs LOW
RR Interval	Previous Dose	86	804.4	128.6	-73.1	117.1	<.001	.038
	Lower Dose	77	800.2	134.8	-38.4	107.6	.004	
PR Interval	Previous Dose	86	137.3	17.4	-0.5	14.8	.797	.979
	Lower Dose	77	139.2	21.1	-0.4	17.4	.880	
QRS Interval	Previous Dose	86	77.7	6.6	2.2	6.8	.002	.957
	Lower Dose	77	79.4	8.2	1.8	8.1	.054	
QT Interval	Previous Dose	86	358.8	24.9	-8.6	21.4	<.001	.134
	Lower Dose	77	359.2	25.6	-4.7	22.7	.132	
QTcB	Previous Dose	86	402.2	22.0	9.5	24.9	<.001	.281
	Lower Dose	77	403.9	21.9	4.7	25.0	.149	
QTcF	Previous Dose	86	386.9	18.4	2.8	19.4	.135	.823
	Lower Dose	77	388.1	17.9	1.3	20.9	.613	
QTcD	Previous Dose	86	392.0	19.0	5.0	20.9	.019	.578
	Lower Dose	77	393.4	18.6	2.4	21.9	.395	
Heart Rate	Previous Dose	86	76.4	12.0	7.7	11.8	<.001	.019
	Lower Dose	77	77.1	12.9	3.9	10.5	.002	

Abbreviations: ECG = electrocardiogram; PRV = previous dose; QTcB = Bazett-corrected QT interval; QTcD = data-corrected QT interval; QTcF = Fridericia-corrected QT interval; SD = standard deviation. Baseline: last visit prior to Atomoxetine, Endpoint: atomoxetine visits after Study Period III randomization

Categorical Analysis of Changes in QTc Intervals and Heart Rate

Atomoxetine Nonresponders

Changes in corrected QT interval and heart rate following baseline in Study Period III were analyzed. For each criterion, the percentage of patients meeting the criteria in a treatment-emergent manner at any Study Period III visit was computed for each dosing

group. Patients meeting the criteria at baseline were excluded from the analysis. No statistically significant differences were observed.

Atomoxetine Responders

Changes in corrected QT interval and heart rate values following baseline in Study Period III were analyzed. No statistically significant differences were observed.

Other Safety Analyses

Patients Randomized to Methylphenidate in Study Period II and Switched to Atomoxetine in Study Period III

Treatment-emergent adverse events (TEAEs) were examined in the subgroup of patients who were randomized to methylphenidate during acute treatment (Study Period II) and switched to atomoxetine. Table LYBI.41 summarizes TEAEs that occurred after patients were switched to atomoxetine. The events are organized by decreasing frequency.

Table LYBI.41. Summary of Treatment-Emergent Adverse Events With >2% Frequency Methylphenidate Patients Switched to Atomoxetine

Event	Atomoxetine N=178 n (%)
Headache	15 (8.4)
Vomiting	15 (8.4)
Pyrexia	10 (5.6)
Decreased appetite	9 (5.1)
Fatigue	9 (5.1)
Gastroenteritis viral	8 (4.5)
Irritability	8 (4.5)
Nasopharyngitis	7 (3.9)
Nausea	7 (3.9)
Upper respiratory tract infection	7 (3.9)
Diarrhoea	6 (3.4)
Ear infection	5 (2.8)
Influenza	5 (2.8)
Nasal congestion	5 (2.8)
Pharyngitis streptococcal	5 (2.8)
Somnolence	5 (2.8)
Dizziness	4 (2.2)
Pharyngolaryngeal pain	4 (2.2)
Rhinorrhoea	4 (2.2)

Population: Methylphenidate patients who switched to acute atomoxetine treatment.

Atomoxetine Poor Metabolizer (PM) Nonresponders and Intolerant Extensive Metabolizer (EM) Nonresponders

A total of 13 patients who enrolled in Study Period III were not rerandomized because they were either atomoxetine PM nonresponder patients or EM nonresponder patients intolerant of dose increases. Subgroup analyses are not reported due to the small number of patients in this group.

One EM patient, who was randomized to atomoxetine during Study Period II, completed the study period but was intolerant of dose increases. Thus, this patient was not rerandomized in Study Period III and remained at previous dose atomoxetine. At Visit 8, the patient was discontinued from the study because of an AE, which was mapped to the MedDRA preferred term depression.

References

[CPMP] Committee for Proprietary Medicinal Products. 1997. Points to consider: the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. CPMP/986/96. Available at: <http://www.emea.eu.int/index/indexh1.htm>. Accessed 15 March 2005.

National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. 1996. Update on the 1987 task force report on high blood pressure in children and adolescents: a working group report from the National High Blood Pressure Education Program. *Pediatrics* 98(4):649-658.

Summary ID# 6066

Clinical Study Summary: Study B4Z-MC-LYBN

Noradrenergic Augmentation of SSRI Therapy in Patients with Depression Unresponsive or Incompletely Responsive to SSRI Monotherapy

Date summary approved by Lilly: 28 March 2006

Brief Summary of Results

- **Primary Analysis:** The augmentation of sertraline (SERT) with atomoxetine (ATX) for the treatment of depression in subjects with no or partial response to an adequate trial with SERT alone was not statistically significantly different than treatment with SERT alone, as measured by the Maier and Philipp Severity (MPS) subscale of the 17-item version of the Hamilton Depression Rating Scale (HAMD-17) using analysis of covariance (ANCOVA).
- **Secondary and Health Outcomes Analyses:** The augmentation of SERT with ATX was not statistically significantly different from treatment with SERT alone on any of the measures of depression severity, cognition, and sexual functioning. Subjects homozygous or heterozygous for the short (s) allele were not statistically different from subjects homozygous for the long (l) allele of the serotonin transporter, as measured by mean change from baseline to last observation MPS and HAMD-17 total scores.
- **Safety Analyses:** The most commonly reported treatment-emergent adverse events were nausea, dry mouth, headache, and diarrhoea during open-label treatment with SERT. During double-blind treatment, dry mouth, insomnia, and constipation were reported statistically significantly more often by the SERT+ATX treatment group compared with the SERT+placebo (PBO) treatment group. There were no statistically significant differences for any analyte in the incidence of treatment-emergent abnormal laboratory values.

The categorical assessment of vital signs and weight showed no statistically significant differences between randomized treatments during double-blind treatment. Categorical assessments of changes in QT intervals showed no statistically significant differences between randomized treatment groups during double-blind treatment.

- Pharmacokinetics Analyses: Atomoxetine concentrations in cytochrome P450 2D6 (CYP2D6) extensive metabolizer (EM) and poor metabolizer (PM) subjects taking SERT+ATX were consistent with historical data; however, concentrations in several EM subjects were somewhat higher than historical average concentrations.

Title of Study: Noradrenergic Augmentation of SSRI Therapy in Patients with Depression Unresponsive or Incompletely Responsive to SSRI Monotherapy	
Investigator(s): This multicenter study included 16 principal investigators.	
Study Center(s): This study was conducted at 16 study centers in one country.	
Length of Study: 19 months. Date first subject enrolled: 18 June 2003. Date last subject completed: 28 January 2005.	Phase of Development: 4
Objectives: The primary objective was to assess whether augmentation of sertraline (SERT) with atomoxetine (ATX) for approximately 8 weeks would result in a statistically significantly greater symptom reduction in depressed subjects with no or partial response after an adequate trial with SERT alone compared with continued therapy with SERT alone. The primary outcome measure was the mean reduction in the Maier and Philipp Severity (MPS) subscale of the 17-item version of the Hamilton Depression Rating Scale (HAMD-17). Secondary objectives compared subjects randomized to sertraline plus atomoxetine (SERT+ATX) with subjects randomized to sertraline plus placebo (SERT+PBO) on the following: - change in HAMD-17 total score in subjects partially responsive or nonresponsive to an adequate trial with SERT monotherapy. - change in the HAMD-17 MPS subscale and HAMD-17 total score in the following subgroups: - subjects partially responsive to an adequate trial of SERT monotherapy - subjects nonresponsive to an adequate trial of SERT monotherapy. - change in the HAMD-17 MPS subscale and HAMD-17 total score in the following subgroup: - subjects with less than 50% reduction in baseline symptom severity after an adequate trial with SERT monotherapy. - effects on cognition in subjects partially responsive or nonresponsive to an adequate trial with SERT monotherapy on the following measures: - modified version of the Verbal Learning and Recall Test (VLRT) - Digit Symbol Substitution Test (DSST) - Two Digit Cancellation Test (2DCT) - Letter-Number Sequencing Test (LNST). - remission rates in subjects partially responsive or nonresponsive to an adequate trial with SERT monotherapy. Two additional secondary objectives were designed to assess the following: - whether subjects homozygous or heterozygous for the short (s) allele of the serotonin transporter (5-HTT) are less responsive to SERT than subjects homozygous for the long (l) allele, as measured by mean change in the MPS and total HAMD-17 scores. - whether subjects homozygous or heterozygous for the short (s) allele of the serotonin transporter who are partial responders or nonresponders to SERT therapy will respond when ATX is added to the treatment regimen together with SERT (SERT+ATX).	
Study Design: This was a multicenter, randomized, double-blind, outpatient study comparing SERT+ATX with SERT alone in subjects with persistent depressive symptoms. After approximately 8 weeks of open-label treatment with SERT, symptom response was evaluated, and subjects continued to receive double-blind treatment for approximately 8 additional weeks as follows: subjects with no or partial response were randomly assigned (1:1) to double-blind treatment with SERT+ATX or SERT+PBO; subjects who met the remission criteria continued to receive double-blind treatment with SERT monotherapy supplemented with placebo to maintain the blind.	

Number of Subjects:

Planned: Approximately 360 subjects, with approximately 166 SERT nonresponders or partial responders.

Study Period II (Open-Label SERT Lead-in Phase):

Enrolled: 276 SERT monotherapy (n=227* completed Study Period II).

*Note that 14 of the 227 Study Period II completers discontinued prior to enrolling in Study Period III.

Study Period III (Double-Blind Treatment):

Randomized Partial and Nonresponder Subjects: 72 SRT+ATX (n=59 completed), 74 SRT+PBO (n=61 completed).

Enrolled Remitter Subjects: 67 continued double-blind SERT monotherapy (n=55 completed).

Diagnosis and Main Criteria for Inclusion: Subjects were males or females aged 18 years or older. For inclusion, subjects had to have a diagnosis of major depression without psychotic features, as determined by clinical assessment and confirmed by semi-structured interview with the Structured Clinical Interview for DSM-IV Axis Disorders-Modified-Patient Edition (SCID-IP), a score ≥ 18 on the HAM-D-17 rating scale at Visit 1, and a history of at least 1 episode of major depression in the 3 years prior to study entry.

Test Product, Dose, and Mode of Administration: Atomoxetine.

Study Period II (Open-Label SERT Lead-in Phase): No ATX was given.

Study Period III (Double-Blind Treatment): Atomoxetine, at doses ranging from 40 mg/day up to a maximum dose of 120 mg/day, given orally once or twice daily in 40-mg capsules. The exact dose was based on clinical response and tolerability.

Reference Therapy, Dose, and Mode of Administration: Sertraline.

Study Period II (Open-Label SERT Lead-in Phase): Sertraline, initiated at 100 mg/day and increased up to a maximum dose of 200 mg/day, given orally once or twice daily in 50-mg capsules. The exact dose was based on clinical response and tolerability.

Study Period III (Double-Blind Treatment): Sertraline, at a dose of 150 mg/day or the final Study Period II dose if it was less, given orally once or twice daily in 50-mg capsules, and augmented with either ATX (up to 120 mg/day in 40-mg capsules) or placebo. Treatment was double blind.

Duration of Treatment:

Study Period II (Open-Label SERT Lead-in Phase): 8 weeks of open-label treatment with SERT.

Study Period III (Double-Blind Treatment): 8 weeks of double-blind treatment with SERT+ATX or SERT+PBO.

Variables:

Efficacy: The primary efficacy measure was the change from baseline to endpoint in the MPS subscale of the HAM-D-17. Secondary efficacy measures included change from baseline to endpoint on the total score of the HAM-D-17, the Clinical Global Impressions-Severity (CGI-S) scale, the VLRT, the DSST, 2DCT, and the LNST.

Safety: Adverse events, laboratory tests, vital signs and weight, and electrocardiograms (ECGs) were evaluated.

Bioanalytical: Single blood samples were collected at the end of the study for determination of SERT, ATX, 4-hydroxyatomoxetine, and N-desmethyatomoxetine concentrations in plasma.

Pharmacokinetic: Plasma concentrations of SERT, ATX, 4-hydroxyatomoxetine, and N-desmethyatomoxetine.

Health Outcomes: Total and subscale scores of the Changes in Sexual Functioning Questionnaire (CSFQ).

Evaluation Methods:

Statistical: The primary efficacy analysis was a comparison of the MPS scores between SERT+PBO and SERT+ATX using an analysis of covariance (ANCOVA) model with terms for treatment, investigator site, and baseline MPS score. Summary statistics (mean, standard deviation [SD]) and 2-sided 95% confidence intervals were computed for secondary variables. Analysis of covariance models used change from baseline to last observation endpoints. Fisher's exact test compared treatment differences for remission rates at endpoint. Analyses of change from baseline scores using an ANCOVA model were also performed by SERT genotype. The sample size calculation was based on a 2-sided, two sample t-test at the 0.05 level. Percentages of treatment-emergent adverse events were summarized using descriptive statistics, and change from baseline to last observation for laboratory data, vital signs and weight, and ECG intervals were computed. Wilcoxon's signed-rank test was used to assess changes within treatment groups. Fisher's exact test was used for treatment comparisons in categorical data.

For the purpose of determining response categories and for analyses, partial response was defined as a $\geq 30\%$ reduction from baseline (Visit 2) in the Visit 5 MPS subscale score, but not a complete response (remission). Remission was defined as a Visit 5 MPS subscale score ≤ 4 and a rating of no more than 1 on all of the individual items of the MPS subscale (items 1, 2, 7, 8, 9, 10). No or minimal response (nonresponder) was defined as less than 30% improvement (reduction) from baseline (Visit 2) in the Visit 5 MPS subscale score. Definitions for partial response, remission, and no response were detailed in a separate document to Institutional Review Boards (IRBs), and investigators and subjects remained blinded to this information throughout the study.

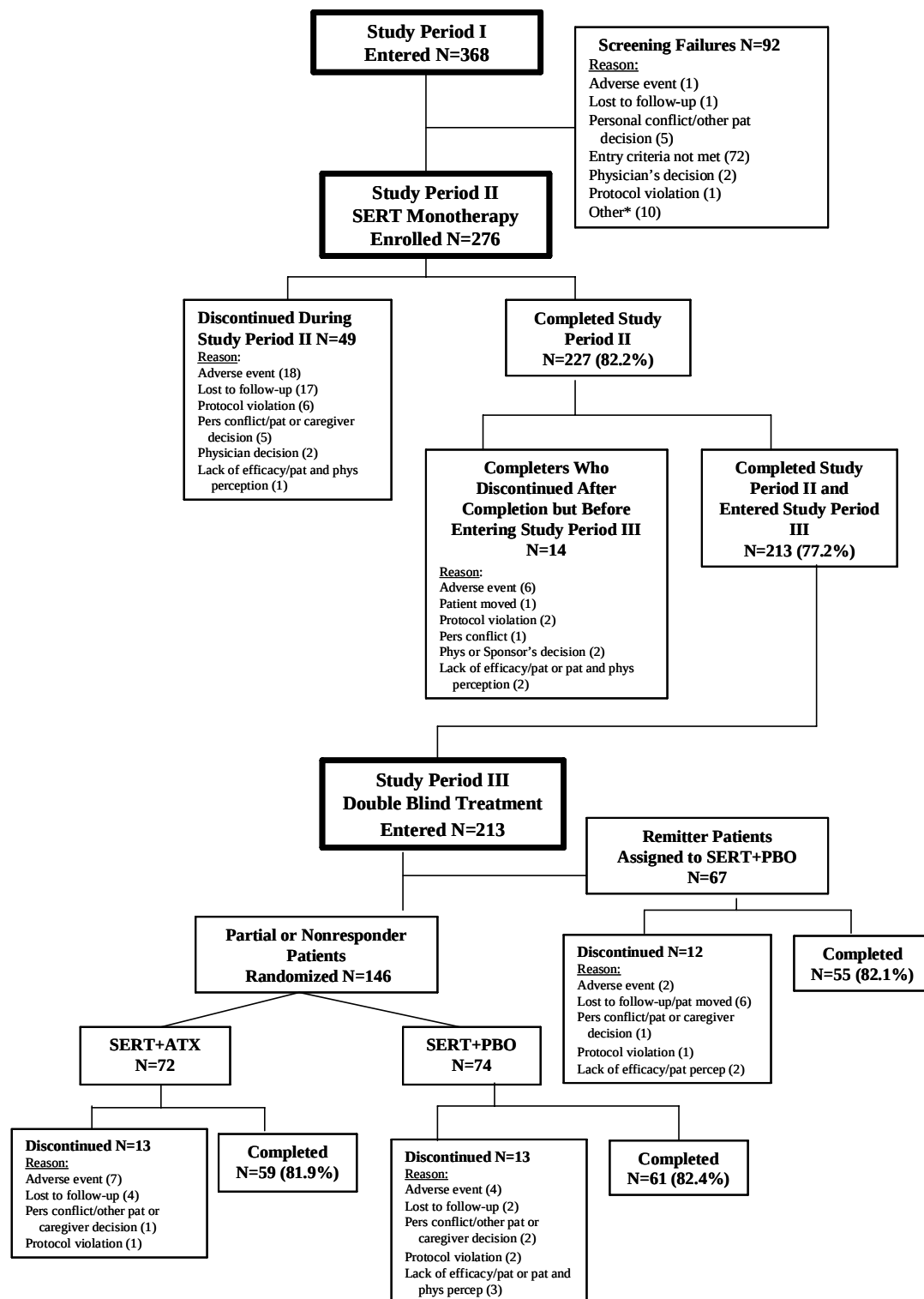
Pharmacokinetic/Pharmacodynamic: Sertraline plasma concentrations were graphically compared between SERT+ATX and SERT+PBO to assess the effects of ATX on SERT plasma concentrations. Atomoxetine concentrations were graphically compared to historical data to evaluate the effects of SERT on ATX plasma concentrations.

Bioanalytical: Heparinized human plasma samples were analyzed for ATX, 4-hydroxyatomoxetine, and N-desmethyatomoxetine using a validated liquid chromatography- atmospheric pressure chemical ionization tandem mass spectrometry (LC-APCI-MS/MS) method over the concentration ranges of 1.00 to 800.00 ng/mL for 4-hydroxyatomoxetine and N-desmethyatomoxetine, and 2.50 to 2000.00 ng/mL for ATX. Further analysis was conducted using a lower-range validated LC/APCI/MS/MS method over the concentration ranges of 1.00 to 100.00 ng/mL for 4-hydroxyatomoxetine and N-desmethyatomoxetine, and 0.25 to 25.00 ng/mL for ATX. Human plasma samples were also analyzed for SERT using a validated liquid chromatography with tandem mass spectrometry method over the concentration range 0.100 ng/mL to 50.0 ng/mL.

Results:

Subject Disposition

A total of 368 subjects entered the study (Study Period I). Of this total, 276 subjects enrolled in the SERT lead-in period (Study Period II), at the end of which response to SERT was assessed. A total of 213 subjects entered the double-blind treatment period. Sixty-seven subjects met the remission criteria, while 146 subjects met the criteria for no or partial response and were randomized to double-blind treatment with SERT+ATX (n=72) or SERT+PBO (n=74). The reasons for failing to enroll or discontinuing from the study are summarized in Figure 1, along with completion rates.



Abbreviations: pat = patient; percep = perception; pers = personal; phys = physician; SERT = sertraline;
SERT+ATX = sertraline plus atomoxetine; SERT+PBO = sertraline plus placebo.
Source: RMP.B4ZO.LYBNSTAT.FINAL (SMRDCA11) (SMRDCA21)

Figure 1. Subject disposition.

There were no statistically significant differences between treatment groups with respect to proportions of randomized subjects discontinuing for any of the primary reasons for study discontinuation during double-blind treatment (Table 1). The most common reason for discontinuation in either treatment group was adverse event.

**Table 1. Summary of Primary Reason for Study Discontinuation
Randomized Subjects
Double-Blind Treatment**

Primary Reason For Discontinuation	SERT+ATX (N=72) n (%)	SERT+PBO (N=74) n (%)	TOTAL (N=146) n (%)	p-value*
Protocol completed	59 (81.9)	61 (82.4)	120 (82.2)	1.00
Adverse event	7 (9.7)	4 (5.4)	11 (7.5)	.364
Unable to contact pat (lost to follow-up)	4 (5.6)	2 (2.7)	6 (4.1)	.438
Personal conflict or other pat/carg dec	1 (1.4)	2 (2.7)	3 (2.1)	1.00
Protocol Violation	1 (1.4)	2 (2.7)	3 (2.1)	1.00
Lack of efficacy, patient perception	0 (0.0)	2 (2.7)	2 (1.4)	.497
Lack of efficacy, pat and MD perception	0 (0.0)	1 (1.4)	1 (0.7)	1.00

Abbreviations: ATX = atomoxetine; carg dec = caregiver's decision; N = total number of patients;
n = number of patients reporting reason for discontinuation; pat = patient; PBO = Placebo;
SERT = sertraline.

*p-values were calculated using Fisher's exact test.

Subject Demographics

Table 2 summarizes baseline characteristics for the 276 subjects who enrolled in the study. Most of the enrolled subjects were Caucasian and most were female. The mean age was 42.4 years, and most subjects (99.6%) met the diagnostic criteria for Major Depressive Disorder (MDD) on the Structured Clinical Interview for DSM-IV Axis Disorders-Modified-Patient Edition (SCID-IP).

**Table 2. Summary of Subject Characteristics at Baseline
Enrolled Subjects, SERT Lead-In Period**

Characteristic	n (%)
Age	
mean years (SD)	42.4 (13.3)
Sex: n (%)	
Male	96 (34.8%)
Female	180 (65.2%)
Race Origin: n (%)	
Caucasian	218 (79.0%)
African descent	28 (10.1%)
Asian (western and east/southeast)	16 (5.9%)
Hispanic	11 (4.0%)
Other	3 (1.1%)
Diagnosis from SCID-IP Present: n (%)	
Major Depressive Disorder	275 (99.6%)
Social Phobia	9 (3.3%)
Anxiety Disorder NOS	8 (2.9%)
Generalized Anxiety Disorder	7 (2.5%)
CYP2D6 Phenotype: n (%)	
Extensive	253 (94.0%)
Poor	16 (6.0%)
Serotonin Transporter Genotype: n (%)	
l/l	79 (30.3%)
l/xl	3 (1.2%)
s/l	126 (48.3%)
s/s	51 (19.5%)
s/xl	2 (0.8%)

Abbreviations: CYP2D6 = cytochrome P450 2D6; l = long allele; NOS = not otherwise specified;
S = short allele; SCID-IP = Structured Clinical Interview for DSM-IV Axis Disorders-Modified-Patient
Edition; SD = standard deviation; SERT = sertraline; xl = extra long allele.

Baseline characteristics were compared for randomized subjects enrolled in double-blind treatment (Table 3). There were no statistically significant differences between treatment groups for any characteristic or SCID-IP diagnosis.

**Table 3. Summary of Subject Characteristics at Baseline
Randomized Subjects, Double-Blind Period**

Characteristic	SERT+ATX	SERT+PBO	p-value
Age			
No. of subjects	72	74	.491
mean years (SD)	44.0 (12.3)	45.9 (13.8)	
Sex (n/%)			1.00
Male	25 (34.7)	25 (33.8)	
Female	47 (65.3)	49 (66.2)	
Race Origin (n/%)			.182
Caucasian	56 (77.8)	62 (83.8)	
African descent	12 (16.7)	5 (6.8)	
Asian (western and east/southeast)	1 (1.4)	4 (5.4)	
Hispanic	3 (4.2)	2 (2.7)	
Other	0 (0.0)	1 (1.4)	
Diagnosis from SCID-IP Present (n/%)			
Major Depressive Disorder	71 (98.6)	74 (100.0)	.493
Social Phobia	0 (0.0)	5 (6.8)	.058
Anxiety Disorder NOS	0 (0.0)	5 (6.8)	.058
Generalized Anxiety Disorder	2 (2.8)	3 (4.1)	1.00
CYP2D6 Phenotype (n/%)			.272
Extensive	61 (87.1)	67 (93.1)	
Poor	9 (12.9)	5 (6.9)	
Serotonin Transporter Genotype (n/%)			.278
l/l	22 (32.4)	16 (22.9)	
l/xl	2 (2.9)	0 (0.0)	
s/l	32 (47.1)	36 (51.4)	
s/s	12 (17.7)	17 (24.3)	
s/xl	0 (0.0)	1 (1.4)	

Abbreviations: ATX = atomoxetine; CYP2D6 = cytochrome P450 2D6; l = long allele; PBO = placebo;
No. = number; NOS = not otherwise specified; s = short allele; SCID-IP = Structured Clinical Interview
for DSM-IV Axis Disorders-Modified-Patient Edition; SD = standard deviation; SERT = sertraline;
xl = extra long allele.

Frequencies were analyzed using Fisher's exact test.

Primary Efficacy Results

The primary analysis compared mean change from baseline to last observation during double blind treatment on the MPS subscale of the HAMD-17 for all randomized subjects with both a baseline and at least one postbaseline MPS score. There was no statistically significant difference between treatment groups (Table 4).

**Table 4. MPS Subscale Score on the HAMD-17
Randomized Subjects, Double-Blind Period**

HAMD-17	n	Baseline (SD)	Mean Change (SD)	Within-Group p-value*	Between-Group p-value**
MPS Score					
SERT+ATX	70	7.67 (3.07)	-2.91 (3.48)	<.001	.597
SERT+PBO	71	8.06 (3.09)	-2.69 (3.81)	<.001	

Abbreviations: HAMD-17 = Hamilton Depression Rating Scale–17 Item Version; MPS = Maier and Philipp Severity Subscale; n = number of subjects with a baseline and postbaseline measurement; SD = standard deviation; SERT+ATX = sertraline plus atomoxetine; SERT+PBO = sertraline plus placebo.

* P-value was from a Wilcoxon signed-rank test.

** P-value was based on an ANCOVA on change from baseline scores with terms for baseline MPS Score, treatment and investigator site.

Baseline: Visit 5; Endpoint: Visit 6-8.

Secondary Efficacy Results

SERT Lead-In Period

During the SERT lead-in period, mean change from baseline scores on the total and subscale scores of the HAMD-17 and the CGI-S score were statistically significantly lower at endpoint (Table 5). There were no statistically significant differences between subjects homozygous or heterozygous for the short (s) allele of the serotonin transporter (5-HTT) compared with subjects homozygous for the long (l) allele, as measured by mean change in the total and subscale scores of the HAMD-17 (Table 6). Within-treatment-group changes were statistically significant on the Immediate Recall subscale of the VLRT, and on the scores of the DSST, 2DCT, and LNST (Table 7).

**Table 5. HAMD-17 Total and Subscale Scores and CGI-S Score
Enrolled Subjects, SERT Lead-In**

	n	Baseline (SD)	Endpoint (SD)	Change (SD)	p-value*
HAMD-17 Total Score	249	22.84 (3.63)	12.37 (7.26)	-10.48 (6.93)	<.001
HAMD-17 MPS Score	250	12.11 (1.97)	6.23 (4.09)	-5.88 (3.99)	<.001
HAMD-17 Core Mood	249	9.54 (1.59)	4.73 (3.40)	-4.80 (3.39)	<.001
HAMD-17 Anxiety	249	6.92 (1.88)	3.83 (2.61)	-3.10 (2.67)	<.001
HAMD-17 Retardation	249	8.15 (1.56)	4.41 (2.86)	-3.75 (2.83)	<.001
HAMD-17 Sleep	249	3.71 (1.66)	2.06 (1.86)	-1.65 (2.02)	<.001
CGI-S	247	4.45 (0.62)	3.00 (1.31)	-1.45 (1.31)	<.001

Abbreviations: CGI-S = Clinical Global Impressions-Severity; HAMD-17 = Hamilton Depression Rating Scale–17 Item Version; MPS = Maier and Philipp Severity Subscale; n = number of subjects with a baseline and at least one postbaseline measurement; SD = standard deviation.

* P-value was from a Wilcoxon signed-rank test.
Baseline: Visit 1-2; Endpoint: Visit 3-5.

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Table 6. HAMD-17 Total and Subscale Scores by Genotype Enrolled Subjects, SERT Lead-In

Variable	Genotype	n	Baseline		Endpoint		Change				Within Group	Between Group
			Mean	SD	Mean	SD	Mean	SD	LCI	UCI	p-value*	p-value**
HAMD-17 Total Score	s/s and s/l	162	23.06	3.61	12.65	7.25	-10.41	7.19	-11.52	-9.29	<.001	.839
	l/l	70	22.61	3.92	12.14	7.68	-10.47	6.64	-12.06	-8.89	<.001	
HAMD-17 Core Mood Factors	s/s and s/l	162	9.58	1.58	4.84	3.44	-4.74	3.52	-5.29	-4.19	<.001	.468
	l/l	70	9.46	1.70	4.43	3.44	-5.03	3.19	-5.79	-4.27	<.001	
HAMD-17 Maier	s/s and s/l	162	12.14	1.92	6.36	4.09	-5.78	4.12	-6.42	-5.14	<.001	.541
	l/l	71	12.11	2.15	6.00	4.28	-6.11	3.85	-7.02	-5.20	<.001	
HAMD-17 Anxiety	s/s and s/l	162	7.10	1.98	3.91	2.65	-3.19	2.83	-3.62	-2.75	<.001	.727
	l/l	70	6.66	1.73	3.83	2.68	-2.83	2.32	-3.38	-2.27	<.001	
HAMD-17 Retardation	s/s and s/l	162	8.14	1.60	4.52	2.90	-3.62	2.82	-4.06	-3.19	<.001	.343
	l/l	70	8.24	1.49	4.20	2.85	-4.04	2.87	-4.73	-3.36	<.001	
HAMD-17 Sleep	s/s and s/l	162	3.70	1.73	2.12	1.84	-1.57	1.92	-1.87	-1.28	<.001	.592
	l/l	70	3.73	1.55	2.00	1.93	-1.73	2.30	-2.28	-1.18	<.001	

Abbreviations: HAMD-17 = Hamilton Depression Rating Scale, 17-item version; l/l = homozygous for the long(l) allele; n = number of subjects with a baseline and at least one postbaseline measurement and who took at least one dose of sertraline; SD = standard deviation; Change = endpoint-baseline; C.I. = 95% 2-sided Confidence Interval of Change; LCI = Lower Bound of 95% C.I.; UCI = Upper Bound of 95% C.I.; s/s and s/l = homozygous or heterozygous for the short(s) allele of 5-HTT;

Baseline: Visit 1-2; Endpoint: Visit 3-5.

*P-values were from Wilcoxon's signed-rank test.

**P-values were based on an ANCOVA on change from baseline scores with terms for baseline and genotype.

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**Table 7. Cognitive Assessments
Enrolled Subjects, SERT Lead-In**

Variable	Treatment	n	Baseline		Endpoint		Change				p-value*
			Mean	SD	Mean	SD	Mean	SD	LCI	UCI	
VLRT Immediate Recall	Sertraline	240	9.67	1.82	9.92	2.10	0.25	1.85	0.01	0.48	.030
VLRT Delayed Recall	Sertraline	240	10.23	2.75	10.31	3.06	0.08	2.84	-0.28	0.44	.699
VLRT Retention Score	Sertraline	240	-0.06	0.21	-0.03	0.22	0.03	0.26	-0.01	0.06	.109
DSST Number Correct	Sertraline	240	67.32	18.43	70.30	20.57	2.99	16.65	0.87	5.10	.004
2DCT Targets Hit	Sertraline	239	38.74	40.74	45.96	49.49	7.22	32.94	3.02	11.42	<.001
LNST Score	Sertraline	164	11.33	2.55	12.31	3.09	0.98	2.88	0.54	1.43	<.001

Abbreviations: 2DCT = Two Digit Cancellation Test; Change = endpoint-baseline; C.I. = 95% 2-sided Confidence Interval of Change; DSST = Digit Symbol Substitution Test; LCI = Lower Bound of 95% C.I.; LNST = Letter Number Sequencing Test; n = number of subjects with a baseline and at least one postbaseline measurement who took at least one dose of study drug; SD = standard deviation; UCI = Upper Bound of 95% C.I.; VLRT = Verbal Learning and Recall Test.

Baseline: Visit 1-2; Endpoint: Visit 3-5.

*P-values were from Wilcoxon's signed-rank test.

Double-Blind Period

There were no statistically significant differences between randomized treatment groups on the total or any of the subscales of the HAMD-17 and CGI-S during the double-blind treatment period (Table 8).

Table 8. HAMD-17 Total and Subscale Scores and CGI-S Score Randomized Subjects, Double-Blind Period

	n	Baseline (SD)	Endpoint (SD)	Change (SD)	Between-Group p-value*
HAMD-17 Total Score					
SRT+ATX	70	14.29 (5.73)	9.34 (6.55)	-4.94 (6.23)	.378
SRT+PBO	71	15.01 (5.46)	10.86 (7.15)	-4.15 (5.74)	
HAMD-17 Core Mood					
SRT+ATX	70	6.04 (2.73)	3.49 (3.31)	-2.56 (2.88)	.404
SRT+PBO	71	6.08 (2.57)	3.93 (3.16)	-2.15 (3.04)	
HAMD-17 Anxiety					
SRT+ATX	70	4.34 (2.09)	2.83 (2.21)	-1.51 (2.41)	.216
SRT+PBO	71	4.49 (2.29)	3.44 (2.65)	-1.06 (2.20)	
HAMD-17 Retardation					
SRT+ATX	70	5.47 (2.49)	3.47 (2.89)	-2.00 (2.72)	.640
SRT+PBO	71	5.42 (2.20)	3.68 (2.68)	-1.75 (2.46)	
HAMD-17 Sleep					
SRT+ATX	70	1.84 (1.59)	1.69 (1.71)	-0.16 (1.78)	.756
SRT+PBO	71	2.48 (1.82)	1.96 (1.72)	-0.52 (1.65)	
CGI-S Score					
SRT+ATX	66	3.32 (1.03)	2.35 (1.27)	-0.97 (1.18)	.376
SRT+PBO	70	3.50 (0.91)	2.70 (1.36)	-0.80 (1.08)	

Abbreviations: CGI-S = Clinical Global Impressions-Severity; HAMD-17 = Hamilton Depression Rating Scale-17 Item Version; n = number of subjects with baseline and at least one postbaseline measurement; SD = standard deviation; SERT+ATX = sertraline plus atomoxetine; SERT+PBO = sertraline plus placebo.

* P-values were from a Wilcoxon signed-rank test.

Baseline: Visit 5; Endpoint: Visit 6-8

Remission rates were compared between randomized groups, and no statistically significant differences were observed (Table 9). There were no statistically significant differences between treatment groups for subjects who were homozygous or heterozygous for the short (s) allele of the serotonin transporter.

**Table 9. Comparison of Remission Rates
Randomized Subjects, Double-Blind Period**

Population	SERT+ATX		SERT+PBO		Total		p-value*
	n/N	%	n/N	%	n/N	%	
All Randomized Subjects	29/72	40.3	28/74	37.8	57/146	39.0	.865
Nonresponders	5/26	19.2	7/28	25.0	12/54	22.2	.747
Partial responders	24/46	52.2	21/46	45.7	45/92	48.9	.677
Subjects <50% reduction in baseline symptom severity	10/48	20.8	16/51	31.4	26/99	26.3	.261
Genotype = s/s or s/l	21/44	47.7	21/53	39.6	42/97	43.3	.537

Abbreviations: N = number of subjects in each treatment group; n = number of subjects meeting symptomatic remission criteria; s/s and s/l = homozygous or heterozygous for the short (s) allele of the serotonin transporter (5-HTT); SERT+ATX = sertraline plus atomoxetine; SERT+PBO = sertraline plus placebo.

* P-value is from a Fisher's exact test.

In the randomized treatment groups, mean change from baseline to last observation endpoint analyses showed no statistically significant between-group differences on any of the following secondary cognition measures: VLRT subscales, DSST, 2DCT, and the LNST (Table 10).

**Table 10. Cognitive Assessments
Randomized Subjects, Double-Blind Period**

Measure	n	Baseline (SD)	Change (SD)	Within-Group p-value*	Between-Group p-value*
VLRT Immediate Recall					
SERT+ATX	66	10.10 (2.12)	0.29 (1.77)	.167	.684
SERT+PBO	70	9.83 (2.10)	0.18 (1.65)	.218	
VLRT Delayed Recall					
SERT+ATX	65	10.11 (3.12)	0.80 (2.90)	.010	.667
SERT+PBO	70	10.43 (2.94)	0.49 (2.35)	.031	
VLRT Retention Score					
SERT+ATX	65	0.00 (0.23)	-0.03 (0.29)	.124	.655
SERT+PBO	70	-0.06 (0.22)	-0.02 (0.24)	.314	
DSST # Correct					
SERT+ATX	66	71.05 (20.47)	1.09 (13.61)	.863	.780
SERT+PBO	70	67.00 (20.17)	2.47 (14.12)	.835	
2DCT Targets Hit					
SERT+ATX	66	40.82 (38.79)	-5.73 (25.61)	<.001	.285
SERT+PBO	69	42.39 (48.01)	0.20 (22.29)	<.001	
LNST Score					
SERT+ATX	49	12.69 (3.19)	-0.27 (2.75)	.289	.870
SERT+PBO	49	11.80 (3.04)	-0.12 (2.95)	.576	

Abbreviations: DDST = Digit Symbol Substitution Test; LNST = Letter-Number Sequencing Test; n = number of subjects with a baseline and at least one postbaseline measurement; SD = standard deviation; SERT+ATX = sertraline plus atomoxetine; SERT+PBO = sertraline plus placebo; 2DCT = Two Digit Cancellation Test; VLRT = Verbal Learning and Recall Test (modified version).

* P-values were from a Wilcoxon signed-rank test.

** P-values were based on an ANCOVA on change from baseline scores with terms for baseline, treatment and investigator.

Baseline: Visit 5; Endpoint: Visit 6-8.

The MPS and total HAMD-17 score comparisons in subgroups of randomized subjects (partial responders, nonresponders, and subjects with less than a 50% reduction in baseline severity), showed no statistically significant differences between ATX or PBO augmentation of SERT (Table 11). Correlations between SERT plasma concentrations and the total HAMD-17 and MPS subscale scores also showed no statistically significant relationships for either treatment group (Table 12).

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**Table 11. HAMD-17 Total and MPS Subscale Score by Subgroup
Randomized Subjects, Double-Blind Period**

											Within Group	Between Group
Variable	Treatment	n	Baseline		Endpoint		Change				p-value*	p-value**
			Mean	SD	Mean	SD	Mean	SD	LCI	UCI		
PARTIAL RESPONDERS												
HAMD-17 Total Score	Sertraline+ATX	44	11.23	4.14	7.27	5.29	-3.95	5.02	-5.48	-2.43	<.001	.344
	Sertraline+PBO	44	12.30	3.89	9.11	6.46	-3.18	5.39	-4.82	-1.54	<.001	
HAMD-17 Maier	Sertraline+ATX	44	5.80	1.89	3.45	3.17	-2.34	2.61	-3.13	-1.55	<.001	.365
	Sertraline+PBO	44	6.30	1.85	4.45	3.42	-1.84	3.14	-2.80	-0.89	<.001	
NONRESPONDERS												
HAMD-17 Total Score	Sertraline+ATX	26	19.46	4.12	12.85	7.07	-6.62	7.69	-9.72	-3.51	<.001	.642
	Sertraline+PBO	27	19.44	4.73	13.70	7.42	-5.74	6.02	-8.12	-3.36	<.001	
HAMD-17 Maier	Sertraline+ATX	26	10.85	1.78	6.96	4.10	-3.88	4.50	-5.70	-2.07	<.001	.911
	Sertraline+PBO	27	10.93	2.51	6.85	4.27	-4.07	4.43	-5.83	-2.32	<.001	
<50% REDUCTION BASELINE SEVERITY												
HAMD-17 Total Score	Sertraline+ATX	47	16.91	4.77	11.66	6.17	-5.26	7.17	-7.36	-3.15	<.001	.631
	Sertraline+PBO	49	17.04	5.02	12.35	7.39	-4.69	5.95	-6.40	-2.99	<.001	
HAMD-17 Maier	Sertraline+ATX	47	9.26	2.34	6.23	3.70	-3.02	3.99	-4.19	-1.85	<.001	.854
	Sertraline+PBO	49	9.43	2.64	6.16	4.12	-3.27	4.10	-4.44	-2.09	<.001	
SUBJECTS S/S and S/L FOR 5-HTT												
HAMD-17 Total Score	Sertraline+ATX	42	14.02	5.13	8.21	5.87	-5.81	5.49	-7.52	-4.10	<.001	.142
	Sertraline+PBO	50	14.56	4.60	10.26	6.52	-4.30	6.15	-6.05	-2.55	<.001	
HAMD-17 Maier	Sertraline+ATX	42	7.67	2.93	4.17	3.59	-3.50	3.26	-4.52	-2.48	<.001	.183
	Sertraline+PBO	50	7.64	2.69	5.10	3.55	-2.54	4.03	-3.68	-1.40	<.001	

Abbreviations: ATX = Atomoxetine; Change = endpoint-baseline; C.I. = 95% 2-sided Confidence Interval of Change; HAMD-17 = Hamilton Depression Rating Scale: 17-Item Version; LCI = Lower Bound of 95% C.I.; MPS = Maier Philipp Severity; n=number of subjects with a baseline and at least one postbaseline measurement; PBO = Placebo; SD = standard deviation; s/s and s/l=homozygous or heterozygous for the short(s) allele of the serotonin transporter (5-HTT); UCI = Upper Bound of 95% C.I.

Baseline: Visit 5; Endpoint: Visit 6-8.

*P-values were from Wilcoxon's signed-rank test.

**P-values were based on an ANCOVA on change from baseline scores with terms for baseline score and treatment.

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**Table 12. HAMD-17 Total and MPS Subscale Correlation with Sertraline Plasma Concentrations
Randomized Subjects, Double-Blind Period**

Variable	Treatment	n	Change		Concentration		P*	p-value
			Mean	SD	Mean	SD		
HAMD-17 Total	Setraline + ATX	46	-4.96	5.55	71.80	40.80	-.0446	.768
	Setraline + PBO	46	-4.13	5.71	74.18	50.93	0.1006	.506
HAMD-17 Maier	Setraline + ATX	46	-3.04	3.39	71.80	40.80	-.0266	.861
	Setraline + PBO	46	-2.46	3.74	74.18	50.93	0.0108	.943

Abbreviations: ATX = Atomoxetine; PBO = Placebo; HAMD-17 = Hamilton Depression Rating Scale: 17-Item Version; n = number of subjects with a baseline and at least one postbaseline measurement and who took at least one dose of study drug; MPS = Maier Philipp Severity; SD = standard deviation; Change = endpoint-baseline.

*Pearson's correlation coefficient.

Safety

Dose

Mean final prescribed dose and mean days on therapy are summarized during the SERT lead-in period (Table 13) and double-blind treatment period (Table 14).

**Table 13. Final Dose and Total Days on Drug
Enrolled Subjects, SERT Lead-In Period**

VARIABLE	Sertraline (N=275)
Final Prescribed Daily Dose (mg)	
No. of Subjects	256
Mean	137.50
Median	150.00
Standard Deviation	35.42
Minimum	50.00
Maximum	200.00
Total Days on Sertraline	
No. of Subjects	267
Mean	51.62
Median	56.00
Standard Deviation	18.68
Minimum	1.00
Maximum	81.00

Abbreviations: No. = number; SERT = sertraline.

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Table 14. Final and Maximum Mean Dose and Total Days on Drug Randomized Subjects, Double-Blind Period

VARIABLE	Sertraline+ATX (N=72)	Sertraline+PBO (N=74)	Total (N=146)	p-value*
<u>Final Prescribed Daily Sertraline Dose (mg)</u>				
No. of Subjects	66	69	135	.837
Mean	143.94	144.93	144.44	
Median	150.00	150.00	150.00	
Standard Deviation	29.76	25.93	27.77	
Minimum	50.00	50.00	50.00	
Maximum	200.00	200.00	200.00	
<u>Total Days on Sertraline</u>				
No. of Subjects	70	72	142	.171
Mean	50.37	53.94	52.18	
Median	56.00	56.00	56.00	
Standard Deviation	16.79	14.08	15.52	
Minimum	1.00	1.00	1.00	
Maximum	68.00	71.00	71.00	
<u>Final Prescribed Daily Atomoxetine Dose (mg)</u>				
No. of Subjects	72	NA	NA	
Mean	66.11	NA	NA	
Median	40.00	NA	NA	
Standard Deviation	30.14	NA	NA	
Minimum	40.00	NA	NA	
Maximum	120.00	NA	NA	
<u>Total Days on Atomoxetine</u>				
No. of Subjects	70	NA	NA	
Mean	50.37	NA	NA	
Median	56.00	NA	NA	
Standard Deviation	16.79	NA	NA	
Minimum	1.00	NA	NA	
Maximum	68.00	NA	NA	

Abbreviations: ATX=Atomoxetine, N = number of subjects who took at least one dose of study drug; No. = number; PBO=Placebo.

*Means analyzed using type III sum of squares analysis of variance (ANOVA).

Adverse Events

There were no deaths during the study. Seven serious adverse events were reported by 4 subjects, 2 of whom discontinued from the study due to a serious adverse event (1 suicide attempt; 1 depression suicidal). Three of the 4 subjects reporting a serious adverse event did not continue beyond the SERT lead-in period and the fourth met the remission criteria and was assigned to SERT+PBO during the double-blind period. The discontinuation rates due to adverse events for the randomized treatment groups were not statistically significantly different (SERT+ATX=9.7%, SERT+PBO=5.4%; $p=.364$) during double-blind treatment.

Table 15 summarizes treatment-emergent adverse events by decreasing frequency that were reported with greater than 5% incidence rate during the SERT lead-in period. The most commonly reported treatment-emergent adverse events were nausea (26.6%), dry mouth (18.9%), headache (16.7%), and diarrhoea (15.6%). Table 16 summarizes treatment-emergent adverse events by decreasing frequency that were reported with greater than a 5% incidence rate during double-blind treatment. Dry mouth ($p<.001$), insomnia ($p=.017$), and constipation ($p=.006$) were all reported statistically significantly more often by the SERT+ATX treatment group compared with the SERT+PBO treatment group.

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**Table 15. Treatment-Emergent Adverse Events with Greater than 5% Incidence
Enrolled Subjects, SERT Lead-In Period**

Preferred Term	Sertraline (N= 275) n (%)
SUBJECTS WITH ≥1 TESS	250 (90.91)
SUBJECTS WITH NO TESS	25 (9.09)
Nausea	73 (26.55)
Dry mouth	52 (18.91)
Headache	46 (16.73)
Diarrhoea	43 (15.64)
Insomnia	34 (12.36)
Dizziness	29 (10.55)
Libido decreased	25 (9.09)
Fatigue	25 (9.09)
Decreased appetite	24 (8.73)
Somnolence	18 (6.55)
Tremor	17 (6.18)
Hyperhidrosis	14 (5.09)

Abbreviations: N = Number of all enrolled subjects who took at
least one dose of sertraline in Study Period II; SERT = sertraline.
MedDRA VERSION: 7.0

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**Table 16. Treatment-Emergent Adverse Events with Greater than 5% Incidence
Randomized Subjects, Double-Blind Period**

Preferred Term	Sertraline+ATX (N=72) n (%)	Sertraline+PBO (N=74) n (%)	TOTAL (N=146) n (%)	p-value*
SUBJECTS WITH ≥1 TESS	56 (77.8)	52 (70.3)	108 (74.0)	.348
SUBJECTS WITH NO TESS	16 (22.2)	22 (29.7)	38 (26.0)	.348
Dry mouth	16 (22.2)	1 (1.4)	17 (11.6)	<.001
Fatigue	6 (8.3)	4 (5.4)	10 (6.8)	.530
Headache	4 (5.6)	6 (8.1)	10 (6.8)	.745
Nausea	7 (9.7)	3 (4.1)	10 (6.8)	.206
Diarrhoea	4 (5.6)	5 (6.8)	9 (6.2)	1.00
Insomnia	8 (11.1)	1 (1.4)	9 (6.2)	.017
Depressed mood	3 (4.2)	5 (6.8)	8 (5.5)	.719
Hyperhidrosis	6 (8.3)	2 (2.7)	8 (5.5)	.163
Constipation	7 (9.7)	0	7 (4.8)	.006
Dizziness	5 (6.9)	1 (1.4)	6 (4.1)	.114
Flatulence	1 (1.4)	4 (5.4)	5 (3.4)	.367
Nasopharyngitis	1 (1.4)	4 (5.4)	5 (3.4)	.367
Tremor	1 (1.4)	4 (5.4)	5 (3.4)	.367
Feeling jittery	4 (5.6)	0	4 (2.7)	.057

Abbreviations: ATX = Atomoxetine; N = Number of subjects who took at least one dose of drug in each treatment group; PBO = Placebo.

*P-values were calculated using a Fisher's exact test.

MedDRA VERSION: 7.0

Clinical Laboratory Values

Table 17 summarizes the incidence of subjects with treatment-emergent abnormal laboratory values during the SERT lead-in period. During double-blind treatment, there were no statistically significant differences between treatment groups for any analyte (Table 18).

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**Table 17. Treatment-Emergent Abnormal Laboratory Values
Enrolled Subjects, SERT Lead-In Period**

Laboratory Group: Clinical Chemistry				
Lab Test	Direction	----Sertraline----		
		N	n	Percent
ALBUMIN	High	223	1	0.4
	Low	227	0	0.0
ALKALINE PHOSPHATASE	High	224	1	0.4
	Low	226	0	0.0
ALT/SGPT	High	226	0	0.0
	Low	226	0	0.0
AST/SGOT	High	221	1	0.5
	Low	221	0	0.0
BILIRUBIN, TOTAL	High	204	1	0.5
	Low	209	0	0.0
CALCIUM	High	217	2	0.9
	Low	228	1	0.4
CHOLESTEROL	High	226	3	1.3
	Low	223	4	1.8
CREATINE PHOSPHOKINASE	High	222	2	0.9
	Low	227	0	0.0
CREATININE	High	225	2	0.9
	Low	228	0	0.0
GGT (GGPT/SGGT/YGGT)	High	225	1	0.4
	Low	227	0	0.0
GLUCOSE, NON-FASTING	High	223	1	0.4
	Low	218	3	1.4
INORGANIC PHOSPHORUS	High	219	0	0.0
	Low	222	4	1.8
TOTAL PROTEIN	High	225	0	0.0
	Low	228	0	0.0
UREA NITROGEN	High	225	3	1.3
	Low	228	1	0.4
URIC ACID	High	225	1	0.4
	Low	228	2	0.9
BANDS	High	229	0	0.0
	Low	229	0	0.0
BASOPHILS	High	228	0	0.0
	Low	229	0	0.0

(continued)

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**Table 17. Treatment-Emergent Abnormal Laboratory Values
Enrolled Subjects, SERT Lead-In Period (concluded)**

Laboratory Group: Hematology				
-----Sertraline-----				
Lab Test	Direction	N	n	Percent
EOSINOPHILS	High	227	3	1.3
	Low	229	0	0.0
ERYTHROCYTE COUNT	High	225	0	0.0
	Low	229	0	0.0
HEMATOCRIT	High	223	0	0.0
	Low	225	1	0.4
HEMOGLOBIN	High	228	0	0.0
	Low	227	2	0.9
LEUKOCYTE COUNT	High	227	2	0.9
	Low	229	1	0.4
LYMPHOCYTES	High	228	2	0.9
	Low	229	1	0.4
MEAN CELL VOLUME (MCV)	High	225	0	0.0
	Low	223	1	0.4
MONOCYTES	High	226	1	0.4
	Low	229	0	0.0
NEUTROPHILS, SEGMENTED	High	227	2	0.9
	Low	229	0	0.0
PLATELET COUNT	High	222	0	0.0
	Low	226	0	0.0
BICARBONATE, HCO ₃	High	228	0	0.0
	Low	206	7	3.4
CHLORIDE	High	225	1	0.4
	Low	227	0	0.0
POTASSIUM	High	220	2	0.9
	Low	220	2	0.9
SODIUM	High	224	1	0.4
	Low	227	1	0.4
THYROID STIMULATING HORMONE	High	1	0	0.0
	Low	1	0	0.0
UA-SPECIFIC GRAVITY	High	226	2	0.9
	Low	228	4	1.8

Abbreviations: N = number of at risk subjects with a baseline and postbaseline measurement; n = number of at risk subjects with the specific lab result (e.g. High); SERT = sertraline.

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**Table 18. Treatment-Emergent Abnormal Laboratory Values
Randomized Subjects, Double-Blind Period**

Lab Test	Direction	---Sertraline + ATX---			---Sertraline + PBO---			P-value*
		N	n	Percent (%)	N	n	Percent (%)	
ALBUMIN	High	56	0	0.0	61	0	0.0	
	Low	56	0	0.0	61	1	1.6	1.00
ALKALINE PHOSPHATASE	High	55	0	0.0	59	1	1.7	1.00
	Low	56	1	1.8	59	0	0.0	.487
ALT/SGPT	High	56	0	0.0	59	1	1.7	1.00
	Low	56	0	0.0	59	0	0.0	
AST/SGOT	High	54	0	0.0	59	0	0.0	
	Low	54	0	0.0	59	0	0.0	
BILIRUBIN, TOTAL	High	51	0	0.0	52	0	0.0	
	Low	51	0	0.0	53	0	0.0	
CALCIUM	High	54	0	0.0	59	0	0.0	
	Low	56	0	0.0	61	0	0.0	
CHOLESTEROL	High	55	1	1.8	58	0	0.0	.487
	Low	54	0	0.0	60	0	0.0	
CREATINE PHOSPHOKINASE	High	55	1	1.8	59	0	0.0	.482
	Low	55	0	0.0	59	0	0.0	
CREATININE	High	55	2	3.6	61	0	0.0	.223
	Low	56	0	0.0	61	0	0.0	
GGT (GGPT/SGGT/YGGT)	High	55	1	1.8	58	0	0.0	.487
	Low	56	0	0.0	59	0	0.0	
GLUCOSE, NON-FASTING	High	56	1	1.8	60	1	1.7	1.00
	Low	55	3	5.5	59	3	5.1	1.00
INORGANIC PHOSPHORUS	High	56	0	0.0	60	0	0.0	
	Low	55	0	0.0	59	4	6.8	.119
TOTAL PROTEIN	High	56	0	0.0	61	0	0.0	
	Low	56	0	0.0	61	0	0.0	
UREA NITROGEN	High	53	0	0.0	61	1	1.6	1.00
	Low	56	0	0.0	61	1	1.6	1.00
URIC ACID	High	56	0	0.0	61	0	0.0	
	Low	55	0	0.0	60	0	0.0	
BANDS	High	57	0	0.0	60	0	0.0	
	Low	57	0	0.0	60	0	0.0	
BASOPHILS	High	57	1	1.8	60	0	0.0	.487
	Low	57	0	0.0	60	0	0.0	
EOSINOPHILS	High	57	0	0.0	59	1	1.7	1.00
	Low	57	0	0.0	60	0	0.0	

(continued)

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**Table 18. Treatment-Emergent Abnormal Laboratory Values
Randomized Subjects, Double-Blind Period (concluded)**

Lab Test	Direction	---Sertraline + ATX---			---Sertraline + PBO---			P-value*
		N	n	Percent (%)	N	n	Percent (%)	
ERYTHROCYTE COUNT	High	57	0	0.0	59	0	0.0	
	Low	57	0	0.0	60	0	0.0	
HEMATOCRIT	High	56	0	0.0	60	0	0.0	
	Low	56	0	0.0	60	1	1.7	1.00
HEMOGLOBIN	High	57	0	0.0	59	0	0.0	
	Low	57	0	0.0	58	1	1.7	1.00
LEUKOCYTE COUNT	High	57	1	1.8	58	1	1.7	1.00
	Low	57	0	0.0	60	1	1.7	1.00
LYMPHOCYTES	High	57	0	0.0	59	0	0.0	
	Low	57	2	3.5	60	1	1.7	.612
MEAN CELL VOLUME (MCV)	High	56	0	0.0	60	0	0.0	
	Low	56	0	0.0	59	0	0.0	
MONOCYTES	High	56	0	0.0	60	0	0.0	
	Low	57	0	0.0	60	0	0.0	
NEUTROPHILS, SEGMENTED	High	57	2	3.5	59	1	1.7	.615
	Low	57	0	0.0	60	0	0.0	
PLATELET COUNT	High	56	0	0.0	60	1	1.7	1.00
	Low	56	0	0.0	60	1	1.7	1.00
BICARBONATE, HCO ₃	High	56	0	0.0	61	0	0.0	
	Low	53	1	1.9	56	0	0.0	.486
CHLORIDE	High	56	0	0.0	60	0	0.0	
	Low	56	0	0.0	61	0	0.0	
POTASSIUM	High	56	1	1.8	59	0	0.0	.487
	Low	54	0	0.0	59	0	0.0	
SODIUM	High	56	0	0.0	61	0	0.0	
	Low	56	0	0.0	60	0	0.0	
UA-SPECIFIC GRAVITY	High	58	1	1.7	63	0	0.0	.479
	Low	58	0	0.0	62	1	1.6	1.00

Abbreviation: ATX = Atomoxetine; PBO = Placebo; N = number of at risk subjects with a baseline and postbaseline measurement;
n = number of at risk subjects with the specific lab result (e.g. High).

*p-values were calculated using a Fisher's Exact test

Vital Signs and Weight

Nine subjects met the criterion (at least a 3.5% decrease in baseline weight) for a categorical change in weight during the open-label SERT lead-in period (Table 19). The categorical assessment of vital signs and weight showed no statistically significant differences between randomized treatments during double-blind treatment (Table 20).

Table 19. Categorical Changes in Vital Signs and Weight Enrolled Subjects, SERT Lead-In Period

Vitals	Direction	N	n	Percent
Pulse ^a -Supine	High	264	0	0.0
	Low	264	2	0.8
Systolic Blood Pressure ^b -Supine	High	264	0	0.0
	Low	264	3	1.1
Diastolic Blood Pressure ^c -Supine	High	264	0	0.0
	Low	264	0	0.0
Weight ^d in kg	High	264	2	0.8
	Low	264	9	3.4
Temp ^e in Centigrade				
Standardized to PO	High	264	0	0.0

Abbreviations: N = number of at risk subjects with a baseline and postbaseline measurement; n = number of at risk subjects with the specific vital sign (e.g. High); PO = by mouth, referring to temperature taken orally; Temp = temperature.

^a Low = decrease of at least 15 to a value less than 50. High = increase of at least 15 to a value of more than 120.

^b Low = decrease of at least 20 to a value of at most 90. High = increase of at least 20 to a value of at least 180.

^c Low = decrease of at least 15 to a value of at most 50. High = increase of at least 15 to a value of at least 105.

^d Low = decrease of at least 7%. High = increase of at least 7%.

^e High = increase of at least 1.1 to a value of at least 38.3.

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**Table 20. Categorical Changes in Vital Signs and Weight
Randomized Subjects, Double-Blind Period**

Vitals	Direction	---Sertraline+ATX---			---Sertraline+PBO---			P-value*
		N	n	Percent	N	n	Percent	
Pulse-Supine	High	70	0	(0.0)	72	0	(0.0)	1.00
	Low	70	0	(0.0)	72	0	(0.0)	1.00
Systolic Blood Pressure-Supine	High	70	0	(0.0)	72	0	(0.0)	1.00
	Low	70	1	(1.4)	72	0	(0.0)	.493
Diastolic Blood Pressure-Supine	High	70	1	(1.4)	72	0	(0.0)	.493
	Low	70	0	(0.0)	72	1	(1.4)	1.00
Weight in kg	High	70	2	(2.9)	72	2	(2.8)	1.00
	Low	70	2	(2.9)	72	0	(0.0)	.241
Temp in Centigrade Standardized to PO	High	70	0	(0.0)	72	1	(1.4)	1.00

Abbreviations: ATX = Atomoxetine; PBO=Placebo; N = number of at risk subjects with a baseline and postbaseline measurement;
n = number of at risk subjects with the specific vital sign (e.g. High).
*p-values were calculated using Fisher's Exact test.

Electrocardiograms

Categorical assessments of changes in QT intervals were conducted by study period using the Committee for Proprietary Medicinal Products (CPMP) criteria for potentially clinically significant changes in corrected QT intervals (Table 21). There were no statistically significant differences between randomized treatment groups during double-blind treatment (Table 22).

**Table 21. Categorical Changes in ECG Values
Enrolled Subjects, SERT Lead-In Period**

Criteria (a)	Sertraline N	n (%)
QTcF Increase $\geq$ 30	238	5 (2.1%)
QTcF Increase $\geq$ 60	238	1 (0.4%)
QTcF Inc from Normal to Borderline	238	0 (0.0%)
QTcF Inc from Normal to Prolonged	238	0 (0.0%)
QTcF Increase to $\geq$ 500 (b)	238	0 (0.0%)
QTcD Increase $\geq$ 30	238	6 (2.5%)
QTcD Increase $\geq$ 60	238	1 (0.4%)
QTcD Inc from Normal to Borderline	238	0 (0.0%)
QTcD Inc from Normal to Prolonged	238	0 (0.0%)
QTcD Increase to $\geq$ 500 (b)	238	0 (0.0%)
QTcB Increase $\geq$ 30	238	9 (3.8%)
QTcB Increase $\geq$ 60	238	1 (0.4%)
QTcB Inc from Normal to Borderline	238	0 (0.0%)
QTcB Inc from Normal to Prolonged	238	0 (0.0%)
QTcB Increase to $\geq$ 500 (b)	238	0 (0.0%)

Abbreviations: ECG = electrocardiogram; QTcD = QT interval data correction; QTcF = QT interval Fridericia correction; QTcB = QT interval Bazett Correction; SERT = sertraline.

(a) Increase $\geq$ 30: Increase of at least 30 from baseline (visits 1-2) at endpoint.
Increase $\geq$ 60: Increase of at least 60 from baseline (visits 1-2) at endpoint.
Increase from Normal to Borderline (males $\geq$ 430 to <450, females $\geq$ 450 to <470).
Increase from Normal to Prolonged (males $\geq$ 450, females $\geq$ 470).
Value $\geq$ 500: Increase to $\geq$ 500.
(b) Subjects with baseline values $\geq$ 500 excluded.
Baseline visits: 1-2, Endpoint visits :3-5.

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**Table 22. Categorical Changes in ECG Values
Randomized Subjects, Double-Blind Period**

Criteria(a)	Sertraline+ATX		Sertraline+PBO		Total		p-Value*
	N	n (%)	N	n (%)	N	n (%)	
QTcF Increase >= 30	64	0 (0.0%)	65	1 (1.5%)	129	1 (0.8%)	1.000
QTcF Increase >= 60	64	0 (0.0%)	65	0 (0.0%)	129	0 (0.0%)	
QTcF Inc from Normal to Borderline	64	0 (0.0%)	65	0 (0.0%)	129	0 (0.0%)	
QTcF Inc from Normal to Prolonged	64	0 (0.0%)	65	0 (0.0%)	129	0 (0.0%)	
QTcF Increase to >=500 (b)	64	0 (0.0%)	65	0 (0.0%)	129	0 (0.0%)	
QTcD Increase >= 30	64	0 (0.0%)	65	1 (1.5%)	129	1 (0.8%)	1.000
QTcD Increase >= 60	64	0 (0.0%)	65	0 (0.0%)	129	0 (0.0%)	
QTcD Inc from Normal to Borderline	64	0 (0.0%)	65	0 (0.0%)	129	0 (0.0%)	
QTcD Inc from Normal to Prolonged	64	0 (0.0%)	65	0 (0.0%)	129	0 (0.0%)	
QTcD Increase to >=500 (b)	64	0 (0.0%)	65	0 (0.0%)	129	0 (0.0%)	
QTcB Increase >= 30	64	6 (9.4%)	65	1 (1.5%)	129	7 (5.4%)	.062
QTcB Increase >= 60	64	0 (0.0%)	65	1 (1.5%)	129	1 (0.8%)	1.000
QTcB Inc from Normal to Borderline	64	0 (0.0%)	65	0 (0.0%)	129	0 (0.0%)	
QTcB Inc from Normal to Prolonged	64	0 (0.0%)	65	0 (0.0%)	129	0 (0.0%)	
QTcB Increase to >=500 (b)	64	0 (0.0%)	65	0 (0.0%)	129	0 (0.0%)	

Abbreviations: ATX = Atomoxetine; PBO = Placebo; QTcD = QT interval data correction; QTcF = QT interval Fridericia correction; QTcB = QT interval Bazett Correction.

(a) Increase >= 30: Increase of at least 30 from baseline (visit 5) at endpoint.
Increase >= 60: Increase of at least 60 from baseline (visit 5) at endpoint.
Increase from Normal to Borderline (males >=430 to <450, females <=450 to <470).
Increase from Normal to Prolonged (males >=450, females >=470).
Value >=500: Increase to >=500

(b) Subjects with baseline values >=500 excluded

Baseline visit: 5, Endpoint visits: 6-8.

*p-values were calculated based on Fisher's exact test.

Pharmacokinetic/Pharmacodynamic Outcomes

Blood samples for determination of SERT, ATX, *N*-desmethyatomoxetine, and 4-hydroxyatomoxetine concentrations in plasma were collected at the end of the study for each subject. At the time samples were collected, daily doses of SERT ranged from 50 to 200 mg, while ATX daily doses ranged from 40 to 120 mg or 0.3 to 2 mg/kg. Table 23 summarizes data disposition.

Table 23. Data Disposition Summary

	Sertraline	Atomoxetine	<i>N</i> -Desmethyl-atomoxetine	4-Hydroxy-atomoxetine
Number of quantifiable samples	151	40	38	32
Number of samples removed due to				
missing dosing information	2	2	1	1
missing sample information	2	0	0	0
missing CYP2D6 information	NA	1	1	1
samples taken >36 h post dose	13	0	0	0
Samples included in analysis	134	37	36	30

Abbreviations: CYP2D6 = cytochrome P450 2D6; h = hours; NA = not applicable.

Figure 2 shows SERT concentrations for subjects receiving SERT+PBO or SERT+ATX. For comparison purposes, SERT concentrations were normalized for prescribed daily dose (mg). Atomoxetine (40 to 120 mg/day) had no apparent effect on SERT concentrations. Sertraline is metabolized by multiple cytochrome (CYP) P450 isoforms (DeVane et al. 2002).

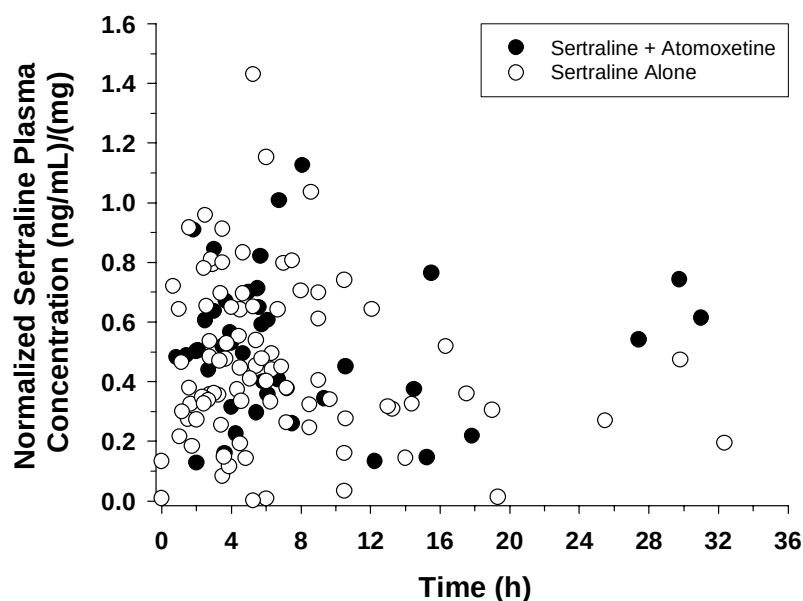
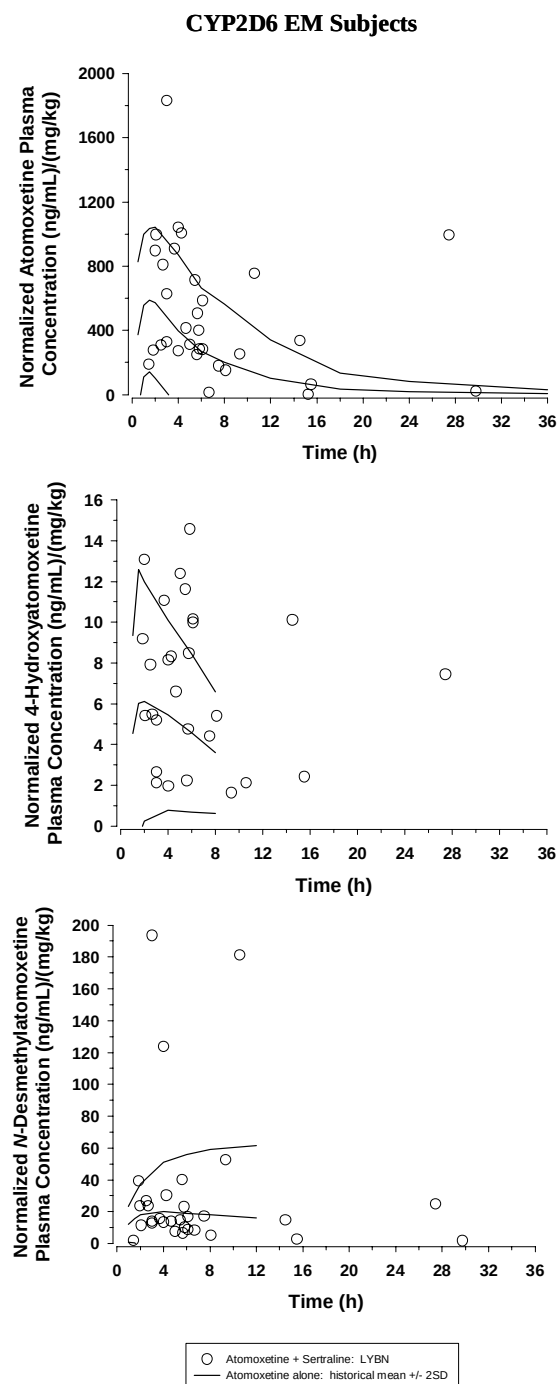


Figure 2. Dose-normalized SERT concentrations over time for subjects receiving SERT+PBO or SERT+ATX.

To assess the effect of SERT on ATX pharmacokinetics, concentrations from subjects receiving ATX and SERT were compared with historical data for ATX, *N*-desmethyatomoxetine, and 4-hydroxyatomoxetine. For comparison purposes, concentrations were normalized for prescribed daily dose of ATX (mg/kg). Figure 3 shows concentrations for CYP2D6 EM subjects. Although the study (LYBN) concentrations were consistent with historical data (Study B4Z-LC-HFBJ), several Study LYBN concentrations were somewhat higher than historical average concentrations. This can be explained, in part, by the fact that SERT has been shown to be a relatively modest inhibitor of the CYP2D6 pathway (DeVane et al. 2002). As shown in Figure 4, ATX concentrations in PM subjects (n=5 subjects) were similar to historical data (Study LYBJ). Metabolite concentrations for Study LYBN PM subjects were similar to historical data (Study B4Z-LC-LYAE), where ATX was administered twice-daily; however, no directly comparable metabolite data is available in PMs following once-daily administration.



For N-desmethyatomoxetine, lines shown are mean and mean + 2 SD.

Figure 3.

Comparison of dose/weight-normalized ATX and metabolite concentrations for EM subjects over time for SERT+ATX (LYBN) or alone (historical mean $\pm$ 2 SD from Study B4Z-LC-HFBJ).

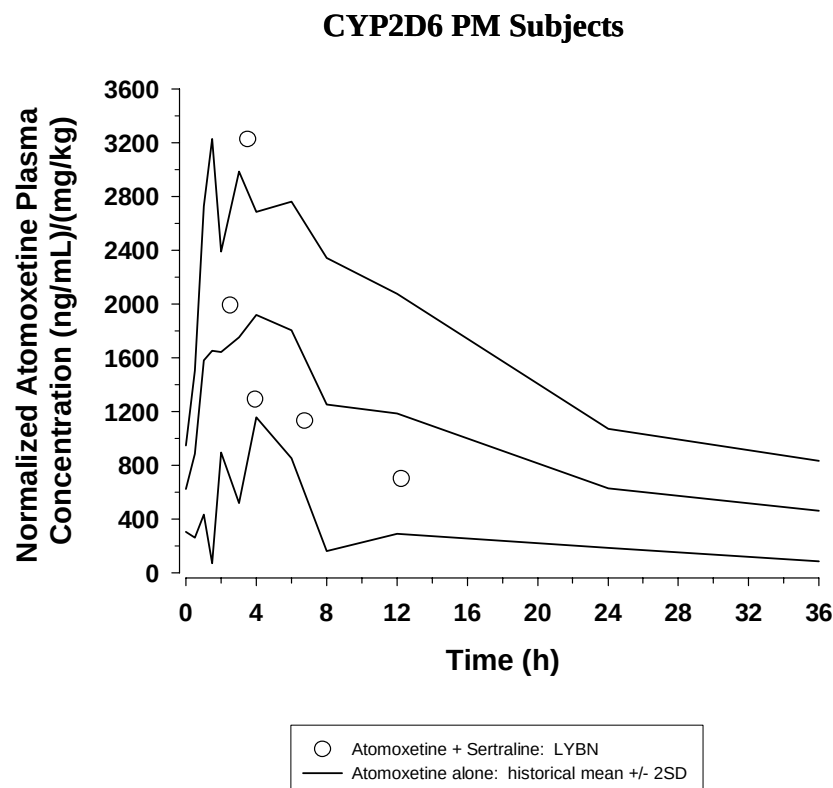


Figure 4. Comparison of dose/weight-normalized ATX concentrations over time for PM subjects for SERT+ATX (LYBN) or alone (historical mean $\pm$ 2 SD from Study B4Z-LC-LYBJ).

Health Outcomes

Change from baseline to last observation was summarized for the CSFQ, a measure designed to evaluate the quality of an individual's sex life. Statistically significant changes within gender were observed during the open-label SERT lead-in period (Table 24). There were no statistically significant differences between randomized treatment groups on the total or any of the subscale scores during double-blind treatment (Table 25).

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**Table 24. Sexual Functioning Questionnaire
Change from Baseline to Endpoint
Enrolled Subjects, SERT Lead-In Period**

Variable	Gender	n	Baseline		Endpoint		Change				p-value*
			Mean	SD	Mean	SD	Mean	SD	LCI	UCI	
Sexual Desire/Frequency	Male	70	6.71	1.50	6.63	1.44	-0.09	1.52	-0.45	0.28	.465
	Female	114	5.10	1.81	5.17	1.84	0.07	1.34	-0.18	0.32	.453
Sexual Desire/Interest	Male	70	9.76	2.63	9.73	2.73	-0.03	1.87	-0.48	0.42	.543
	Female	111	7.41	2.42	7.47	2.38	0.06	2.06	-0.33	0.45	.559
Sexual Pleasure	Male	37	2.70	1.00	2.92	1.12	0.22	1.11	-0.15	0.59	.278
	Female	62	2.52	1.13	2.74	1.14	0.23	1.00	-0.03	0.48	.094
Arousal/Excitement	Male	68	10.85	2.74	11.07	2.40	0.22	2.15	-0.30	0.74	.595
	Female	109	8.56	2.85	8.62	2.62	0.06	2.02	-0.32	0.45	.892
Orgasm/Completion	Male	60	11.47	1.94	10.87	1.92	-0.60	1.72	-1.04	-0.16	.003
	Female	106	9.11	2.83	8.84	2.89	-0.27	2.54	-0.76	0.22	.334
Total Score	Male	30	51.37	8.02	51.07	7.50	-0.30	6.66	-2.79	2.19	.169
	Female	56	42.59	9.38	43.70	8.97	1.11	7.10	-0.79	3.01	.331
Total Score Imputed	Male	56	52.60	7.37	51.60	6.93	-0.99	6.12	-2.63	0.65	.024
	Female	101	41.52	9.30	42.06	8.97	0.54	6.70	-0.79	1.86	.337

Abbreviations: Change = endpoint-baseline; C.I. = 95% 2-sided Confidence Interval of Change; LCI = Lower Bound of 95% C.I.; n = number of subjects with a baseline and at least one post baseline measurement; SD = standard deviation; SERT = sertraline; UCI = Upper Bound of 95% C.I.

Baseline: Visit 1-2; Endpoint: Visit 3-5.

*P-values were from Wilcoxon's signed-rank test.

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**Table 25. Sexual Functioning Questionnaire
Change from Baseline to Endpoint
Randomized Subjects, Double-Blind Period**

Variable	Treatment	n	Baseline		Endpoint		Change				Within Group	Between Group
			Mean	SD	Mean	SD	Mean	SD	LCI	UCI	p-value*	p-value**
FEMALES												
Sexual Desire/Frequency	Sertraline+ATX	37	5.05	1.67	5.24	1.79	0.19	1.22	-0.22	0.60	.429	.385
	Sertraline+PBO	32	4.78	2.01	4.78	2.01	0.00	0.98	-0.35	0.35	1.00	
MALES												
Sexual Desire/Frequency	Sertraline+ATX	12	5.83	1.70	6.42	1.78	0.58	1.08	-0.11	1.27	.148	.665
	Sertraline+PBO	22	6.95	1.13	7.14	1.49	0.18	1.22	-0.36	0.72	.269	
FEMALES												
Sexual Desire/Interest	Sertraline+ATX	37	7.32	2.14	7.46	2.04	0.14	1.78	-0.46	0.73	.778	.436
	Sertraline+PBO	32	7.09	2.53	7.00	2.50	-0.09	1.59	-0.67	0.48	.853	
MALES												
Sexual Desire/Interest	Sertraline+ATX	11	8.27	3.82	8.64	3.04	0.36	2.58	-1.37	2.10	.195	.747
	Sertraline+PBO	23	10.57	1.93	10.26	2.09	-0.30	1.84	-1.10	0.49	.542	
FEMALES												
Sexual Pleasure	Sertraline+ATX	21	2.67	0.86	3.00	0.71	0.33	0.86	-0.06	0.72	.146	.278
	Sertraline+PBO	18	2.56	1.10	2.67	1.19	0.11	0.76	-0.27	0.49	.766	
MALES												
Sexual Pleasure	Sertraline+ATX	7	3.00	0.82	3.00	0.58	0.00	0.82	-0.76	0.76	1.00	.270
	Sertraline+PBO	9	3.33	1.41	3.56	1.13	0.22	0.67	-0.29	0.73	.625	
FEMALES												
Arousal/Excitement	Sertraline+ATX	36	8.03	2.37	8.44	2.52	0.42	1.83	-0.20	1.03	.209	.246
	Sertraline+PBO	33	8.12	2.88	7.97	3.27	-0.15	2.17	-0.92	0.62	.886	
MALES												
Arousal/Excitement	Sertraline+ATX	12	9.25	2.86	9.58	3.18	0.33	1.56	-0.66	1.32	.523	.872
	Sertraline+PBO	23	11.39	1.47	11.39	2.44	0.00	2.17	-0.94	0.94	.869	
FEMALES												
Orgasm/Completion	Sertraline+ATX	33	8.55	2.62	9.00	2.70	0.45	1.58	-0.11	1.02	.135	.487
	Sertraline+PBO	30	8.67	3.22	8.87	3.03	0.20	1.16	-0.23	0.63	.333	
MALES												
Orgasm/Completion	Sertraline+ATX	8	9.13	2.30	9.50	2.62	0.38	1.06	-0.51	1.26	.531	.451
	Sertraline+PBO	21	11.62	1.36	11.00	2.21	-0.62	2.01	-1.53	0.30	.237	

(continued)

Atomoxetine

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**Table 25. Sexual Functioning Questionnaire
Change from Baseline to Endpoint
Randomized Subjects, Double-Blind Period (concluded)**

Variable	Treatment	n	Baseline		Endpoint		Change				Within Group	Between Group
			Mean	SD	Mean	SD	Mean	SD	LCI	UCI	p-value*	p-value**
FEMALES												
Total Score	Sertraline+ATX	19	41.89	7.29	44.05	7.02	2.16	6.69	-1.06	5.38	.130	.489
	Sertraline+PBO	12	44.33	10.11	44.58	10.59	0.25	2.93	-1.61	2.11	.916	
MALES												
Total Score	Sertraline+ATX	4	45.00	2.16	47.25	3.20	2.25	3.10	-2.68	7.18	.375	.654
	Sertraline+PBO	7	56.86	2.67	55.86	4.98	-1.00	5.16	-5.78	3.78	.531	
FEMALES												
Total Score Imputed	Sertraline+ATX	35	40.60	7.20	42.09	7.45	1.49	5.62	-0.44	3.42	.107	.379
	Sertraline+PBO	29	40.08	10.64	40.58	10.62	0.50	3.88	-0.98	1.97	.628	
MALES												
Total Score Imputed	Sertraline+ATX	5	41.80	7.40	43.83	8.13	2.03	2.73	-1.35	5.41	.250	.944
	Sertraline+PBO	21	53.77	4.66	53.34	7.29	-0.42	6.63	-3.44	2.59	.899	

Abbreviations: ATX = Atomoxetine; Change = endpoint-baseline; C.I. = 95% 2-sided Confidence Interval of Change; LCI= Lower Bound of 95% C.I.; PBO = Placebo; n = number of subjects with a baseline and at least one postbaseline measurement; SD = standard deviation; UCI = Upper Bound of 95% C.I.

Baseline: Visit 5; Endpoint: Visit 6-8.

*P-values were from Wilcoxon's signed-rank test.

**P-values were based on an ANCOVA on change from baseline scores with terms for baseline and treatment.

References

DeVane CL, Liston HL, Markowitz JS. 2002. Clinical pharmacokinetics of sertraline.
Clin Pharmacokinet 41(15):1247-66.

Summary ID#6425

Clinical Study Summary: Study B4Z-MC-LYBO

Date summary approved by Lilly: 10 August 2005

Title of Study: A Randomized, Double-Blind, Placebo- and Comparator-Controlled Study of Atomoxetine Hydrochloride in a Drug-Abusing Population	
Investigator: This single-center study included 1 principal investigator.	
Study Centers: This study was conducted at 1 study center in one country.	
Length of Study: Approximately 10 months Date first patient enrolled: 30 May 2002 Date last patient completed: 10 March 2003	Phase of Development: 1/2
Objectives: The primary objective of this study was to assess the desirability of atomoxetine as an abusable drug by comparing the subjective, euphoriant effects of atomoxetine (45 mg, 90 mg, and 180 mg) with placebo, methylphenidate (90 mg), phentermine (60 mg free base), and desipramine (100 mg and 200 mg) in drug-abusing adults with the extensive metabolizer (EM) genotype for cytochrome P450 2D6 (CYP2D6) substrates. The primary assessment was a comparison between low-dose atomoxetine and phentermine as assessed by the "liking" score ("Do you like the drug effect you are feeling now?") from the Drug Rating Questionnaire-Subject (DRQ-S) during Study Period III. The secondary objectives of this study were to assess the desirability of atomoxetine as an abusable drug by comparing the subjective, euphoriant effects of atomoxetine (45 mg, 90 mg, and 180 mg) with placebo, methylphenidate (90 mg), phentermine (60 mg free base), and desipramine (100 mg and 200 mg) in EM drug-abusing adults using secondary abuse-potential measures; to determine the minimum single dose of atomoxetine that produces a detectable subjective effect in EM adult drug-abusers; to determine the single dose of desipramine that produces the maximum, favorable subjective response in EM adult drug-abusers; to assess the safety and tolerability of single atomoxetine doses up to 240 mg (default high dose was set at 180 mg in a protocol amendment) in EM adult drug-abusers and determine the maximum single dose that does not impair the ability of these subjects to consistently and accurately report their experiences; to assess the safety and tolerability of single desipramine doses up to 200 mg in EM adult drug-abusers and determine the maximum single dose that produces primarily noradrenergic effects without impairing the ability of these subjects to consistently and accurately report their experiences; and to evaluate the pharmacokinetics of atomoxetine at supratherapeutic doses in EM substance abusers.	
Study Design: Study LYBO was an abuse-potential study that included an in-patient dose-ranging phase for desipramine and atomoxetine, followed by a randomized, double-blind, balanced Latin square crossover phase comparing atomoxetine with placebo, methylphenidate, phentermine, and desipramine in drug-abusing adults aged 21 through 55 years. The study consisted of three study periods: • Study Period I: A 7- to 91-day screening phase during which subjects were consented (Visit 1) and screened (Visit 1 and Visit 2). A blood sample was taken to determine each subject's metabolic status. Subjects who were poor metabolizers (PM) of the CYP2D6 substrates were excluded from the study. Subjects had a history (previous 30 days) of stimulant abuse (including cocaine and/or amphetamines). Screening assessments were conducted according to protocol. • Study Period II: An in-patient, single-blind, dose-ranging phase to evaluate the subjective effects of single, low doses of atomoxetine and desipramine to select appropriate and safe doses for use in Study Period III. Methylphenidate was included as a "positive control" to assure that subjects had a response	

during the second session of this study period. During subsequent sessions, subjects received ascending doses of desipramine followed by ascending doses of atomoxetine. A minimum of 6 and a maximum of 8 subjects were to participate in Study Period II. The “feel the drug” and the “liking” scales of the DRQ-S were administered according to the Study Schedule. Pharmacological effects, safety, drug tolerability, and subjective impact were also measured. The maximum dose of atomoxetine was 180 mg (the default high dose set in a protocol), and the maximum dose of desipramine was 200 mg.

- **Study Period III:** An in-patient, randomized, double-blind, multiple-dose, placebo- and comparator-controlled, balanced Latin square crossover phase designed to assess the abuse potential of atomoxetine. The positive control for a medication of high abuse potential was methylphenidate (a Schedule II amphetamine). The positive control for a medication of lesser abuse potential was phentermine (a Schedule IV amphetamine). Negative controls were placebo and desipramine, which is an unscheduled medication that is psychoactive and was expected to produce noradrenergic effects that do not lead to abuse. Treatments (placebo, methylphenidate 90 mg, phentermine 60 mg, desipramine 100 mg and 200 mg, and atomoxetine 45 mg, 90 mg, and 180 mg) were assigned in random order, given orally under double-blind and double-dummy conditions. Each subject received only one dose of each treatment, separated by a 48-hour period. In this study period, the maximum single doses were as follows: atomoxetine did not exceed 180 mg and desipramine did not exceed 200 mg. The exact doses of desipramine that were used during Study Period III were determined by the investigator, after consultation with a Lilly Physician and recommendations from the FDA, and were based upon review of the subjective ratings and safety and tolerability results obtained during Study Period II. The low dose of atomoxetine was fixed at 45 mg. The study continued until a total of 40 subjects had completed all treatments.

Number of Patients:

Study Period II:

Planned: 6 to 8 subjects

Enrolled: 8 subjects

Completed: 8 subjects

Study Period III:

Planned: 40 subjects

Randomized: 46 subjects

Completed: 40 subjects

Diagnosis and Main Criteria for Inclusion: Eligible men and women aged 21 through 55 years who met the following criteria: having the EM genotype for CYP2D6 substrates; having abused stimulants within the last 30 days prior to study enrollment based on medical history, examination, and/or laboratory results; and having no clinical or physical abnormalities that precluded enrollment as judged by the investigator and based on clinical examination and laboratory results. Subjects who participated in Study Period II were not eligible to participate in Study Period III.

Test Product, Dose, and Mode of Administration: Capsules were prepared by a research pharmacist using 5-mg, 20-mg, and 40-mg strengths of atomoxetine. Each dose was given as a single dose in the morning.

Study Period II: Atomoxetine 45-mg, 60-mg, 100-mg, and 180-mg capsules were given single-blind in ascending doses.

Study Period III: Atomoxetine 45-mg, 90-mg, and 180-mg capsules were given double-blind, according to the balanced Latin square design treatment sequence.

Duration of Treatment:

Study Period II: 12 to 24 days

Study Period III: 16 to 32 days

Reference Therapy, Dose, and Mode of Administration: Capsules were prepared by a research pharmacist using 5-mg and 10-mg strengths of methylphenidate, 30-mg strengths of phentermine, and 25-mg and 50-mg strengths of desipramine. Each dose was given as a single dose in the morning.

Study Period II: Methylphenidate: 45 mg; desipramine: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, and 200 mg; placebo. Treatments were given single-blind, and desipramine was given in ascending doses.

Study Period III: Methylphenidate: 90 mg; phentermine: 60 mg; desipramine: 100 mg and 200 mg; placebo. Treatments were given double-blind, according to the balanced Latin square design treatment sequence.

Variables:

Abuse Potential: The primary analysis variable in this study was the Liking Score from the DRQ-S during Study Period III. Other measures included the scales or subscales of the Addiction Research Center Inventory (ARCI); the other subscales of the DRQ-S; the observer-rated DRQ (DRQ-O); the Drug Identification Questionnaire (DIQ); the Specific Drug Effect Questionnaire (SDEQ-S and SDEQ-O for subject- and observer-rated versions, respectively); a sleep chart; the Treatment Enjoyment Assessment Questionnaire (TEAQ); and the Street Value Assessment Questionnaire (SVAQ).

Safety: Adverse events, vital signs, laboratory tests, and electrocardiograms (ECG).

Pharmacokinetic: Blood samples collected 1.5 hours postdose to measure the plasma concentrations of atomoxetine and its primary metabolites; plasma concentrations of other drugs.

Evaluation Methods:

Statistical: For each measure, the maximum score over the first 6 hours postdose was computed for each subject at each Study Period III visit. The primary analysis compared treatment differences between atomoxetine 45 mg and phentermine in maximum DRQ-S Liking Scores using an analysis of variance (ANOVA) model. Following the balanced Latin square design, the ANOVA model included terms for treatment, visit, and subject and used type III sums of squares. Pairwise comparisons between treatment groups were conducted using least squares means from the ANOVA model. For safety, treatment-emergent adverse events were summarized by treatment.

Summary:

Patient Disposition: Figure LYBO.1 presents a summary of subject disposition. A total of 98 subjects were screened during Study Period I. Of the 98 subjects who entered the study, 44 were discontinued and did not enroll in either Study Period II or Study Period III. The most common reason for discontinuation following screening was because protocol entry criteria were not met (n=25).

Eight subjects were enrolled in Study Period II and completed the dose-ranging period.

Forty-six subjects were randomized in Study Period III, and 40 subjects completed the multiple drug/dose administration and evaluation period.

Patient Demographics: Table LYBO.1 summarizes demographic data for subjects who were enrolled in Study Period II. Table LYBO.2 summarizes demographic data for all enrolled subjects in Study Period III.

Abuse Potential:

Study Period II: Table LYBO.3 and Table LYBO.4 summarize changes in the DRQ-S and DRQ-O scores, respectively, for each treatment group in Study Period II. Dose determinations for Study Period III were made by the investigator in consultation with the Lilly physician responsible for the study, and were based on the Study Period II values on the DRQ-S and DRQ-O. In brief, these data indicated that 100- and 200-mg doses of desipramine were required to reliably produce detectable subjective and behavioral effects. Atomoxetine 45 mg was at or below the threshold for detecting a difference from placebo, while atomoxetine 100-mg and 180-mg doses were psychoactive and separated from placebo. One of the first two subjects who received 180 mg of atomoxetine during Study Period II experienced marked peripheral

vasoconstriction (coded as blood pressure increased) and chills (coded as rigors). The investigator and the Lilly clinical research physician agreed that these adverse events were dose limiting in this population. Further, the two physicians agreed that the upper limit for atomoxetine in Study Period III would be 180 mg, and no subjects would receive 240 mg as was originally planned in Protocol B4Z-MC-LYBO(a).

Study Period III: Table LYBO.5 summarizes the primary analysis variable (DRQ-S Liking score) during the doubleblind, multiple drug/dose administration and evaluation phase for all subjects who completed Study Period III. Under double-blind conditions using the DRQ-S Liking Score, methylphenidate (a Schedule II amphetamine) differentiated from placebo. Atomoxetine 45 mg also demonstrated a statistically significantly lower mean response (less liking) compared with phentermine, which is a Schedule IV amphetamine. Other pairwise comparisons from this analysis showed the following: all atomoxetine doses (45 mg, 90 mg, and 180 mg) demonstrated statistically significantly less liking than methylphenidate; all atomoxetine doses demonstrated statistically significantly less liking than phentermine; no atomoxetine dose was found to be statistically significantly different than any dose of desipramine (an unscheduled drug), except that atomoxetine 180 mg demonstrated statistically significantly less liking than desipramine 100 mg; both desipramine doses demonstrated statistically significantly less liking than methylphenidate; desipramine 200 mg demonstrated statistically significantly less liking than phentermine, while desipramine 100 mg was not statistically significantly different; and desipramine 200 mg was not statistically significantly different than placebo, while desipramine 100 mg demonstrated statistically significantly more liking than placebo.

Secondary measures of abuse potential included: the Disliking and Feeling subscales of the DRQ-S; the Liking, Disliking, and Feeling subscales of the DRQ-O; the Morphine Benzedrine Group (MBG), the Amphetamine (AMPH), the Benzedrine Group (BG), the Lysergic Acid Diethylamide (LSD), and the Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) subscales of the ARCI; the DIQ; the SDEQ-S; the SDEQ-O; a sleep chart; the TEAQ; and the SVAQ. The following paragraphs present the results for these secondary measures.

Table LYBO.6 summarizes 6-hour maximum scores on the DRQ-S Disliking subscale for all subjects who completed Study Period III. The mean DRQ-S Disliking score was statistically significantly higher for both methylphenidate and atomoxetine 90 mg as compared to the placebo group.

Table LYBO.7 summarizes 6-hour maximum scores on the DRQ-S Feeling subscale for all subjects who completed Study Period III. Methylphenidate demonstrated a statistically significantly higher mean response compared with all other treatments. Desipramine 100 mg, phentermine, and atomoxetine (90 and 180 mg) all demonstrated statistically significantly higher mean response than placebo. There were no statistically significant differences between atomoxetine 45 mg and placebo and between desipramine 200 mg and placebo. The results were similar whether the analysis included all subjects who completed or all subjects who were randomized.

Table LYBO.8 summarizes 6-hour maximum scores on the DRQ-O Liking subscale for all subjects who completed Study Period III. There were no statistically significant differences between any of the three doses of atomoxetine and placebo. Methylphenidate and phentermine demonstrated statistically significantly higher mean response (liking) compared with placebo and compared with each dose of atomoxetine. The results were similar whether the analysis included all subjects who completed or all subjects who were randomized.

Table LYBO.9 summarizes 6-hour maximum scores on the DRQ-O Disliking subscale for all subjects who completed Study Period III. There were no statistically significant treatment differences between each dose of atomoxetine compared with placebo. Methylphenidate demonstrated statistically significantly higher mean response (dislike) compared with placebo. The results were similar whether the analysis included all subjects who completed or all subjects who were randomized.

Table LYBO.10 summarizes 6-hour maximum scores on the DRQ-O Feeling subscale for all subjects who completed Study Period III. Atomoxetine 180 mg, methylphenidate, and phentermine all demonstrated a statistically significantly higher mean response (feel the effect) compared with placebo. The mean response for methylphenidate was also statistically significantly higher than all other treatment groups. The results were similar whether the analysis included all subjects who completed or all subjects who were randomized.

Table LYBO.11 summarizes 6-hour maximum scores on the MBG subscale of the ARCI for subjects who completed Study Period III. Both methylphenidate and phentermine demonstrated statistically significantly higher mean response (euphoric effects) as compared with each dose of atomoxetine, each dose of desipramine, and placebo. There were no statistically significant treatment differences between each dose of atomoxetine versus placebo or between each dose of atomoxetine versus desipramine. Similar results were observed when 6-hour maximum MBG scores were analyzed for all randomized subjects.

Table LYBO.12 summarizes 6-hour maximum scores on the AMPH subscale of the ARCI for subjects who completed Study Period III. Atomoxetine 90 mg, methylphenidate, and phentermine all had a statistically significantly higher mean response (stimulant effect) compared with placebo. The highest mean scores were observed for methylphenidate and phentermine, which demonstrated a statistically significantly higher mean response compared with each dose of atomoxetine and with each dose of desipramine. No dose of atomoxetine was significantly different from any dose of desipramine. When 6-hour maximum AMPH scores were analyzed for all randomized subjects, there was no statistical difference between any dose of atomoxetine versus placebo. The effects observed for methylphenidate and phentermine were consistent whether the analysis included all subjects who completed or all subjects who were randomized.

Table LYBO.13 summarizes 6-hour maximum scores on the BG subscale of the ARCI for subjects who completed Study Period III. Atomoxetine 90 mg, methylphenidate, and phentermine all had a statistically significantly higher mean response difference compared with placebo. The highest mean scores were observed for methylphenidate and phentermine, which demonstrated a statistically significantly higher mean response compared with each dose of atomoxetine and with each dose of desipramine. No dose of atomoxetine was significantly different from any dose of desipramine. Similar results were observed when 6-hour maximum BG scores were analyzed for all randomized subjects.

Table LYBO.14 summarizes 6-hour maximum scores on the LSD subscale of the ARCI for subjects who completed Study Period III. Atomoxetine 90 mg, methylphenidate, and phentermine all had a statistically significantly higher mean response difference compared with placebo. The highest mean scores were observed for methylphenidate, which demonstrated a statistically significantly higher mean response than all other treatments. Similar results were observed when 6-hour maximum LSD scores were analyzed for all randomized subjects.

Table LYBO.15 summarizes 6-hour maximum scores on the PCAG subscale of the ARCI for subjects who completed Study Period III. Desipramine 200 mg and methylphenidate demonstrated a statistically significantly higher mean response (sedation) compared with placebo. No statistically significant differences between each dose of atomoxetine versus placebo or desipramine were observed. When 6-hour maximum PCAG scores were analyzed for all randomized subjects, the results were similar with the exception that atomoxetine 180 mg also had a statistically significantly higher mean score than placebo.

Table LYBO.16 summarizes the results of the DIQ. Following treatment with methylphenidate, 64.29% of subjects identified the effects as like that of a stimulant. Following treatment with phentermine, 43.90% of subjects identified the effects as like that of a stimulant. Overall, the pattern of responses for atomoxetine was different from the stimulants (more identification as downers than stimulants). Similarly, the effects of desipramine 100 and 200 mg were more commonly identified as like that of a downer.

Table LYBO.17 summarizes the results of the SDEQ-S. The pattern of responses observed for atomoxetine was not suggestive of that of a stimulant. The most common specific drug effect associated

with placebo was feeling relaxed (27.91%); for desipramine (100, 200 mg), feeling relaxed (46.51%, 30.95%, respectively) and sleepy (37.21%, 38.10%, respectively). Methylphenidate was most commonly associated with feeling relaxed (57.14%), full of energy (45.24%), and surroundings seemed different or unreal (47.62%). The most common specific drug effects associated with atomoxetine (45, 90, 180 mg) were feeling relaxed (39.53%, 40.48%, and 53.66%, respectively by increasing dose) and sleepy (27.91%, 28.57%, and 34.15%, respectively by increasing dose).

Table LYBO.18 summarizes results of the SDEQ-O. The pattern of responses observed for atomoxetine was not suggestive of that of a stimulant. The most common specific drug effect associated with placebo was feeling relaxed (44.19%); for desipramine (100, 200 mg) the most common specific drug effects were feeling relaxed (46.51% and 57.14%, respectively) and sleepy (41.86% and 50.00%, respectively). The most common specific drug effects associated with methylphenidate and phentermine were the same: feeling relaxed (61.90% and 56.10%, respectively) and talking (57.14% and 41.46%, respectively). The most common specific drug effects associated with atomoxetine (45, 90, 180 mg) were feeling relaxed (53.49%, 45.24%, and 63.41%, respectively by increasing dose) and sleepy (34.88%, 38.10%, and 58.54%, respectively by increasing dose).

Table LYBO.19 summarizes mean hours of sleep by treatment for subjects who completed Study Period III, according to the subjects' sleep charts. Regardless of treatment, mean observed sleep times were higher than subject sleep estimates. The lowest mean sleep hours were in the phentermine treatment group.

Table LYBO.20 shows the results of the TEAQ. The first drug of choice was methylphenidate (31.58%), followed by phentermine (15.79%), and none of the treatments (15.79%). Atomoxetine 45 and 90 mg were less likely to be selected than placebo, while atomoxetine 180 mg was as likely to be selected as placebo.

Table LYBO.21 summarizes the postdose value from the SVAQ for all subjects who completed Study Period III. Subjects reported a higher mean value for methylphenidate, phentermine, and desipramine 100 mg than for placebo. The highest value was associated with methylphenidate, which was statistically significantly higher than all other treatment groups. Each dose of atomoxetine was not valued statistically significantly different than placebo. The results using all randomized subjects were similar to the results for all subjects who completed, with the exception of no statistically significant difference between desipramine 100 mg and placebo.

Safety:

Study Period II: Table LYBO.22 summarizes treatment-emergent adverse events during Study Period II by decreasing frequency using MedDRA preferred terms. The most commonly reported events across all treatments included blood pressure increased, tachycardia NOS, euphoric mood, and somnolence. After taking atomoxetine, the most commonly reported treatment-emergent adverse events were headache, blood pressure increased, blood pressure decreased, dizziness, and euphoric mood. No subjects discontinued from Study Period II due to an adverse event.

A by-subject review of blood pressure values showed changes in vital signs, which were consistent with the drugs received. A slight elevation in orthostatic pulse was noted in 2 subjects after taking desipramine and after taking atomoxetine. Treatment differences were not tested due to the small sample size (N=8) in this study period.

Electrocardiogram measurements were obtained at admission and at discharge for the 4 subjects who received 180 mg of atomoxetine during Study Period II. Both the investigator and a Lilly physician reviewed each subject's ECG measurements.

Study Period III: Table LYBO.23 summarizes treatment-emergent adverse events by decreasing frequency using MedDRA preferred terms organized by system organ class. Across all treatments, the most commonly reported (>10%) treatment-emergent adverse events were: feeling relaxed (33.4%), somnolence (29.0%), tachycardia NOS (19.9%), orthostatic hypotension (17.6%), blood pressure increased (17.3%), dry mouth (13.2%), headache (12.3%), euphoric mood (12.0%), nausea (11.7%), and dizziness (11.4%). A binary repeated measures ANOVA model was used to test treatment effects for adverse events with an occurrence of >10%. A statistically significant overall treatment effect was observed for dry mouth ($p=.003$) and euphoric mood ($p=.045$). In both of these cases, the highest incidence was observed in subjects taking methylphenidate. After taking atomoxetine, the most commonly reported treatment-emergent adverse events were feeling of relaxation, somnolence, tachycardia NOS, and orthostatic hypotension. The frequency of reported events increased as dose increased for nausea, dyspepsia, sluggishness, rigors, feeling hot, somnolence, headache, and dysuria.

Table LYBO.24 and Table LYBO.25 summarize changes from baseline to 1.5 hours postdose in orthostatic and supine heart rate (pulse) and systolic and diastolic blood pressure by treatment for all randomized males and females, respectively. The following treatment differences were observed: a statistically significantly greater change from baseline to 1.5-hour supine heart rate (pulse) was observed in methylphenidate compared with all other treatments; statistically significantly greater change from baseline to 1.5-hour supine systolic and diastolic blood pressure was observed in phentermine compared with all other treatments; statistically significantly greater change from baseline to 1.5-hour orthostatic heart rate (pulse) was observed in all three atomoxetine doses and in methylphenidate compared with placebo, each dose of desipramine, and phentermine; statistically significantly greater change from baseline to 1.5-hour orthostatic systolic blood pressure was observed in methylphenidate and phentermine compared with placebo, each dose of atomoxetine, and each dose of desipramine; a statistically significantly greater change from baseline to 1.5-hour orthostatic diastolic blood pressure was observed in methylphenidate compared with placebo, each dose of atomoxetine, and each dose of desipramine.

Electrocardiogram measurements were taken at discharge during Study Period III. Table LYBO.26 summarizes change from baseline (screening) to endpoint in ECG measurements. Both the investigator and a Lilly physician reviewed each subject's ECG measurements.

Pharmacokinetic:

Study Period II: The pharmacokinetics of atomoxetine, 4-hydroxyatomoxetine, and *N*-desmethyлатomoxetine were similar to those observed at lower doses. Atomoxetine was rapidly absorbed and eliminated. The *N*-desmethyлатomoxetine and 4-hydroxyatomoxetine metabolites circulated in plasma at low concentrations and exhibited a longer half-life when compared with atomoxetine.

Study Period III: Table LYBO.27 summarizes plasma levels for each drug. The plasma results confirm that methylphenidate, phentermine, and desipramine concentrations were present in plasma at 1.5 hours following administration of these drugs on all but one occasion. A single below quantifiable limits (BQL) value for desipramine was observed following a 100-mg desipramine dose. The mean plasma levels for atomoxetine, *N*-desmethyлатomoxetine, and 4-hydroxyatomoxetine at 1.5 hours post atomoxetine doses were as expected in EM subjects.

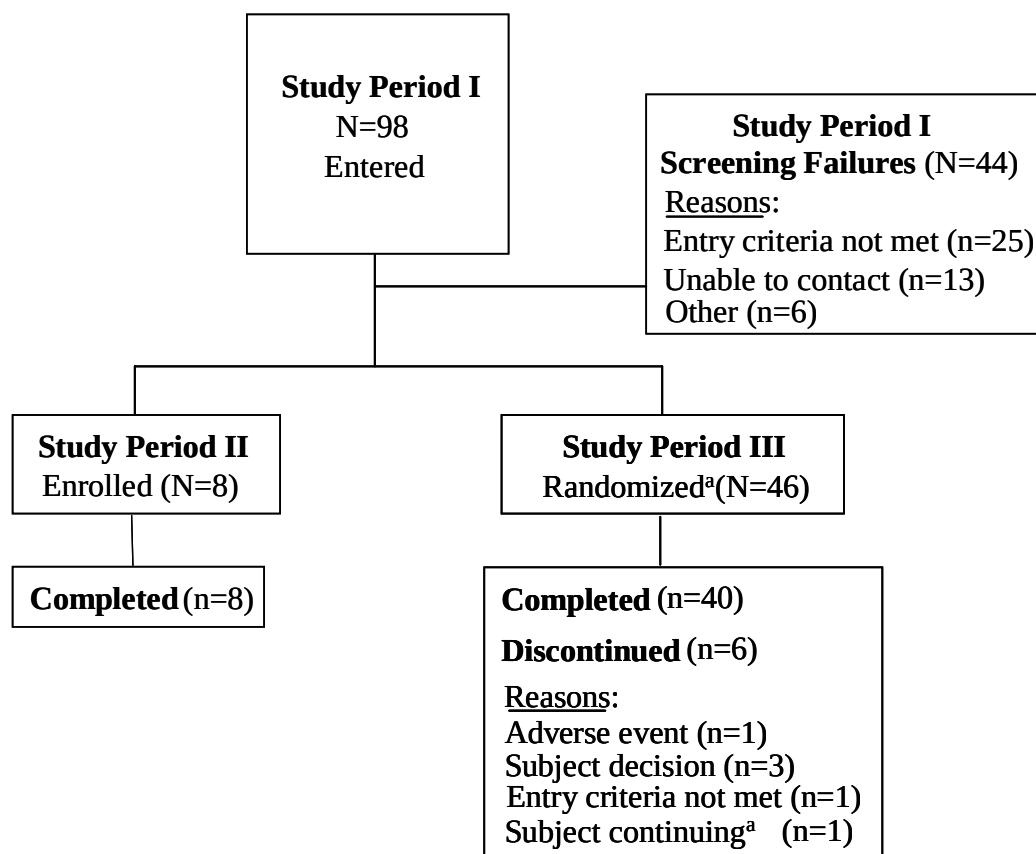


Figure LYBO.1. Overview of subject disposition.

^a One subject (LYBO-240-8060) was randomized (assigned to a therapy sequence) in Study Period III, but discontinued at Visit 2 (did not meet entry criteria due to elevated blood pressure [hypertensive]) without taking any study drug, and is listed as “subject continuing” under the discontinuations for Study Period III.

**Table LYBO.1. Summary of Demographics
Study Period II**

Variable	All_TRTs (N=54)
----------	--------------------

Sex: No. (%) (Visit: 103)

No. Patients	8
Male	8 (100)

Origin: No. (%) (Visit: 103)

No. Patients	8
African Descent	7 (87.5)
Caucasian	1 (12.5)

Age (Visit: 103)

No. Patients	8
Mean	41.44
Median	42.36
Standard Dev.	3.61
Minimum	33.57
Maximum	44.65

Population: All Enrolled Patients.
Study Period II

**Table LYBO.2. Summary of Demographics
All Enrolled Subjects
Study Period III**

Variable	All_TRTs

Sex: No. (%)	
No. Subjects	46
Female	11 (23.9)
Male	35 (76.1)
Origin: No. (%)	
No. Subjects	46
African Descent	44 (95.7)
Caucasian	1 (2.2)
East/Southeast Asian	1 (2.2)
Age	
No. Subjects	46
Mean	41.81
Median	41.63
Standard Dev.	4.79
Minimum	32.04
Maximum	53.87

Abbreviations: No=number; Standard Dev=Standard deviation,

TRTs=treatments.

Population: All Enrolled Subjects

Study Period III

Atomoxetine hydrochloride

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**Table LYBO.3. DRQ-S Liking, Disliking, and Feeling Scores
Summary Statistics on 6-Hour Maximum
Scores By Treatment for All Randomized Patients
Study Period II**

DRQ-S LIKING SCORE			
	6 HOUR MAXIMUM		
	N	MEAN	STD
TREATMENT			
PLA	8	5.0	8.3
DMI 025	4	1.3	0.5
DMI 050	4	3.0	4.0
DMI 075	2	1.5	0.7
DMI 100	2	8.5	4.9
DMI 150	2	1.0	0.0
DMI 200	2	9.5	3.5
MPH 045	8	6.1	4.8
ATX 045	4	2.0	2.0
ATX 060	4	1.5	1.0
ATX 100	4	11.5	7.5
ATX 180	4	11.8	7.7

ABBREVIATIONS: ATX=ATOMOXETINE, DMI=DESIPRAMINE, MPH=METHYLPHENIDATE, PHN=PHENTERMINE, PLA=PLACEBO, SD= STANDARD DEVIATION
PROGRAM: \\MC1STAT02\MC1STAT02.GRP\RMP\B4ZS\LYBO\ANOVA_DRQS_LIKE_SP2_YN_1.SAS

(continued)

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Table LYBO.3. DRQ-S Liking, Disliking, and Feeling Scores
Summary Statistics on 6-Hour Maximum
Scores By Treatment for All Randomized Patients
Study Period II (continued)

DRQ-S DISLIKING SCORE			
	HOUR MAXIMUM		
	N	MEAN	STD
TREATMENT			
PLA	8	1.0	0.0
DMI 025	4	7.8	13.5
DMI 050	4	1.0	0.0
DMI 075	2	1.0	0.0
DMI 100	2	3.0	2.8
DMI 150	2	1.0	0.0
DMI 200	2	6.5	7.8
MPH 045	8	4.6	9.9
ATX 045	4	1.0	0.0
ATX 060	4	1.0	0.0
ATX 100	4	5.5	9.0
ATX 180	4	14.0	11.7

ABBREVIATIONS: ATX=ATOMOXETINE, DMI=DESIPRAMINE, MPH=METHYLPHENIDATE, PHN=PHENTERMINE, PLA=PLACEBO, SD= STANDARD DEVIATION
PROGRAM: \\MC1STAT02\MC1STAT02.GRP\RMP\B4ZS\LYBO\ANOVA_DRQS_DISLIKE_SP2_YN_1.SAS

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**Table LYBO.3. DRQ-S Liking, Disliking, and Feeling Scores
Summary Statistics on 6-Hour Maximum
Scores By Treatment for All Randomized Patients
Study Period II (concluded)**

DRQ-S FEELING SCORE			
	6 HOUR MAXIMUM		
	N	MEAN	STD
TREATMENT			
PLA	8	3.9	4.5
DMI 025	4	1.3	0.5
DMI 050	4	1.8	1.5
DMI 075	2	1.5	0.7
DMI 100	2	3.0	0.0
DMI 150	2	3.0	2.8
DMI 200	2	2.0	0.0
MPH 045	8	3.9	1.4
ATX 045	4	2.0	2.0
ATX 060	4	1.5	1.0
ATX 100	4	8.0	6.8
ATX 180	4	9.3	7.3

ABBREVIATIONS: ATX=ATOMOXETINE, DMI=DESIPRAMINE, MPH=METHYLPHENIDATE, PHN=PHENTERMINE, PLA=PLACEBO, SD= STANDARD DEVIATION

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**Table LYBO.4. DRQ-O Liking, Disliking, and Feeling Scores
Summary Statistics on 6-Hour Maximum
Scores By Treatment for All Randomized Patients
Study Period II**

DRQ-O LIKING SCORE			
	6 HOUR MAXIMUM		
	N	MEAN	STD
TREATMENT			
PLA	8	7.1	11.0
DMI 025	4	1.3	0.5
DMI 050	4	3.0	4.0
DMI 075	2	1.0	0.0
DMI 100	2	13.5	16.3
DMI 150	2	1.0	0.0
DMI 200	2	17.5	3.5
MPH 045	8	4.1	3.5
ATX 045	4	2.0	2.0
ATX 060	4	1.5	1.0
ATX 100	4	5.8	3.4
ATX 180	4	5.3	6.7

ABBREVIATIONS: ATX=ATOMOXETINE, DMI=DESIPRAMINE, MPH=METHYLPHENIDATE, PHN=PHENTERMINE, PLA=PLACEBO, SD= STANDARD DEVIATION

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**Table LYBO.4. DRQ-O Liking, Disliking, and Feeling Scores
Summary Statistics on 6-Hour Maximum
Scores By Treatment for All Randomized Patients
Study Period II (continued)**

DRQ-O DISLIKING SCORE			
	6 HOUR MAXIMUM		
	N	MEAN	STD
TREATMENT			
PLA	8	1.3	0.7
DMI 025	4	7.8	13.5
DMI 050	4	1.3	0.5
DMI 075	2	1.0	0.0
DMI 100	2	3.0	2.8
DMI 150	2	1.0	0.0
DMI 200	2	3.0	2.8
MPH 045	8	4.5	9.9
ATX 045	4	1.0	0.0
ATX 060	4	4.5	7.0
ATX 100	4	4.5	7.0
ATX 180	4	10.8	11.3

ABBREVIATIONS: ATX=ATOMOXETINE, DMI=DESIPRAMINE, MPH=METHYLPHENIDATE, PHN=PHENTERMINE, PLA=PLACEBO, SD= STANDARD DEVIATION

(continued)

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**Table LYBO.4. DRQ-O Liking, Disliking, and Feeling Scores
Summary Statistics on 6-Hour Maximum
Scores By Treatment for All Randomized Patients
Study Period II (concluded)**

DRQ-O FEELING SCORE			
	6 HOUR MAXIMUM		
	N	MEAN	STD
TREATMENT			
PLA	8	4.1	5.4
DMI 025	4	1.3	0.5
DMI 050	4	2.0	1.4
DMI 075	2	1.0	0.0
DMI 100	2	6.0	5.7
DMI 150	2	3.0	2.8
DMI 200	2	10.0	0.0
MPH 045	8	4.1	2.9
ATX 045	4	2.0	2.0
ATX 060	4	3.0	2.3
ATX 100	4	8.3	5.9
ATX 180	4	11.5	8.1

ABBREVIATIONS: ATX=ATOMOXETINE, DMI=DESIPRAMINE, MPH=METHYLPHENIDATE, PHN=PHENTERMINE, PLA=PLACEBO, SD= STANDARD DEVIATION

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Table LYBO.5. DRQ-S Liking Score
6-Hour Maximum Score by Treatment
All Subjects Who Completed Study Period III

	6 Hour Maximum			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
Treatment										
PLA	40	3.5	5.6							
DMI 100	40	6.6	9.0	.022						
DMI 200	40	4.3	6.0	.562	.086					
MPH 090	40	10.6	10.2	<.001	.003	<.001				
PHN 060	40	8.6	9.7	<.001	.130	.001	.130			
ATX 045	40	5.2	7.4	.211	.295	.501	<.001	.011		
ATX 090	40	4.2	6.7	.600	.076	.955	<.001	.001	.466	
ATX 180	40	3.7	5.4	.881	.032	.667	<.001	<.001	.270	.708

Linear Trend ATX (with placebo) p-value*=0.821

Linear Trend ATX (without placebo) p-value*=0.296

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, Std=Standard Deviation, VS=versus.

Pairwise treatment comparison p-values are from ANOVA model: 6 hour maximum= treatment visit subject

* Test for linear dose effect from the ANOVA model using contrast of least squares means

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Table LYBO.6. DRQ-S Disliking Score
6-Hour Maximum Score by Treatment
All Subjects Who Completed Study Period III

	6 Hour Maximum			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
Treatment										
PLA	40	4.0	7.4							
DMI 100	40	5.7	9.1	.310						
DMI 200	40	4.7	6.6	.684	.542					
MPH 090	40	9.4	11.0	.002	.031	.006				
PHN 060	40	6.3	9.9	.182	.749	.353	.066			
ATX 045	40	4.9	8.0	.591	.632	.896	.009	.424		
ATX 090	40	7.4	11.2	.046	.324	.111	.240	.504	.143	
ATX 180	40	6.4	10.0	.160	.695	.317	.077	.942	.384	.552

Linear Trend ATX (with placebo) p-value*=0.119

Linear Trend ATX (without placebo) p-value*=0.528

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, Std=Standard Deviation, VS=versus.

Pairwise treatment comparison p-values are from ANOVA model: 6 hour maximum= treatment visit subject

* Test for linear dose effect from the ANOVA model using contrast of least squares means

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**Table LYBO.7. DRQ-S Feeling Score
6-Hour Maximum Score by Treatment
All Subjects Who Completed Study Period III**

	6 Hour Maximum			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
Treatment										
PLA	40	3.1	4.4							
DMI 100	40	5.6	6.5	.041						
DMI 200	40	4.2	5.4	.358	.259					
MPH 090	40	12.2	9.4	<.001	<.001	<.001				
PHN 060	40	7.1	6.9	<.001	.202	.017	<.001			
ATX 045	40	4.9	6.3	.138	.572	.572	<.001	.066		
ATX 090	40	6.7	8.8	.003	.326	.035	<.001	.770	.122	
ATX 180	40	6.2	7.8	.011	.616	.103	<.001	.439	.286	.630

Linear Trend ATX (with placebo) p-value*=0.010

Linear Trend ATX (without placebo) p-value*=0.409

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, Std=Standard Deviation, VS=versus.

Pairwise treatment comparison p-values are from ANOVA model: 6 hour maximum= treatment visit subject

* Test for linear dose effect from the ANOVA model using contrast of least squares means

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Table LYBO.8. DRQ-O Liking Score
6-Hour Maximum Score by Treatment
All Subjects Who Completed Study Period III

	6 Hour Maximum			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
Treatment										
PLA	40	3.5	5.7							
DMI 100	40	6.0	8.1	.064						
DMI 200	40	4.7	7.2	.383	.325					
MPH 090	40	11.7	9.4	<.001	<.001	<.001				
PHN 060	40	8.8	10.0	<.001	.037	.002	.037			
ATX 045	40	3.2	5.1	.809	.037	.265	<.001	<.001		
ATX 090	40	3.2	4.2	.824	.038	.274	<.001	<.001	.985	
ATX 180	40	4.7	5.2	.393	.316	.985	<.001	.002	.274	.282

Linear Trend ATX (with placebo) p-value*=0.328
 Linear Trend ATX (without placebo) p-value*=0.234

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, Std=Standard Deviation, VS=versus.
 Pairwise treatment comparison p-values are from ANOVA model: 6 hour maximum= treatment visit subject
 * Test for linear dose effect from the ANOVA model using contrast of least squares means

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Table LYBO.9. DRQ-O Disliking Score
6-Hour Maximum Score by Treatment
All Subjects Who Completed Study Period III

	Change to 6 Hour Maximum			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
Treatment										
PLA	40	2.9	5.4							
DMI 100	40	4.5	8.0	.344						
DMI 200	40	4.0	6.1	.524	.756					
MPH 090	40	6.8	9.2	.016	.141	.075				
PHN 060	40	5.0	8.4	.203	.744	.524	.251			
ATX 045	40	3.4	7.2	.792	.494	.709	.032	.313		
ATX 090	40	6.0	9.9	.055	.328	.198	.619	.514	.097	
ATX 180	40	4.9	8.6	.226	.792	.566	.226	.950	.344	.475

Linear Trend ATX (with placebo) p-value*=0.151
Linear Trend ATX (without placebo) p-value*=0.502

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, SD=Standard Deviation, VS=versus.
Pairwise treatment comparison p-values are from ANOVA model: change to maximum= treatment visit subject
* Test for linear dose effect from the ANOVA model using contrast of least squares means

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**Table LYBO.10. DRQ-O Feeling Score
6-Hour Maximum Score by Treatment
All Subjects Who Completed Study Period III**

	Change to 6 Hour Maximum			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
Treatment										
PLA	40	4.2	5.1							
DMI 100	40	5.0	5.2	.545						
DMI 200	40	5.4	6.3	.347	.738					
MPH 090	40	11.9	7.7	<.001	<.001	<.001				
PHN 060	40	7.6	7.2	.005	.026	.058	<.001			
ATX 045	40	4.8	5.8	.661	.867	.616	<.001	.017		
ATX 090	40	6.2	6.7	.108	.316	.504	<.001	.218	.242	
ATX 180	40	7.8	7.1	.003	.018	.041	<.001	.884	.011	.168

Linear Trend ATX (with placebo) p-value*=0.001
Linear Trend ATX (without placebo) p-value*=0.012

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, Std=Standard Deviation, VS=versus.

Pairwise treatment comparison p-values are from ANOVA model: change to maximum= treatment visit subject

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**Table LYBO.11. ARCI Morphine-Benzedrine Group (MBG) Score
6-Hour Maximum Score by Treatment
All Subjects Who Completed Study Period III**

	6 Hour Maximum			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
Treatment										
PLA	40	0.9	2.5							
DMI 100	40	1.4	3.3	.395						
DMI 200	40	1.2	2.6	.610	.734					
MPH 090	40	4.1	4.8	<.001	<.001	<.001				
PHN 060	40	4.2	5.2	<.001	<.001	<.001	.966			
ATX 045	40	1.1	3.2	.734	.610	.865	<.001	<.001		
ATX 090	40	2.1	4.2	.057	.288	.161	<.001	<.001	.117	
ATX 180	40	1.5	3.0	.350	.932	.671	<.001	<.001	.552	.329

Linear Trend ATX (with placebo) p-value*=0.266

Linear Trend ATX (without placebo) p-value*=0.760

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, Std=Standard Deviation, VS=versus.

Pairwise treatment comparison p-values are from ANOVA model: 6 hour maximum= treatment visit subject

* Test for linear dose effect from the ANOVA model using contrast of least squares means

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**Table LYBO.12. ARCI Amphetamine (AMPH) Score
6-Hour Maximum by Treatment
All Subjects Who Completed Study Period III**

	6 Hour Maximum			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
Treatment										
PLA	40	1.0	2.0							
DMI 100	40	1.2	2.0	.581						
DMI 200	40	1.1	2.2	.730	.836					
MPH 090	40	2.9	2.7	<.001	<.001	<.001				
PHN 060	40	2.9	3.1	<.001	<.001	<.001	1.00			
ATX 045	40	1.1	2.1	.730	.836	1.00	<.001	<.001		
ATX 090	40	1.7	2.6	.039	.130	.086	.002	.002	.086	
ATX 180	40	1.3	2.0	.302	.629	.491	<.001	<.001	.491	.302

Linear Trend ATX (with placebo) p-value*=0.217

Linear Trend ATX (without placebo) p-value*=0.707

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, Std=Standard Deviation, VS=versus.

Pairwise treatment comparison p-values are from ANOVA model: 6 hour maximum= treatment visit subject

* Test for linear dose effect from the ANOVA model using contrast of least squares means

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**Table LYBO.13. ARCI Bazedrine Group (BG) Score
6-Hour Maximum Score by Treatment
All Subjects Who Completed Study Period III**

	Change to 6 Hour Maximum			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
Treatment										
PLA	40	4.4	0.8							
DMI 100	40	4.8	1.7	.205						
DMI 200	40	4.6	1.7	.446	.612					
MPH 090	40	6.0	2.4	<.001	<.001	<.001				
PHN 060	40	6.1	2.4	<.001	<.001	<.001	.800			
ATX 045	40	4.8	1.6	.205	1.00	.612	<.001	<.001		
ATX 090	40	5.1	2.0	.018	.272	.109	.003	.001	.272	
ATX 180	40	4.8	1.7	.151	.866	.498	<.001	<.001	.866	.352

Linear Trend ATX (with placebo) p-value*=0.170

Linear Trend ATX (without placebo) p-value*=0.956

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, Std=Standard Deviation, VS=versus.

Pairwise treatment comparison p-values are from ANOVA model: change to maximum= treatment visit subject

* Test for linear dose effect from the ANOVA model using contrast of least squares means

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**Table LYBO.14. ARCI Lysergic Acid Diethylamide (LSD) Score
6-Hour Maximum Score by Treatment
All Subjects Who Completed Study Period III**

	Change to 6 Hour Maximum			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
Treatment										
PLA	40	4.1	0.5							
DMI 100	40	4.4	0.8	.311						
DMI 200	40	4.3	0.8	.407	.854					
MPH 090	40	5.8	2.4	<.001	<.001	<.001				
PHN 060	40	5.0	1.6	.002	.035	.022	.002			
ATX 045	40	4.5	1.1	.141	.645	.519	<.001	.098		
ATX 090	40	4.8	1.8	.010	.118	.081	<.001	.581	.269	
ATX 180	40	4.6	1.0	.081	.461	.357	<.001	.168	.782	.407

Linear Trend ATX (with placebo) p-value*=0.097

Linear Trend ATX (without placebo) p-value*=0.952

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, Std=Standard Deviation, VS=versus.

Pairwise treatment comparison p-values are from ANOVA model: change to maximum= treatment visit subject

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**Table LYBO.15. ARCI Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) Score
6-Hour Maximum Score by Treatment
All Subjects Who Completed Study Period III**

	Change to 6 Hour Maximum			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
Treatment										
PLA	40	4.5	1.4							
DMI 100	40	4.6	1.0	.947						
DMI 200	40	5.3	2.2	.042	.048					
MPH 090	40	5.4	2.3	.018	.022	.741				
PHN 060	40	5.1	2.3	.166	.187	.509	.323			
ATX 045	40	4.7	1.4	.741	.792	.087	.042	.291		
ATX 090	40	5.2	2.1	.100	.114	.692	.468	.792	.187	
ATX 180	40	5.3	2.0	.056	.065	.895	.644	.598	.114	.792

Linear Trend ATX (with placebo) p-value*=0.033

Linear Trend ATX (without placebo) p-value*=0.151

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, Std=Standard Deviation, VS=versus.

Pairwise treatment comparison p-values are from ANOVA model: change to maximum= treatment visit subject

* Test for linear dose effect from the ANOVA model using contrast of least squares means

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Table LYBO.16. **Drug Identification Questionnaire (DIQ) Score**
Percentage of Positive Responses by Treatment
All Randomized Subjects

TREATMENT	POSSIBLE DRUG CHOICE					OPIATE ANTAGONIST %
	ANTI-DEPRESSANTS %	BENZODIAZEPINES %	DOWNERS %	HALLUCINOGENS %	OPIATES %	
PLA	4.65	9.30	4.65	0.00	0.00	4.65
DMI 100	2.33	11.63	20.93	0.00	0.00	6.98
DMI 200	0.00	9.52	23.81	4.76	0.00	7.14
MPH 090	0.00	9.52	7.14	0.00	2.38	9.52
PHN 060	0.00	4.88	9.76	0.00	0.00	9.76
ATX 045	2.33	6.98	11.63	0.00	0.00	4.65
ATX 090	2.38	7.14	26.19	2.38	0.00	11.90
ATX 180	7.32	7.32	19.51	0.00	2.44	9.76

(continued)

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**Table LYBO.16. Drug Identification Questionnaire (DIQ) Score
Percentage of Positive Responses by Treatment
All Randomized Subjects (concluded)**

TREATMENT	POSSIBLE DRUG CHOICE		
	PHENCYCLIDINE %	PHENOTHIAZINES %	STIMULANTS %
PLA	0.00	0.00	13.95
DMI 100	0.00	0.00	16.28
DMI 200	0.00	0.00	14.29
MPH 090	2.38	0.00	64.29
PHN 060	0.00	0.00	43.90
ATX 045	2.33	0.00	18.60
ATX 090	0.00	2.38	9.52
ATX 180	0.00	0.00	19.51

Abbreviations: ATX=atomoxetine, DMI=desipramine, MPH=methylphenidate, PHN=phentermine, PLA=placebo

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**Table LYBO.17. SDEQ-S Score
Percentage of Positive Responses by Treatment
All Randomized Subjects**

Treatment	SDEQ-S Items												
	SDEQS01 (%)	SDEQS02 (%)	SDEQS03 (%)	SDEQS04 (%)	SDEQS05 (%)	SDEQS06 (%)	SDEQS07 (%)	SDEQS08 (%)	SDEQS09 (%)	SDEQS10 (%)	SDEQS11 (%)	SDEQS12 (%)	SDEQS13 (%)
PLA	4.65	27.91	0.00	11.63	0.00	0.00	11.63	4.65	0.00	4.65	0.00	4.65	2.33
DMI 100	6.98	46.51	11.63	37.21	0.00	4.65	11.63	4.65	4.65	9.30	0.00	4.65	2.33
DMI 200	2.38	30.95	14.29	38.10	2.38	2.38	11.90	11.90	11.90	11.90	4.76	2.38	4.76
MPH 090	2.38	57.14	4.76	16.67	0.00	26.19	45.24	30.95	19.05	23.81	4.76	14.29	2.38
PHN 060	7.32	56.10	9.76	21.95	0.00	12.20	31.71	12.20	4.88	19.51	0.00	7.32	2.44
ATX 045	0.00	39.53	11.63	27.91	0.00	4.65	6.98	4.65	4.65	13.95	2.33	0.00	2.33
ATX 090	2.38	40.48	9.52	28.57	0.00	9.52	16.67	2.38	9.52	14.29	2.38	4.76	2.38
ATX 180	2.44	53.66	12.20	34.15	0.00	4.88	21.95	4.88	19.51	14.63	2.44	7.32	2.44

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Table LYBO.17. SDEQ-S Score
Percentage of Positive Responses by Treatment
All Randomized Subjects (concluded)

Treatment	SDEQ-S Items								
	SDEQS14 (%)	SDEQS15 (%)	SDEQS16 (%)	SDEQS17 (%)	SDEQS18 (%)	SDEQS19 (%)	SDEQS20 (%)	SDEQS21 (%)	SDEQS22 (%)
PLA	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	9.30
DMI 100	0.00	0.00	0.00	2.33	2.33	0.00	0.00	2.33	9.30
DMI 200	7.14	2.38	0.00	7.14	7.14	2.38	0.00	7.14	16.67
MPH 090	11.90	4.76	0.00	7.14	7.14	7.14	7.14	11.90	47.62
PHN 060	9.76	0.00	2.44	4.88	4.88	2.44	2.44	4.88	26.83
ATX 045	6.98	0.00	4.65	2.33	2.33	2.33	0.00	0.00	13.95
ATX 090	14.29	0.00	4.76	2.38	2.38	2.38	2.38	4.76	21.43
ATX 180	12.20	0.00	4.88	2.44	2.44	2.44	2.44	2.44	14.63

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo; SDEQ-S=Specific Drug Effect Questionnaire-Subject, SDEQS1=skin itchy, SDEQS2=relaxed, SDEQS3=nodding, SDEQS4=sleepy, SDEQS5=drunk, SDEQS6=nervous, SDEQS7=full of energy, SDEQS8=need to talk, SDEQS9=sick to your stomach, SDEQS10=stomach turning, SDEQS11=distances, colors or shapes appear changed, SDEQS12=hearing changed, SDEQS13=hallucinating and seeing lights or spots, SDEQS14=dizzy, SDEQS15=hallucinating and hearing sounds or voices, SDEQS16=hallucinating and seeing things, animals, insects or people, SDEQS17=confused, SDEQS18=afraid, SDEQS19=paranoid, SDEQS20=depressed or sad, SDEQS21=body feels different, changed or unreal, SDEQS22=surroundings seem different or unreal.

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Table LYBO.18. SDEQ-O Score
Percentage of Positive Responses by Treatment
All Randomized Subjects

Treatment	SDEQ-O Items												
	SDEQO01 (%)	SDEQO02 (%)	SDEQO03 (%)	SDEQO04 (%)	SDEQO05 (%)	SDEQO06 (%)	SDEQO07 (%)	SDEQO08 (%)	SDEQO09 (%)	SDEQO10 (%)	SDEQO11 (%)	SDEQO12 (%)	SDEQO13 (%)
PLA	0.00	2.33	44.19	4.65	20.93	0.00	0.00	0.00	20.93	4.65	0.00	0.00	2.33
DMI 100	6.98	6.98	46.51	9.30	41.86	0.00	0.00	2.33	18.60	11.63	2.33	0.00	2.33
DMI 200	4.76	11.90	57.14	11.90	50.00	2.38	2.38	0.00	16.67	9.52	0.00	0.00	0.00
MPH 090	2.38	14.29	61.90	2.38	11.90	0.00	21.43	26.19	57.14	38.10	0.00	0.00	0.00
PHN 060	4.88	17.07	56.10	7.32	24.39	2.44	17.07	19.51	41.46	24.39	2.44	0.00	2.44
ATX 045	2.33	9.30	53.49	4.65	34.88	0.00	4.65	4.65	16.28	9.30	0.00	0.00	4.65
ATX 090	0.00	9.52	45.24	9.52	38.10	0.00	4.76	4.76	7.14	7.14	2.38	0.00	2.38
ATX 180	0.00	17.07	63.41	12.20	58.54	2.44	4.88	7.32	19.51	7.32	0.00	2.44	2.44

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Table LYBO.18. SDEQ-O Score
Percentage of Positive Responses by Treatment
All Randomized Subjects (concluded)

Treatment	SDEQ-O Items								
	SDEQO14 (%)	SDEQO15 (%)	SDEQO16 (%)	SDEQO17 (%)	SDEQO18 (%)	SDEQO19 (%)	SDEQO20 (%)	SDEQO21 (%)	SDEQO22 (%)
PLA	0.00	2.33	0.00	2.33	2.33	4.65	0.00	2.33	0.00
DMI 100	0.00	2.33	2.33	0.00	0.00	2.33	2.33	0.00	0.00
DMI 200	2.38	7.14	0.00	0.00	0.00	7.14	2.38	2.38	0.00
MPH 090	0.00	4.76	4.76	9.52	9.52	7.14	7.14	16.67	0.00
PHN 060	0.00	2.44	4.88	4.88	4.88	9.76	2.44	7.32	0.00
ATX 045	2.33	6.98	2.33	6.98	6.98	11.63	0.00	2.33	6.98
ATX 090	0.00	2.38	4.76	4.76	4.76	2.38	0.00	4.76	0.00
ATX 180	0.00	4.88	2.44	7.32	7.32	0.00	0.00	2.44	0.00

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, SDEQ-O=Specific Drug Effect Questionnaire-Observer, SDEQO1=scratching, SDEQO2=withdrawn/detached, SDEQO3=relaxed, SDEQO4=nodding, SDEQO5=sleepy, SDEQO6=drunk, SDEQO7=nervous, SDEQO8=anxious, SDEQO9=talking, SDEQO10=active, SDEQO11=vomiting, SDEQO12=hallucinating (auditory), SDEQO13=hallucinating (visual), SDEQO14=hallucinating (tactile), SDEQO15=confused, SDEQO16=paranoid, SDEQO17=depressed, SDEQO18=forgetful, SDEQO19=perspiring, SDEQO20=tremulous, SDEQO21=showing red eye, SDEQO22=restless.

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Table LYBO.19. Sleep Chart Score
Mean Hours of Sleep (Scores) by Treatment
All Subjects Who Completed Study Period III

	Subject Sleep Estimate			Total Observed Sleep Time		
	N	Mean	Std	N	Mean	Std
Treatment						
PLA	40	4.5	1.6	40	4.9	1.6
DMI 100	40	4.9	1.2	40	5.6	1.2
DMI 200	40	4.9	2.0	40	5.7	1.9
MPH 090	40	4.2	1.9	40	5.1	1.8
PHN 060	40	2.3	1.9	40	2.8	2.0
ATX 045	40	4.6	1.4	40	5.1	1.5
ATX 090	40	4.7	1.4	40	5.4	1.5
ATX 180	40	4.7	1.4	40	5.4	1.4

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, Std=standard deviation.

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**Table LYBO.20. Treatment Enjoyment Assessment Questionnaire (TEAQ)
 Percentage of Subjects Selecting Each Drug
 All Subjects Who Completed Study Period III**

TRT	Frequency	Percent

PLA	3	7.89
DMI 100	2	5.26
DMI 200	3	7.89
MPH 090	12	31.58
PHN 060	6	15.79
ATX 045	1	2.63
ATX 090	2	5.26
ATX 180	3	7.89
NONE	6	15.79

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, TRT=treatment.
 Sample Size = 38

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**Table LYBO.21. Street Value Assessment Questionnaire (SVAQ)
6-Hour Maximum by Treatment
All Subjects Who Completed Study Period III**

	SVAQ			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
Treatment										
PLA	40	0.4	1.1							
DMI 100	40	1.7	3.3	.023						
DMI 200	39	1.3	3.0	.133	.446					
MPH 090	40	4.7	4.1	<.001	<.001	<.001				
PHN 060	40	2.8	3.5	<.001	.078	.012	<.001			
ATX 045	39	1.5	3.3	.057	.723	.686	<.001	.036		
ATX 090	40	1.1	2.4	.272	.236	.679	<.001	.003	.411	
ATX 180	40	1.5	3.1	.071	.635	.771	<.001	.026	.907	.477

Linear Trend ATX (with placebo) p-value*=0.166
Linear Trend ATX (without placebo) p-value*=0.958

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, Std=Standard Deviation

Pairwise treatment comparison p-values are from ANOVA model: SVAQ= treatment visit subject

* Test for linear dose effect from the ANOVA model using contrast of least squares means

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**Table LYBO.22. Summary of Treatment-Emergent Adverse Events by Decreasing Frequency
Using MedDRA Preferred Terms Ordered by System Organ Class
All Enrolled Subjects, Study Period II**

Event	PLA N=8 (%)	MPH 45mg N=8 (%)	DMI 25mg N=4 (%)	DMI 50mg N=4 (%)	DMI 75mg N=2 (%)	DMI 100mg N=2 (%)	DMI 150mg N=2 (%)	DMI 200mg N=2 (%)	ATX 45mg N=4 (%)	ATX 60mg N=4 (%)	ATX 100mg N=4 (%)	ATX 180mg N=4 (%)	TOTAL (%)
Cardiac Disorders													
Tachycardia NOS	62.5	12.5	0.0	0.0	50.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14.6
Palpitations	0.0	0.0	0.0	0.0	0.0	0.0	0.0	50.0	0.0	0.0	25.0	0.0	4.2
Ear and Labyrinth Disorders													
Tinnitus	0.0	25.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	6.3
Eye Disorders													
Eye pain	0.0	12.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	0.0	0.0	4.2
Eye irritation	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	0.0	0.0	2.1
Eye redness	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	0.0	0.0	2.1
Lacrimation increased	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	0.0	0.0	2.1
Gastrointestinal Disorders													
Dyspepsia	12.5	25.0	0.0	0.0	0.0	50.0	0.0	0.0	0.0	0.0	0.0	0.0	8.3
Dry mouth	25.0	12.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6.3
Nausea	0.0	12.5	25.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	6.3
Abdominal discomfort	0.0	12.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.1
Abdominal distension	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	0.0	2.1
Abdominal pain NOS	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	2.1
Loose stools	0.0	12.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.1
Salivary hypersecretion	0.0	0.0	0.0	25.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.1
General Disorders and Administration Site Conditions													
Fatigue	12.5	0.0	0.0	0.0	0.0	0.0	100	0.0	25.0	0.0	0.0	0.0	8.3
Feeling of relaxation	0.0	12.5	0.0	0.0	0.0	100	0.0	0.0	0.0	0.0	0.0	25.0	8.3
Sluggishness	0.0	12.5	25.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.2
Asthenia	12.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.1
Chest discomfort	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	0.0	2.1
Chest pain	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	0.0	2.1

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**Table LYBO.22. Summary of Treatment-Emergent Adverse Events by Decreasing Frequency
Using MedDRA Preferred Terms Ordered by System Organ Class
All Enrolled Subjects, Study Period II (continued)**

Event	PLA N=8 (%)	MPH 45mg N=8 (%)	DMI 25mg N=4 (%)	DMI 50mg N=4 (%)	DMI 75mg N=2 (%)	DMI 100mg N=2 (%)	DMI 150mg N=2 (%)	DMI 200mg N=2 (%)	ATX 45mg N=4 (%)	ATX 60mg N=4 (%)	ATX 100mg N=4 (%)	ATX 180mg N=4 (%)	TOTAL (%)
General Disorders and Administration Site Conditions													
Energy increased	0.0	12.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.1
Feeling abnormal	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	2.1
Feeling hot	0.0	0.0	0.0	0.0	0.0	50.0	0.0	0.0	0.0	0.0	0.0	0.0	2.1
Feeling jittery	0.0	12.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.1
Rigors	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	2.1
Injury, Poisoning and Procedural Complications													
Hypothermia	25.0	12.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	0.0	8.3
Investigations													
Blood pressure increased	50.0	12.5	0.0	25.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	25.0	16.7
Blood pressure decreased	0.0	0.0	25.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	0.0	25.0	6.3
Metabolism and Nutrition													
Anorexia	0.0	12.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.1
Neoplasms Benign and Malignant													
Neoplasm eye NOS	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	0.0	0.0	2.1
Nervous System Disorders													
Somnolence	50.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	0.0	10.4
Dysgeusia	12.5	0.0	25.0	25.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	8.3
Headache	0.0	12.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	50.0	8.3
Dizziness	0.0	0.0	0.0	0.0	50.0	0.0	0.0	0.0	0.0	0.0	0.0	50.0	6.3
Hypoaesthesia	0.0	0.0	0.0	0.0	0.0	0.0	50.0	0.0	25.0	0.0	0.0	0.0	4.2
Dizziness postural	12.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.1
Paraesthesia	0.0	12.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.1
Paraesthesia oral	0.0	12.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.1

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**Table LYBO.22. Summary of Treatment-Emergent Adverse Events by Decreasing Frequency
Using MedDRA Preferred Terms Ordered by System Organ Class
All Enrolled Subjects, Study Period II (concluded)**

Event	PLA N=8 (%)	MPH 45mg N=8 (%)	DMI 25mg N=4 (%)	DMI 50mg N=4 (%)	DMI 75mg N=2 (%)	DMI 100mg N=2 (%)	DMI 150mg N=2 (%)	DMI 200mg N=2 (%)	ATX 45mg N=4 (%)	ATX 60mg N=4 (%)	ATX 100mg N=4 (%)	ATX 180mg N=4 (%)	TOTAL (%)
Psychiatric Disorders													
Euphoric mood	12.5	50.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	50.0	14.6
Logorrhoea	0.0	25.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.2
Irritability	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	0.0	0.0	0.0	2.1
Respiratory, Thoracic and Mediastinal Disorders													
Hyperventilation	0.0	0.0	0.0	0.0	0.0	0.0	0.0	50.0	0.0	0.0	0.0	0.0	2.1
Skin and Subcutaneous Tissues Disorders													
Sweating increased	0.0	12.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.1
Vascular Disorders													
Orthostatic hypotension	0.0	12.5	0.0	0.0	0.0	0.0	0.0	100	0.0	0.0	0.0	0.0	6.3
Flushing	0.0	0.0	25.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.1
Hypotension NOS	0.0	0.0	0.0	0.0	0.0	50.0	0.0	0.0	0.0	0.0	0.0	0.0	2.1
Hypertension NOS	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Abbreviations: ATX=Atomoxetine; DMI=desipramine; MPH=methylphenidate; NOS=not otherwise specified; PHN=phentermine; PLA=placebo.
Population: All Randomized Subjects in Study Period II.
For each treatment, N represents the number of subjects taking the treatment.
The denominator for the Total column (48) is the total number of subject visits on a study treatment during the study.

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**Table LYBO.23. Summary of Treatment-Emergent Adverse Events by Decreasing Frequency
Using MedDRA Preferred Terms Ordered by System Organ Class
All Randomized Subjects, Study Period III**

	PLA	MPH	PHN	DMI	DMI	ATX	ATX	ATX	TOTAL
	90mg	60mg	100mg	200mg	45mg	90mg	180mg		
	N=43	N=42	N=43	N=43	N=43	N=43	N=42	N=42	
System Organ Class									
Event	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Cardiac Disorders									
Tachycardia NOS	20.9	23.8	18.6	18.6	20.9	25.6	14.3	16.7	19.9
Palpitations	0.0	14.3	7.0	0.0	0.0	0.0	0.0	0.0	2.6
Bradycardia NOS	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.0	0.3
Cardiac flutter	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.0	0.3
Ear and Labyrinth Disorders									
Hyperacusis	0.0	2.4	4.7	2.3	2.3	0.0	2.4	2.4	2.1
Hearing impaired	0.0	2.4	0.0	0.0	2.3	0.0	0.0	0.0	0.6
Cerumen impaction	0.0	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.3
Ear pain	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Sensation of block in ear	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.0	0.3
Tinnitus	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Eye Disorders									
Lacrimation increased	0.0	7.1	2.3	4.7	2.3	0.0	11.9	4.8	4.1
Vision blurred	2.3	11.9	4.7	0.0	0.0	0.0	0.0	0.0	2.3
Visual disturbance NOS	0.0	0.0	0.0	0.0	4.7	0.0	0.0	2.4	0.9
Asthenopia	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.0	0.3
Eye redness	0.0	0.0	0.0	0.0	0.0	2.3	0.0	0.0	0.3

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**Table LYBO.23. Summary of Treatment-Emergent Adverse Events by Decreasing Frequency
Using MedDRA Preferred Terms Ordered by System Organ Class
All Randomized Subjects, Study Period III (continued)**

System Organ Class Event	PLA N=43	MPH 90mg N=42	PHN 60mg N=43	DMI 100mg N=43	DMI 200mg N=43	ATX 45mg N=43	ATX 90mg N=42	ATX 180mg N=42	TOTAL
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Gastrointestinal Disorders									
Dry mouth	4.7	38.1	16.3	7.0	14.0	7.0	11.9	7.1	13.2
Nausea	2.3	21.4	11.6	7.0	9.3	11.6	14.3	16.7	11.7
Dyspepsia	4.7	16.7	11.6	7.0	7.0	4.7	7.1	9.5	8.5
Abdominal pain upper	0.0	2.4	2.3	0.0	0.0	0.0	4.8	2.4	1.5
Constipation	0.0	0.0	2.3	0.0	2.3	0.0	2.4	4.8	1.5
Flatulence	0.0	9.5	0.0	0.0	0.0	0.0	2.4	0.0	1.5
Vomiting NOS	0.0	2.4	0.0	2.3	0.0	0.0	7.1	0.0	1.5
Tongue disorder NOS	0.0	4.8	2.3	0.0	0.0	0.0	0.0	0.0	0.9
Abdominal pain NOS	0.0	0.0	2.3	0.0	0.0	2.3	0.0	0.0	0.6
Eructation	0.0	2.4	0.0	0.0	0.0	0.0	0.0	2.4	0.6
Loose stools	0.0	2.4	2.3	0.0	0.0	0.0	0.0	0.0	0.6
Salivary hypersecretion	0.0	2.4	0.0	0.0	2.3	0.0	0.0	0.0	0.6
Diarrhoea NOS	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.4	0.3
Faeces hard	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.4	0.3
Hypoaesthesia oral	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.3
General Disorders and Administration Site Conditions									
Feeling of relaxation	25.6	40.5	37.2	32.6	37.2	32.6	26.2	35.7	33.4
Sluggishness	2.3	7.1	4.7	7.0	16.3	4.7	7.1	11.9	7.6
Energy increased	2.3	19.0	9.3	7.0	4.7	0.0	9.5	4.8	7.0
Feeling abnormal	0.0	7.1	0.0	2.3	9.3	4.7	2.4	7.1	4.1
Fatigue	2.3	7.1	2.3	2.3	4.7	4.7	4.8	2.4	3.8
Rigors	2.3	0.0	7.0	2.3	2.3	2.3	4.8	9.5	3.8
Feeling hot	0.0	2.4	4.7	0.0	4.7	2.3	2.4	7.1	2.9
Feeling jittery	2.3	14.3	0.0	0.0	0.0	0.0	0.0	0.0	2.1
Unexpected therapeutic drug effect	0.0	2.4	2.3	0.0	7.0	0.0	2.4	2.4	2.1
Chest pain	0.0	0.0	2.3	2.3	0.0	0.0	2.4	2.4	1.2
Chest discomfort	0.0	2.4	0.0	0.0	0.0	0.0	0.0	2.4	0.6

(continued)

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**Table LYBO.23. Summary of Treatment-Emergent Adverse Events by Decreasing Frequency
Using MedDRA Preferred Terms Ordered by System Organ Class
All Randomized Subjects, Study Period III (continued)**

System Organ Class Event	PLA N=43	MPH 90mg N=42	PHN 60mg N=43	DMI 100mg N=43	DMI 200mg N=43	ATX 45mg N=43	ATX 90mg N=42	ATX 180mg N=42	TOTAL
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
General Disorders and Administration Site Conditions (continued)									
Asthenia	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Gait abnormal	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.0	0.3
Hyperpyrexia	0.0	0.0	0.0	0.0	0.0	2.3	0.0	0.0	0.3
Lethargy	0.0	0.0	0.0	0.0	2.3	0.0	0.0	0.0	0.3
Sensation of foreign body NOS	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Infections and Infestations									
Furuncle	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.4	0.3
Injury, Poisoning and Procedural Complications									
Hypothermia	2.3	0.0	2.3	2.3	2.3	0.0	0.0	2.4	1.5
Investigations									
Blood pressure increased	25.6	28.6	9.3	11.6	14.0	23.3	14.3	11.9	17.3
Heart rate irregular	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.4	0.3
Urine output increased	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Metabolism and Nutrition									
Appetite decreased NOS	0.0	7.1	4.7	4.7	2.3	0.0	2.4	0.0	2.6
Hunger	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.0	0.3
Musculoskeletal and Connective Tissues Disorders									
Arthralgia	0.0	0.0	0.0	2.3	0.0	0.0	0.0	2.4	0.6
Groin pain	0.0	0.0	2.3	0.0	0.0	0.0	0.0	2.4	0.6
Muscle weakness NOS	0.0	0.0	2.3	0.0	2.3	0.0	0.0	0.0	0.6
Sensation of heaviness	0.0	0.0	2.3	0.0	0.0	0.0	0.0	2.4	0.6
Back pain	0.0	0.0	0.0	0.0	2.3	0.0	0.0	0.0	0.3
Muscle twitching	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.4	0.3

(continued)

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**Table LYBO.23. Summary of Treatment-Emergent Adverse Events by Decreasing Frequency
Using MedDRA Preferred Terms Ordered by System Organ Class
All Randomized Subjects, Study Period III (continued)**

System Organ Class Event	PLA N=43	MPH 90mg N=42	PHN 60mg N=43	DMI 100mg N=43	DMI 200mg N=43	ATX 45mg N=43	ATX 90mg N=42	ATX 180mg N=42	TOTAL
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Nervous System Disorders									
Somnolence	20.9	14.3	18.6	39.5	39.5	27.9	33.3	38.1	29.0
Headache	7.0	16.7	9.3	14.0	16.3	4.7	11.9	19.0	12.3
Dizziness	9.3	19.0	7.0	9.3	11.6	11.6	9.5	14.3	11.4
Paraesthesia	2.3	14.3	16.3	9.3	7.0	4.7	16.7	9.5	10.0
Sensory disturbance NOS	2.3	14.3	9.3	2.3	7.0	7.0	9.5	2.4	6.7
Dysgeusia	4.7	11.9	9.3	7.0	4.7	2.3	4.8	2.4	5.9
Nodding of head	2.3	2.4	2.3	4.7	9.3	4.7	2.4	7.1	4.4
Tremor	2.3	7.1	9.3	0.0	2.3	4.7	4.8	0.0	3.8
Dysarthria	0.0	9.5	4.7	2.3	2.3	2.3	0.0	4.8	3.2
Psychomotor hyperactivity	2.3	4.8	4.7	0.0	2.3	0.0	0.0	2.4	2.1
Parosmia	4.7	2.4	0.0	0.0	0.0	2.3	2.4	2.4	1.8
Sedation	2.3	2.4	0.0	2.3	0.0	2.3	2.4	0.0	1.5
Dizziness postural	0.0	2.4	0.0	0.0	2.3	0.0	0.0	0.0	0.6
Formication	0.0	0.0	0.0	0.0	0.0	2.3	0.0	0.0	0.3
Memory impairment	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.0	0.3
Paralysis NOS	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.4	0.3
Psychiatric Disorders									
Euphoric mood	9.3	31.0	23.3	7.0	4.7	7.0	4.8	9.5	12.0
Insomnia	9.3	2.4	20.9	2.3	2.3	4.7	0.0	2.4	5.6
Logorrhoea	2.3	19.0	2.3	4.7	2.3	2.3	0.0	0.0	4.1
Nervousness	0.0	19.0	4.7	0.0	0.0	4.7	4.8	0.0	4.1
Anxiety	0.0	16.7	7.0	4.7	2.3	0.0	0.0	0.0	3.8
Decreased activity	0.0	14.3	2.3	0.0	2.3	0.0	0.0	4.8	2.9
Confusional state	0.0	2.4	2.3	0.0	2.3	2.3	0.0	4.8	1.8
Depressed mood	0.0	4.8	0.0	0.0	4.7	0.0	2.4	2.4	1.8
Hallucination, visual	2.3	0.0	2.3	2.3	0.0	2.3	2.4	2.4	1.8
Hypervigilance	2.3	2.4	4.7	2.3	2.3	0.0	0.0	0.0	1.8
Irritability	0.0	2.4	4.7	0.0	2.3	0.0	2.4	2.4	1.8
Mood alteration NOS	0.0	2.4	2.3	2.3	2.3	0.0	2.4	0.0	1.5

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**Table LYBO.23. Summary of Treatment-Emergent Adverse Events by Decreasing Frequency
Using MedDRA Preferred Terms Ordered by System Organ Class
All Randomized Subjects, Study Period III (continued)**

System Organ Class Event	PLA N=43	MPH 90mg N=42	PHN 60mg N=43	DMI 100mg N=43	DMI 200mg N=43	ATX 45mg N=43	ATX 90mg N=42	ATX 180mg N=42	TOTAL
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Psychiatric Disorders (continued)									
Inappropriate affect	2.3	4.8	0.0	0.0	0.0	2.3	0.0	0.0	1.2
Restlessness	0.0	2.4	4.7	0.0	2.3	0.0	0.0	0.0	1.2
Social avoidant behaviour	2.3	2.4	0.0	0.0	4.7	0.0	0.0	0.0	1.2
Paranoia	0.0	2.4	2.3	0.0	0.0	0.0	2.4	0.0	0.9
Affect lability	0.0	2.4	2.3	0.0	0.0	0.0	0.0	0.0	0.6
Abnormal dreams	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Agitation	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Anger	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Anxiety disorder	0.0	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.3
Bradyphrenia	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Depression	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Hallucination NOS	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.0	0.3
Hallucination, tactile	0.0	0.0	0.0	0.0	2.3	0.0	0.0	0.0	0.3
Mood swings	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Nightmare	0.0	0.0	0.0	0.0	0.0	2.3	0.0	0.0	0.3
Sleep disorder NOS	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.0	0.3
Renal and Urinary Disorders									
Dysuria	0.0	0.0	2.3	0.0	0.0	2.3	2.4	9.5	2.1
Pollakiuria	2.3	2.4	2.3	2.3	0.0	0.0	2.4	0.0	1.5
Urinary hesitation	0.0	0.0	0.0	0.0	0.0	0.0	2.4	0.0	0.3
Reproductive System and Breast Disorders									
Dysmenorrhoea*	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10.0	1.2
Vaginal discharge*	0.0	0.0	0.0	0.0	0.0	0.0	10.0	0.0	1.2
Vaginal odour*	10.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.2

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**Table LYBO.23. Summary of Treatment-Emergent Adverse Events by Decreasing Frequency
Using MedDRA Preferred Terms Ordered by System Organ Class
All Randomized Subjects, Study Period III (continued)**

System Organ Class Event	PLA N=43	MPH 90mg N=42	PHN 60mg N=43	DMI 100mg N=43	DMI 200mg N=43	ATX 45mg N=43	ATX 90mg N=42	ATX 180mg N=42	TOTAL
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Respiratory, Thoracic and Mediastinal Disorders									
Rhinorrhoea	4.7	7.1	4.7	0.0	2.3	4.7	4.8	0.0	3.5
Nasal congestion	0.0	2.4	0.0	2.3	0.0	2.3	2.4	0.0	1.2
Cough	0.0	2.4	2.3	2.3	0.0	0.0	0.0	0.0	0.9
Dry throat	0.0	2.4	2.3	0.0	2.3	0.0	0.0	0.0	0.9
Pharyngolaryngeal pain	0.0	2.4	0.0	0.0	0.0	2.3	2.4	0.0	0.9
Dyspnoea	0.0	2.4	0.0	0.0	0.0	0.0	0.0	2.4	0.6
Yawning	0.0	0.0	0.0	0.0	2.3	0.0	0.0	2.4	0.6
Hoarseness	0.0	0.0	0.0	0.0	0.0	0.0	2.4	0.0	0.3
Hyperventilation	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Nasal passage irritation	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Paranasal sinus hypersecretion	0.0	0.0	0.0	0.0	0.0	0.0	2.4	0.0	0.3
Productive cough	0.0	0.0	0.0	0.0	0.0	2.3	0.0	0.0	0.3
Sinus pain	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.0	0.3
Sneezing	0.0	0.0	0.0	0.0	0.0	0.0	2.4	0.0	0.3
Tachypnoea	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Throat irritation	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.0	0.3
Skin and Subcutaneous Tissues Disorders									
Sweating increased	2.3	9.5	7.0	2.3	0.0	0.0	0.0	4.8	3.2
Pruritus	0.0	0.0	4.7	7.0	2.3	0.0	2.4	2.4	2.3
Piloerection	0.0	2.4	0.0	2.3	0.0	0.0	2.4	2.4	1.2
Cold sweat	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Scar	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.3

(continued)

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**Table LYBO.23. Summary of Treatment-Emergent Adverse Events by Decreasing Frequency
Using MedDRA Preferred Terms Ordered by System Organ Class
All Randomized Subjects, Study Period III (concluded)**

System Organ Class Event	PLA	MPH	PHN	DMI	DMI	ATX	ATX	ATX	TOTAL
		90mg	60mg	100mg	200mg	45mg	90mg	180mg	
	N=43	N=42	N=43	N=43	N=43	N=43	N=42	N=42	
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Surgical and Medical Procedures									
Patient isolation	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.4	0.3
Vascular Disorders									
Orthostatic hypotension	11.6	16.7	23.3	16.3	20.9	14.0	9.5	28.6	17.6
Flushing	0.0	2.4	2.3	2.3	0.0	0.0	2.4	2.4	1.5
Hypertension NOS	0.0	0.0	0.0	0.0	0.0	0.0	2.4	0.0	0.3
Peripheral coldness	2.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3

Abbreviations: ATX=atomoxetine; DMI=desipramine; MPH=methylphenidate; NOS=not otherwise specified; PLA=placebo.

Population: All Randomized Subjects. For each treatment, N represents the number of subjects taking the treatment.

The denominator for the Total column (341) is the total number of subject visits on a study treatment during the study.

* Denominator based on total number of possible female visits (N=80). All female subjects (N=10) completed Study Period III (8 visits per subject).

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Table LYBO.24. Vital Signs
Summary Statistics on Baseline Change to 1.5 Hours Post Dose
Scores by Treatment for All Male Randomized Subjects

SUPINE PULSE

Treatment	Baseline			Change to 1.5 Hours Post Dose			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
PLA	33	66.6	10.6	33	-0.5	7.5							
DMI 100	33	65.5	9.5	33	-1.4	6.8	.289						
DMI 200	32	63.3	10.4	32	0.3	5.7	.489	.725					
MPH 090	32	64.9	12.1	32	8.1	11.7	<.001	<.001	<.001				
PHN 060	32	65.7	10.2	32	-0.8	7.9	.691	.513	.766	<.001			
ATX 045	33	67.9	11.4	33	-0.7	8.4	.744	.169	.317	<.001	.472		
ATX 090	32	67.3	11.9	32	1.0	8.0	.206	.022	.057	.001	.100	.345	
ATX 180	32	65.1	10.9	32	3.2	6.9	.082	.006	.016	.005	.034	.159	.638

Linear Trend ATX (with placebo) p-value*=.058
 Linear Trend ATX (without placebo) p-value*=.183

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, SD= Standard Deviation
 Pairwise treatment comparison p-values are from ANOVA model: change to 1.5 hours post dose= baseline treatment visit patient
 * Test for linear dose effect from the ANOVA model using contrast of least squares means

(continued)

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Table LYBO.24. Vital Signs
Summary Statistics on Baseline Change to 1.5 Hours Post Dose
Scores by Treatment for All Male Randomized Subjects (continued)

SUPINE SYSTOLIC BLOOD PRESSURE

Treatment	Baseline			Change to 1.5 Hours Post Dose			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
PLA	33	117.5	11.6	33	0.3	7.4							
DMI 100	33	120.2	10.7	33	1.3	8.9	.275						
DMI 200	32	116.3	12.1	32	6.2	10.2	.045	.355					
MPH 090	32	117.2	9.4	32	11.0	14.8	<.001	.004	.047				
PHN 060	32	118.7	13.3	32	21.9	22.5	<.001	<.001	<.001	<.001			
ATX 045	33	118.2	11.2	33	10.5	12.9	<.001	.004	.051	.960	<.001		
ATX 090	32	116.8	11.3	32	11.1	11.0	<.001	.004	.052	.964	<.001	.996	
ATX 180	32	117.7	11.2	32	10.5	10.0	<.001	.004	.052	.966	<.001	.994	.998

Linear Trend ATX (with placebo) p-value*=.001
 Linear Trend ATX (without placebo) p-value*=.994

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, SD= Standard Deviation
 Pairwise treatment comparison p-values are from ANOVA model: change to 1.5 hours post dose= baseline treatment visit patient
 * Test for linear dose effect from the ANOVA model using contrast of least squares means

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Table LYBO.24. Vital Signs
Summary Statistics on Baseline Change to 1.5 Hours Post Dose
Scores by Treatment for All Male Randomized Subjects (continued)

SUPINE DIASTOLIC BLOOD PRESSURE

Treatment	Baseline			Change to 1.5 Hours Post Dose			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
PLA	33	69.5	8.6	33	0.2	8.8							
DMI 100	33	69.9	9.9	33	2.8	7.8	.062						
DMI 200	32	66.7	7.5	32	4.3	6.5	.179	.618					
MPH 090	32	67.4	7.6	32	8.9	8.9	<.001	.011	.002				
PHN 060	32	69.1	9.7	32	12.7	12.3	<.001	<.001	<.001	.002			
ATX 045	33	69.8	9.2	33	5.2	8.7	.001	.156	.059	.246	<.001		
ATX 090	32	69.3	7.1	32	6.0	8.3	<.001	.086	.029	.397	<.001	.753	
ATX 180	32	69.6	8.8	32	7.4	8.4	<.001	.007	.002	.871	.004	.184	.312

Linear Trend ATX (with placebo) p-value*<.001
Linear Trend ATX (without placebo) p-value*=.168

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, SD= Standard Deviation
Pairwise treatment comparison p-values are from ANOVA model: change to 1.5 hours post dose= baseline treatment visit patient
* Test for linear dose effect from the ANOVA model using contrast of least squares means

(continued)

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Table LYBO.24. Vital Signs
Summary Statistics on Baseline Change to 1.5 Hours Post Dose
Scores by Treatment for All Male Randomized Subjects (continued)

ORTHO PULSE													
	Baseline			Change to 1.5 Hours Post Dose			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
Treatment													
PLA	33	87.5	14.2	33	-1.3	12.4							
DMI 100	33	89.8	13.2	33	-5.6	12.1	.267						
DMI 200	32	83.7	13.6	32	1.8	12.8	.740	.158					
MPH 090	32	87.5	13.2	32	10.9	15.2	<.001	<.001	<.001				
PHN 060	32	86.1	13.1	32	2.8	14.2	.231	.023	.389	.002			
ATX 045	33	91.5	15.6	33	5.6	11.6	.002	<.001	.006	.251	.055		
ATX 090	32	89.4	14.7	32	9.3	13.6	<.001	<.001	<.001	.870	.004	.323	
ATX 180	32	86.6	13.2	32	15.3	12.6	<.001	<.001	<.001	.187	<.001	.014	.139

Linear Trend ATX (with placebo) p-value*<.001
 Linear Trend ATX (without placebo) p-value*=.014

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, SD= Standard Deviation
 Pairwise treatment comparison p-values are from ANOVA model: change to 1.5 hours post dose= baseline treatment visit patient
 * Test for linear dose effect from the ANOVA model using contrast of least squares means

(continued)

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Table LYBO.24. Vital Signs
Summary Statistics on Baseline Change to 1.5 Hours Post Dose
Scores by Treatment for All Male Randomized Subjects (continued)

ORTHO SYSTOLIC BLOOD PRESSURE

Treatment	Baseline			Change to 1.5 Hours Post Dose			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
PLA	33	118.9	17.3	33	0.8	10.5							
DMI 100	33	117.7	12.6	33	3.6	10.0	.389						
DMI 200	32	118.3	15.2	32	4.8	12.5	.142	.538					
MPH 090	32	114.6	10.9	32	12.2	11.4	<.001	.010	.052				
PHN 060	32	119.1	16.9	32	13.3	19.2	<.001	<.001	<.001	.143			
ATX 045	33	117.0	15.2	33	2.4	10.6	.809	.536	.220	.002	<.001		
ATX 090	32	116.0	13.0	32	3.6	7.9	.654	.686	.311	.003	<.001	.834	
ATX 180	32	116.8	14.4	32	1.7	10.5	.935	.350	.124	<.001	<.001	.748	.597

Linear Trend ATX (with placebo) p-value*=.905
 Linear Trend ATX (without placebo) p-value*=.692

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, SD= Standard Deviation
 Pairwise treatment comparison p-values are from ANOVA model: change to 1.5 hours post dose= baseline treatment visit patient
 * Test for linear dose effect from the ANOVA model using contrast of least squares means

(continued)

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Table LYBO.24. Vital Signs
Summary Statistics on Baseline Change to 1.5 Hours Post Dose
Scores by Treatment for All Male Randomized Subjects (concluded)

ORTHO DIASTOLIC BLOOD PRESSURE

Treatment	Baseline			Change to 1.5 Hours Post Dose			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
PLA	33	79.9	10.9	33	0.8	8.3							
DMI 100	33	80.2	9.7	33	1.2	7.2	.758						
DMI 200	32	79.3	10.1	32	4.3	10.2	.054	.103					
MPH 090	32	77.5	10.1	32	9.7	7.9	<.001	<.001	.018				
PHN 060	32	80.8	11.3	32	5.8	10.0	<.001	.002	.145	.365			
ATX 045	33	78.5	9.6	33	5.6	6.7	.022	.048	.732	.041	.262		
ATX 090	32	79.5	9.1	32	3.7	7.7	.095	.172	.793	.009	.086	.545	
ATX 180	32	78.5	10.5	32	4.5	8.9	.089	.162	.820	.010	.093	.568	.972

Linear Trend ATX (with placebo) p-value*=.224
 Linear Trend ATX (without placebo) p-value*=.624

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, SD= Standard Deviation
 Pairwise treatment comparison p-values are from ANOVA model: change to 1.5 hours post dose= baseline treatment visit patient
 * Test for linear dose effect from the ANOVA model using contrast of least squares means

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Table LYBO.25. Vital Signs
Summary Statistics on Baseline Change to 1.5 Hours Post Dose
Scores by Treatment for All Female Randomized Subjects

SUPINE PULSE

Treatment	Baseline			Change to 1.5 Hours Post Dose			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
PLA	10	67.2	10.9	10	3.0	7.0							
DMI 100	10	69.8	12.1	10	-0.2	8.0	.588						
DMI 200	10	66.7	9.3	10	0.8	8.3	.582	.984					
MPH 090	10	66.6	9.9	10	13.8	11.9	<.001	<.001	<.001				
PHN 060	9	72.3	10.4	9	1.1	8.3	.643	.320	.328	.003			
ATX 045	10	69.0	11.2	10	4.2	4.7	.430	.185	.190	.004	.769		
ATX 090	10	70.8	10.4	10	5.2	6.0	.118	.037	.042	.037	.289	.431	
ATX 180	9	69.1	9.1	8	3.4	5.2	.297	.123	.126	.019	.561	.752	.673

Linear Trend ATX (with placebo) p-value*=.306
 Linear Trend ATX (without placebo) p-value*=.856

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, SD= Standard Deviation
 Pairwise treatment comparison p-values are from ANOVA model: change to 1.5 hours post dose= baseline treatment visit patient
 * Test for linear dose effect from the ANOVA model using contrast of least squares means

(continued)

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Table LYBO.25. Vital Signs
Summary Statistics on Baseline Change to 1.5 Hours Post Dose
Scores by Treatment for All Female Randomized Subjects (continued)

SUPINE SYSTOLIC BLOOD PRESSURE

Treatment	Baseline			Change to 1.5 Hours Post Dose			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
PLA	10	107.3	10.0	10	-2.5	7.8							
DMI 100	10	106.2	10.3	10	4.9	14.8	.192						
DMI 200	10	114.0	14.6	10	5.4	9.3	.041	.419					
MPH 090	10	108.8	10.3	10	8.6	17.8	.022	.307	.869				
PHN 060	9	109.7	9.7	9	15.1	14.5	<.001	.028	.162	.204			
ATX 045	10	104.8	8.2	10	5.2	10.2	.218	.941	.385	.271	.024		
ATX 090	10	107.1	12.4	10	7.3	8.6	.068	.605	.743	.607	.081	.556	
ATX 180	9	108.3	10.4	8	2.3	10.0	.538	.542	.176	.120	.009	.587	.275

Linear Trend ATX (with placebo) p-value*=.655
 Linear Trend ATX (without placebo) p-value*=.482

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, SD= Standard Deviation
 Pairwise treatment comparison p-values are from ANOVA model: change to 1.5 hours post dose= baseline treatment visit patient
 * Test for linear dose effect from the ANOVA model using contrast of least squares means

(continued)

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Table LYBO.25. Vital Signs
Summary Statistics on Baseline Change to 1.5 Hours Post Dose
Scores by Treatment for All Female Randomized Subjects (continued)

SUPINE DIASTOLIC BLOOD PRESSURE

Treatment	Baseline			Change to 1.5 Hours Post Dose			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
PLA	10	65.7	10.6	10	-1.9	6.9							
DMI 100	10	63.6	7.1	10	2.9	6.7	.182						
DMI 200	10	71.0	15.3	10	1.3	5.1	.085	.655					
MPH 090	10	66.1	9.9	10	7.8	11.7	.001	.047	.137				
PHN 060	9	65.7	8.4	9	7.6	7.6	.002	.065	.172	.924			
ATX 045	10	63.5	7.5	10	2.6	8.1	.266	.818	.506	.026	.040		
ATX 090	10	69.3	10.4	10	1.4	7.9	.070	.631	.986	.129	.166	.481	
ATX 180	9	65.3	6.8	8	3.8	5.8	.210	.995	.675	.064	.085	.825	.656

Linear Trend ATX (with placebo) p-value*=.240
 Linear Trend ATX (without placebo) p-value*=.927

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, SD= Standard Deviation
 Pairwise treatment comparison p-values are from ANOVA model: change to 1.5 hours post dose= baseline treatment visit patient
 * Test for linear dose effect from the ANOVA model using contrast of least squares means

(continued)

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Table LYBO.25. Vital Signs
Summary Statistics on Baseline Change to 1.5 Hours Post Dose
Scores by Treatment for All Female Randomized Subjects (continued)

ORTHO PULSE

Treatment	Baseline			Change to 1.5 Hours Post Dose			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
PLA	10	93.0	19.3	10	-5.0	8.9							
DMI 100	10	86.4	19.5	10	1.3	5.8	.639						
DMI 200	10	84.7	9.8	10	3.8	11.8	.313	.576					
MPH 090	10	89.1	13.7	10	6.0	14.8	.081	.197	.482				
PHN 060	9	90.8	12.6	9	5.4	15.2	.026	.077	.228	.588			
ATX 045	10	88.3	17.5	10	6.5	12.6	.084	.201	.489	.990	.581		
ATX 090	10	89.8	13.3	10	10.9	11.0	.003	.013	.058	.208	.492	.204	
ATX 180	9	86.3	10.5	8	9.6	10.5	.016	.044	.139	.400	.754	.394	.736

Linear Trend ATX (with placebo) p-value*=.019
 Linear Trend ATX (without placebo) p-value*=.507

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, SD= Standard Deviation
 Pairwise treatment comparison p-values are from ANOVA model: change to 1.5 hours post dose= baseline treatment visit patient
 * Test for linear dose effect from the ANOVA model using contrast of least squares means

(continued)

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Table LYBO.25. Vital Signs
Summary Statistics on Baseline Change to 1.5 Hours Post Dose
Scores by Treatment for All Female Randomized Subjects (continued)

ORTHO SYSTOLIC BLOOD PRESSURE

Treatment	Baseline			Change to 1.5 Hours Post Dose			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
PLA	10	106.4	12.4	10	2.3	13.1							
DMI 100	10	110.3	7.5	10	0.5	8.8	.970						
DMI 200	10	114.6	12.5	10	-0.1	9.3	.858	.827					
MPH 090	10	112.6	13.0	10	9.4	18.9	.028	.024	.045				
PHN 060	9	111.7	10.8	9	8.7	11.7	.070	.061	.102	.727			
ATX 045	10	104.2	11.9	10	6.1	5.4	.492	.475	.638	.125	.250		
ATX 090	10	108.3	9.7	10	-1.9	7.2	.492	.520	.403	.005	.014	.179	
ATX 180	9	111.1	16.2	8	-0.6	10.6	.812	.838	.683	.021	.052	.391	.694

Linear Trend ATX (with placebo) p-value*=.583
 Linear Trend ATX (without placebo) p-value*=.509

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, SD= Standard Deviation
 Pairwise treatment comparison p-values are from ANOVA model: change to 1.5 hours post dose= baseline treatment visit patient
 * Test for linear dose effect from the ANOVA model using contrast of least squares means

(continued)

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Table LYBO.25. Vital Signs
Summary Statistics on Baseline Change to 1.5 Hours Post Dose
Scores by Treatment for All Female Randomized Subjects (concluded)

ORTHO DIASTOLIC BLOOD PRESSURE

Treatment	Baseline			Change to 1.5 Hours Post Dose			VS. PLA	VS. D100	VS. D200	VS. M90	VS. PH60	VS. A45	VS. A90
	N	Mean	Std	N	Mean	Std	P-value	P-value	P-value	P-value	P-value	P-value	P-value
PLA	10	74.6	10.8	10	-4.3	5.4							
DMI 100	10	75.2	8.2	10	0.2	7.8	.177						
DMI 200	10	79.2	16.0	10	-0.4	11.6	.082	.659					
MPH 090	10	74.8	11.5	10	8.9	11.5	<.001	.003	.014				
PHN 060	9	78.1	4.0	9	1.0	3.9	.016	.252	.485	.074			
ATX 045	10	71.2	8.9	10	4.7	5.1	.031	.395	.699	.031	.750		
ATX 090	10	77.3	10.2	10	-1.7	7.6	.145	.919	.731	.005	.291	.459	
ATX 180	9	76.3	8.7	8	4.1	7.7	.019	.260	.485	.090	.980	.738	.300

Linear Trend ATX (with placebo) p-value*=.051
 Linear Trend ATX (without placebo) p-value*=.608

Abbreviations: ATX=Atomoxetine, DMI=Desipramine, MPH=Methylphenidate, PHN=Phentermine, PLA=Placebo, SD= Standard Deviation
 Pairwise treatment comparison p-values are from ANOVA model: change to 1.5 hours post dose= baseline treatment visit patient
 * Test for linear dose effect from the ANOVA model using contrast of least squares means

**Table LYBO.26. Condensed Summary of ECG Data
Mean Change from Baseline to Endpoint**

Variables Analyzed	Therapy	n	-----Baseline-----		Change to -----Endpoint-----	
			Mean	SD	Mean	SD
RR	ATX45	5	1118.264	100.747	-403.189	164.718
	ATX90	5	936.906	245.258	-266.355	187.970
	METH90	6	980.209	204.543	-247.791	172.698
	PLACEBO	5	1228.688	167.406	-412.953	101.979
	ATX180	7	1044.376	163.647	-210.447	111.354
	DES100	5	1026.513	109.527	-240.427	170.605
	DES200	6	971.090	223.628	-229.667	213.588
	PHEN60	7	935.072	147.510	-297.490	97.514
PR	ATX45	5	158.000	35.637	-2.000	10.954
	ATX90	5	166.000	16.733	-4.000	15.166
	METH90	6	147.500	16.047	-2.500	8.803
	PLACEBO	5	174.000	16.733	-12.000	13.038
	ATX180	7	168.571	14.639	0.000	11.547
	DES100	5	154.000	26.077	4.000	5.477
	DES200	6	165.000	25.100	-5.000	15.166
	PHEN60	7	148.571	12.150	-7.143	11.127
QRS	ATX45	5	88.000	4.472	-6.000	8.944
	ATX90	5	84.000	5.477	-4.000	5.477
	METH90	6	93.333	10.328	-1.667	14.720
	PLACEBO	5	92.000	8.367	0.000	7.071
	ATX180	7	90.000	8.165	0.000	5.774
	DES100	5	84.000	5.477	-2.000	4.472
	DES200	6	95.000	13.784	-3.333	5.164
	PHEN60	7	91.429	10.690	-5.714	7.868
QT	ATX45	5	430.000	33.166	-76.000	33.615
	ATX90	5	400.000	41.231	-46.000	40.373
	METH90	6	398.333	29.269	-43.333	18.619
	PLACEBO	5	430.000	20.000	-54.000	8.944
	ATX180	7	417.143	24.976	-38.571	29.114
	DES100	5	426.000	31.305	-58.000	14.832
	DES200	6	405.000	37.283	-43.333	44.572
	PHEN60	7	405.714	33.094	-64.286	20.702
QTcB	ATX45	5	407.200	25.292	13.800	35.787
	ATX90	5	417.800	23.435	16.000	24.950
	METH90	6	405.500	19.857	11.000	25.612
	PLACEBO	5	389.800	22.621	29.400	22.941
	ATX180	7	410.286	20.377	6.286	9.499
	DES100	5	422.000	40.094	-6.800	31.823
	DES200	6	415.167	32.811	5.667	24.262
	PHEN60	7	421.571	29.370	6.429	32.284
QTcF	ATX45	5	414.424	26.572	-17.241	28.758
	ATX90	5	411.172	16.749	-5.926	25.151
	METH90	6	402.697	12.798	-7.992	15.092
	PLACEBO	5	402.476	17.775	1.521	17.381
	ATX180	7	412.318	14.265	-9.298	14.891
	DES100	5	423.275	35.979	-24.338	21.189
	DES200	6	411.346	24.456	-11.396	23.751
	PHEN60	7	415.945	26.272	-19.212	27.111

(continued)

Table LYBO.26. **Condensed Summary of ECG Data**
Mean Change from Baseline to Endpoint (concluded)

Variables Analyzed	Therapy	n	-----Baseline-----		Change to -----Endpoint-----	
			Mean	SD	Mean	SD
QTCD	ATX45	5	411.862	25.974	-6.741	30.452
	ATX90	5	413.362	16.997	1.352	24.275
	METH90	6	403.606	14.102	-1.610	18.246
	PLACEBO	5	398.044	19.212	11.042	19.280
	ATX180	7	411.615	15.623	-4.128	12.598
	DES100	5	422.856	37.298	-18.330	24.574
	DES200	6	412.652	26.292	-5.779	22.672
	PHEN60	7	417.811	26.803	-10.753	28.772
HR	ATX45	5	54.000	4.796	31.600	15.915
	ATX90	5	67.800	18.144	22.600	11.845
	METH90	6	63.500	13.308	20.500	13.278
	PLACEBO	5	49.600	7.057	26.000	8.718
	ATX180	7	58.857	10.605	15.714	12.919
	DES100	5	59.000	6.481	18.600	13.088
	DES200	6	64.667	15.280	16.667	14.473
	PHEN60	7	65.571	10.518	30.000	8.307

Legend of Variable Abbreviations:

Abbrev.	Description
HR	ECG Heart Rate
PR	PR Interval
QRS	QRS Interval
QT	QT Interval
QTCB	Bazett QTC Interval
QTCD	QT/
QTCF	Fridericia QTC Interval
RR	RR Interval

Table LYBO.27. Summary of Plasma Levels (ng/ml) for the Specific Drug Given at the Visit Study Period III

	N	Mean	(SD)	Min	Max	BQL (n)
M90	41	37.2	(17.9)	6.1	74.9	0
P60	41	130.2	(50.8)	11	220	0
D100	43	7.9	(8.6)	0.7	34.9	1
D200	42	15.9	(13.7)	0.8	70.4	0
A45						
parent	43	344.7	(154.5)	49.5	833.4	0
N-atx	43	8.7	(9.4)	2.1	59.7	1
4-Hydroxy	43	3.7	(3.1)	1.4	16.4	2
A90						
parent	41	670.0	(306.3)	136.8	1773.1	0
N-atx	41	16.0	(11.7)	2.4	59.3	0
4-Hydroxy	41	6.5	(4.5)	1.2	21.0	0
A180						
parent	41	1151.3	(648.4)	148.7	3242.3	0
N-atx	41	27.6	(25.0)	1.3	133.5	0
4-Hydroxy	41	10.6	(7.7)	1.6	29.8	1

Abbreviations: 4-Hydroxy = 4-hydroxyatomoxetine; A45 = atomoxetine 45 mg; A90 = atomoxetine 90 mg; A180 = atomoxetine 180 mg; BQL = below quantifiable limits; D100 = desipramine 100 mg; D200 = desipramine 200 mg; M90 = methylphenidate 90 mg; N-atx = N-desmethyatomoxetine; Parent = atomoxetine; P60 = phentermine 60 mg; SD = standard deviation.

Summary ID# 6477(a)

Clinical Study Summary: Study B4Z-US-LYBP (Acute Therapy Phase)

**Title of Study: A Randomized, Double-Blind, Placebo-
Controlled Study of Atomoxetine Hydrochloride in
Children and Adolescents with Attention-
Deficit/Hyperactivity Disorder and Comorbid Anxiety**

Date summary approved by Lilly: 03 April 2006

Brief Summary of Results

Both primary outcomes of this study, the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) and Pediatric Anxiety Rating Scale (PARS) scores showed statistically significant improvement in patients treated with atomoxetine compared with patients treated with placebo. Results of secondary outcome, the Child Health Questionnaire-Parent-Completed Full Length (CHQ-PF50) Psychosocial Summary score, showed statistically significant improvement in patients treated with atomoxetine compared with patients treated with placebo. Other secondary outcomes also showed statistically significant improvement in the atomoxetine treatment group compared with the placebo treatment group, including the Multidimensional Anxiety Scale for Children (MASC) Self-rated Anxiety scale.

There were no patient deaths in this study. There were no statistically significant differences between treatment groups for the incidence of reasons for discontinuation. During the double-blind treatment period, 2 of 87 atomoxetine-treated patients and 1 of 89 placebo-treated patients discontinued due to an adverse event. There were 72.73% of patients in the atomoxetine treatment group and 56.25% of patients in the placebo treatment group who reported at least one Treatment-emergent adverse event (TEAE)

Title of Study: A Randomized, Double-Blind, Placebo-Controlled Study of Atomoxetine Hydrochloride in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder and Comorbid Anxiety	
Investigator(s): This multicenter study included 14 principal investigators.	
Study Center(s): This study was conducted at 14 study centers.	
Length of Study: approximately 24 months Date first patient enrolled: 17 September 2002 Date last patient completed: 28 May 2004 (acute phase) Date last patient completed: 21 September 2004 (open-label phase)	Phase of Development: 3b

Objectives:

Primary Objectives:

- To assess the efficacy of atomoxetine compared with placebo in reducing signs and symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD) and anxiety in children and adolescents as measured by (1) the Attention-Deficit/Hyperactivity Disorder Rating Scale–IV–Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) and (2) the PARS after approximately 12 weeks of double-blind treatment.

Secondary Objectives:

- to test the hypothesis that atomoxetine was superior to placebo in improving psychosocial functioning in children and adolescents with ADHD and anxiety as assessed by parental reports of change in the CHQ-PF50 and by the Family Assessment Measure-Version III (FAM-III).
- to test the hypothesis that atomoxetine improved symptoms of ADHD and anxiety in patients as measured by the Clinical Global Impressions–Overall–Severity (CGI-O-S). Improvement was measured using the Clinical Global Impressions–Overall–Improvement (CGI-O-I).
- to test the hypothesis that atomoxetine was superior to placebo in improving outcomes in social, emotional, cognitive, educational, and affiliative functioning as assessed by the Life Participation Scale for ADHD–Revised (LPS-ADHD-R).
- to test the hypothesis that atomoxetine was superior to placebo in reducing behavioral symptoms of ADHD, oppositional defiant disorder (ODD), and conduct disorder (CD) as assessed by the Attention-Deficit/Hyperactivity Disorder Symptom Checklist–4–Behavior (ADHD-SC4).
- to compare the changes in symptoms between atomoxetine and placebo treatment groups in children and adolescents with ADHD and comorbid anxiety as measured by the General Impressions Scale: Child and General Impressions Scale: Parent (GIS-C and GIS-P).
- to test the hypothesis that atomoxetine was superior to placebo in reducing the signs and symptoms of anxiety as assessed by the MASC.
- to assess the safety and tolerability of atomoxetine at total daily doses up to 1.8 mg/kg/day.

Study Design: Figure LYBP.1 presents an illustration of the study design. Study B4Z-US-LYBP was a Phase 3b, multicenter, randomized, double-blind, placebo-controlled clinical trial of atomoxetine hydrochloride in children and adolescents with ADHD and comorbid anxiety. After screening at Visit 1 and Visit 2 (Study Period I), eligible patients were randomized (at Visit 3) to double-blind treatment (Study Period II) with up to 1.8 mg/kg/day of atomoxetine or placebo for approximately 12 weeks. Patients and all site personnel were blinded to the commencement of active treatment (double-blind placebo lead-in); this information was provided to each site's Ethical Review Board by the sponsor in a separate document. Active medication was administered at Visit 4. The active treatment period was followed by an extended open-label period (Study Period III) in which all eligible patients received treatment with atomoxetine. Results of the open-label period will be published in a separate summary. Upon approval to market atomoxetine in the United States (US), the study was ended early, and no patients entered the final open-label extension phase (Study Period IV).

Number of Patients

Planned: Approximately 180 patients (90 patients atomoxetine; 90 patients placebo)

Randomized: 87 active drug, 89 placebo

Completed: Double-Blind Treatment: 66 active drug, 66 placebo

Diagnosis and Main Criteria for Inclusion: Male and female, child or adolescent patients who were at least 8 years of age, but had not yet reached their 18th birthday. Patients must have met <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</i>TM (DSM-IVTM; APA, 1994) criteria for ADHD and for at least one of the following anxiety disorders: separation anxiety disorder, generalized anxiety disorder, or social phobia. At Visit 2 and at Visit 3, patients must have had an ADHDRS-IV-Parent:Inv score that was at least 1.5 standard deviations above age and gender norms for at least one of the three following scores: Inattention Subscale score, the Hyperactivity/Impulsivity Subscale score or the Total Subscale score, and must have had a Total PARS score ≥ 15.
Study Drug, Dose, and Mode of Administration: Study Period II (double-blind): Atomoxetine initiated at 0.8 mg/kg/day for 3 days and then increased to a target dose of 1.2 mg/kg/day given twice daily as capsules (2.5-, 5-, 10-, 20-, 25-, and 40-mg strengths) from blister cards. Maximum dose was not to exceed 1.8 mg/kg/day (120 mg/day). Study Period III (open label): Data from Study Period III will be presented in a separate summary.
Reference Therapy, Dose, and Mode of Administration: Placebo: Identical in appearance and administration to study drug.
Duration of Treatment: Approximately 12 weeks Double-blind Placebo lead-in, twice daily: Approximately 2 weeks Atomoxetine, twice daily: Approximately 10 weeks Placebo, twice daily: Approximately 10 weeks
Variables: <u>Efficacy:</u> • <u>Primary:</u> ADHDRS-IV-Parent:Inv Total score and PARS Total score. • <u>Secondary:</u> CHQ-PF50 Psychosocial Summary Score; FAM-III Overall Rating Score and subscores; CGI-O-S; CGI-O-I; LPS-ADHD-R Total Score; ADHD-SC4 Scores (Peer Conflict and Oppositional Defiant); GIS-C Morning, Evening, and Daily Scores; GIS-P Morning, Evening, and Daily Scores; MASC Total Score; ADHDRS-IV-Parent:Inv Inattention and Hyperactivity/Impulsivity subscales; all remaining component scores of the CHQ-PF50; all remaining subscales of the FAM-III; remaining items of PARS; ADHD-SC4 Stimulant side effect score. <u>Safety:</u> Study Period II: Treatment differences in percentages of treatment-emergent adverse events (TEAEs); changes from baseline to endpoint for laboratory data, vital signs (including height and weight), and electrocardiogram (ECG) intervals. <u>Health Outcomes:</u> CHQ-PF50 and FAM III variables were secondary outcomes of this study as described above.
Evaluation Methods: <u>Statistical:</u> The primary efficacy variables were the PARS Total score and the ADHDRS-IV-Parent-Inv Total score. The primary efficacy analysis for each of these variables was an analysis of covariance (ANCOVA) on the mean change from baseline to last-observation-carried-forward (LOCF) endpoint scores during Study Period II. The ANCOVA model contained terms for baseline values, treatment groups, and pooled investigational sites. The primary analyses included only qualified patients. Patients were classified as qualified for the primary analysis if they showed no more than a 25% reduction on the PARS Total score during the blinded placebo lead-in between Visit 3 and Visit 4. The sample size in this study provided over 80% power to detect a difference between treatment groups of a least 3 points in mean change from baseline to endpoint PARS with a standard deviation of no more than 6 points. To control for multiplicity, the gatekeeper method was used to hold the family-wise alpha level for pre-specified comparisons for possible label inclusion to 0.05.

I Screening/ Assessment Phase			II Double-blind Treatment with *Atomoxetine or Placebo						III Open-label Treatment with Atomoxetine				IV Open-label Extension Phase a			
V1 – V2 5–28 Days (7 Days Suggested)			V3-V9 9-18 Days (14 Days Suggested)						V9 – V11 9 – 18 Days (14 Days Suggested)				V11 – V13 30 - 60 Days (45 Days Suggested)		V13 - V16 30-90 Days (60 Days Suggested)	
All Patients			Atomoxetine						Atomoxetine				Atomoxetine			
			Placebo lead-in													
			Placebo													
			*Randomization (1:1)													
Visit	1	2	*3	4	5	6	7	8	9	10	11	12	13	14	15	16

^a = This was to assure that if atomoxetine had not received marketing approval by the end of Study Period III, the open-label treatment period could be extended.

Figure LYBP.1. Illustration of study design.

Results:

Patient Disposition

Figure LYBP.2 presents patient disposition by Study Period. Of the 269 patients who entered the study, 176 were randomized to one of the two treatment groups (87 patients were randomized to the atomoxetine treatment group and 89 patients were randomized to the placebo treatment group). In all, 132 patients (66 patients from each group) completed Study Period II. There were no statistically significant differences between treatment groups for incidence of reasons for discontinuation. The most common reasons for discontinuing the study were lack of efficacy and personal conflict/other patient/caregiver decision.

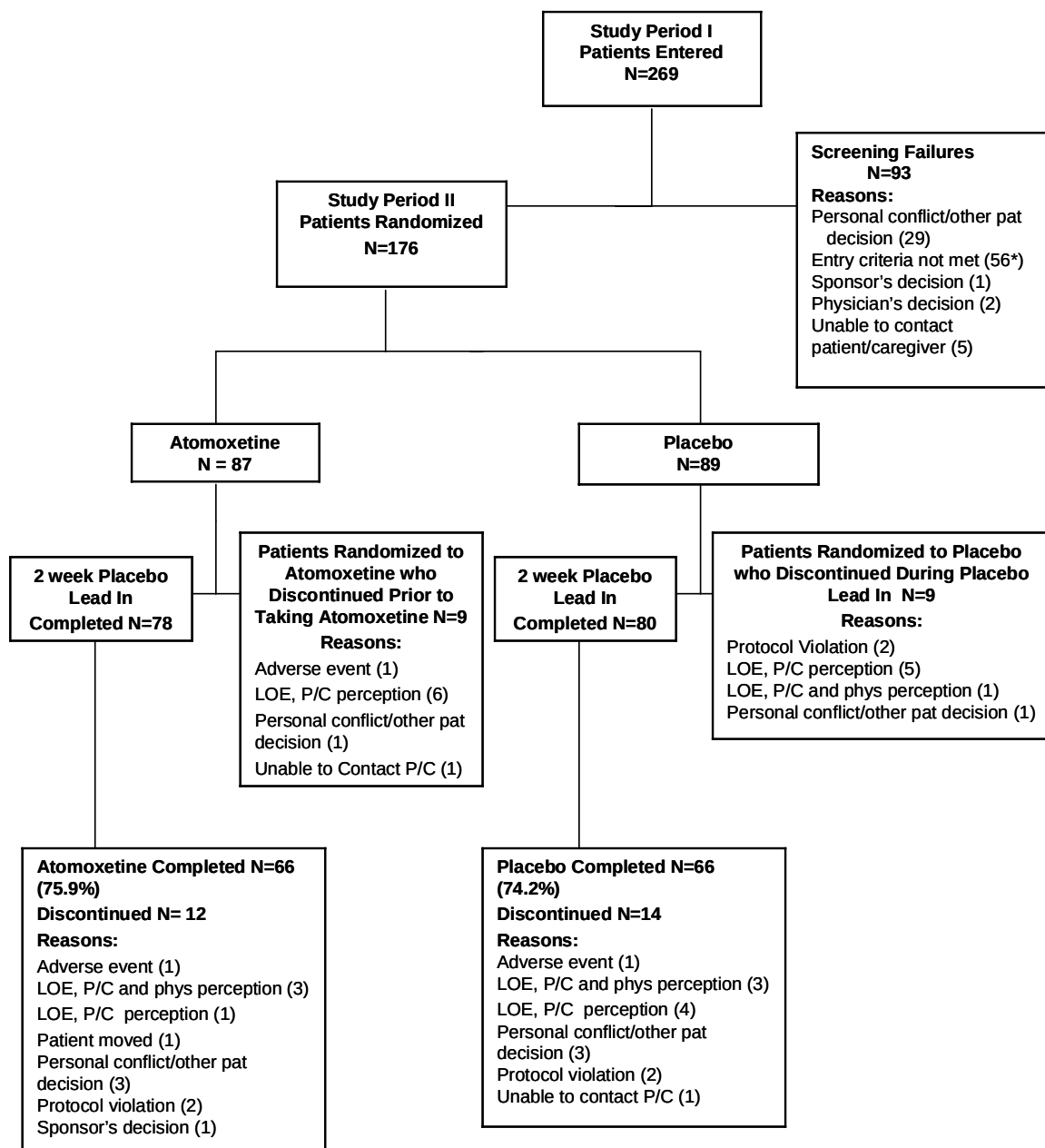


Figure LYBP.2. Patient disposition.

Abbreviations: LOE = lack of efficacy; Pat = patient; P/C = patient/caregiver; phys = physician.

* One patient did not meet entry criteria and was discontinued at Visit 1. A summary packet was not completed for this patient and, therefore, this patient was not included in the source document report.

Patient Demographics

Table LYBP.1 displays sex, ethnic origin, age, cytochrome P450 2D6 (CYP2D6) genotype, Visit 1 height, Visit 1 weight, ADHD subtype, family history variables, and prior stimulant exposure for all randomized patients.

Diagnosis of ADHD and anxiety was confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL). The K-SADS-PL is a semi-structured diagnostic interview which is used to confirm that the clinical diagnosis meets DSM-IV criteria. Table LYBP.2 summarizes K-SADS-PL present diagnosis at baseline for ADHD and comorbid diseases for all randomized patients. The two treatment groups were comparable at baseline with no statistically significant differences in ADHD or any comorbid disease. The most common comorbid anxiety disease in both the atomoxetine treatment group and the placebo treatment group was Anxiety-General Anxiety (68.97% atomoxetine, 62.92% placebo); followed by Anxiety-Separation (29.89% atomoxetine, 37.08% placebo); and Anxiety-Avoidance/Social Phobia (24.14% atomoxetine, 22.47% placebo). In addition, Behavior-Opposition Defiant was also present in 47.13% of patients in the atomoxetine treatment group and 38.20% of patients in the placebo group. Presence at baseline of other evaluated comorbid diseases was low (<6.0%) in both treatment groups.

Table LYBP.3 summarizes disease severity at baseline for all randomized patients as assessed by the ADHDRS-IV-Parent:Inv Total score, the PARS Total score, and the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) Total score. Patients had moderate to severe ADHD as indicated by the ADHDRS-IV-Parent:Inv Total t-score, which was greater than 80 (mean ADHD t-score was 81; t-score range was 57 to 112). T-scores are a transformation of the raw scores based on normative data and a patient's gender and age. The transformation gives the scale a mean of 50 and a standard deviation of 10 for a normal population.

**Table LYBP.1. Patient Demographics at Baseline
All Randomized Patients**

DEMOGRAPHIC INFORMATION		TMX		PLA		P-
		N	PERCENT	N	PERCENT	VALUE
AT LEAST ONE DOSE OF STUDY DRUG	YES	85	98.84 %	89	100.00 %	
	UNKNOWN	1	1.16 %	0	0.00 %	.491
CY2D6 PHENOTYPE	EXTN	82	95.35 %	77	89.53 %	.248
EXTN SLOW	SLOW	4	4.65 %	9	10.47 %	
DSM-IV ADHD SUBTYPE	HYP/IMP	1	1.15 %	1	1.12 %	.930
	INATTN	20	22.99 %	22	24.72 %	
	MIXED	66	75.86 %	66	74.16 %	
FAMILY HISTORY OF ADHD-FATHER	YES	25	28.74 %	26	29.21 %	
	NO	53	60.92 %	51	57.30 %	.820
	UNKNOWN	9	10.34 %	12	13.48 %	
FAMILY HISTORY OF ADHD-GRANDPARENTS	YES	10	11.49 %	8	8.99 %	
	NO	68	78.16 %	68	76.40 %	.677
	UNKNOWN	9	10.34 %	13	14.61 %	
FAMILY HISTORY OF ADHD-MOTHER	YES	22	25.29 %	21	23.60 %	

(Continued)

**Table LYBP.1. Patient Demographics at Baseline
All Randomized Patients**

DEMOGRAPHIC INFORMATION		TMX		PLA		P-
		N	PERCENT	N	PERCENT	VALUE
FAMILY HISTORY OF ADHD-MOTHER	NO	63	72.41 %	60	67.42 %	.181
	UNKNOWN	2	2.30 %	8	8.99 %	
FAMILY HISTORY OF ADHD- SIBLINGS	YES	32	36.78 %	31	34.83 %	
	NO	45	51.72 %	48	53.93 %	.842
	UNKNOWN	6	6.90 %	4	4.49 %	
	NOT APPLICABLE	4	4.60 %	6	6.74 %	
GENDER	FEMALE	33	37.93 %	29	32.58 %	.529
	MALE	54	62.07 %	60	67.42 %	
ORIGIN	AFRICAN DESCENT	4	4.60 %	3	3.37 %	.797
	CAUCASIAN	69	79.31 %	73	82.02 %	
	HISPANIC	14	16.09 %	12	13.48 %	
	OTHER	0	0.00 %	1	1.12 %	
PREVIOUS STIMULANT USE	YES	53	60.92 %	57	64.04 %	
	NO	34	39.08 %	32	35.96 %	.756

(Continued)

Atomoxetine hydrochloride

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**Table LYBP.1. Patient Demographics at Baseline
All Randomized Patients (Concluded)**

DEMOGRAPHIC INFORMATION		N	MEAN	MEDIAN	STD	MAX	MIN	P-VALUE
AGE	TMX	87	12.22	11.99	2.81	17.95	8.01	0.283
	PLA	89	11.79	11.54	2.53	17.66	8.03	
BODY MASS INDEX AT VISIT 1	TMX	87	20.61	20.16	4.47	36.05	14.66	0.218
	PLA	89	19.82	18.98	3.97	32.09	13.91	
HEIGHT AT VISIT 1	TMX	87	150.18	150.00	16.23	180.00	117.00	0.977
	PLA	89	150.12	150.00	14.18	183.00	121.00	
WEIGHT AT VISIT 1	TMX	87	47.77	43.00	16.69	90.00	22.30	0.406
	PLA	89	45.77	42.70	15.06	86.30	24.50	

**Table LYBP.2. K-SADS (Present) Diagnoses at Baseline
All Randomized Patients**

		TMX		PLA		P
		N	PERCENT	N	PERCENT	VALUE
AFFECTIVE-- ADJUSTMENT	N	86	98.85 %	88	98.88 %	1.000
	NA	1	1.15 %	1	1.12 %	
AFFECTIVE-- DYSTHYMIA	N	86	98.85 %	88	98.88 %	1.000
	NA	1	1.15 %	1	1.12 %	
AFFECTIVE-- MAJOR DEPRESSION	N	82	94.25 %	86	96.63 %	.494
	Y	5	5.75 %	3	3.37 %	
AFFECTIVE-- OTHER DISORDER	N	84	96.55 %	86	96.63 %	.855
	NA	1	1.15 %	2	2.25 %	
	Y	2	2.30 %	1	1.12 %	
AFFECTIVE-- SEASONAL PATTERN	N	86	98.85 %	87	97.75 %	1.000
	NA	1	1.15 %	1	1.12 %	
	Y	0	0.00 %	1	1.12 %	
ANXIETY-- AGORAPHOBIA	N	87	100.00 %	89	100.00 %	

(Continued)

**Table LYBP.2. K-SADS (Present) Diagnoses at Baseline
All Randomized Patients**

		TMX		PLA		P
		N	PERCENT	N	PERCENT	VALUE
ANXIETY--	N	66	75.86 %	69	77.53 %	.859
AVOID/SOCIAL						
PHOBIA	Y	21	24.14 %	20	22.47 %	
ANXIETY--	N	27	31.03 %	33	37.08 %	.429
GENERAL						
ANXIETY	Y	60	68.97 %	56	62.92 %	
ANXIETY--	N	86	98.85 %	89	100.00 %	.494
OBSESSIVE						
COMPULSIVE	Y	1	1.15 %	0	0.00 %	
ANXIETY--	N	87	100.00 %	89	100.00 %	
PANIC						
ANXIETY--	N	61	70.11 %	56	62.92 %	.341
SEPARATION						
	Y	26	29.89 %	33	37.08 %	
BEHAVIOR--	N	2	2.30 %	0	0.00 %	.243
ADHD						
	Y	85	97.70 %	89	100.00 %	
BEHAVIOR--	N	83	95.40 %	89	100.00 %	.058
CONDUCT						
DISORDER	Y	4	4.60 %	0	0.00 %	

(Continued)

**Table LYBP.2. K-SADS (Present) Diagnoses at Baseline
All Randomized Patients (Concluded)**

		TMX		PLA		P
		N	PERCENT	N	PERCENT	VALUE
BEHAVIOR--	N	46	52.87 %	55	61.80 %	.286
OPPOSITION						
DEFIANT	Y	41	47.13 %	34	38.20 %	
POST	N					
TRAUMATIC						
STRESS LIFE		87	100.00 %	89	100.00 %	

P-VALUE IS FROM FISHER'S EXACT TEST

Abbreviations: TMX = Atomoxetine, PLA = Placebo

Table LYBP.3. Severity of Disease at Baseline
ADHDRS-IV-Parent:Inv, PARS, CY-BOCS Total Scores
All Randomized Patients

		N	MEAN	MEDIAN	STD	MIN	MAX	P-VALUE
ADHDRS-INV HYP/IMP SCORE IMPUT	TREATMENT							
	TMX	87	15.97	16.00	6.05	1.00	27.00	.141
	PLA	89	17.29	18.00	6.22	0.00	27.00	
ADHDRS-INV HYP/IMP T- SCORE	TMX	87	76.81	75.66	14.66	43.69	113.56	.604
	PLA	89	77.88	79.47	13.62	41.39	112.30	
ADHDRS-INV INATTEN SCORE IMPUT	TMX	87	21.53	22.00	3.74	12.00	27.00	.605
	PLA	89	21.80	23.00	3.85	13.00	27.00	
ADHDRS-INV INATTEN T- SCORE	TMX	87	80.81	81.72	8.65	58.45	100.07	.763
	PLA	89	80.40	80.68	8.88	61.64	102.36	
ADHDRS-INV TOTAL SCORE IMPUTED	TMX	87	37.49	37.00	8.12	20.00	53.00	.184
	PLA	89	39.09	40.00	8.73	19.00	54.00	
ADHDRS-INV TOTAL T-SCORE	TMX	87	81.18	78.71	10.57	58.39	104.22	.873
	PLA	89	81.40	80.48	10.65	56.63	111.84	
CYBOC TOTAL COMPULSIVE	TMX	87	0.71	0.00	1.96	0.00	9.00	.553
	PLA	89	0.54	0.00	1.60	0.00	8.00	

(Continued)

Table LYBP.3. Severity of Disease at Baseline
ADHDRS-IV-Parent:Inv, PARS, CY-BOCS Total Scores
All Randomized Patients (Concluded)

		N	MEAN	MEDIAN	STD	MIN	MAX	P-VALUE
CYBOC TOTAL OBSESSIVE	TREATMENT							
	TMX	87	0.80	0.00	2.02	0.00	9.00	.457
	PLA	89	0.58	0.00	1.72	0.00	7.00	
PARS TOTAL SCORE	TMX	87	18.22	17.00	2.57	14.00	25.00	.577
	PLA	89	17.94	18.00	2.31	15.00	24.00	

P-VALUES ARE BASED ON AN ANOVA MODEL WITH TERMS FOR TREATMENT AND POOLED INVESTIGATOR
 Abbreviations: TMX = Atomoxetine, PLA = Placebo

Efficacy Data

In general, all enrolled patients who had a baseline and at least one postbaseline score were included in the analyses of questionnaire data, according to the treatment group to which they were randomized (whether the drug was actually taken or not). The only exception was for the primary efficacy analyses, in which only qualified patients with at least one postbaseline measure were included. Patients were classified as qualified for the primary analysis if they showed no more than a 25% reduction on the PARS Total score during the blinded placebo lead-in between Visit 3 and Visit 4. Therefore, Visit 1 through Visit 4 served as the baseline period, and Visit 5 through Visit 9 served as the endpoint period for analyses of the acute treatment phase.

Primary Outcomes

ADHDRS-IV-Parent:Inv

One primary efficacy measure was the ADHDRS-IV-Parent:Inv Total score. The Total score is the sum of the scores for each of the 18 items, with higher scores indicating greater severity of ADHD symptoms. Each item is scored on a 0 to 3 point scale (total score ranges from 0 to 54), and each item corresponds to 1 of the 18 Diagnostic and DSM-IV symptoms of ADHD.

Table LYBP.4 provides the ADHDRS-IV-Parent:Inv Total score mean change from baseline to LOCF endpoint. Results of the mean change from baseline to LOCF endpoint demonstrated statistically significantly greater improvement ($p < .001$) in the atomoxetine treatment group compared with the placebo treatment group.

**Table LYBP.4. ADHDRS-IV-Parent:Inv Total Score
Mean Change from Baseline to LOCF Endpoint
All Qualified Patients—Acute Therapy Phase**

TREATMENT GROUP		BASELINE		ENDPOINT		CHANGE		P-VAL (A)	P-VAL (B)
		N	MEAN	SD	MEAN	SD	MEAN		
TMX	55	33.85	8.94	23.38	12.23	-10.47	10.62	<.001	<.001
PLA	58	34.24	10.69	32.81	12.36	-1.43	8.26	.192	----
95% CONFIDENCE INTERVAL ON CHANGE FROM BASELINE TO LOCF ENDPOINT									
		TMX		PLACEBO		TREATMENT DIFFERENCE			
		(-14.41, -9.07)		(-5.26, -0.09)		(-12.56, -5.58)			

A) P-VALUE IS FROM STUDENT'S T-TEST.

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORE USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH POOLED INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE.

Abbreviations: TMX = Atomoxetine, PLA = Placebo

PARS

The other primary efficacy measure was the PARS Total score. The Total score for the PARS is derived by summing five of the seven severity/impairment/interference items (2, 3, 5, 6, and 7). Items 1 (overall number of anxiety symptoms) and 4 (overall severity of physical symptoms) are not included in the Total score calculation. The Total score ranges from 0 to 25 with higher scores indicating greater severity of anxiety symptoms.

As illustrated in Table LYBP.5, the mean change from baseline to LOCF endpoint for the PARS Total score demonstrated statistically significant improvement ($p=.011$) in the atomoxetine treatment group compared to the placebo treatment group.

Table LYBP.5. PARS Total Score
Mean Change from Baseline to LOCF Endpoint
All Qualified Patients—Acute Therapy Phase

LAST OBSERVATION CARRIED FORWARD SUMMARY TABLE

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VAL (A)	P-VAL (B)
		MEAN	SD	MEAN	SD	MEAN	SD		
TMX	55	17.49	2.97	11.98	5.31	-5.51	4.78	<.001	.011
PLA	58	17.03	2.52	13.88	5.43	-3.16	4.95	<.001	----
95% CONFIDENCE INTERVAL ON CHANGE FROM BASELINE TO LOCF ENDPOINT									
		TMX		PLACEBO		TREATMENT DIFFERENCE			
		(-7.56, -4.89)		(-5.26, -2.66)		(-4.01, -0.52)			

A) P-VALUE IS FROM STUDENT'S T-TEST.

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORE USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH POOLED INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE.

Abbreviations: TMX = Atomoxetine, PLA = Placebo

Secondary Outcomes:

Secondary Analyses of the ADHDRS-IV-Parent:Inv

Table LYBP.6. illustrates the results of a repeated measures analysis for the change from baseline scores at every postbaseline visit (Visit 5 through Visit 9) of the ADHDRS-IV-Parent:Inv Total score. Statistically significant improvement in the atomoxetine treatment group compared to the placebo group was demonstrated at every postbaseline visit (Visit 5, $p=.002$; Visit 6, $p<.001$; Visit 7, $p<.001$; Visit 8, $p<.001$; Visit 9, $p<.001$).

Analyses of subscale scores of the ADHDRS-IV-Parent:Inv also showed statistically significant improvement in the atomoxetine treatment group compared with the placebo treatment group on the mean change from baseline to LOCF endpoint for the Total t-score (atomoxetine [baseline 77.64, change -11.81], placebo [baseline 76.48, change -1.45], $p < .001$), the Inattention subscale score (atomoxetine [baseline 19.47, change -5.42], [placebo, baseline 19.17, change -0.36], $p<.001$); and the Hyperactivity/Impulsivity subscale score (atomoxetine [baseline 14.38, change -5.05], placebo [baseline 15.07, change -1.07], $p<.001$).

**Table LYBP.6. ADHDRS-IV-Parent:Inv Total Score
Repeated Measures Analysis
Change From Baseline
All Qualified Patients—Acute Therapy Phase**

Atomoxetine				Placebo			TREATMENT DIFFERENCE		
VISIT	LS MEAN	SE	P-VAL (C)	LS MEAN	SE	P-VAL (C)	LS MEAN	SE	P-VAL (D)
5	-6.14	1.07	<.001	-1.69	1.04	.107	-4.45	1.43	.002
6	-8.28	1.13	<.001	-1.47	1.11	.190	-6.81	1.53	<.001
7	-10.68	1.21	<.001	-2.35	1.17	.048	-8.34	1.63	<.001
8	-10.25	1.39	<.001	-2.85	1.34	.036	-7.40	1.88	<.001
9	-12.53	1.37	<.001	-2.62	1.32	.050	-9.91	1.85	<.001
95% CONFIDENCE INTERVAL ON CHANGE FROM BASELINE AT VISIT 9 USING REPEATED MEASURES									
(-15.23 , -9.82)			(-5.24 , 0.00)			(-13.57 , -6.24)			
SUMMARY OF MODEL PARAMETERS						F-VALUE	P-VAL (E)		
BASELINE						9.94	.002		
TREATMENT						31.94	<.001		
INVP						1.59	.129		
VISIT						4.05	.004		
TREATMENT*VISIT						2.34	.060		

RESULTS FOR REPEATED MEASURES BASED ON A MIXED MODEL WITH TERMS FOR BASELINE, TREATMENT, POOLED INVESTIGATOR, VISIT, AND TREATMENT BY VISIT INTERACTION USING AN UNSTRUCTURED COVARIANCE MATRIX TO MODEL CORRELATIONS WITHIN PATIENT ACROSS VISITS.

C) P-VALUES ARE FROM T-TESTS FOR A NONZERO LEAST SQUARES MEAN AT THE GIVEN VISIT.

D) P-VALUES ARE FROM T-TESTS FOR A TREATMENT DIFFERENCE IN LEAST SQUARES MEANS AT THE GIVEN VISIT.

E) P-VALUES ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE.

Abbreviations: TMX = Atomoxetine, PLA = Placebo

Secondary Analyses of the PARS

Table LYBP.7 illustrates a repeated measure analysis of the mean PARS Total Score for both treatment groups at each postbaseline visit. Statistically significant improvement was demonstrated in the atomoxetine treatment group compared with the placebo treatment group at every visit (Visit 5, p=.017; Visit 6, p=.006; Visit 7, p=.003; Visit 8, p=.003; Visit 9, p=.012).

**Table LYBP.7. PARS Total Score
Repeated Measures Analysis
Change From Baseline
All Qualified Patients—Acute Therapy Phase**

TMX				PLA			TREATMENT DIFFERENCE		
VISIT	LS MEAN	SE	P-VAL (C)	LS MEAN	SE	P-VAL (C)	LS MEAN	SE	P-VAL (D)
5	-3.33	0.50	<.001	-1.71	0.49	<.001	-1.62	0.67	.017
6	-5.18	0.57	<.001	-3.00	0.56	<.001	-2.18	0.77	.006
7	-5.96	0.59	<.001	-3.59	0.57	<.001	-2.37	0.79	.003
8	-6.80	0.67	<.001	-4.08	0.64	<.001	-2.72	0.91	.003
9	-6.40	0.68	<.001	-4.04	0.66	<.001	-2.37	0.93	.012
95% CONFIDENCE INTERVAL ON CHANGE FROM BASELINE AT VISIT 9 USING REPEATED MEASURES									
(-7.76 , -5.05)			(-5.35 , -2.72)			(-4.21 , -0.52)			
SUMMARY OF MODEL PARAMETERS						F-VALUE	P-VAL (E)		
BASELINE						0.07	.796		
TREATMENT						12.99	<.001		
INVP						3.93	<.001		
VISIT						11.11	<.001		
TREATMENT*VISIT						0.36	.838		

RESULTS FOR REPEATED MEASURES BASED ON A MIXED MODEL WITH TERMS FOR BASELINE, TREATMENT, POOLED INVESTIGATOR, VISIT, AND TREATMENT BY VISIT INTERACTION USING AN UNSTRUCTURED COVARIANCE MATRIX TO MODEL CORRELATIONS WITHIN PATIENT ACROSS VISITS.

C) P-VALUES ARE FROM T-TESTS FOR A NONZERO LEAST SQUARES MEAN AT THE GIVEN VISIT.

D) P-VALUES ARE FROM T-TESTS FOR A TREATMENT DIFFERENCE IN LEAST SQUARES MEANS AT THE GIVEN VISIT.

E) P-VALUES ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE.

Abbreviations: TMX = Atomoxetine, PLA = Placebo

Secondary Efficacy Variables:

Table LYBP.8 illustrates a summary of results of secondary efficacy variables in the hierarchical order determined in the *a priori* analysis plan. The mean baseline and endpoint scores for each outcome for both treatment groups are provided.

The CHQ-PF50 Psychosocial Summary Score mean change from baseline to LOCF endpoint, demonstrated statistically significantly greater improvement in the atomoxetine treatment group compared to the placebo treatment group. Outcome of the mean change to LOCF endpoint of the FAM-III Overall Score did not demonstrate a statistically significant difference between treatment groups. Improvement of signs and symptoms of both ADHD and anxiety as measured by the mean change to LOCF endpoint of the CGI-O-S and repeated measures analysis of the CGI-O-I at every postbaseline visit (Visit 5 through Visit 9) demonstrated statistically significantly greater improvement in atomoxetine-treated patients compared with placebo-treated patients. Results of the GIS-C (child rated) Daily Score evaluating improvement in the patient's overall well being did not show statistically significant separation between treatment groups. Results of the GIS-P (parent rated) Daily Score did demonstrate statistically significant greater improvement in the atomoxetine treated group compared to the placebo treated group. Atomoxetine-treated patients demonstrated statistically significantly greater improvement compared with placebo-treated patients in symptoms of anxiety measured by the self-rated MASC. Outcomes of social, emotional, cognitive, educational, and affiliative functioning using the LPS-ADHD-R scale also demonstrated statistically significantly greater improvement in atomoxetine-treated patients compared with placebo-treated patients. Atomoxetine-treated patients showed statistically significantly greater improvement compared with placebo-treated patients in reducing behavioral symptoms of peer conflict and oppositional defiance as demonstrated by results of the ADHD-SC4.

Atomoxetine hydrochloride

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Table LYBP.8. Secondary Efficacy Outcomes
Mean Change from Baseline to LOCF Endpoint
All Randomized Patients

Secondary Outcome	Atomoxetine Mean Scores (SD)		Placebo Mean Scores (SD)		p-Value*	Statistically Significantly Greater Improvement with Atomoxetine vs. Placebo
	Baseline	Endpoint	Baseline	Endpoint		
<u>CHQ-PF50</u> Psychosocial Summary Score	N=75 29.68 (9.89)	36.53 (12.20)	N=77 28.58 (10.07)	31.86 (11.06)	.019	Yes
<u>FAM III</u> Overall Rating Score	N=71 60.17 (3.23)	59.27 (3.68)	N=76 59.24 (3.42)	59.42 (3.47)	.187	No
<u>CGI-O-S</u>	N=78 4.28 (0.95)	3.37 (1.25)	N=78 4.37 (0.85)	4.00 (1.17)	.002	Yes
<u>CGI-O-I**</u>						
Visit 5		2.93 (.012)		3.46 (0.12)	.002	Yes
Visit 6		2.70 (.012)		3.43 (0.13)	<.001	Yes
Visit 7		2.59 (.012)		3.33 (0.12)	<.001	Yes
Visit 8		2.62 (.012)		3.27 (0.12)	<.001	Yes
Visit 9		2.64 (.013)		3.10 (0.13)	.009	Yes
<u>LPS-ADHD-R</u>	N=76		N=76			
Total Score	30.78 (9.02)	40.31 (13.07)	32.05 (9.96)	35.11 (11.57)	.002	Yes

(Continued)

Atomoxetine hydrochloride

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Table LYBP.8. Secondary Efficacy Outcomes
Mean Change from Baseline to LOCF Endpoint
All Randomized Patients (Concluded)

Secondary Outcome	Atomoxetine Mean Scores (SD)		Placebo Mean Scores (SD)		p-Value*	Statistically Significantly Greater Improvement with Atomoxetine vs. Placebo
	Baseline	Endpoint	Baseline	Endpoint		
<u>ADHD-SC4</u> Peer Conflict Score	N=77 2.83 (4.14)	2.42 (4.21)	N=76 3.28 (4.39)	4.09 (4.84)	.005	Yes
<u>ADHD-SC4</u> Oppositional Defiant Score	N=77 10.08 (5.79)	8.53 (6.13)	N=77 9.30 (5.24)	10.18 (6.19)	.003	Yes
<u>GIS-C</u> Daily Score	N=77 3.40 (1.40)	3.16 (1.58)	N=78 3.68 (1.29)	3.53 (1.37)	.252	No
<u>GIS-P</u> Daily Score	N=78 3.64 (0.90)	3.22 (1.37)	N=78 3.90 (1.05)	3.83 (1.21)	.016	Yes
<u>MASC</u> Total Score	N=75 51.76 (20.48)	47.16 (19.66)	N=76 48.33 (19.52)	50.40 (18.77)	.009	Yes

Abbreviations: ADHD-SC4 = Attention-Deficit/Hyperactivity Disorder Symptom Checklist–4–Behavior; CHQ-PF50 = Child Health Questionnaire-Parent-Completed Full Length; CGI-O-I = Clinical Global Impressions–Overall–Improvement; CGI-O-S = Clinical Global Impressions–Overall–Severity; FAM III = Family Assessment Measure-Version III; GIS-C = General Impressions Scale: Child; GIS-P = General Impressions Scale: Parent; LOCF = last-observation-carried-forward; LPS-ADHD-R = Life Participation Scale for ADHD–Revised; MASC = Multidimensional Anxiety Scale for Children; SD = standard deviation; vs - versus.

*p-values represent between treatment group differences calculated from baseline to LOCF endpoint scores using least squares means from an ANCOVA model with terms for pooled investigator, treatment, and baseline as a covariate.

**Because the CGI-O-I is a scale that assesses improvement, there were no baseline scores. A repeated measures analysis was performed at Visit 5 through Visit 9 comparing scores between treatment groups at each visit.

Health Outcomes

The CHQ-PF50 and the FAM-III Health Outcome Measures were secondary variables of the study, and the summary results are included in Table LYBP.8 above. Results of the mean change from baseline to LOCF endpoint CHQ-PF50 Psychosocial Summary Scores demonstrated statistically significantly greater improvement in the atomoxetine treatment group compared with the placebo treatment group ($p=.019$). Results of the FAM-III Overall Rating Score did not show statistically significant separation between treatment groups.

Safety

There were no patient deaths in this study. During the double-blind period, two of 87 atomoxetine-treated patients and one of 89 placebo-treated patients discontinued due to an adverse event. In the atomoxetine treatment group, one patient discontinued due to constipation, and one patient discontinued due to initial insomnia. In the placebo group, one patient discontinued because of depressive symptoms. One patient in the atomoxetine treatment group reported a serious adverse event (SAE) of aseptic meningitis in the acute phase of this study. The patient was hospitalized for treatment and fully recovered. This SAE was determined by the attending physician to be unrelated to study drug, and the patient was not discontinued from the study. The patient missed 3 days of atomoxetine treatment while in the hospital before resuming participation in the study. No SAEs were reported in the placebo treatment group.

Because patients did not receive active medication until Visit 4, the first postbaseline visit for treatment-emergent adverse events (TEAEs) or other safety measures was Visit 5. There were a number of patients who discontinued at Visit 4, before administration of active study drug. Thus, the 157 patients who continued beyond the placebo lead-in and took at least one dose of study drug were included in the analysis of adverse events. Patients who received study medication were assumed to have taken one dose, unless it was documented otherwise or missing. For inclusion into the analysis of clinical laboratory values, vital signs, and ECG data, patients were required to have a baseline measurement, at least one dose of drug, and at least one postbaseline measurement. The number of patients included within each analysis may have varied because it was possible for a patient to have baseline and postbaseline values for one safety endpoint and not for another.

Treatment-emergent adverse events (TEAEs) were grouped by occurrence using the Medical Dictionary for Regulatory Activities® (MedDRA®) terminology to classify events. The MedDRA terminology permits event terms to be grouped into different levels (for example, high level or preferred term). Table LYBP.10 summarizes TEAEs by MedDRA Preferred Term, in order of decreasing frequency. This summary only includes TEAEs that were reported in at least 5% of randomized patients who had taken at least one dose of study medication. There were 72.73% of patients in the atomoxetine treatment group and 56.25% of patients in the placebo treatment group who reported at

least one TEAE. The most commonly reported adverse events ($\geq 10\%$) for atomoxetine-treated patients were decreased appetite, headache, abdominal pain upper, and vomiting. For placebo-treated patients, the most common adverse event was headache.

Table LYBP.11 provides a summary of statistically significant differences between treatment groups in mean change from baseline to LOCF endpoint for laboratory analytes. One patient had aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) enzyme levels above the upper limit of normal (U/L) range at Visit 9 (the last visit in the acute phase); (AST, 91.0 U/L; ALT 125.0 U/L). Upon examination of this patient's data during the open-label phase of this trial (Visit 10 through Visit 13), enzyme levels were still elevated at Visit 10 (AST, 92.0 U/L; ALT 118.0 U/L), but spontaneously returned to near-normal limits by Visit 13 (AST, 48 U/L; ALT 40.0 U/L). All data from the open-label phase of Study LYBP will be published in a separate summary.

Table LYBP.12 provides a summary of statistically significant differences between treatment groups in mean change from baseline to LOCF endpoint for ECGs, vital signs and weight.

Table LYBP.10. Treatment-Emergent Adverse Events (Occurring in $\geq 5\%$ of Drug-Treated Patients) by MedDRA Preferred Terms, Decreasing Frequency, All Randomized Patients Who Took At Least One Dose of Study Drug Acute Therapy Phase

Event Classification	ATX		PLA		TOTAL		Fisher's Exact P-value
	N= (77)		N= (80)		N= (157)		
	n	%	n	%	n	%	
Patients with >=1 TESS	56	72.73 %	45	56.25 %	101	64.33 %	.045
Patients with no TESS	21	27.27 %	35	43.75 %	56	35.67 %	
Decreased appetite	11	14.29 %	3	3.75 %	14	8.92 %	.025
Headache	11	14.29 %	7	8.75 %	18	11.46 %	.323
Abdominal pain upper	9	11.69 %	4	5.00 %	13	8.28 %	.155
Vomiting	8	10.39 %	4	5.00 %	12	7.64 %	.241
Irritability	5	6.49 %	3	3.75 %	8	5.10 %	.490
Nasopharyngitis	5	6.49 %	5	6.25 %	10	6.37 %	1.000
Nausea	5	6.49 %	2	2.50 %	7	4.46 %	.270
Cough	4	5.19 %	5	6.25 %	9	5.73 %	1.000
Influenza	4	5.19 %	1	1.25 %	5	3.18 %	.204
Sinusitis	4	5.19 %	3	3.75 %	7	4.46 %	.716

(Continued)

Table LYBP.10. Treatment-Emergent Adverse Events (Occurring in $\geq 5\%$ of Study Drug-Treated Patients) by MedDRA Preferred Terms, Decreasing Frequency, All Randomized Patients Who Took At Least One Dose of Study Drug Acute Therapy Phase (Concluded)

Event Classification	ATX		PLA		TOTAL		Fisher's Exact P-value
	N= (77)		N= (80)		N= (157)		
	n	%	n	%	n	%	
Nasal congestion	3	3.90 %	7	8.75 %	10	6.37 %	.329
Pharyngolaryngeal pain	3	3.90 %	4	5.00 %	7	4.46 %	1.000

P-VALUES ARE BASED ON FISHER'S EXACT TEST
 Abbreviations: TMX = Atomoxetine, PLA = Placebo

Table LYBP.11. Laboratory Analysis with Statistically Significant Differences Between Treatment Groups in Mean Change from Baseline to LOCF Endpoint for Laboratory Analytes All Randomized Patients Who Took At Least One Dose of Study Drug Acute Therapy Phase

Analyte	Treatment Group	N	Baseline		Change		Overall p-Value*	Overall Ranked p-Value**
			Mean	SD	Mean	SD		
Albumin	Atomoxetine	71	44.75	2.52	0.42	2.80	.012	.071
	Placebo	70	44.30	3.09	-0.49	3.08		
ALT/SGPT	Atomoxetine	71	18.80	8.73	-0.39	14.12	.384	.029
	Placebo	70	17.43	6.11	1.96	7.56		
Creatine Phosphokinase	Atomoxetine	71	135.72	81.34	-7.21	76.13	.178	.026
	Placebo	70	116.44	54.95	16.03	76.93		
Creatinine	Atomoxetine	72	51.25	11.76	2.74	10.48	.042	.239
	Placebo	70	47.13	10.84	0.89	9.61		
Total Protein	Atomoxetine	72	72.51	4.69	1.56	3.97	.002	.008
	Placebo	70	72.44	4.70	-0.37	4.10		

Abbreviations: ALT/SGPT = alanine transaminase/serum glutamic pyruvic transaminase, ANCOVA = analysis of covariance, ANOVA = analysis of variance, LOCF = last-observation-carried-forward, SD = standard deviation

* Overall p-value is based on an ANCOVA model with terms for baseline, treatment, and pooled investigator using raw data.

** Overall Ranked p-value is based on an ANOVA model with terms for treatment and pooled investigator using ranked data.

Table LYBP.12. ECG, Vital Signs, and Weight with Statistically Significant Differences Between Treatment Groups in Mean Change from Baseline to LOCF Endpoint
All Randomized Patients Who Took At Least One Dose of Study Drug
Acute Therapy Phase

Vital Sign and ECG	Treatment Group	N	Baseline		Change		p-Value*
			Mean	SD	Mean	SD	
ECG Heart Rate	Atomoxetine	73	76.04	12.88	5.68	11.11	<.001
	Placebo	76	77.79	10.59	-0.68	9.97	
ECG RR Interval	Atomoxetine	73	812.25	145.48	-58.49	109.10	<.001
	Placebo	76	785.47	106.81	5.69	104.04	
ECG QT Interval	Atomoxetine	73	361.78	27.50	-10.82	19.49	<.001
	Placebo	76	362.24	24.53	3.29	20.03	
Fridericia QTC Interval	Atomoxetine	73	389.11	21.08	-2.28	18.27	.002
	Placebo	76	393.36	19.37	2.66	20.29	
Database Corrected QTC Interval	Atomoxetine	73	394.08	21.95	-0.68	19.74	.016
	Placebo	76	398.99	19.74	2.54	21.67	
Diastolic BP	Atomoxetine	77	62.96	7.71	3.40	8.51	.046
	Placebo	78	63.69	6.51	1.23	7.22	
Weight	Atomoxetine	77	49.58	17.43	-0.55	2.25	<.001
	Placebo	78	47.03	15.03	1.39	1.69	
Pulse	Atomoxetine	77	78.69	10.74	6.84	11.75	<.001
	Placebo	78	80.65	10.08	-1.90	12.96	

Abbreviations: ANCOVA = analysis of covariance, BP = blood pressure, ECG = electrocardiogram,

LOCF = last-observation-carried-forward, SD = standard deviation.

* p-value is from baseline to LOCF endpoint scores using least squares means from an ANCOVA model.

Summary ID# 6477b

Clinical Study Summary: Study B4Z-US-LYBP (Open-Label Phase)

A Randomized, Double-Blind, Placebo-Controlled Study of Atomoxetine Hydrochloride in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder and Comorbid Anxiety

Date summary approved by Lilly: 18-October-2007

Brief Summary of Results

The outcomes of the primary and secondary objectives of the randomized, double-blind, placebo-controlled phase of this study (acute therapy phase) were posted in a separate Clinical Study Summary ID# 6477a. Presented here are data results collected from the optional open-label extension phase of Study B4Z-US-LYBP, which allowed enrolled patients to receive atomoxetine hydrochloride (hereafter referred to as atomoxetine) until it became commercially available in the United States (US). The results of the open-label extension phase are as follows:

- Results of mean change from baseline to endpoint of both primary efficacy measures—the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) Total score and the Pediatric Anxiety Rating Scale (PARS) Total score—computed for the open-label phase showed statistically significant attention-deficit/hyperactivity disorder (ADHD) and anxiety symptom improvement.

- The mean change from baseline to last-observation-carried-forward (LOCF) endpoint on the ADHDRS-IV-Parent:Inv Total score and the PARS Total score by original randomization group did not demonstrate a statistically significant difference between groups, while the within-group analysis was statistically significant.
- Analyses of secondary efficacy measures showed statistically significant symptom improvement in mean change from baseline to endpoint for the following: Child Health Questionnaire–Parent Form 50 (CHQ-PF50), Multidimensional Anxiety Scale for Children (MASC) Total score, Clinical Global Impressions – Overall-Severity (CGI-O-S), Life Participation Scale for ADHD – Revised (LPD-ADHD-R), ADHD Symptom Checklist - 4 (ADHD-SC4) for both Conflict and Oppositional Defiant Scores, and General Impressions Scale: Child and Parent Daily Scores (GIS-C and GIS-P). The Family Assessment Measure, Version III (FAM-III) Overall Rating score was not found to be statistically significant.
- There were no deaths in this study. During the open-label phase, 4 patients discontinued the study due to an adverse event (AE). A total of 77 (58.8%) patients experienced at least 1 treatment-emergent adverse event (TEAE). The most common reported TEAEs ($\geq 5\%$) were: headache (14; 10.7%), nasopharyngitis (13; 9.92%), upper abdominal pain (10; 7.63%), decreased appetite (10; 7.63%), and nausea (8; 6.11%).

Title of Study: A Randomized, Double-Blind, Placebo-Controlled Study of Atomoxetine Hydrochloride in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder and Comorbid Anxiety	
Investigator(s): This multicenter study included 14 principal investigators.	
Study Center(s): This study was conducted at 14 study centers in 1 country.	
Length of Study (open-label phase): Approximately 21 months	Phase of Development: 3b
Open-label study phase: Date first patient entered: 01 December 2002 Date last patient completed: 21 September 2004	
Objectives: The objectives of this study were evaluated during the double-blind, placebo-controlled, acute therapy phase, and the results were published in a separate summary (CT# 6477a). During the open-label extension phase, some efficacy measures were evaluated by prior treatment group to examine attention-deficit/hyperactivity disorder (ADHD) and anxiety symptom improvement with atomoxetine treatment in patients who had been randomized to placebo during the acute phase. Continuation of symptom improvement during the open-label extension phase was also evaluated in patients who had been randomized to the atomoxetine treatment group during the acute phase. Safety measures were evaluated for all patients who entered the open-label extension phase and took at least 1 dose of study drug.	
For Study Period III (open-label extension phase), the objectives evaluated were: <u>Primary:</u> - to assess the efficacy of atomoxetine compared with placebo in reducing signs and symptoms of ADHD and anxiety in children and adolescents as measured by Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) Total score and Pediatric Anxiety Rating Scale (PARS) Total score. <u>Secondary:</u> - to test the hypothesis that atomoxetine was superior to placebo in improving psychosocial functioning in children and adolescents with ADHD and anxiety as assessed by parental reports of change in the Child Health Questionnaire–Parent-Completed Full Length (CHQ-PF50) and Family Assessment Measure, Version III (FAM-III). - to test the hypothesis that atomoxetine improved symptoms of ADHD and anxiety in patients as measured by the Clinical Global Impressions–Overall-Severity (CGI-O-S). Improvement was measured using the Clinical Global Impressions–Overall-Improvement (CGI-O-I). - to test the hypothesis that atomoxetine was superior to placebo in improving outcomes in social, emotional, cognitive, educational, and affiliative functioning as assessed by the Life Participation Scale for ADHD-Revised (LPS-ADHD-R). - to test the hypothesis that atomoxetine was superior to placebo in reducing behavioral symptoms of ADHD, oppositional defiant disorder (ODD), and conduct disorder (CD) as assessed by the Attention-Deficit/Hyperactivity Disorder Symptom Checklist-4-Behavior (ADHD-SC4). - to compare the changes in symptoms between atomoxetine and placebo treatment groups in children and adolescents with ADHD and comorbid anxiety as measured by the General Impressions Scale-Child (GIS-C) and General Impressions Scale-Parent (GIS-P). - to test the hypothesis that atomoxetine was superior to placebo in reducing the signs and symptoms of anxiety as assessed by Multidimensional Anxiety Scale for Children (MASC). - to assess the safety and tolerability of atomoxetine at total daily doses up to 1.8 mg/kg/day.	
Study Design: The acute treatment phase of Study LYBP was a Phase 3b, multicenter, randomized, double-blind, placebo-controlled clinical trial of atomoxetine in children and adolescents with ADHD and comorbid anxiety (Summary CT# 6477a). The acute treatment phase was followed by an extended open-label phase (Study Period III and Study Period IV) for all eligible patients to receive treatment with atomoxetine until commercially available in the United States (US). Because atomoxetine became	

commercially available in the US during the study, Study Period III ended early and Study Period IV did not occur. This report summarizes the results of the open-label phase of the study (Study Period III).
Number of Patients: Study Period III (open-label): Entered Open-Label Phase: 132 (original randomization: 66 atomoxetine, 66 placebo) Completed Open-Label Phase: 0 (Study ended early)
Diagnosis and Main Criteria for Inclusion: Male and female child or adolescent patients who were at least 8 years of age but had not yet reached their 18th birthday. Patients must have met the <i>Diagnostic and Statistical Manual of Mental Disorders</i>, 4th Edition (DSM-IV; APA, 1994) criteria for ADHD and for at least 1 of the following anxiety disorders: separation anxiety disorder, generalized anxiety disorder, or social phobia. At Visit 2 and Visit 3, patients must have had an ADHDRS-IV-Parent:Inv score at least 1.5 standard deviations above age and gender norms for at least 1 of the 3 following scores: Inattention Subscale score, the Hyperactivity-Impulsivity Subscale score, or the Total Subscale score. They also must have had a total PARS score ≥ 15. To be eligible to continue into Study Period III (the open-label extension phase), patients must have completed Study Period II (the acute treatment phase).
Test Product, Dose, and Mode of Administration: Study Period III (open-label): atomoxetine initiated at 0.8 mg/kg/day for 3 days and then increased to a target dose of 1.2 mg/kg/day, given twice daily as capsules (2.5-, 5-, 10-, 20-, 25-, and 40-mg strengths) from blister cards. Maximum dose was not to exceed 1.8 mg/kg/day (120 mg/day).
Reference Therapy, Dose, and Mode of Administration: None in the open-label phase.
Duration of Treatment: Study Period III (open-label): Patients were to receive atomoxetine until it became commercially available in the US.
Variables: Study Period III (open-label): The baseline was the last of Visit 4 through Visit 9 in Study Period II. The endpoint measure was defined as the last-observation-carried-forward (LOCF) collected during Study Period III. <u>Efficacy:</u> <u>Primary:</u> ADHDRS-IV-Parent:Inv Total score and PARS Total score. <u>Secondary:</u> CHQ-PF50 Psychosocial Summary score; FAM-III Overall Rating score; CGI-O-S; CGI-O-I; LPS-ADHD-R Total score; ADHD-SC4 Behavior scores (Peer Conflict and Oppositional Defiant); GIS-C Daily scores; GIS-P Daily scores; MASC Total score; ADHDRS-IV-Parent:Inv Inattention and Hyperactivity-Impulsivity subscales; all remaining component scores of the CHQ-PF50. <u>Safety:</u> Treatment differences in percentages of treatment-emergent adverse events (TEAEs); changes from baseline to endpoint for laboratory data, vital signs (including height and weight), and electrocardiogram (ECG) intervals. <u>Health Outcomes:</u> CHQ-PF50 and FAM-III variables were secondary outcomes as described above.
Evaluation Methods: Statistical: The primary efficacy variables (the ADHDRS-IV-Parent:Inv Total score, PARS Total score, CGI-O-I, and CGI-O-S) were analyzed for mean change from baseline (by original randomization) to LOCF endpoint. Safety: Mean change from baseline to LOCF endpoint values were evaluated for laboratory analytes, vital signs, and ECGs. Values from the last visit with nonmissing data from Visit 4 through Visit 9 of all enrolled patients who entered the open-label phase were used to compute mean baseline values.

Results

Disposition

A total of 132 patients entered the open-label phase (Study Period III, beginning at Visit 10). During the study, atomoxetine became commercially available in the US, and the study ended early; therefore, no patients completed Study Period III, and Study Period IV did not occur. Additionally, most patients (101; 76.52%) who entered the open-label phase completed Visit 10 through Visit 13 and discontinued because of sponsor decision (Table LYBP.1). Other reasons for discontinuation from the study included patient moved (1; 0.76%); unable to contact patient/caregiver (5; 3.79%); physician decision (1; 0.76%); personal conflict or other patient/caregiver decision (7; 5.30%); protocol violation (4; 3.03%); lack of efficacy, patient/caregiver perception (7; 5.30%); lack of efficacy, patient/caregiver and physician perception (2; 1.52%); and adverse events (4; 3.03%).

Table LYBP.1. Reasons for Discontinuation (N = 132)

Reason for Discontinuation	n	Percentage
Adverse event	4	3.03
Patient moved	1	0.76
Unable to contact patient/caregiver	5	3.79
Sponsor decision	101	76.52
Physician decision	1	0.76
Personal conflict or other patient/caregiver decision	7	5.30
Protocol violation	4	3.03
Lack of efficacy, physician perception	0	0
Lack of efficacy, patient/caregiver perception	7	5.30
Lack of efficacy, patient/caregiver and physician perception	2	1.52
Death	0	0
Study Period 3 completed	0	0
Protocol completed	0	0

Abbreviations: N = total number of patients; n = number of patients with same discontinuation reason.
Population: All patients who entered the open-label phase.

Patient Demographics

Table LYBP.2 and Table LYBP.3 provides patient demographic information. Of the 132 patients who entered the open-label phase of the study, 46 (34.85%) were female and 86 (65.15%) were male, 102 (77.27%) were Caucasian, 50 (37.88%) had no prior stimulant exposure, and 9 (6.98%) were determined by genotyping to be slow metabolizers of cytochrome P450 2D6 (CYP2D6). The patients ranged in age from 8.01 years to 17.95 years, and the mean age was 12.23 years. All patients who entered the open-label phase had ADHD and 1 or more of the following comorbid anxiety disorders: general anxiety (85; 64.39%), and/or social phobia (32; 24.24%), and/or separation disorder (45; 34.09%). One patient also had obsessive-compulsive disorder (OCD). Most patients (71.21%) met the criteria for the Combined ADHD subtype. Of the remaining patients, 27.27% met the criteria for the predominantly Inattentive ADHD subtype, and 1.52% met the criteria for the predominantly Hyperactive-Impulsive ADHD subtype.

Table LYBP.2. Patient Demographics History

Demographic Information	N	Percentage
At least 1 dose of study drug		
Yes	131	99.24
Unknown	1	0.76
CYP2DP Phenotype		
Extensive	120	93.02
Slow	9	6.98
DSM-IV ADHD Subtype		
Hyperactive/impulsive	2	1.52
Inattentive	36	27.27
Mixed	94	71.21
Family History of ADHD – Father		
Yes	35	26.52
No	83	62.88
Unknown	14	10.61
Family History of ADHD – Grandparents		
Yes	11	8.33
No	103	78.03
Unknown	18	13.64
Family History of ADHD – Mother		
Yes	32	24.24
No	92	69.70
Unknown	8	6.06
Family History of ADHD – Siblings		
Yes	49	37.12
No	66	50.00
Unknown	8	6.06
Not Applicable	9	6.82
Gender		
Female	46	34.85
Male	86	65.15
Origin		
African Descent	5	3.79
Caucasian	102	77.27
Hispanic	24	18.18
Other	1	0.76
Previous Stimulant Use		
Yes	82	62.12
No	50	37.88

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; N = Number of patients.
Population: All patients who entered the open label period.

**Table LYBP.3. Patient Demographics
Vital Signs**

Demographic Information	N	Mean	Median	STD	MAX	MIN
Age	132	12.23	12.20	2.64	17.95	8.01
Body Mass Index at Visit 1	132	20.44	19.52	4.44	36.05	13.91
Height at Visit 1 (cm)	132	151.41	151.00	14.97	183.00	117.00
Weight at Visit 1 (kg)	132	47.96	44.50	15.86	90.00	22.30

Abbreviations: N = Number of patients; MAX = Maximum; MIN = Minimum; STD = Standard Deviation

Population: All patients who entered the open label period.

Primary Efficacy Outcomes

Table LYBP.4 summarizes the changes from baseline to LOCF endpoint for the ADHDRS Total score and the PARS Total score evaluated during the open-label phase. Mean change scores included all patients who entered the open-label phase from both original randomization groups. Results of these analyses demonstrated a statistically significant mean reduction in scores from baseline to endpoint on both primary measures ADHDRS-IV-Parent:Inv Total score and PARS Total score.

Table LYBP.4. ADHDRS-IV-Parent:Inv Total Score and PARS Total Score Mean Change from Baseline to LOCF Endpoint

Measure	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	p-Value^a
ADHDRS Total Score	130	25.76 (12.65)	19.94 (10.87)	-5.82 (11.53)	<.001
PARS Total Score	130	11.47 (5.83)	8.42 (5.46)	-3.05 (5.75)	<.001

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored; LOCF = last-observation-carried-forward; N = number of patients; PARS = Pediatric Anxiety Rating Scale; SD = standard deviation.

^a p-Values are from Student's t-tests.

Population: All patients who entered the open-label phase.

Table LYBP.5 provides a summary of results for the primary efficacy outcomes during the open-label phase by original randomization group. The mean change from baseline to LOCF endpoint on the ADHDRS-IV-Parent:Inv Total score and the PARS Total score by original randomization group did not demonstrate a statistically significant difference between groups, while the within-group analysis was statistically significant.

**Table LYBP.5. ADHDRS-IV-Parent:Inv Total Score and PARS Total Score
Mean Change from Baseline to LOCF Endpoint
Computed by Original Randomization Group**

Measure	Acute Treatment	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	Within-Group p-Value ^a	Between-Group p-Value ^b
ADHDRS Total Score	ATX	65	21.18 (11.77)	17.98 (9.30)	-3.20 (10.30)	.015	.894
	PLA	65	30.34 (11.89)	21.90 (11.98)	-8.44 (12.16)	<.001	
PARS Total Score	ATX	65	10.68 (5.62)	7.92 (5.35)	-2.75 (6.02)	<.001	.553
	PLA	65	12.26 (5.97)	8.91 (5.57)	-3.35 (5.50)	<.001	

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale–IV–Parent Version: Investigator-Administered and Scored; ATX = atomoxetine; N = number of patients; PARS = Pediatric Anxiety Rating Scale; PLA = placebo; SD = standard deviation.

^a p-Values are from Student's t-tests.

^b Between-treatment-group p-values are from baseline to LOCF endpoint scores using least-squares means from an ANCOVA model with terms for pooled investigator, treatment, and baseline as covariates.

Population: All patients who entered the open-label phase.

Secondary Efficacy Outcomes

Table LYBP.6 summarizes the changes from baseline to LOCF endpoint for the secondary efficacy outcomes evaluated during the open-label phase. Mean change scores include all patients from both original randomization groups who entered the open-label phase and had a baseline and a postbaseline score. Symptom improvement was observed on all secondary outcomes prespecified in the protocol except the FAM-III Overall Rating Total score. These results are similar to those seen in the acute study phase in patients who were treated with atomoxetine (CT# 6477a).

The results of the MASC Total score mean change from baseline to LOCF endpoint analysis, evaluated by original randomization group, also demonstrated statistically significant improvement in symptoms of anxiety in both treatment groups (placebo $p<.001$, atomoxetine $p=.005$), supporting the results demonstrated in the PARS Total score.

The overall efficacy response rates were defined as $\geq 25\%$ decrease in ADHD symptoms as measured by an ADHDRS-IV Parent:Inv Total score using the last value of Visit 4 through Visit 9 for baseline, a Clinical Global Impressions–Overall Improvement (CGI-O-I) score ≤ 2 at endpoint, and a Clinical Global Impressions–Overall Severity (CGI-O-S) score ≤ 2 at endpoint. The CGI-O-I scores yielded a large percentage (72.88% placebo, 75% atomoxetine) of responders, and results were similar between treatment groups ($p=.834$). The ADHDRS-IV-Parent:Inv Total score yielded a larger percentage of responders (56.92%) in patients who had been in the placebo treatment group during the

acute treatment phase compared with the percentage of responders (32.81%) who had been in the atomoxetine treatment group during the acute treatment phase ($p=.008$). The CGI-O-S score percentage of responders was similar between treatment groups ($p=.190$: 33.33% placebo, 45.61% atomoxetine).

**Table LYBP.6. Secondary Efficacy Outcomes
Mean Change from Baseline to LOCF Endpoint**

Secondary Outcome	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	p-Value^a
CHQ-PF50 Psychosocial Summary Score	115	35.48 (10.77)	39.82 (11.84)	4.34 (12.07)	<.001
FAM-III Overall Rating Score	107	59.34 (3.85)	58.82 (2.81)	-0.52 (3.59)	.139
CGI-O-S	117	3.56 (1.21)	2.87 (1.09)	-0.69 (1.14)	<.001
CGI-O-I ^b	115	N/A	2.08 (0.97)	N/A	N/A
LPS-ADHD-R Total Score	116	38.22 (12.20)	42.75 (13.26)	4.53 (15.81)	.003
ADHD-SC4 Peer Conflict Score	116	2.88 (4.17)	2.09 (3.63)	-0.78 (3.15)	.008
ADHD-SC4 Oppositional Defiant Score	116	8.74 (5.67)	7.61 (5.43)	-1.13 (5.46)	.027
GIS-C Daily Score	130	3.17 (1.41)	2.83 (1.34)	-0.34 (1.50)	.011
GIS-P Daily Score	130	3.32 (1.17)	2.75 (1.20)	-0.58 (1.51)	<.001
MASC Total Score	115	47.59 (19.48)	41.88 (16.97)	-5.72 (13.11)	<.001

Abbreviations: ADHD-SC4 = Attention-Deficit/Hyperactivity Disorder Symptom Checklist-4-Behavior; CGI-O-I = Clinical Global Impressions–Overall Improvement; CGI-O-S = Clinical Global Impressions–Overall Severity; CHQ-PF50 = Child Health Questionnaire Parent Form 50 FAM-III = Family Assessment Measure, Version III; GIS-C = General Impressions Scale–Child; GIS-P = General Impressions Scale–Parent; LOCF = last-observation-carried-forward; LPS-ADHD-R = Life Participation Scale for ADHD–Revised; MASC = Multidimensional Anxiety Scale for Children; N/A = not applicable; N = number of patients; SD = standard deviation.

^a p-Values are from Student's t-tests.

^b This measure is not designed to include baseline scores.

Population: All patients who entered the open-label phase.

Safety

The mean final daily dose prescribed was 65.06 mg (1.33 mg/kg), and the maximum daily dose prescribed was 120 mg (2.61 mg/kg). The mean time on therapy was 193.89 days. Mean change from baseline (last of Visit 4 through Visit 9) to LOCF endpoint analyses were computed for laboratory values, vital signs, height, weight, and electrocardiograms (ECGs) for patients who took at least 1 dose of study drug during the open-label phase.

Adverse Events (AE)

No deaths occurred in this study. During the open-label phase, 4 patients discontinued due to an adverse events (AE: irritability, Visit 10; homicidal ideation, Visit 11; middle insomnia, Visit 12; and vomiting, Visit 12). A total of 77 (58.8%) patients experienced at least 1 treatment-emergent adverse event (TEAE). The most common AE was headache (14; 10.7%). Table LYBP.7 provides a summary of TEAEs occurring in 3 ($\geq 2.29\%$) or more patients.

Table LYBP.7. Treatment-Emergent Adverse Events ($\geq 2.29\%$)
N = 131

Treatment-Emergent Adverse Event	n	Percentage
Headache	14	10.7%
Nasopharyngitis	13	9.92%
Upper Abdominal Pain	10	7.63%
Decreased Appetite	10	7.63%
Nausea	8	6.11%
Fatigue	6	4.58%
Somnolence	6	4.58%
Vomiting	6	4.58%
Dizziness	4	3.05%
Cough	3	2.29%
Nasal Congestion	3	2.29%
Pharyngolaryngeal	3	2.29%
Seasonal Allergy	3	2.29%
Sedation	3	2.29%

Abbreviation: N = total number of patients; n = number of patients with the event.

Population: All patients who took at least 1 dose of study drug during the open-label phase.

Laboratory Values

Table LYBP.8 provides a summary of all laboratory analytes that showed a statistically significant mean change from baseline to LOCF endpoint for all patients who took at least 1 dose of study drug during the open-label phase. Mean laboratory values for all analytes at endpoint were within normal range. One patient had aspartate transaminase/serum glutamic-oxaloacetic transaminase (AST/SGOT) and alanine transaminase/serum glutamic-pyruvic transaminase (ALT/SGPT) enzyme levels above the upper limit of normal (U/L) range at Visit 9 (the last visit in the acute phase; AST 91.0 U/L, ALT 125.0 U/L). Upon examination of this patient's data during the open-label phase of this trial (Visit 10 through Visit 13), enzyme levels were still elevated at Visit 10 (AST 92.0 U/L, ALT 118.0 U/L) but spontaneously returned to near-normal limits by Visit 13 (AST 48 U/L, ALT 40.0 U/L).

Table LYBP.8. Laboratory Analytes
Mean Change from Baseline to LOCF Endpoint

Analyte	N	Baseline Mean (SD)	Change Mean (SD)	p-Value ^a
Albumin	105	44.41 (3.05)	0.63 (2.97)	.034
Alkaline phosphatase	106	236.11 (89.73)	-16.54 (41.94)	<.001
Alanine aminotransaminase	105	19.37 (12.52)	-2.60 (11.02)	.018
Aspartate aminotransaminase	104	26.16 (9.21)	-1.86 (6.52)	.005
Bicarbonate	105	23.28 (2.26)	0.89 (2.48)	<.001
Chloride	106	106.23 (2.32)	-0.64 (2.66)	.016
Cholesterol	106	4.22 (0.79)	0.12 (0.50)	.018
Creatine kinase	105	126.62 (87.88)	-12.65 (56.04)	.023
Hematocrit	106	0.41 (0.03)	0.01 (0.03)	.001
Mean cell volume	106	84.60 (5.19)	1.29 (3.92)	.001
Platelet count	106	306.07 (68.95)	-9.63 (45.62)	.033
Blood urea nitrogen	106	4.91 (1.27)	-0.30 (1.31)	.020

Abbreviations: LOCF = last-observation-carried-forward; N = number of patients; SD = standard deviation.

^a p-Values are from Students' t-tests.

Population: All patients who took at least 1 dose of study drug during the open-label phase.

Vital Signs, Height, and Weight

Vital signs and weight were obtained at every visit. Height was collected for patients at their last visit of the open-label phase. No statistically significant changes from baseline to LOCF endpoint were observed for weight, systolic blood pressure, or pulse. Table LYBP.9 provides a summary of statistically significant mean changes from baseline to LOCF endpoint in vital signs. There was a statistically significant mean increase from baseline to LOCF endpoint in height and a statistically significant decrease in body mass index. There was also a statistically significant increase in diastolic blood pressure.

Table LYBP.9. Vital Signs
Mean Change from Baseline to LOCF Endpoint

Vital Signs	N	Baseline Mean (SD)	Change Mean (SD)	p-Value^a
Height (cm)	116	151.97 (14.63)	1.63 (2.44)	<.001
Diastolic BP	129	65.91 (6.72)	2.08 (8.59)	.007
BMI	116	20.67 (4.44)	-0.40 (1.23)	<.001

Abbreviation: BMI = body mass index; BP = blood pressure; LOCF = last-observation-carried-forward; N = number of patients; SD = standard deviation.

^a p-Values are from Student's t-tests.

Population: All patients who took at least 1 dose of study drug during the open-label phase.

Electrocardiograms (ECGs)

There were no statistically significant mean changes from baseline to LOCF endpoint for ECG PR interval, ECG QRS interval, or ECG QT interval. Table LYBP.10 provides a summary of ECGs that showed a statistically significant change from baseline to endpoint. Statistically significant mean change from baseline to LOCF endpoint values were seen for ECG heart rate, ECG derived RR interval, Fridericia-corrected QT interval, and database-corrected QT interval.

Table LYBP.10. ECGs
Mean Change from Baseline to LOCF Endpoint

Electrocardiograms (ECGs)	N	Baseline Mean (SD)	Change Mean (SD)	p-Value^a
ECG Heart Rate	109	80.21 (12.29)	4.04 (13.48)	.002
ECG Derived RR Interval ^b	109	766.20 (123.82)	-34.00 (129.34)	.007
Fridericia QTc Interval	109	390.27 (18.44)	3.81 (19.82)	.047
Database-Corrected QT Interval	109	396.49 (19.06)	4.97 (20.93)	.015

Abbreviations: LOCF = last-observation-carried-forward; N = number of patients; SD = standard deviation.

^a p-Values are from Student's t-tests.

^b Derived: RR interval = 1000*60/heart rate.

Population: All patients who took at least 1 dose of study drug during the open-label phase.

References

[APA]American Psychiatric Association. 1994. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association. 943 p.

Summary ID# 6639

Clinical Study Summary: Study B4Z-UT-S003

An Open-Label Pilot Study of Atomoxetine for Attention Deficit and Hyperactive/Impulsive Behavior Problems in Children and Adolescents with Autistic Spectrum Disorders

Date summary approved by Lilly: 27 February 2007

Brief Summary of Results

The aim of this Phase 4 pilot study was to examine tolerability and effectiveness of atomoxetine on attention deficit/hyperactivity (ADHD) symptoms and autistic features in children and adolescents with autism spectrum disorder (ASD). The results of the study are as follows:

- Atomoxetine statistically significantly reduced symptoms of ADHD: ADHD-Rating Scale-IV (ADHD-RS-IV); 44% decrease vs. baseline, $p=.003$ (Last observation carried forward, LOCF). All 7 completers were rated as “much” or “very much improved” on the Clinical Global Impressions (CGI) scale.
- Statistically significant changes were observed for the Conners’ Parent Rating Scale—revised: short form ([CPRS-R:S] 25% in the subscale “Cognitive Problems,” $p=0.028$; 32% in “Hyperactivity,” $p=0.030$; and 23% in “ADHD index,” $p=0.023$). There were no statistically significant changes in any of the other subscales.
- Anorexia, irritability, and sleep problems were the most frequently reported side-effects.
- No deaths occurred during this study.

Title of Study: An Open-Label Pilot Study of Atomoxetine for Attention Deficit and Hyperactive/Impulsive Behaviour Problems in Children and Adolescents with Autistic Spectrum Disorders	
Investigator(s): This single-center study included 1 principal investigator(s).	
Study Center(s): This study was conducted at 1 study center(s) in 1 country.	
Length of Study: 8 months from first patient visit (FPV) to last patient visit (LPV) Date of first patient visit: 25 Feb 2004 Date of last patient visit for entire study: 20 Oct 2004	Phase of Development: 4
Objectives: The primary objective of this study: - To test the hypothesis that atomoxetine, titrated to a maximum of 1.8 mg/kg/day for 10 weeks, is effective in reducing symptoms of inattention and overactivity/impulsivity as measured by mean change in ADHD-RS-IV-Parent: Inv. Scale from baseline to endpoint in a population of pediatric outpatients, aged 6 through 17 years, with autistic spectrum disorders, accompanied by attention deficit and hyperactivity/impulsive behavior problems (LOCF). The secondary objectives of this study: - To assess whether atomoxetine will be effective in reducing symptoms of inattention and overactivity/impulsivity as measured by mean change from baseline to endpoint in the scales of the Clinical Global Impressions – Attention-deficit/Hyperactivity Disorder – Improvement (CGI-ADHD-I), the Conners' Parent Rating Scale – revised: short form (CPRS-R:S), and the Conners' Teacher Rating Scale – revised: short form (CTRS-R:S). - To assess whether atomoxetine will be effective for improving social functioning and personal sufficiency in children and adolescents with ASD+ADHD as measured by mean change from baseline to endpoint in two subscales of the Aberrant Behavior Checklist (Social Withdrawal, Inappropriate Speech), on two subscales of the Children's Social Behaviour Questionnaire ([CSBQ]; Social Contact Problems, Social Insight Problems), and on 4 domains of the Vineland Behavior Scales. - To assess whether atomoxetine has a positive or negative effect on frequently associated symptoms as impulsive aggression, agitation, self-injurious behavior, troublesome repetitive behavior and poor motor coordination as measured by mean changes from baseline to endpoint in two subscales of the Aberrant Behavior Checklist (Irritability, Stereotypy), two subscales of the CSBQ (Acting out, Anxious Rigid, Stereotypical), the Children Yale Brown Obsessive Compulsive Disorder Scale (CYBOCS), a subscale (Maladaptive) of the Vineland Behavior Scales and the Conduct Problem subscale of the Nisonger Child Behavior Rating Form. - To assess whether atomoxetine has a positive or negative effect on neuropsychological functioning, as measured by a clinical psychologist with a set of cognitive measures, including the Dual Working Memory Task, the Stroop Color Word Test (Stroop), the Trail Making Test (Trails A and B), the Working Memory Subtests of the Wechsler Intelligence Scale for Children - Third Edition and the Maze Subtest of the Wechsler Intelligence Scale for Children - Third Edition. This will be measured by mean change from baseline to endpoint in each of the tasks. - To assess the overall influence on functioning and burden on the family as measured by mean change from baseline to endpoint with the CHIP-CE (Child Health and Illness Profile-child evaluated). - To monitor clinical safety and side effects as assessed by adverse events elicited during open-ended questioning.	

Study Design:

Study B4Z-UT-S003 was a ten-week open-label pilot trial with atomoxetine in pediatric patients (outpatient) aged 6 yrs to 17 yrs with an autistic spectrum disorder diagnosis accompanied with attention deficit and hyperactivity/impulsive behavior problems. Patients must have met Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV) criteria for ADHD as well as DSM-IV TR criteria for Autistic Disorder or Asperger syndrome or Pervasive Developmental Disorder – Not Otherwise Specified (PDDNOS) as well as criteria detailed in the inclusion criteria. The study comprised two study periods (see Table 1 and Figure 1).

Study period I:

Study period 1 was a 3- to 28-day screening and medication washout period. Prior to or at Visit 1, the patient was *prescreened*. In this period the purpose and procedures of the study were explained, informed consent was obtained from a parent and assent obtained from the patient (when appropriate) prior to the administration of any study-specific procedures at Visit 1.

The following assessments were completed in the first period:

The Autism Diagnostic Interview (ADI), was completed for each patient. The Children's Social Behavior Questionnaire (CSBQ), the Aberrant Behavior Checklist (ABC), the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S), the Conners' Teacher Rating Scale- Revised: Short Form (CTRS-R: S), the Child Health and Illness Profile (CHIP-CE), the ADHD-RS-IV-Parent, the Clinical Global Impression of Severity (CGI-S) and the Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity (CGI-ADHD-S); the Nisonger Child Behavior Rating Form (N-CBRF) and the Children Yale Brown Obsessive Compulsive Disorder Scale (CYBOCS) had to be completed for evaluation of entry criteria. Intellectual functioning was assessed (intelligence quotient [IQ]) by Wechsler scales.

Study period II:

At Visit 2 (baseline), in addition to the measures mentioned at V1 (except for the IQ and the ADI), the Vineland Behavior Scales and the Cognitive Measures were completed.

Study Period II was an approximately 10-week period (Visit 2 through Visit 12), with weekly follow-up visits, during which atomoxetine was titrated to a target dose of 1.2 mg/kg/day but flexibility between 0.5 mg/kg/day to a maximum of 1.8 mg/kg/day, based on efficacy and tolerability, was allowed. The total dose was administered once daily or as 2 equal divided doses in the morning and late afternoon or early evening. Prior to enrollment, patients must have met the symptom severity criteria, Disease Diagnostic Criteria, at both Visit 1 and Visit 2. At the end of Visit 2, patients who completed all assessments and who were eligible to enroll in the treatment phase of this study were assigned to treatment with atomoxetine.

At the Visit 12 endpoint visit (endpoint in the trial), patients returned for an extended visit. Once all behavioral ratings and blood tests were completed, the research team determined the next phase of the child's treatment, based on study results and parental preference.

If a clinically significant increase in the QTc interval from baseline was present, then the patient was assessed by the investigator for symptoms (such as palpitations, near syncope, or syncope). Any clinically significant findings that resulted in a diagnosis was captured on the Adverse Events/Pre-existing Condition page of the CRF. Any clinically significant findings that did not result in a diagnosis was documented in the Visit Comments page of the CRF.

Number of Patients:

Planned: 12

Randomized/Entered: 12 patients (10 males, 2 females), with a mean age of 10.2 ± 2.8 years were enrolled and started open-label treatment with atomoxetine for 10 weeks

Completed: 7 children completed the full 10 weeks on atomoxetine. The mean maximum total daily dose (TDD) of atomoxetine prescribed ranged from 0.49 mg/kg/day to 1.72 mg/kg/day, with an overall mean TDD of 1.19 ± 0.41 mg/kg/day.

Main Criteria for Inclusion:

All children had to meet DSM-IV text revision (TR) criteria for a pervasive developmental disorder, that is, autistic disorder, Asperger's disorder, or a pervasive developmental disorder not otherwise specified. These diagnoses were made by use of the Autism Diagnostic Interview-Revised Scale complemented with a clinical judgment. The Autism Diagnostic Interview (ADI) is a highly structured method of eliciting information from a parent to confirm a clinical impression of autism in children and adults. Moreover, patients were required to meet the DSM-IV TR criteria for ADHD by clinical assessment and also had to have a symptom severity score at least 1.7 standard deviations above age and gender norms on the total, the inattentive, or the hyperactivity/impulsive subscale scores on the ADHD Rating Scale-IV-Parent Version (Investigator Administered and Scored) (ADHDRS). Other enrollment criteria included an age of 6 to 17 years, and a weight of 20 to 60 kg.

Study Drug, Dose, and Mode of Administration: Atomoxetine was titrated to a target dose of 1.2 mg/kg/day with flexibility of dose between 0.5 mg/kg/day and 1.8 mg/kg/day, based on efficacy and tolerability. The total dose was administered as a single daily dose in the morning or as a twice daily divided dose.

Comparator/placebo, Dose, and Mode of Administration: Not applicable

Duration of Treatment: 10 weeks

Variables:

Efficacy: see Table 3 - Efficacy Outcomes at Baseline and End of Study for Twelve Children with Symptoms of ADHD Treated for up to 10 Weeks with Atomoxetine.

Safety: Safety and tolerability were assessed by weekly open-ended questioning for adverse events and monitoring of vital signs.

Evaluation Methods:

Statistical: The primary efficacy measure was the baseline to endpoint change in ADHDRS severity. Intent-to-treat analyses were applied to data from all patients enrolled for ongoing therapy. If a patient withdrew from study prior to study completion, their data were examined by using the last observation carried forward model. Descriptive statistics were presented as mean $\pm$ SD. Differences between baseline and end-of-study were examined using Wilcoxon signed rank tests (two-tailed). In all tests, p-values of less than .05 were used to indicate statistical significance. Statistical analyses were performed by use of the SPSS statistical program, version 12.0.1. As this was a pilot study, corrections for multiple comparisons were not made.

Results:

Study Design

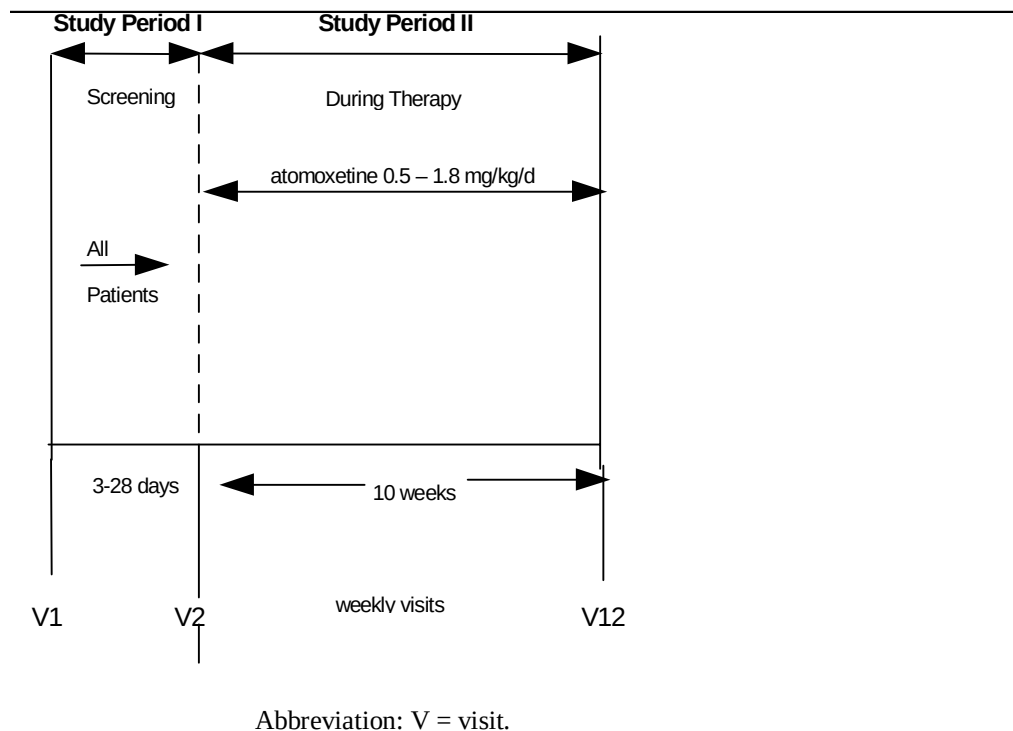


Figure 1. Illustration of study design for Study B4Z-UT-S003.

Table 1 details the study periods and the associated visit numbers and intervals allowed during the study.

Table 1. Visit Intervals for Patients Participating in Study B4Z-UT-S003

Study Period	Visit Numbers	Visit Interval Allowed (days)	Suggested Visit Interval (days)
I Screening, Medication Washout, and Assessment Period	1	3-28	7
II Open-label, Treatment Period	2-12	7	+/- 2

Patient Demographics

Of the 47 patients who showed initial interest to participate, 35 did not meet inclusion criteria or were unwilling to give final consent. The remaining 12 patients (10 males, 2 females), with a mean age of 10.2 ± 2.8 years were enrolled and started open-label treatment with atomoxetine. Baseline characteristics are summarized in Table 2.

Table 2. Clinical Characteristics of 12 Children Enrolled in Open-Label Treatment with Atomoxetine

Baseline Characteristic	Atomoxetine (N=12)
Age years:	
Mean	10.2
Minimum	6.0
Maximum	14.0
Standard Deviation	2.8
Gender No.	
Male	10
Female	2
DSM-IV TR Diagnosis of PDD	
Autistic Disorder	6
PDDNOS	5
Asperger's Disorder	1
Mental Development	
Mild Retardation	0
Borderline IQ	8
Average IQ	4
Previous Drugs	
Clonidine	1
Dextroamphetamine	3
Melatonin	2
Methylphenidate	7
Pipamperone	2
Quetiapine	1
Risperidone	5

Abbreviations: DSM-IV TR = Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition Text Revision; IQ = intelligence quotient; N = total number of patients; No = number; PDD = Pervasive Developmental Disorder; PDDNOS = Pervasive Developmental Disorder – Not Otherwise Specified.

Patient Disposition

Ten patients completed at least 6 weeks of the study, and 7 patients completed the whole study. A total of five patients discontinued because of side effects (Figure 2).

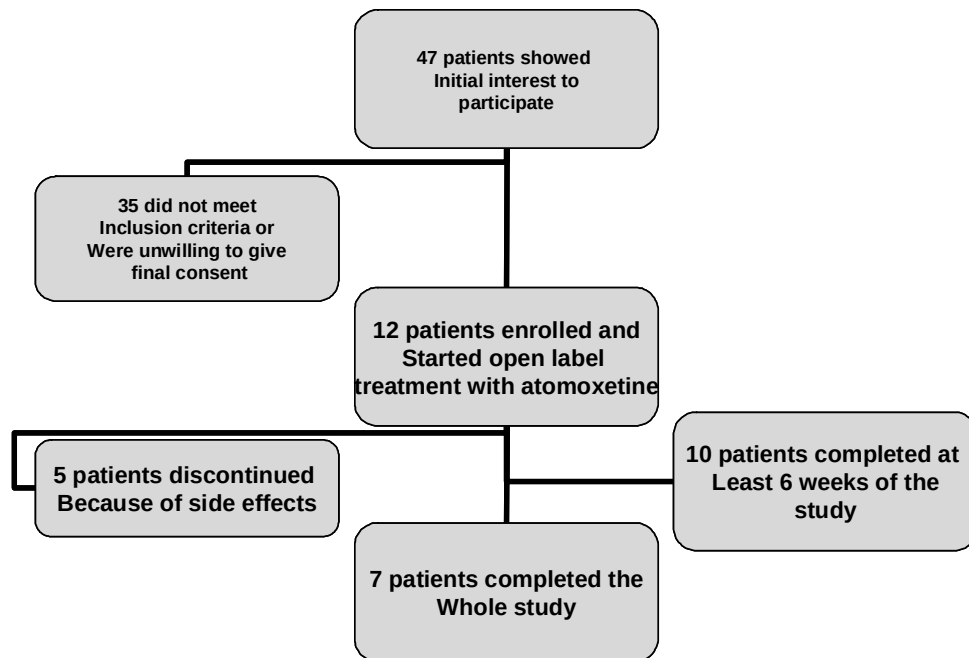


Figure 2. Patient disposition.

Reasons for Discontinuation

A total of five patients discontinued because of side effects: 1 patient after receiving one dose of atomoxetine because of nausea, 1 patient after 3 weeks because of anxiety, 1 patient after 6 weeks because of increased aggression/agitation, 1 patient after 8 weeks because of nausea/vomiting, and 1 patient after 9 weeks because of loss of appetite and for the weight loss (3.3 kg) being unacceptable to the parents.

Primary and Secondary Efficacy Measures

Results of the primary and secondary efficacy measures are shown in Table 3.

Atomoxetine statistically significantly reduced symptoms of ADHD: ADHD-Rating Scale-IV (ADHD-RS-IV); 44% decrease vs. baseline, $p=.003$ (LOCF). All 7 completers were rated as “much” or “very much improved” on the Clinical Global Impressions (CGI) scale.

Statistically significant changes were observed for the CPRS-R:S 25% in the subscale “Cognitive Problems,” $p=0.028$; 32% in “Hyperactivity,” $p=0.030$; and 23% in “ADHD index,” $p=0.023$). There were no statistically significant changes in any of the other subscales.

Table 3. Efficacy Outcomes at Baseline and End of Study for Twelve Children with Symptoms of ADHD Treated for up to 10 Weeks with Atomoxetine^a

Measure	Baseline	End-of-Study	p-Value ^b	Z	ES ^c
ADHD-Rating Scale-IV, Parent Version, Investigator Scored-Total score	40.33±5.61	22.42±9.49	.003	-2.982	2.30
Connors' Parent Rating Scale-R-S subscales (total score of subscales)					
Oppositional subscale	9.17±5.20	8.17±5.59	.609	-.512	0.19
Cognitive Problems subscale	12.42±4.83	9.33±4.48	.028	-2.197	0.66
Hyperactivity subscale	9.83±3.93	6.67±5.66	.030	-2.169	0.66
Attention Deficit Hyperactivity Disorder Index	24.25±7.91	18.67±9.83	.023	-2.273	0.63
Aberrant Behavior Checklist subscales					
Irritability	15.83±9.45	14.50±12.82	.610	-.511	0.12
Social withdrawal	8.92±5.85	7.17±7.04	.183	-1.483	0.27
Stereotype	3.42±3.09	2.58±3.31	.140	-1.476	0.26
Hyperactivity	23.58±7.86	17.67±13.78	.071	-1.806	0.44
Inappropriate speech	3.33±2.61	3.75±3.67	.478	-.710	-0.13

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; ES =Effect Size ; R-S = revised – short form; Z = Z score.

^a Last observation carried forward. Mean ± SD.

^b Comparisons made with a two-tailed, Wilcoxon Signed Rank test.

^c Effect sizes were calculated by dividing the difference in mean scores at Baseline and End of Study by the pooled standard deviation.

Safety

The most common adverse events reported were anorexia (n=10), irritability (n=9), and sleep problems (n=7). All side effects were in the mild-to-moderate range. Mean heart rate statistically significantly increased from baseline to endpoint (85 vs. 93 bpm; p<.022), no statistically significant differences were observed in blood pressure. Analysis of electrocardiograms (ECGs) revealed no evidence of effects of atomoxetine on mean conduction, repolarization, or rhythm (PR, QRS, and QTC intervals all unchanged). There were no clinically meaningful changes in individual or mean

laboratory test results, vital signs, and ECG assessments (relative to pre-study situation) as assessed by the investigator.

Health Outcomes

At the end of the study, 9 of the 12 children (75 %) were rated as “much improved” or “very much improved” on the CGI-ADHD-S scale.

Summary ID# 6671

Clinical Study Summary: Study B4Z-SO-LY15

A Randomized, Double Blind Placebo Controlled Study of the Broader Efficacy of Atomoxetine Hydrochloride in the Treatment of Attention-Deficit/Hyperactivity Disorder in Swedish Children and Adolescents

Date summary approved by Lilly: 16 October 2007

Brief Summary of Results

The primary efficacy variable of this Phase 3b study was the change from baseline to endpoint in the Achievement domain of the Child Health and Illness Profile-Child Edition (CHIP-CE) parent form. Results are as follows:

Primary efficacy variable (Study Period II)

- The least squares (LS) mean change from baseline to endpoint in the Achievement domain score was 6.9 in the atomoxetine group and 3.0 in the placebo group. The corresponding difference between treatment groups of 3.9 was statistically significant (95% confidence interval [CI]: 0.9, 6.8; $p=0.010$) and thus, the primary objective to show the superiority of atomoxetine over placebo in the CHIP-CE Achievement domain was met.

Secondary efficacy variables (Study Period II)

- Between-treatment differences for the CHIP-CE total score and domains other than the Achievement domain were not statistically significant, with the exception of the Risk avoidance domain (LS mean difference: 3.2; 95% CI: 0.1, 6.3; $p=0.041$).

- In both treatment groups, the Family Burden of Illness Module (FBIM) total score as well as the Emotional and Restriction domain scores decreased from baseline to endpoint in Study Period II. The LS mean change from baseline to endpoint in the FBIM total score was -2.2 with atomoxetine and -0.5 with placebo (difference between treatments: -1.8; 95% CI: -3.5, -0.0; p=0.046).
- The mean Attention-Deficit/Hyperactivity Disorder - Rating Scale (ADHD-RS) total score as well as the mean ADHD-RS subscale scores decreased (i.e., improved) in both treatment groups. Statistically significantly higher decreases in the atomoxetine group compared to the placebo group were observed for the total score and the subscale scores (all p<0.001).
- At the end of Study Period II (Week 10), total costs and indirect costs as assessed by the Resource Utilization Questionnaire (RUQ) had decreased in the atomoxetine group but increased in the placebo group. The difference between treatment groups was statistically significant for the indirect costs (p=0.018) and the total costs (p=0.001).

Efficacy in Study Period III

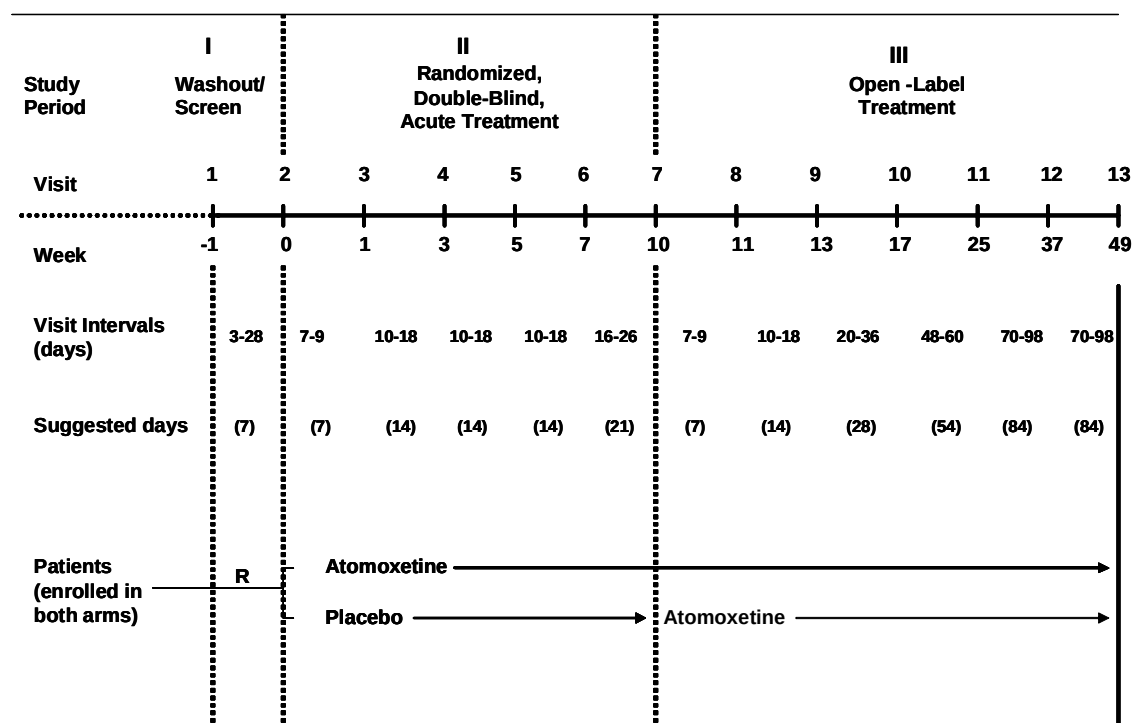
- Efficacy variables assessed in the atomoxetine open-label treatment period (Study Period III) showed at least stable values for both previous treatment groups (based on the treatment previously received in Study Period II).

Safety

- During Study Period II, 44 patients in the atomoxetine group (89.8%) and 37 patients in the placebo group (74.0%) reported at least 1 treatment-emergent adverse event (TEAE) (p=0.066). Statistically significantly higher incidences in the atomoxetine group occurred for the TEAEs of headache, upper abdominal pain, anorexia, and nausea.
- No serious adverse events (SAEs), deaths, or adverse events (AEs) leading to discontinuation were reported in Study Period II.
- During Study Period III, 73 patients (73.7%) reported at least 1 TEAE; fewer patients in the previous atomoxetine group (59.2%) reported TEAEs than patients in the previous placebo group (88.0%). One SAE (orthopedic procedure) was reported, which was not related to atomoxetine. A total of 7 patients (7.1%) discontinued the study prematurely due to an AE during Period III. No deaths were reported in Study Period III.

Title of Study: A Randomized, Double Blind, Placebo Controlled Study of the Broader Efficacy of Atomoxetine Hydrochloride in the Treatment of Attention-Deficit/Hyperactivity Disorder in Swedish Children and Adolescents	
Investigators: This multicentre study included 9 principal investigators.	
Study Centers: This study was conducted at 9 study centers in 1 country.	
Length of Study: 1 year and 5 months Date first patient enrolled: 30 March 2005 Date last patient completed: 21 August 2006	Phase of Development: 3b
Objectives: <u>Primary objective:</u> To test the hypothesis that atomoxetine and psychoeducation given for 10 weeks is superior to placebo and psychoeducation in improving overall functioning of patients, age 7-15 years, with Attention-Deficit/Hyperactivity Disorder (ADHD), as measured by the mean change in the total score of the Child Health and Illness Profile-Child Edition-Parent form (CHIP-CE-Parent form) domain Achievement <u>Secondary objectives:</u> • To compare the effects of atomoxetine and psychoeducation with those of placebo and psychoeducation at 10 weeks in patients with ADHD using the CHIP-CE-Parent form domains Satisfaction, Comfort, Resilience, and Risk avoidance, all CHIP-CE-Parent form subdomains, the CHIP-CE-Parent form total score, the Attention-Deficit/Hyperactivity Disorder - Rating Scale (ADHD-RS) total score regarding core ADHD symptoms, the Clinical Global Impressions-Severity (CGI-S) and -Improvement (CGI-I) regarding severity of illness and improvement, the "I Think I Am" ("Jag tycker jag är") tool regarding self-perception, the Appraisal of Stress in Child-Rearing (ASCR) regarding family stress, and the Family Burden of Illness Module (FBIM; also known as the Family Strain Index [FSI]) regarding family burden of illness. • To investigate the concurrent validity of the FBIM and the ASCR. • To assess whether the changes in scores on the aforementioned rating scales are maintained over the longer term. • To investigate if the results are modified by comorbid and/or developmental problems as measured by the "Five to Fifteen" (FTF) and Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS). • To assess the long-term safety of atomoxetine. • To assess the utilization of resources and costs to families and society between atomoxetine and placebo during the 10-week double-blind treatment period and for each patient during the following open-label extension period, using the Resource Utilization Questionnaire (RUQ).	
Study Design: This study was a Phase 3b multicentre, randomized, placebo-controlled, double-blind study (Figure 1).	
Number of Patients: Planned: 50 atomoxetine, 50 placebo Randomized: 49 atomoxetine, 50 placebo Completed Study Period II: 49 atomoxetine, 50 placebo Entered Study Period III: 99 atomoxetine (49 received atomoxetine and 50 placebo in Study Period II) Completed Study Period III: 70 atomoxetine (38 received atomoxetine and 32 placebo during Study Period II); 39 completed all 13 scheduled visits, 31 discontinued according to the protocol when atomoxetine became commercially available in Sweden.	
Diagnosis and Main Criteria for Inclusion: Patients had to meet the criteria for ADHD of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV™) as well as a symptom severity threshold of 1.5 standard deviations above age and sex norms for their diagnostic subtype on the Attention-Deficit/Hyperactivity Disorder Rating Scale-Parent Version (ADHDRS-IV-Parent); had to be between 7 and 15 years of age; had not to be previously treated with central stimulants. The diagnosis of ADHD and	

comorbid diagnoses were established by using the K-SADS diagnostic interview.
Test Product, Dose, and Mode of Administration: Atomoxetine, 0.5 mg/kg/day (patients weighing <70 kg) or 40 mg/day (patients weighing 70 kg or more) during the first week of Study Periods II and III. Thereafter (Study Periods II and III), the dose was to be titrated upwards to a maintenance dose of 1.2 mg/kg/day (patients weighing <70 kg) or 80 mg/day (patients weighing 70 kg or more). Atomoxetine was orally administered.
Reference Therapy, Dose, and Mode of Administration: Placebo, 0.5 mg/kg/day (patients weighing <70 kg) or 40 mg/day (patients weighing 70 kg or more) during the first week of Study Period II. Thereafter (Study Period II), the dose was to be titrated upwards to a maintenance dose of 1.2 mg/kg/day (patients weighing <70 kg) or 80 mg/day (patients weighing 70 kg or more). Placebo was orally administered.
Duration of Treatment: Maximum of 49 weeks (Study Period II, a double-blind placebo-controlled period of 10 weeks, followed by Study Period III, an optional open-label extension period of 39 weeks on active treatment)
Variables: <u>Efficacy:</u> Primary: CHIP-CE-Parent form, Achievement domain Secondary: CHIP-CE-Parent form (other domains, subdomains, and total score), ADHD-RS total and sub scores, CGI-ADHD-S and CGI-ADHD-I, the “I Think I Am” (“Jag tycker jag är”) tool, the Appraisals of Stress in Child-Rearing (ASCR), the FBIM, and the FTF <u>Safety:</u> Serious adverse events (SAEs) and adverse events (AEs), vital signs <u>Health Outcomes:</u> RUQ
Methods: <u>Statistical:</u> The primary efficacy variable was the mean score on the Achievement domain of the CHIP-CE. The primary efficacy analysis was a last observation carried forward (LOCF) analysis of covariance (ANCOVA) on the change from baseline (scores obtained at Visit 2) to Visit 7 (end of Study Period II). The model contained terms for baseline score, treatment, site, visit, treatment-by-visit interaction (removed if not significant, i.e., $p \geq 0.05$), and the Children’s Depression Rating Scale-Revised (CDRS-R) baseline score as a covariate. Significance was shown with a p-value of <0.05 (2-sided). A similar ANCOVA model was used for the secondary variables derived from the CHIP-CE. The LOCF ANCOVA change from baseline to endpoint was used to analyze the secondary variables FBIM, “I Think I Am” (“Jag tycker jag är”), ADHD-RS, CGI-ADHD-S, ASCR, and FTF. The model included terms for baseline, treatment, and site. The endpoint value of the CGI-ADHD-I was analyzed using an ANOVA model including terms for treatment and site. A restricted maximum likelihood based mixed-model repeated measures (MMRM) model was used for ADHD-RS, CGI-ADHD-S, and CGI-ADHD-I post-baseline scores. Study Period III data was descriptively summarized by treatment group based on the treatment previously received in Study Period II.



Key: R = Randomization at Visit 2.

Figure 1. Illustration of study design for Study B4Z-SO-LY15

Results:

Patient Demographics

Table 1 summarizes baseline demographic characteristics for all randomized patients. There were no statistically significant differences in patient characteristics between treatment groups (Fisher's exact test for categorical data; ANOVA with treatment as the independent effect for continuous data). Of the 99 randomized patients, 80.8% were male and 93.9% were Caucasian. The mean and median age were 11.5 years (range of 7.3 to 15.8 years) with 56.6% of patients aged 6-11 years. The mean body mass index (BMI) was 29.6 kg/m² (median of 27.8 kg/m²; range of 17.7 to 73.2 kg/m²).

**Table 1. Patient Demographics
Descriptive Statistics
Full Analysis Set**

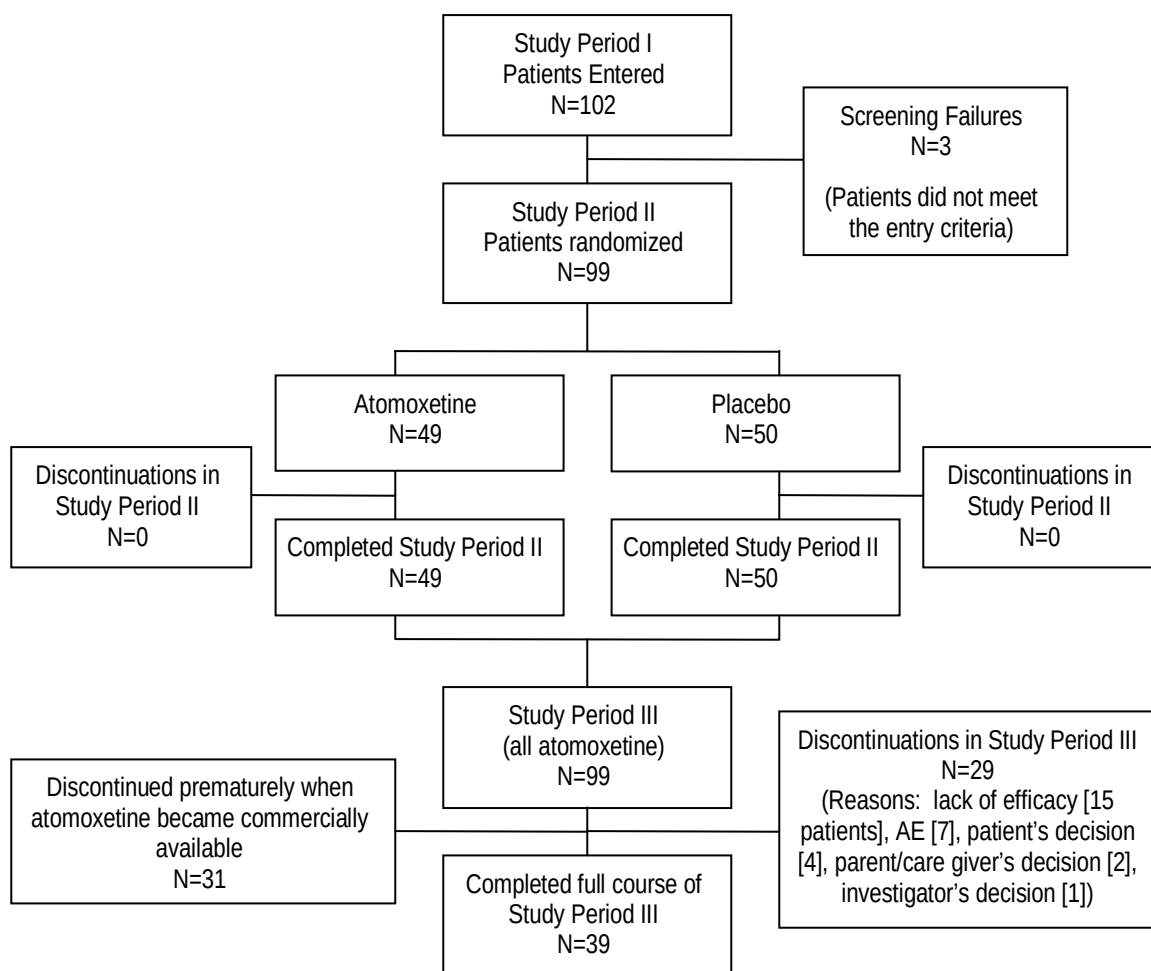
	Atomoxetine (N=49)	Placebo (N=50)	Total (N=99)	p-value
Sex (n [%])				0.803
Female	10 (20.4)	9 (18.0)	19 (19.2.x)	
Male	39 (79.6)	41 (82.0)	80 (80.8)	
Origin (n [%])				0.083
African	0 (0.0)	1 (2.0)	1 (1.0)	
Caucasian	44 (89.8)	49 (98.0)	93 (93.9)	
East Asian	2 (4.1)	0 (0.0)	2 (2.0)	
Hispanic	1 (2.0)	0 (0.0)	1 (1.0)	
Native American	1 (2.0)	0 (0.0)	1 (1.0)	
West Asian	1 (2.0)	0 (0.0)	1 (1.0)	
Age (years)				0.511
n	49	50	99	
Mean (SD)	11.6 (2.3)	11.3 (2.1)	11.5 (2.2)	
Median (range)	12.1 (7.3, 15.8)	11.3 (7.5, 15.6)	11.5 (7.3, 15.8)	
Age groups (n[%])				0.158
6 – 11 years	24 (49.0)	32 (64.0)	56 (56.6)	
12 – 15 years	25 (51.0)	18 (36.0)	43 (43.4)	
Weight (kg)				0.553
n	49	50	99	
Mean (SD)	46.4 (17.6)	44.3 (17.7)	45.3 (17.6)	
Median (range)	47.0 (22.0, 126.6)	40.3 (22.0, 130.6)	40.9 (22.0, 130.6)	
Height (cm)				0.589
n	49	50	99	
Mean (SD)	150.7 (14.5)	149.2 (14.1)	150.0 (14.3)	
Median (range)	152.5 (121.7, 180.0)	148.7 (117.0, 185.5)	149.5 (117.0, 185.5)	
BMI (kg/m ²)				0.535
n	49	50	99	
Mean (SD)	30.2 (8.9)	29.1 (8.6)	29.6 (8.8)	
Median (range)	30.0 (17.7, 73.2)	27.3 (18.2, 70.4)	27.8 (17.7, 73.2)	

Abbreviations: N = total number of patients; n = number of patients in the category; SD = standard deviation.

Patient Disposition

Figure 2 presents a summary of patient disposition for the entire study. Of the 102 enrolled patients, 99 were randomized, 49 to atomoxetine and 50 to placebo. All of these patients completed the full course of the 10-week double-blind treatment period (Study Period II) and entered Study Period III to receive open-label atomoxetine.

The full 9-month duration of Study Period III was completed by 39 patients and 31 patients discontinued Study Period III according to the protocol when atomoxetine became commercially available in Sweden. The remaining 29 patients discontinued Study Period III prematurely for the following reasons: 15 patients due to lack of efficacy, 7 due to AEs, 4 due to the patient's own decision, 2 due to the decision of the parent/care-giver, and 1 due to the investigator's decision.



Abbreviation: AE = adverse event; N = total number of patients.

Figure 2. Patient disposition.

Primary Efficacy Measure

The primary efficacy variable was the change from baseline to endpoint in the Achievement domain of the CHIP-CE parent form. Descriptive statistics for CHIP-CE baseline scores are given in Table 2.

**Table 2. CHIP-CE Domain Scores and Total Score at Baseline
Descriptive Statistics
Full Analysis Set**

		Atomoxetine (N=49)	Placebo (N=50)
Achievement (primary variable)	n	48	48
	Mean (SD)	29.2 (9.9)	29.8 (8.9)
	Median (Range)	28.7 (7.5, 44.7)	28.7 (12.8, 52.5)
Satisfaction	n	49	49
	Mean (SD)	31.8 (13.4)	34.0 (13.7)
	Median (Range)	32.9 (-0.6, 53.8)	32.9 (-4.8, 55.9)
Comfort	n	49	49
	Mean (SD)	44.1 (9.1)	44.1 (8.7)
	Median (Range)	44.3 (12.8, 59.6)	45.4 (17.1, 60.7)
Resilience	n	49	49
	Mean (SD)	35.8 (11.4)	39.5 (12.2)
	Median (Range)	34.8 (16.3, 64.7)	39.1 (13.5, 64.7)
Risk avoidance	n	48	49
	Mean (SD)	32.7 (12.6)	34.9 (11.9)
	Median (Range)	34.9 (-3.5, 53.3)	31.8 (10.3, 60.8)
Total score	n	48	48
	Mean (SD)	28.3 (10.3)	30.5 (10.8)
	Median (Range)	29.0 (-1.2, 47.4)	30.4 (5.2, 51.5)

Abbreviations: N = total number of patients; n = number of patients in the category; SD = standard deviation.

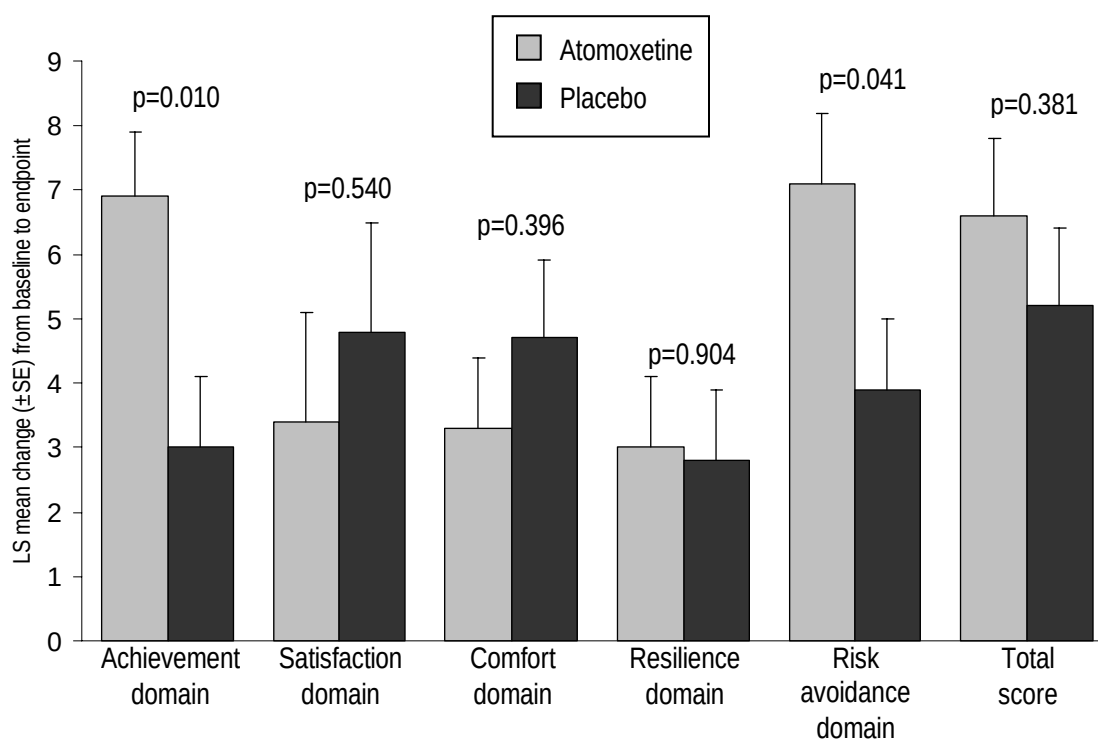
The LS mean change from baseline to endpoint in the Achievement domain score was 6.9 in the atomoxetine group and 3.0 in the placebo group, as given in Table 3 and depicted in Figure 3. The corresponding difference between treatment groups of 3.9 was statistically significant ($p=0.010$) and thus, the primary objective to show the superiority of atomoxetine over placebo in the CHIP-CE Achievement domain was met.

Table 1. Change from Baseline to Endpoint in CHIP-CE Domains and Total Score
ANCOVA
Full Analysis Set

CHIP-CE domain	Atomoxetine (N=49)		Placebo (N=50)		Difference in LS means		
	LSmean	SE	LSmean	SE	Estimate	95%-CI	p-value ¹
Achievement (primary variable)	6.9	1.0	3.0	1.1	3.9	(0.9, 6.8)	0.010
Satisfaction	3.4	1.7	4.8	1.7	-1.4	(-6.1, 3.2)	0.540
Comfort	3.3	1.1	4.7	1.2	-1.4	(-4.5, 1.8)	0.396
Resilience	3.0	1.1	2.8	1.1	0.2	(-3.0, 3.4)	0.904
Risk avoidance	7.1	1.1	3.9	1.1	3.2	(0.1, 6.3)	0.041
Total score	6.6	1.2	5.2	1.2	1.5	(-1.8, 4.8)	0.381

¹ p-value from ANCOVA model with terms for baseline, treatment, site, and CDRS-R score.

Abbreviations: CHIP-CE = Child Health and Illness Profile-Child Edition; CI = confidence interval; CDRS-R = Children's Depression Rating Scale; LS = least squares; N = total number of patients; SE = standard error.



Abbreviations: LS = least squares; SE = standard error.

Figure 1. Change from baseline to endpoint in CHIP-CE domains and the CHIP-CE total score, LS mean and SE, in the full analysis set

Secondary Efficacy Measures

Child Health and Illness Profile-Child Edition (CHIP-CE)

For mean scores in CHIP-CE domains and total score at baseline see Table 2 above. Between-treatment differences for CHIP-CE total score and domains other than the Achievement domain were not statistically significant, with the exception of the Risk avoidance domain (LS mean difference: 3.2; $p=0.041$), as given in Table 3 and Figure 3.

Family Burden of Illness Module (FBIM)

Descriptive statistics for FBIM baseline scores are given in Table 4.

**Table 4. FBIM Total Score and Domain Scores at Baseline
Descriptive Statistics
Full Analysis Set**

FBIM score		Atomoxetine (N=49)	Placebo (N=50)
Total	n	49	48
	Mean (SD)	9.8 (4.7)	8.8 (4.6)
	Median (Range)	9.0 (3.0, 22.0)	8.0 (1.0, 21.0)
Emotional Domain	n	49	48
	Mean (SD)	3.4 (1.7)	3.3 (1.7)
	Median (Range)	3.0 (0.0, 8.0)	3.0 (1.0, 7.0)
Restriction Domain	n	49	48
	Mean (SD)	6.5 (3.2)	5.5 (3.3)
	Median (Range)	6.0 (2.0, 14.0)	5.0 (0.0, 14.0)

Abbreviations: FBIM = Family Burden of Illness Module; N = total number of patients; n = number of patients in the category; SD = standard deviation.

In both treatment groups, the FBIM total score as well as the domain scores decreased from baseline to endpoint in Study Period II. The LS mean change from baseline to endpoint in the FBIM total score was -2.2 with atomoxetine and -0.5 with placebo (difference between treatments: -1.8 ; $p=0.046$). Details are shown in Table 5.

Table 5. Change From Baseline to Endpoint in FBIM Total Score and Domain Scores
ANCOVA
Full Analysis Set

FBIM score	Atomoxetine (N=49)		Placebo (N=50)		Difference in LS means		
	LSmean	SE	LSmean	SE	Estimate	95%-CI	p-value ¹
Total	-2.2	0.6	-0.5	0.6	-1.8	-3.5, -0.0	0.046
Emotional Domain	-0.8	0.2	-0.3	0.2	-0.5	-1.1, 0.1	0.102
Restriction Domain	-1.4	0.5	-0.1	0.5	-1.2	-2.5, 0.0	0.056

¹ p-value from ANCOVA model with terms for baseline, treatment, and site.

Abbreviations: CI = confidence interval; FBIM = Family Burden of Illness Module; LS = least squares; N = total number of patients; SE = standard error.

Children's Depression Rating Scale (CDRS)

Descriptive statistics for the CDRS baseline score are given in Table 6.

Table 6. CDRS Total Score at Baseline
Descriptive Statistics
Full Analysis Set

CDRS score		Atomoxetine (N=49)	Placebo (N=50)
Total	n	49	49
	Mean (SD)	25.8 (7.5)	25.1 (6.7)
	Median (Range)	23.0 (17.0, 54.0)	23.0 (17.0, 45.0)

Abbreviations: CDRS = Children's Depression Rating Scale; N = total number of patients; n = number of patients in the category; SE = standard error.

During Study Period II, an LS mean decrease in the CDRS total score of -3.4 from baseline to endpoint was observed in the atomoxetine group compared with a change of -0.1 in the placebo group (between-treatment difference: -3.3; p=0.033), as shown in Table 7.

**Table 7. Change in CDRS Total Score from Baseline to Endpoint
ANCOVA
Full Analysis Set**

CDRS score	Atomoxetine (N=49)		Placebo (N=50)		Difference in LS means		
	LSmean	SE	LSmean	SE	Estimate	95%-CI	p-value ¹
Total	-3.4	1.1	-0.1	1.1	-3.3	(-6.4, -0.3)	0.033

¹ p-value from ANCOVA model with terms for baseline, treatment, and site.

Abbreviations: ANCOVA = analysis of covariance; CDRS = Children's Depression Rating Scale; CI = confidence interval; LS = least squares; N = total number of patients; SE = standard error.

I think I am (Jag tycker jag är)

Descriptive statistics for "I think I am" baseline scores are given in Table 8.

**Table 8. "I Think I Am" Scores at Baseline
Descriptive Statistics
Full Analysis Set**

I think I Am score		Atomoxetine (N=49)	Placebo (N=50)
Total	n	39	34
	Mean (SD)	4.97 (1.63)	4.85 (1.74)
	Median (Range)	5.00 (1.00, 9.00)	5.00 (2.00, 9.00)
L-Scale Total	n	12	13
	Mean (SD)	5.33 (1.87)	5.31 (1.97)
	Median (Range)	5.00 (2.00, 9.00)	6.00 (2.00, 9.00)
MH-Scale Total	n	27	21
	Mean (SD)	4.81 (1.52)	4.57 (1.57)
	Median (Range)	5.00 (1.00, 9.00)	5.00 (2.00, 7.00)
MH-Scale domains			
Physical abilities	n	31	27
	Mean (SD)	5.42 (1.84)	5.67 (2.02)
	Median (Range)	6.00 (1.00, 9.00)	6.00 (2.00, 9.00)
Performance	n	29	26
	Mean (SD)	4.66 (1.97)	5.46 (1.65)
	Median (Range)	4.00 (1.00, 9.00)	5.50 (2.00, 9.00)
Psychic well being	n	31	29
	Mean (SD)	3.77 (1.54)	3.59 (1.74)
	Median (Range)	4.00 (1.00, 7.00)	3.00 (1.00, 8.00)
Family relations	n	30	29
	Mean (SD)	4.53 (1.94)	4.52 (1.90)
	Median (Range)	4.00 (1.00, 9.00)	5.00 (1.00, 7.00)
Relation to peers	n	28	26
	Mean (SD)	5.54 (1.91)	4.77 (1.95)
	Median (Range)	6.00 (1.00, 9.00)	5.00 (1.00, 8.00)

Abbreviations: L-Scale = Low Scale (referring to the low age range of 7-10 years applicable for this scale); MH-Scale = Middle/High Scale (referring to the higher age range of 11-16 years applicable for this scale); N = total number of patients; n = number of patients in the category; SD = standard deviation.

None of the differences in the "I think I am" total score and domains between treatment groups were statistically significant (Table 9).

Table 9. Change from Baseline to Endpoint in “I Think I Am” Scores ANCOVA Full Analysis Set

I think I am scores	Atomoxetine (N=49)		Placebo (N=50)		Difference in LS means		
	LSmean	SE	LSmean	SE	Estimate	95%-CI	p-value ¹
Total	0.3	0.2	0.1	0.3	0.1	(-0.6, 0.8)	0.671
L-Scale Total	0.6	0.6	0.0	0.6	0.6	(-1.0, 2.3)	0.438
MH-Scale Total	0.1	0.2	0.3	0.3	-0.2	(-0.9, 0.5)	0.553
MH-Scale domains							
Physical abilities	-0.5	0.3	-0.5	0.3	0.0	(-0.8, 0.8)	0.960
Performance	0.3	0.2	-0.2	0.3	0.5	(-0.2, 1.3)	0.147
Psychic well being	0.8	0.2	0.2	0.3	0.5	(-0.2, 1.2)	0.137
Family relations	-0.3	0.3	0.1	0.3	-0.4	(-1.2, 0.5)	0.398
Relation to peers	-0.1	0.3	0.1	0.3	-0.2	(-1.1, 0.6)	0.590

¹ p-value from ANCOVA model with terms for baseline, treatment, and site.

Abbreviations: CI = confidence interval; L-Scale = Low Scale (referring to the low age range of 7-10 years applicable for this scale); LS = least squares; MH-Scale = Middle/High Scale (referring to the higher age range of 11-16 years applicable for this scale); N = total number of patients; SE = standard error.

Attention-Deficit/Hyperactivity Disorder - Rating Scale (ADHD-RS)

Descriptive statistics for ADHD-RS baseline scores are given in Table 10.

Table 10. ADHD-RS Total Score and Subscale Scores at Baseline Descriptive Statistics Full Analysis Set

ADHD-RS score		Atomoxetine (N=49)	Placebo (N=50)
Total	n	49	50
	Mean (SD)	38.9 (7.7)	39.5 (6.7)
	Median (Range)	39.0 (22.0, 54.0)	39.5 (28.0, 52.0)
Inattention Subscale	n	49	50
	Mean (SD)	21.3 (4.1)	21.5 (3.7)
	Median (Range)	22.0 (11.0, 27.0)	21.5 (12.0, 27.0)
Hyperactivity-Impulsivity Subscale	n	49	50
	Mean (SD)	17.6 (6.4)	18.0 (5.9)
	Median (Range)	19.0 (1.0, 27.0)	17.5 (3.0, 27.0)

Abbreviations: ADHD-RS = Attention-Deficit/Hyperactivity Disorder – Rating Scale; N = total number of patients; n = number of patients in the category; SD = standard deviation.

The mean ADHD-RS total score as well as the mean ADHD-RS subscales scores decreased (i.e., improved) in both treatment groups. The ANCOVA change from baseline to endpoint analysis showed statistically significantly higher decreases in the

atomoxetine group compared to the placebo group with $p < 0.001$ for the total score and the subscale scores (Table 11).

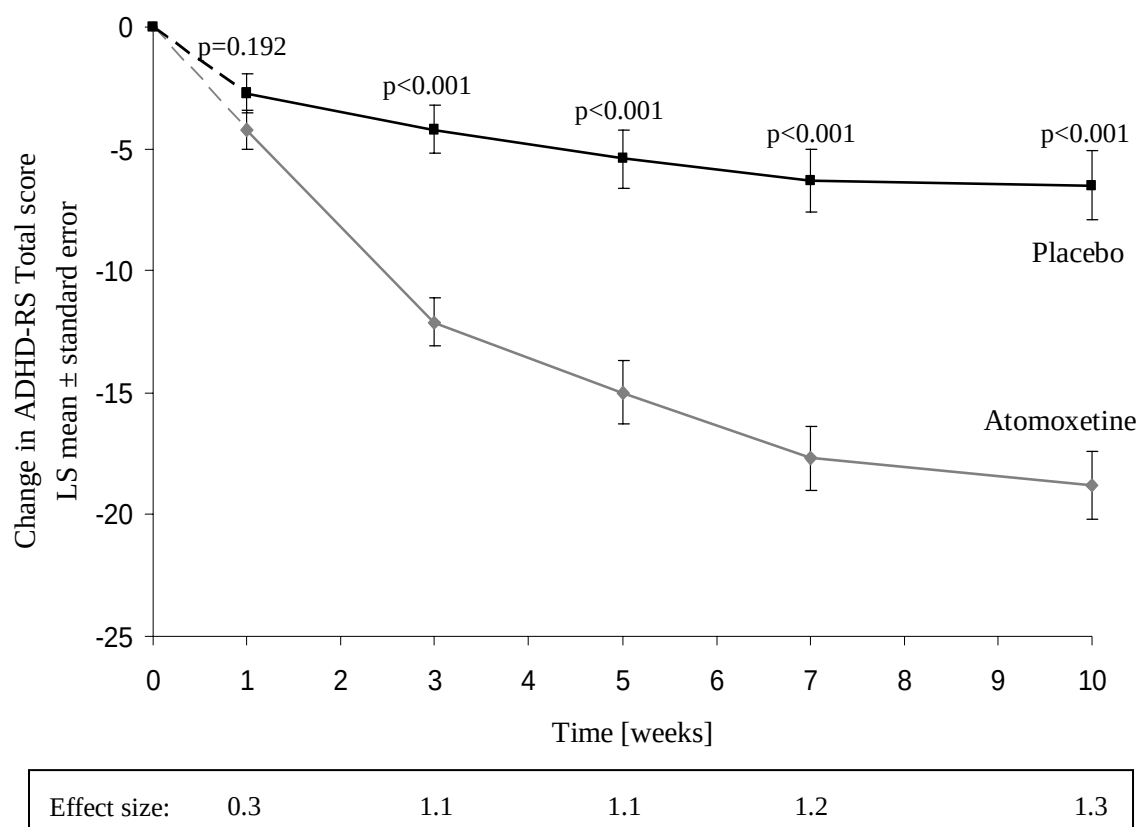
Table 11. Change from Baseline to Endpoint in ADHD-RS Total Score and Subscale Scores
 ANCOVA
 Full Analysis Set

ADHD-RS score	Atomoxetine (N=49)		Placebo (N=50)		Difference in LS means		
	LSmean	SE	LSmean	SE	Estimate	95%-CI	p-value ¹
Total	-19.0	1.5	-6.3	1.5	-12.8	-16.8, -8.8	<0.001
Inattention Subscale	-10.3	0.8	-3.8	0.7	-6.5	-8.6, -4.5	<0.001
Hyperactivity-Impulsivity Subscale	-8.7	0.8	-2.5	0.8	-6.2	-8.5, -4.0	<0.001

¹ p-value from ANCOVA model with terms for baseline, treatment, and site.

Abbreviations: ANCOVA = analysis of covariance; ADHD-RS = Attention-Deficit/Hyperactivity Disorder – Rating Scale; CI = confidence interval; LS = least squares; N = total number of patients; SE = standard error.

The MMRM analysis showed that differences between treatments were statistically significant from Week 3 on, in the total score (Figure 4) and also in the subscale scores.



Abbreviations: ADHD-RS = Attention-Deficit/Hyperactivity Disorder – Rating Scale; LS = least squares.

Figure 4. Repeated measures analysis of the ADHD-RS total score, LS means, standard errors, and effect sizes, in the full analysis set.

The effect size for the ADHD-RS total score was calculated from both the ANCOVA model and the MMRM. The effect size from the ANCOVA analysis was 1.3. The effect size from the MMRM analysis continuously increased during Study Period II to 1.3 at Week 10, with the largest increase observed during the first 3 weeks of double-blind treatment (effect size of 1.1 at Week 3).

Responder analyses showed that 71.4% of atomoxetine patients compared to 28.6% of placebo patients had a 25% improvement from baseline to endpoint, and 63.3% (atomoxetine) versus 14.3% (placebo) had a 40% improvement from baseline to endpoint.

Clinical Global Impressions – Severity (CGI-S)

Descriptive statistics for the CGI-S baseline score are given in Table 12.

Table 12. CGI-Severity at Baseline
Descriptive Statistics
Full Analysis Set

		Atomoxetine (N=49)	Placebo (N=50)
CGI Severity score at baseline	n	49	50
	Mean (SD)	4.8 (0.7)	4.9 (0.7)
	Median (Range)	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)

Abbreviations: CGI = Clinical Global Impressions Scale; N = total number of patients; n = number of patients in the category; SD = standard deviation.

The LS mean change from baseline to endpoint in the CGI-S score showed an improvement for both treatment groups with a statistically significant difference between atomoxetine and placebo ($p < 0.001$) (Table 13).

Table 13. Change in CGI-Severity from Baseline to Endpoint and CGI Improvement at Endpoint
ANCOVA
Full Analysis Set

	Atomoxetine (N=49)		Placebo (N=50)		Difference in LS means		
	LSmean	SE	LSmean	SE	Estimate	95%-CI	p-value ¹
Change in CGI Severity score	-1.8	0.1	-0.3	0.1	-1.5	(-1.9, -1.1)	<0.001

¹ p-value from ANCOVA model with terms for baseline, treatment, and site.

Abbreviations: ANCOVA = analysis of covariance; CGI = Clinical Global Impressions Scale; CI = confidence interval; LS = least squares; N = total number of patients; SE = standard error.

Clinical Global Impressions – Improvement (CGI-I)

The LS mean CGI-I score at endpoint was 2.3 in the atomoxetine group and 3.7 in the placebo group ($p < 0.001$) (Table 14).

Table 14. CGI Improvement at Endpoint
ANOVA
Full Analysis Set

	Atomoxetine (N=49)		Placebo (N=50)		Difference in LS means		
	LSmean	SE	LSmean	SE	Estimate	95%-CI	p-value ¹
CGI Improvement score	2.3	0.2	3.7	0.2	-1.4	(-1.8, -1.0)	<0.001

¹ p-value from ANOVA model with terms for treatment and site.

Abbreviations: ANCOVA = analysis of covariance; CGI = Clinical Global Impressions Scale; CI = confidence interval; LS = least squares; N = total number of patients; SE = standard error.

Five To Fifteen (FTF)

Descriptive statistics for FTF baseline scores are given in Table 15.

**Table 15. Five-To-Fifteen Domain Scores at Baseline
Descriptive Statistics
Full Analysis Set**

FTF domain		Atomoxetine (N=49)	Placebo (N=50)
Motor control	n	49	48
	Mean (SD)	0.58 (0.39)	0.63 (0.45)
	Median (Range)	0.47 (0.00, 1.47)	0.53 (0.00, 1.88)
Executive function	n	49	49
	Mean (SD)	1.42 (0.33)	1.38 (0.36)
	Median (Range)	1.38 (0.33, 2.00)	1.44 (0.44, 1.92)
Perception	n	48	48
	Mean (SD)	0.70 (0.38)	0.54 (0.37)
	Median (Range)	0.71 (0.00, 1.76)	0.44 (0.00, 1.50)
Memory	n	49	48
	Mean (SD)	0.85 (0.47)	0.70 (0.35)
	Median (Range)	0.82 (0.00, 1.82)	0.73 (0.09, 1.55)
Language and Speech	n	49	49
	Mean (SD)	0.60 (0.43)	0.43 (0.30)
	Median (Range)	0.48 (0.05, 1.76)	0.33 (0.00, 1.38)
Learning	n	44	49
	Mean (SD)	1.16 (0.47)	1.13 (0.39)
	Median (Range)	1.23 (0.07, 1.89)	1.11 (0.19, 1.85)
Social Competence	n	49	47
	Mean (SD)	0.76 (0.43)	0.61 (0.44)
	Median (Range)	0.70 (0.00, 1.78)	0.59 (0.00, 1.48)
Emotional/Behavioral	n	49	49
	Mean (SD)	0.60 (0.35)	0.55 (0.33)
	Median (Range)	0.61 (0.06, 1.67)	0.52 (0.00, 1.15)

Abbreviations: FTF = Five-to-Fifteen; N = total number of patients; n = number of patients in the category;
SD = standard deviation.

LS mean scores for each FTF domain decreased (i.e., improved) in both treatment groups with the exception of the Memory domain, which increased in the placebo group. Decreases were greater in the atomoxetine group and the difference between treatment groups was statistically significant for 7 of the 8 domains with corresponding p-values ranging from <0.001 to 0.033 (Table 16).

Table 16. **Change from Baseline to Endpoint in Five-To-Fifteen Domain Scores**
ANCOVA
Full Analysis Set

Five-to-fifteen domain	Atomoxetine (N=49)		Placebo (N=50)		Difference in LS means		
	LSmean	SE	LSmean	SE	Estimate	95%-CI	p-value ¹
Motor control	-0.2	0.0	-0.1	0.0	-0.1	(-0.2, -0.0)	0.012
Executive function	-0.4	0.1	-0.1	0.1	-0.3	(-0.5, -0.2)	<0.001
Perception	-0.2	0.0	-0.0	0.0	-0.2	(-0.3, -0.1)	0.004
Memory	-0.1	0.0	0.0	0.0	-0.1	(-0.3, -0.0)	0.033
Language and Speech	-0.1	0.0	-0.1	0.0	-0.1	(-0.2, 0.0)	0.115
Learning	-0.2	0.0	-0.1	0.0	-0.1	(-0.3, -0.0)	0.020
Social Competence	-0.2	0.0	-0.1	0.0	-0.1	(-0.3, -0.0)	0.009
Emotional/Behavioral	-0.2	0.0	-0.1	0.0	-0.1	(-0.2, -0.0)	0.031

¹ p-value from ANCOVA model with terms for baseline, treatment, and site.

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; N = total number of patients; SE = standard error.

Appraisal of Stress in Child-Rearing (ASCR)

Descriptive statistics for ASCR baseline scores are given in Table 17.

Table 17. ASCR Section (I) Domain Scores and ASCR Section B Score at Baseline
Descriptive Statistics
Full Analysis Set

		Atomoxetine (N=49)	Placebo (N=50)
Section (I)			
Acceptance domain	n	47	48
	Mean (SD)	2.91 (0.36)	2.82 (0.50)
	Median (Range)	3.00 (2.25, 3.50)	3.00 (0.00, 3.25)
Coping domain	n	47	48
	Mean (SD)	2.76 (0.28)	2.83 (0.31)
	Median (Range)	2.75 (2.00, 3.25)	2.81 (2.13, 3.50)
Experiencing problems domain	n	46	48
	Mean (SD)	3.20 (0.43)	3.11 (0.37)
	Median (Range)	3.14 (2.29, 4.14)	3.07 (2.43, 3.86)
Need for a change domain	n	47	48
	Mean (SD)	3.35 (0.59)	3.37 (0.45)
	Median (Range)	3.33 (2.00, 4.50)	3.42 (2.17, 4.33)
Child as a burden domain	n	47	48
	Mean (SD)	3.29 (0.39)	3.15 (0.44)
	Median (Range)	3.29 (2.43, 4.00)	3.14 (2.00, 3.86)
Managing on ones own domain	n	47	48
	Mean (SD)	2.92 (0.42)	2.88 (0.38)
	Median (Range)	3.00 (2.25, 4.00)	3.00 (2.00, 4.00)
Pleasure domain	n	47	48
	Mean (SD)	1.76 (0.58)	1.69 (0.57)
	Median (Range)	1.80 (1.00, 3.40)	1.60 (1.00, 3.00)
Relation domain	n	47	48
	Mean (SD)	3.26 (0.55)	3.33 (0.63)
	Median (Range)	3.40 (2.20, 4.20)	3.30 (2.00, 4.40)
Section B	n	47	48
	Mean (SD)	4.53 (1.43)	4.52 (1.38)
	Median (Range)	5.00 (2.00, 8.00)	4.50 (3.00, 8.00)

Abbreviations: N = total number of patients; n = number of patients in the category; SD = standard deviation.

There were no statistically significant differences between treatment groups in ASCR scores with the exception of the Child as a burden domain of ASCR section (I) (difference between treatments: -0.2; p=0.007). LS mean changes from baseline to endpoint for the ASCR section B score were -0.6 with atomoxetine and -0.4 for placebo (p=0.325). Details are given in Table 18.

Table 18. Change from Baseline to Endpoint in ASCR Section (I)
Domain Scores and ASCR Section B Score
ANCOVA
Full Analysis Set

ASCR score	Atomoxetine (N=49)		Placebo (N=50)		Difference in LS means		
	LSmean	SE	LSmean	SE	Estimate	95%-CI	p-value ¹
Section (I)							
Acceptance domain	0.0	0.1	0.0	0.1	-0.0	-0.1, 0.1	0.888
Coping domain	0.1	0.0	-0.0	0.0	0.1	-0.0, 0.2	0.069
Experiencing problems domain	0.0	0.1	0.0	0.1	-0.0	-0.2, 0.1	0.871
Need for a change domain	0.1	0.1	0.1	0.1	-0.0	-0.1, 0.2	0.549
Child as a burden domain	-0.2	0.1	0.1	0.1	-0.2	-0.4, -0.1	0.007
Managing on ones own domain	0.1	0.1	0.1	0.0	0.0	-0.1, 0.2	0.797
Pleasure domain	-0.2	0.1	-0.1	0.1	-0.1	-0.3, 0.1	0.496
Relation domain	0.1	0.1	0.1	0.1	-0.0	-0.2, 0.2	0.889
Section B	-0.6	0.2	-0.4	0.2	-0.2	-0.6, 0.2	0.325

¹ p-value from ANCOVA model with terms for baseline, treatment, and site.

Abbreviations: ASCR = Appraisal of Stress in Child-Rearing; CI = confidence interval; LS = least squares; N = total number of patients; CI = confidence interval.

Resource Utilization Questionnaire (RUQ)

The number of patients who had no direct costs either at baseline or endpoint was 30.6% (atomoxetine group) and 30.0% (placebo group) at baseline, and 68.8% and 59.2% at endpoint, respectively, and therefore it was decided to not analyze the direct costs with parametric statistical methods, but with a post-hoc bootstrap analysis instead.

At baseline, total costs were higher in the atomoxetine group than in the placebo group, which resulted from higher direct costs in the atomoxetine group. However, the majority of total costs were indirect costs, which were similar between treatment groups at baseline, as shown in Table 19.

Table 19. **ROQ - Costs (SEK) at Baseline**
Descriptive Statistics
Full Analysis Set

Costs (SEK)		Atomoxetine (N=49)	Placebo (N=50)
Direct costs	n	49	50
	Mean (SD)	4308.1 (6517.7)	2697.5 (3019.8)
	Median (Range)	2160.0 (0.0, 33737)	1419.0 (0.0, 10087)
Indirect costs	n	49	50
	Mean (SD)	7367.9 (7977.3)	7486.1 (5683.8)
	Median (Range)	5755.9 (0.0, 56207)	6004.2 (1650.9, 32241)
Total costs	n	49	50
	Mean (SD)	11676 (10183)	10184 (7128.3)
	Median (Range)	7550.5 (0.0, 58007)	7829.9 (1650.9, 37475)

1 SEK ≈ 0.1087 EUR; 9.20 SEK ≈ 1 EUR

Abbreviations: N = total number of patients; n = number of patients in the category; SD = standard deviation.

At endpoint, total costs and indirect costs had decreased in the atomoxetine group, whereas in the placebo group total and indirect costs had increased. The difference between treatment groups was statistically significant for the indirect costs ($p=0.016$) and the total costs ($p=0.001$). Details are given in Table 20. From the post-hoc bootstrap analysis, the mean difference between treatments in the change from baseline in direct costs was -3673.81 SEK with a 95% CI of (-6174.0, -1402.3 SEK).

**Table 20. ROQ – Costs (SEK) at Endpoint
Descriptive Statistics
Full Analysis Set**

Costs (SEK)		Atomoxetine (N=49)	Placebo (N=50)
Direct costs	n	48	49
	Mean (SD)	1690.8 (3297.1)	3451.8 (5471.4)
	Median (Range)	0.0 (0.0, 13413)	0.0 (0.0, 20936)
Indirect costs	n	48	49
	Mean (SD)	6940.0 (7774.0)	9060.5 (10390)
	Median (Range)	5588.2 (31.9, 52106)	6255.2 (2150.8, 70224)
Total costs	n	48	49
	Mean (SD)	8630.8 (8490.0)	12512 (13686)
	Median (Range)	5768.8 (31.9, 52106)	9573.0 (2150.8, 90967)
Change from baseline			
Indirect costs	n	48	49
	Mean (SD)	–497.1 (3757.7)	1483.9 (8761.9)
	Median (Range)	–961.8 (–9179.0, 11167.6)	673.3 (–14318.6, 56351.0)
	p-value ¹		0.016
Total costs	n	48	49
	Mean (SD)	–3204.2 (8043.2)	2285.4 (11484.3)
	Median (Range)	–2154.7 (–24162.9, 16843.6)	75.8 (–15976.0, 67811.0)
	p-value ¹		0.001

¹ 1 SEK ≈ 0.1087 EUR; 9.20 SEK ≈ 1 EUR

¹ p-value for the difference between treatments from ANCOVA model with terms for baseline cost, treatment, and site (costs were log-transformed prior to ANCOVA).

Abbreviations: N = total number of patients; n = number of patients in the category; SD = standard deviation.

Efficacy in Study Period III

Key efficacy variables in Study Period III are summarized in Table 21 by the treatment received during Study Period II, i.e., the term previous atomoxetine group refers to patients who received atomoxetine throughout Periods II and III, and previous placebo group refers to all patients who received placebo during Period II but atomoxetine during Period III.

The full 9-month duration of Study Period III was completed by 39 patients and 31 patients discontinued Study Period III according to the protocol when atomoxetine became commercially available in Sweden. The remaining 29 patients discontinued Study Period III prematurely as described in the Patient Disposition section.

Table 21. Key Efficacy Parameters at Week 10 and Endpoint of Study Period III by Treatment in Study Period II
Descriptive Statistics
Full Analysis Set

	Week 10 (Visit 7)		Endpoint	
	Atomoxetine	Placebo	Atomoxetine	Placebo
CHIP-CE Achievement domain				
n	49	47	49	50
Mean (SD)	36.6 (9.8)	32.4 (9.7)	37.5 (10.4)	38.7 (9.7)
Median (range)	35.8 (7.5, 53.5)	32.3 (14.6, 58.9)	39.4 (11.0, 53.5)	38.5 (14.6, 58.9)
CHIP-CE total score				
n	49	47	49	50
Mean (SD)	35.8 (10.6)	34.8 (10.4)	36.9 (10.9)	39.0 (10.8)
Median (range)	35.7 (3.1, 55.4)	35.9 (9.4, 56.5)	35.3 (9.3; 55.0)	38.5 (9.5, 58.0)
FBIM total score				
n	49	48	47	50
Mean (SD)	7.4 (4.8)	8.5 (5.1)	6.2 (4.3)	6.3 (4.9)
Median (range)	6.0 (0.0, 24.0)	8.0 (0.0, 21.0)	5.0 (0.0, 23.0)	6.0 (0.0, 22.0)
I Think I Am total score				
n	41	36	35	35
Mean (SD)	5.37 (1.85)	4.89 (2.04)	5.63 (2.06)	5.51 (2.05)
Median (range)	5.0 (2.0, 9.0)	5.0 (1.0, 8.0)	6.0 (1.0, 9.0)	5.0 (2.0, 9.0)
ADHD total score				
n	49	49	48	50
Mean (SD)	20.6 (11.2)	33.5 (10.0)	17.4 (9.5)	21.9 (11.2)
Median (range)	17.0 (1.0, 45.0)	33.0 (8.0, 49.0)	16.5 (2.0, 39.0)	20.0 (3.0, 46.0)
CGI-S score				
n	49	49	48	50
Mean (SD)	3.0 (1.4)	4.5 (0.9)	2.7 (1.3)	3.0 (1.2)
Median (range)	3.0 (1.0, 5.0)	5.0 (2.0, 6.0)	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)
CGI-I score				
n	49	49	48	50
Mean (SD)	2.3 (1.1)	3.7 (1.1)	2.0 (1.0)	2.3 (1.1)
Median (range)	2.0 (1.0, 5.0)	4.0 (1.0, 6.0)	2.0 (1.0, 6.0)	2.0 (1.0, 5.0)

Abbreviations: ADHD = attention deficit/hyperactivity disorder; CGI-I = Clinical Global Impressions of Improvement; CGI-S = Clinical Global Impressions of Severity; Child Health and Illness Profile-Child Edition; FBIM = Family Burden of Illness Module; n = number of patients in the category; SD = standard deviation.

Safety

Analysis of AEs included the 99 randomized patients who had taken at least one dose of study medication.

Overall Adverse Event Profile

During Study Period I, before the start of study medication, a total of 8 patients (8.1%) reported 1 AE each. These AEs were isolated events from various system organ classes (SOCs). There were no SAEs or cases of death during Study Period I.

An overview of treatment-emergent adverse events (TEAEs) that occurred during Study Periods II and III is given in Table 22.

**Table 22. Overview of TEAEs during Study Periods II and III
Descriptive Statistics
Safety Population**

Preferred term	Number (%) of patients		
	Atomoxetine	Placebo	Total
Study Period II			
Total number of treated patients	49	50	99
Patients with ≥1 TEAE	44 (89.8)	37 (74.0)	81 (81.8)
possibly related to study medication	29 (59.2)	11 (22.0)	40 (40.4)
with severe intensity	3 (6.1)	0 (0.0)	3 (3.0)
leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Patients with ≥1 serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)
Number of deaths	0 (0.0)	0 (0.0)	0 (0.0)
Study Period III¹			
Total number of treated patients	49	50	99
Patients with ≥1 TEAE	29 (59.2)	44 (88.0)	73 (73.7)
possibly related to study medication	9 (18.4)	31 (62.0)	40 (40.4)
with severe intensity	3 (6.1)	4 (8.0)	7 (7.1)
leading to discontinuation	2 (4.1)	5 (10.0)	7 (7.1)
Patients with ≥1 serious TEAE	0 (0.0)	1 (2.0)	1 (1.0)
Number of deaths	0 (0.0)	0 (0.0)	0 (0.0)

¹ Treatment groups refer to the treatment received during Period II.

Abbreviation: TEAE = treatment-emergent adverse event.

Treatment-Emergent Adverse Events in Study Period II

A TEAE was defined as an event that first occurred or else worsened after randomization (i.e., after the start of Study Period II). A total of 81 patients (81.8%) reported at least 1 TEAE during Study Period II, 89.8% in the atomoxetine group and 74.0% in the placebo group (p=0.066).

The most common TEAEs were headache (38.8% of atomoxetine patients; 18.0% of placebo patients; p=0.026), upper abdominal pain (40.8% atomoxetine; 14.0% placebo;

p=0.003), fatigue (32.7% atomoxetine; 18.0% placebo; p=0.109), anorexia (34.7% atomoxetine; 0.0% placebo; p<0.001), and nausea (28.6% atomoxetine; 4.0% placebo; p<0.001) (Table 23). There were no statistically significant differences between treatment groups in the incidence of other TEAEs.

Table 23. Summary of TEAEs during Study Period II with ≥5% of Patients in any Treatment Group
Descriptive Statistics
Safety Population

Preferred term	Number (%) of patients			p-value
	Atomoxetine (N=49)	Placebo (N=50)	Total (N=99)	
Patients with ≥1 TEAE	44 (89.8)	37 (74.0)	81 (81.8)	0.066
Patients with no TEAE	5 (10.2)	13 (26.0)	18 (18.2)	
Headache	19 (38.8)	9 (18.0)	28 (28.3)	0.026
Abdominal pain upper	20 (40.8)	7 (14.0)	27 (27.3)	0.003
Fatigue	16 (32.7)	9 (18.0)	25 (25.3)	0.109
Anorexia	17 (34.7)	0 (0.0)	17 (17.2)	<0.001
Nausea	14 (28.6)	2 (4.0)	16 (16.2)	<0.001
Vomiting	6 (12.2)	4 (8.0)	10 (10.1)	0.524
Irritability	6 (12.2)	2 (4.0)	8 (8.1)	0.159
Depressive symptom	5 (10.2)	2 (4.0)	7 (7.1)	0.268
Upper respiratory tract infection	5 (10.2)	2 (4.0)	7 (7.1)	0.268
Pyrexia	2 (4.1)	3 (6.0)	5 (5.1)	>0.999
Abdominal pain	3 (6.1)	1 (2.0)	4 (4.0)	0.362
Decreased appetite	3 (6.1)	0 (0.0)	3 (3.0)	0.117
Nasopharyngitis	0 (0.0)	3 (6.0)	3 (3.0)	0.242

Abbreviations: N = total number of patients; TEAE = treatment-emergent adverse event.

For most TEAEs the worst intensity was reported as either mild or moderate. Overall, 3 patients in the atomoxetine group reported a total of 5 TEAEs that were considered severe in intensity: 1 patient with irritability, 1 with fatigue and upper abdominal pain, and another with 2 upper abdominal pain TEAEs.

Most frequently reported (≥5% of patients) TEAEs that were considered possibly related to study medication by the investigator were fatigue (14.3% of atomoxetine patients; 10.0% of placebo patients), upper abdominal pain (20.4% atomoxetine; 2.0% placebo), anorexia (20.4% atomoxetine; 0.0% placebo), nausea (14.3% atomoxetine; 2.0% placebo), and headache (10.2% atomoxetine; 2.0% placebo).

Treatment-Emergent Adverse Events in Study Period III

A total of 73 patients (73.7%) reported at least 1 TEAE during Study Period III, 59.2% in the previous atomoxetine group and 88.0% in the previous placebo group (p=0.001) (Table 24).

The most frequently reported TEAEs were fatigue (16.3% of previous atomoxetine patients; 34.0% of previous placebo patients), upper abdominal pain (16.3% previous atomoxetine; 20.0% previous placebo), headache (12.2% previous atomoxetine; 20.0% previous placebo), anorexia (10.2% previous atomoxetine; 22.0% previous placebo), and nausea (8.2% previous atomoxetine; 20.0% previous placebo). There were no statistically significant differences for any TEAE between treatment groups based on the treatment previously received in Study Period II.

Table 24. Summary of TEAEs During Study Period III With $\geq 5\%$ of Patients in any Treatment Group, by Treatment in Period II Descriptive Statistics Safety Population

Preferred term	Number (%) of patients			p-value
	Atomoxetine (N=49)	Placebo (N=50)	Total (N=99)	
Patients with ≥ 1 TEAE	29 (59.2)	44 (88.0)	73 (73.7)	0.001
Patients with no TEAE	20 (40.8)	6 (12.0)	26 (26.3)	
Fatigue	8 (16.3)	17 (34.0)	25 (25.3)	0.063
Abdominal pain upper	8 (16.3)	10 (20.0)	18 (18.2)	0.795
Headache	6 (12.2)	10 (20.0)	16 (16.2)	0.413
Anorexia	5 (10.2)	11 (22.0)	16 (16.2)	0.171
Nausea	4 (8.2)	10 (20.0)	14 (14.1)	0.147
Gastroenteritis	4 (8.2)	2 (4.0)	6 (6.1)	0.436
Upper respiratory tract infection	3 (6.1)	3 (6.0)	6 (6.1)	>0.999
Nasopharyngitis	2 (4.1)	3 (6.0)	5 (5.1)	>0.999
Pyrexia	2 (4.1)	3 (6.0)	5 (5.1)	>0.999
Vomiting	1 (2.0)	4 (8.0)	5 (5.1)	0.362
Decreased appetite	3 (6.1)	1 (2.0)	4 (4.0)	0.362
Respiratory tract infection	0 (0.0)	3 (6.0)	3 (3.0)	0.242

Abbreviations: N = total number of patients; TEAE = treatment-emergent adverse event.

Deaths and Serious Adverse Events

Study Period II

There were no deaths and no serious adverse events (SAEs) during Study Period II.

Study Period III

There were no deaths during Study Period III.

One SAE occurred during Study Period III. For a 14-year old male patient, an orthopedic (surgical) procedure was reported that required hospitalization of the patient. The SAE was moderate in intensity and not considered related to study medication.

Discontinuations due to Adverse Events

Study Period II

There were no discontinuations due to AEs in Study Period II.

Study Period III

A total of 7 patients (7.1%) discontinued the study prematurely due to an AE during the open-label atomoxetine treatment phase (Study Period III): 2 patients (1 from each pre-treatment group) due to upper abdominal pain, and 1 patient each due to aggression, depressed mood, drug effect decreased, weight decreased (all pre-treated with placebo), and depressive symptom (pre-treated with atomoxetine). With exception of the drug effect decreased AE, all these events were considered related to atomoxetine by the investigator.

Vital Signs

Mean changes from baseline to endpoint of Study Period II in systolic blood pressure were 1.4 mmHg for atomoxetine and 0.3 mmHg for placebo. Corresponding mean changes in diastolic blood pressure were 2.0 mmHg for atomoxetine and -1.8 mmHg for placebo. Mean changes from baseline to endpoint in heart rate were 4.6 beats/min for atomoxetine and 0.8 beats/min for placebo. During Study Period III, the overall mean vital sign values changed from 106.6 mmHg at Week 10 to 107.9 mmHg at endpoint of Period III (systolic blood pressure), from 63.2 to 66.6 mmHg (diastolic blood pressure), and from 75.1 to 78.7 beats/min (heart rate).

Weight

At endpoint of Study Period II, body weight had decreased by a mean of -1.9 kg in the atomoxetine group compared with a change of 0.7 kg in the placebo group, and at endpoint of Study Period III, body weight had changed from baseline by a mean of -1.0 kg in the atomoxetine group and by 0.4 kg in the placebo group.

Height

In this study population of children aged 7-15 years, patients had grown by the end of Study Period II, by 0.9 cm in the atomoxetine group and by 1.4 cm in the placebo group. Over the course of Study Period III, patients further grew in height by an average of 2.7 cm, from 151.1 cm at Week 10 to 153.8 cm at endpoint of Period III.

Summary ID# 6934

Clinical Study Summary: Study B4Z-MC-LYBR

Title of Study: A Randomized, Double-Blind Comparison, Safety and Efficacy Trial of Atomoxetine Hydrochloride and Methylphenidate Hydrochloride in Pediatric Outpatients with DSM-IV Attention-Deficit/Hyperactivity Disorder

Date summary approved by Lilly: 10 August 2005

Brief Summary of Results

Data from this randomized, double-blind study comparing atomoxetine and methylphenidate in 330 pediatric outpatients diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD) showed that:

- After an acute treatment period of approximately 8 weeks, 77.4% of subjects treated with atomoxetine responded to treatment, compared with 81.5% of those on methylphenidate. The results of the primary efficacy analysis demonstrated that atomoxetine is noninferior to methylphenidate in the improvement of ADHD symptoms based on criteria defined *a priori*. Response was defined as a reduction of 40% or greater from baseline to endpoint in the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) scale total score.
- Repeated-measures and last-observation-carried-forward (LOCF) mean change analyses using an analysis of covariance (ANCOVA) model show that both atomoxetine and methylphenidate were associated with statistically significant improvements in ADHD symptoms, including inattention and hyperactivity/impulsivity. Scores for both treatment groups were comparable throughout the acute treatment period. There were no differences based on gender, age, ADHD subtype, prior stimulant medication use, or the presence of comorbid oppositional defiant disorder.

- Atomoxetine was associated with a statistically significantly greater rate of treatment-emergent adverse events (TEAEs) than methylphenidate. Anorexia, nausea, somnolence, dizziness, and vomiting were statistically significantly more likely to be reported in atomoxetine-treated subjects than in those treated with methylphenidate. Subjects treated with atomoxetine also were statistically significantly more likely to experience weight loss. There were no deaths reported during the study. One serious adverse event, a focal motor convulsion, was reported for a subject randomized to atomoxetine.

Title of Study: A Randomized, Double-Blind Comparison, Safety and Efficacy Trial of Atomoxetine Hydrochloride and Methylphenidate Hydrochloride in Pediatric Outpatients with DSM-IV Attention-Deficit/Hyperactivity Disorder	
Investigator(s): This multicenter study included 13 principal investigators.	
Study Center(s): This study was conducted at 13 study centers in 3 countries.	
Length of Study: Approximately 9 months Date first subject enrolled: 06 January 2004 Date last subject completed: 17 October 2004	Phase of Development: 3
Objectives: The <u>primary</u> objective of this study was to test the hypothesis that atomoxetine is noninferior to methylphenidate in improving Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms following a double-blind treatment period of approximately 8 weeks. Assessment was based on a comparison of response rates derived from the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) scale. <u>Secondary</u> objectives included a comparison of the tolerability of atomoxetine and methylphenidate as assessed by treatment-emergent adverse events, and an assessment of the comparability of the efficacy of atomoxetine and methylphenidate based on the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) and the Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity (CGI-ADHD-S) scale.	
Study Design: Study B4Z-MC-LYBR (LYBR) was a multicountry, multicenter, randomized, double-blind study comparing atomoxetine and methylphenidate in 330 pediatric outpatients who met <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</i>TM (DSM-IVTM) diagnostic criteria for ADHD. The trial comprised three study periods and included an initial randomization of all subjects to acute treatment. After an initial screening period, eligible subjects were randomized in a double-blind fashion to receive atomoxetine or methylphenidate for approximately 8 weeks. Study drug dosage was adjusted by the physician based on an assessment of response and tolerability. This phase was followed by a discontinuation phase of approximately 1 week during which physicians assessed each subject's safety and tolerability after study drug discontinuation.	
Number of Subjects: Planned: Approximately 330 pediatric outpatients (165 subjects per treatment group) Randomized: 164 atomoxetine, 166 methylphenidate Completed: 138 atomoxetine, 152 methylphenidate	
Diagnosis and Main Criteria for Inclusion: Subjects 6 through 16 years of age at Visit 1 who met DSM-IV diagnostic criteria for ADHD (any subtype) as determined by a physician investigator's clinical assessment. Diagnosis was confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL) semi-structured interview. Criteria included a severity rating ≥ 25 for boys or ≥ 22 for girls, or a rating > 12 for a specific subtype on the ADHDRS-IV-Parent:Inv score, and a CGI-ADHD-S score ≥ 4 at both Visit 1 and Visit 2.	
Test Product, Dose, and Mode of Administration: Atomoxetine hydrochloride, 0.8 mg/kg/day to 1.8 mg/kg/day, given once daily as oral capsules (in dosage strengths of 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, and 40 mg).	
Reference Therapy, Dose, and Mode of Administration: Methylphenidate hydrochloride, 0.2 mg/kg/day up to 0.6 mg/kg/day, given twice daily as oral capsules (in dosage strengths of 5 mg and 10 mg). [To maintain blinding, subjects in the atomoxetine treatment group also received placebo once daily.]	
Duration of Treatment: 8 weeks of acute treatment: Atomoxetine Frequency: Once daily for 8 weeks Methylphenidate Frequency: Twice daily for 8 weeks	

Variables:

Efficacy: Improvement of ADHD symptoms by comparing the percentage of responders derived from the ADHDRS-IV-Parent:Inv Total score. Secondary efficacy variables included ADHDRS-IV-Parent:Inv Total and subscale scores; subscores of the CPRS-R:S scale; and the CGI-ADHD-S Score.

Safety: Assessment of adverse events (AEs), including serious adverse events (SAEs); vital signs; height and weight; routine laboratory tests; and electrocardiograms (ECGs).

Evaluation Methods:

Statistical: As the primary efficacy analysis, a one-sided 95% exact confidence interval on the difference in percentage of responders (atomoxetine minus methylphenidate) was constructed to test noninferiority between atomoxetine and methylphenidate. Response was defined as a reduction of at least 40% from baseline at endpoint on the ADHDRS-IV-Parent:Inv Total score. Noninferiority was declared if the one-sided 95% lower confidence limit was greater than -18%. Treatment effects over time were evaluated using repeated measures analysis based on the restricted maximum likelihood method, assuming an unstructured covariance matrix. A Satterthwaite approximation was used for the denominator degrees of freedom in the t-test. Totals and subtotals of the efficacy rating scale were also analyzed by calculating the change from baseline to last-observation-carried-forward (LOCF) endpoint using analysis of covariance (ANCOVA). The sample size provided approximately 95% power to declare overall noninferiority of atomoxetine to methylphenidate under the assumption that the 2 treatment groups would have equal response rates of 62%. In particular, the sample size of 240 subjects from one country provided approximately 90% power to declare noninferiority of atomoxetine to methylphenidate under the same assumption.

Results:

Subject Demographics

Table LYBR.1 presents a summary of subject demographics for this study. Of the 330 subjects who were randomized to treatment, 270 (81.8%) were male, 302 (91.5%) were Asian, and 250 (75.8%) had no prior stimulant exposure. Demographics and other characteristics were comparable for the two treatment groups, although the mean age of subjects in the methylphenidate group was statistically significantly higher than that of the atomoxetine group (methylphenidate 9.91 years, atomoxetine 9.40 years, $p=.035$). Overall mean age was 9.65 years (range of 6.22 years to 16.68 years).

At baseline, 59.4% of the randomized subjects met the criteria for the combined ADHD subtype on the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version:Behavioral Disorders Supplement (K-SADS-PL:Behavioral), and 37.6% were classified as predominantly inattentive.

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**Table LYBR.1. Summary of Demographics and Other Subject Characteristics
All Randomized Subjects**

VARIABLE	Atomoxetine (N=164)	Methylphenidate (N=166)	TOTAL (N=330)	P-value
AGE				
No. of Subjects	164	166	330	.035**
Mean	9.40	9.91	9.65	
Median	9.04	9.49	9.24	
Standard Deviation	2.04	2.32	2.19	
Minimum	6.26	6.22	6.22	
Maximum	15.35	16.68	16.68	
AGE < 12 YR	142 (86.6)	131 (78.9)	273 (82.7)	.080*
AGE >= 12 YR	22 (13.4)	35 (21.1)	57 (17.3)	
GENDER				
No. of Subjects	164	166	330	.669*
Female	28 (17.1)	32 (19.3)	60 (18.2)	
Male	136 (82.9)	134 (80.7)	270 (81.8)	

*FREQUENCIES ARE ANALYZED USING A FISHER'S EXACT TEST

**MEANS ANALYZED USING TYPE III SUM OF SQUARES ANALYSIS OF VARIANCE (ANOVA)

(continued)

Atomoxetine hydrochloride

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**Table LYBR.1. Summary of Demographics and Other Subject Characteristics
All Randomized Subjects (Continued)**

VARIABLE	Atomoxetine (N=164)	Methylphenidate (N=166)	TOTAL (N=330)	P-value

ORIGIN				
No. of Subjects	164	166	330	1.00*
East/Southeast Asia	150 (91.5)	152 (91.6)	302 (91.5)	
Hispanic	14 (8.5)	14 (8.4)	28 (8.5)	
HEIGHT				
No. of Subjects	150	159	309	.261**
Mean	136.71	138.49	137.63	
Median	134.00	136.00	135.00	
Standard Deviation	13.60	14.18	13.91	
Minimum	115.00	111.00	111.00	
Maximum	174.00	177.00	177.00	
WEIGHT				
No. of Subjects	153	161	314	.093**
Mean	33.45	35.38	34.44	
Median	31.00	32.50	31.75	
Standard Deviation	9.68	10.55	10.16	
Minimum	20.00	20.20	20.00	
Maximum	60.00	60.00	60.00	

 *FREQUENCIES ARE ANALYZED USING A FISHER'S EXACT TEST

**MEANS ANALYZED USING TYPE III SUM OF SQUARES ANALYSIS OF VARIANCE (ANOVA)

(continued)

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**Table LYBR.1. Summary of Demographics and Other Subject Characteristics
All Randomized Subjects (Continued)**

VARIABLE	Atomoxetine (N=164)	Methylphenidate (N=166)	TOTAL (N=330)	P-value

CY2D6 Phenotype Extn Slow				
No. of Subjects	161	162	323	.574*
ERROR	2 (1.2)	1 (0.6)	3 (0.9)	
EXTN	157 (97.5)	160 (98.8)	317 (98.1)	
SLOW	2 (1.2)	1 (0.6)	3 (0.9)	
DSM-IV ADHD Subtype				
No. of Subjects	164	166	330	.645*
Hyperactive	4 (2.4)	6 (3.6)	10 (3.0)	
Inattentive	59 (36.0)	65 (39.2)	124 (37.6)	
Combined	101 (61.6)	95 (57.2)	196 (59.4)	
Previous Stimulant Use				
No. of Subjects	164	166	330	.701*
No	126 (76.8)	124 (74.7)	250 (75.8)	
Yes	38 (23.2)	42 (25.3)	80 (24.2)	

 *FREQUENCIES ARE ANALYZED USING A FISHER'S EXACT TEST

**MEANS ANALYZED USING TYPE III SUM OF SQUARES ANALYSIS OF VARIANCE (ANOVA)

(continued)

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**Table LYBR.1. Summary of Demographics and Other Subject Characteristics
All Randomized Subjects (Continued)**

VARIABLE	Atomoxetine (N=164)	Methylphenidate (N=166)	TOTAL (N=330)	P-value

Family Hist ADHD-Mother				
No. of Subjects	163	166	329	.750*
No	159 (97.5)	159 (95.8)	318 (96.7)	
Unknown	0 (0.0)	1 (0.6)	1 (0.3)	
Yes	4 (2.5)	6 (3.6)	10 (3.0)	
Family Hist ADHD-Father				
No. of Subjects	163	166	329	.741*
No	145 (89.0)	145 (87.3)	290 (88.1)	
Unknown	3 (1.8)	2 (1.2)	5 (1.5)	
Yes	15 (9.2)	19 (11.4)	34 (10.3)	
Family Hist ADHD-Grandp				
No. of Subjects	163	166	329	1.00
No	149 (91.4)	150 (90.4)	299 (90.9)	
Unknown	12 (7.4)	13 (7.8)	25 (7.6)	
Yes	2 (1.2)	3 (1.8)	5 (1.5)	

 *FREQUENCIES ARE ANALYZED USING A FISHER'S EXACT TEST

**MEANS ANALYZED USING TYPE III SUM OF SQUARES ANALYSIS OF VARIANCE (ANOVA)
 (continued)

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**Table LYBR.1. Summary of Demographics and Other Subject Characteristics
All Randomized Subjects (Concluded)**

VARIABLE	Atomoxetine (N=164)	Methylphenidate (N=166)	TOTAL (N=330)	P-value

Family Hist ADHD-Sib				
No. of Subjects	163	166	329	.805*
No	45 (27.6)	51 (30.7)	96 (29.2)	
Not Applicable	108 (66.3)	104 (62.7)	212 (64.4)	
Unknown	2 (1.2)	1 (0.6)	3 (0.9)	
Yes	8 (4.9)	10 (6.0)	18 (5.5)	

*FREQUENCIES ARE ANALYZED USING A FISHER'S EXACT TEST

**MEANS ANALYZED USING TYPE III SUM OF SQUARES ANALYSIS OF VARIANCE (ANOVA)

Subject Disposition

A total of 361 subjects entered the study at Visit 1, and 330 were assigned to treatment (164 atomoxetine, 166 methylphenidate). Of the 330 subjects randomized, 290 (87.9%) completed acute treatment.

The methylphenidate treatment group had a statistically significantly higher ($p=.044$) completion rate than the atomoxetine group (91.6% versus 84.1%). Statistically significantly more ($p=.011$) atomoxetine-treated subjects discontinued due to adverse events compared with methylphenidate-treated subjects (11% versus 3.6%). An analysis of study discontinuation by visit showed that half of the discontinuations due to adverse events in the atomoxetine group happened early, particularly during the first two visits of the double-blind treatment period.

Figure LYBR.1 presents a summary of subject disposition for the screening/washout and double-blind treatment periods.

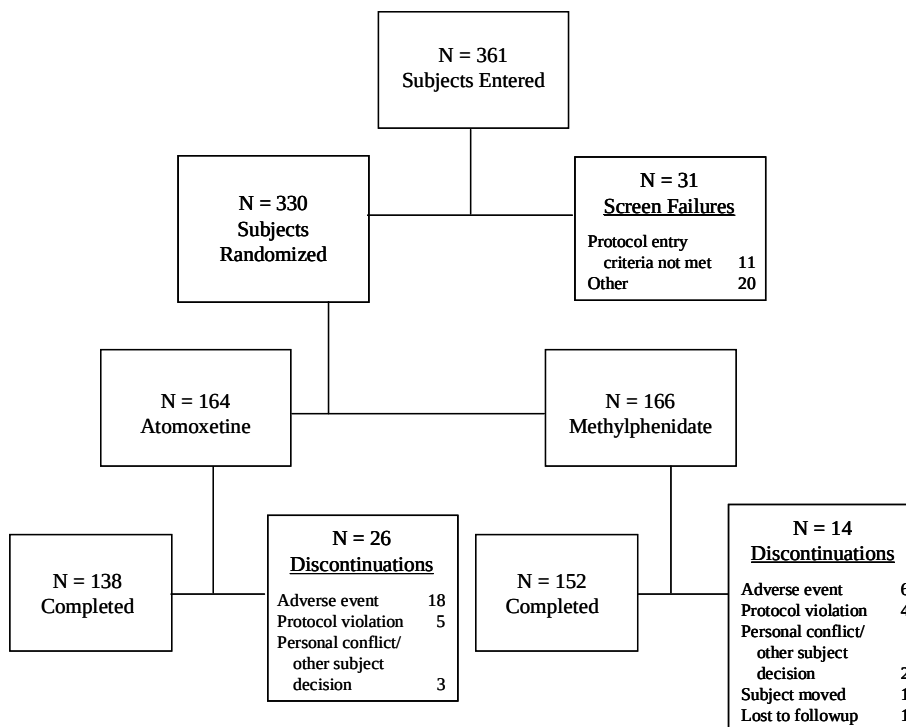


Figure LYBR.1. Subject disposition.

Primary Efficacy Measure

Table LYBR.2 summarizes results of the primary efficacy analysis, which examined noninferiority between atomoxetine and methylphenidate by comparing the response rates for the atomoxetine and methylphenidate treatment groups on the ADHDRS-IV-Parent:Inv Total score. The analysis included randomized subjects with a baseline and at least one postbaseline ADHDRS-IV-Parent:Inv Total score who had no more than one visit during which the subject was noncompliant. Because the lower bound of the 1-sided 95% exact confidence interval (-11.7%) on the difference in response rates (atomoxetine minus methylphenidate) was greater than the pre-specified noninferiority margin (-18%), these results met the primary efficacy objective and supported the hypothesis that atomoxetine was noninferior to methylphenidate in this study. The results from a similar analysis for the intent-to-treat population were consistent with the data shown in Table LYBR.2 (lower bound of the 1-sided 95% exact confidence interval was -12.8%, $p=0.282$).

**Table LYBR.2. Atomoxetine versus Methylphenidate
Response Rates: $\geq 40\%$ Reduction from Baseline
Based on ADHDRS-IV-Parent:Inv Total Score
Compliant Subjects***

Therapy	N	Responders *		95% Confidence Interval For ATX%-MPH%
		N	%	
Atomoxetine	159	123	77.4	1-sided: (-11.7, --) 2-sided: (-13.2, 4.9) p-value**: 0.405
Methylphenidate	157	128	81.5	

Abbreviations: ATX = atomoxetine; MPH = methylphenidate.

* Subjects who had no more than one non-compliant visit.

** P-value is based on Fisher's exact test.

Secondary Efficacy Measures

Secondary efficacy analyses (of the intent-to-treat population) were conducted using the ADHDRS-IV-Parent:Inv Total and subscale scores (Inattention, Hyperactivity/Impulsivity), as well as the Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity (CGI-ADHD-S) scale and Conners' Parent Rating Scale-Revised:Short Form (CPRS-R:S) subscales. These analyses included the following approaches:

- Repeated measures analysis with independent effects for country, investigator (nested within country), treatment, visit, baseline total score, and treatment-by-visit interaction in the model.

- Mean change from baseline to last observation carried forward (LOCF) endpoint with independent effects for country, investigator (nested within country), treatment, and baseline total score in the analysis of covariance (ANCOVA) model.

In all of the secondary efficacy analyses, both treatment groups were associated with statistically significant improvements in ADHD symptoms. Repeated measures analyses comparing the two treatments on the ADHDRS-IV-Parent:Inv Inattention Subscale, ADHDRS-IV-Parent:Inv Hyperactivity-Impulsivity Subscale, and CGI-ADHD-S scale all showed statistically significant improvement for both groups, starting at Visit 3. The improvement noted throughout acute (double-blind) treatment was comparable for the two groups. There were no statistically significant differences between groups at any visit.

Table LYBR.3 presents results for one of the secondary efficacy analyses, showing the least squares means of change from baseline for each treatment group and the treatment comparisons at each postbaseline visit for ADHDRS-IV-Parent:Inv Total scores. The data show that subjects in both treatment groups experienced statistically significant reductions ($p < .001$) in baseline scores at each visit, indicating improvement in their ADHD symptoms (atomoxetine mean change from baseline ranged from -8.17 at Visit 3 to -21.66 at Visit 8; methylphenidate mean change ranged from -6.50 at Visit 3 to -21.85 at Visit 8). The improvement observed throughout the double-blind treatment period was comparable for the two treatment groups, although subjects in the atomoxetine group experienced a statistically significantly greater reduction ($p = .018$) from baseline at Visit 3.

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**Table LYBR.3. Repeated Measures Analysis of ADHDRS-IV-Parent:Inv
Total Score
Change from Baseline
All Randomized Subjects**

VISIT	-----Atomoxetine-----			-----Methylphenidate-----			----- DIFFERENCE -----		
	LS MEAN	SE	P-VAL A	LS MEAN	SE	P-VAL A	LS MEAN	SE	P-VAL B
3	-8.17	0.60	<.001	-6.50	0.60	<.001	1.67	0.70	.018
4	-12.41	0.65	<.001	-11.74	0.64	<.001	0.67	0.78	.392
5	-15.61	0.67	<.001	-15.36	0.66	<.001	0.25	0.81	.757
6	-17.46	0.72	<.001	-16.72	0.71	<.001	0.74	0.90	.410
7	-20.16	0.72	<.001	-20.04	0.70	<.001	0.11	0.88	.899
8	-21.66	0.74	<.001	-21.85	0.72	<.001	-0.19	0.92	.833

GEOCODE	3.32	0.0375
INVP (GEOCODE)	4.94	<.0001
TRTMNT	0.66	0.4159
VISIT	163.38	<.0001
BASELINE	58.83	<.0001
TRTMNT*VISIT	1.26	0.2818

MODEL: CHANGE = COUNTRY CODE,VISIT,IMPUTED BASELINE SCORE,POOLED INVESTIGATOR NUMBER(COUNTRY CODE),
TREATMENT,INTERACTION OF VISIT BY TREATMENT
COVARIANCE STRUCTURE = UNSTRUCTURED, VISITS: 3-8
A P-VALUES ARE FROM TESTS FOR A NONZERO LEAST SQUARES MEAN AT THE GIVEN VISIT
B P-VALUES ARE FROM TESTS FOR A TREATMENT DIFFERENCE IN LEAST SQUARES MEAN AT THE GIVEN VISIT
C P-VALUES ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE

Table LYBR.4 summarizes one of the mean change analyses, showing the mean change from baseline to LOCF endpoint in ADHDRS-IV-Parent:Inv Total and subscale scores (Inattention and Hyperactivity-Impulsivity). Total and subscale scores showed statistically significant changes ($p < .001$) from baseline to endpoint during double-blind treatment for both groups. There were no statistically significant differences between treatment groups.

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Table LYBR.4. ADHDRS-IV-Parent:Inv Total and Subscale Scores
Mean Change from Baseline to Endpoint
All Randomized Subjects

Variable		Baseline		Endpoint		Change		Within Group	Between Group
Treatment	N	Mean	SD	Mean	SD	Mean	SD	p-value (a)	p-value (b)
TOTAL SCORE									
Atomoxetine	162	38.63	7.61	17.57	9.12	-21.06	10.33	<.001	0.155
Methylphenidate	164	37.40	7.64	15.84	8.90	-21.57	9.56	<.001	—
95% Confidence Interval for Treatment Difference: (-0.49 , 3.08)									
INATTENTIVE SUBSCALE									
Atomoxetine	162	21.75	3.53	10.42	4.76	-11.33	5.67	<.001	0.054
Methylphenidate	164	21.40	3.77	9.37	4.90	-12.02	5.40	<.001	—
95% Confidence Interval for Treatment Difference: (-0.02 , 1.97)									
HYP/IMP SUBSCALE									
Atomoxetine	162	16.88	5.56	7.15	5.02	-9.73	5.84	<.001	0.432
Methylphenidate	164	16.01	5.60	6.46	4.85	-9.54	5.48	<.001	—
95% Confidence Interval for Treatment Difference: (-0.56 , 1.30)									

(a): P-value is from paired t-test.

(b): P-value is based on an ANCOVA on change from baseline scores with terms for baseline, treatment, country, investigator(nested within country).

Table LYBR.5 summarizes the mean change from baseline to LOCF endpoint in the CGI-ADHD-S score. Higher scores indicate greater severity. Baseline mean for both therapies was 5.30, which indicates “markedly ill” to “severely ill.” At endpoint, the mean score in the atomoxetine treatment group was 2.97, indicating severity had lessened to “mildly ill,” while 2.80 was the endpoint mean in the methylphenidate treatment group. The results of this analysis show that both atomoxetine and methylphenidate were associated with statistically significant mean change on this scale.

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Table LYBR.5. CGI-ADHD-S
Mean Change from Baseline to Endpoint
All Randomized Subjects

Variable		Baseline		Endpoint		Change		Within Group	Between Group
Treatment	N	Mean	SD	Mean	SD	Mean	SD	p-value (a)	p-value (b)
Atomoxetine	162	5.30	0.81	2.97	1.21	-2.33	1.39	<.001	0.154
Methylphenidate	164	5.30	0.85	2.80	1.16	-2.50	1.33	<.001	—

95% Confidence Interval for Treatment Difference: (-0.07 , 0.42)

(a): P-value is from paired t-test.

(b): P-value is based on an ANCOVA on change from baseline scores with terms for baseline, treatment, country, investigator(nested within country).

Table LYBR.6 summarizes the mean change from baseline to endpoint on the CPRS-R:S ADHD Index, Cognitive Problems/Inattention, Hyperactivity, and Oppositional subscale scores. Higher scores indicate more frequent display of symptoms.

Both atomoxetine and methylphenidate demonstrated statistically significant improvement ($p < .001$) on each of the subscales. There were no statistically significant differences between the two treatment groups on any of the subscales.

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Table LYBR.6. CPRS-R:S
Mean Change from Baseline to Endpoint
All Randomized Subjects

Variable		Baseline		Endpoint		Change		Within Group	Between Group
Treatment	N	Mean	SD	Mean	SD	Mean	SD	p-value (a)	p-value (b)
CPRS ADHD Index									
Atomoxetine	157	26.55	6.13	15.43	6.61	-11.12	7.71	<.001	0.952
Methylphenidate	162	26.30	5.42	15.32	6.76	-10.98	7.77	<.001	—
95% Confidence Interval for Treatment Difference: (-1.34 , 1.42)									
CPRS Cognitive Problems									
Atomoxetine	157	13.67	3.58	7.86	4.01	-5.81	4.24	<.001	0.455
Methylphenidate	162	13.46	3.57	7.45	4.04	-6.01	4.67	<.001	—
95% Confidence Interval for Treatment Difference: (-0.51 , 1.14)									
CPRS Hyperactive Score									
Atomoxetine	157	10.84	4.49	4.97	4.02	-5.87	4.81	<.001	0.190
Methylphenidate	162	10.02	4.20	5.15	3.88	-4.87	4.26	<.001	—
95% Confidence Interval for Treatment Difference: (-1.25 , 0.25)									
CPRS Oppositional Score									
Atomoxetine	157	9.90	3.92	6.89	3.62	-3.01	3.93	<.001	0.084
Methylphenidate	162	9.58	3.98	6.19	3.61	-3.40	4.13	<.001	—
95% Confidence Interval for Treatment Difference: (-0.08 , 1.32)									

(a): P-value is from paired t-test.

(b): P-value is based on an ANCOVA on change from baseline scores with terms for baseline, treatment, country, investigator(nested within country).

Safety

The analysis of adverse events in this study included the 330 enrolled subjects who took at least 1 dose of study drug. Subjects who received study medication (randomized subjects) were assumed to have taken at least 1 dose unless it was documented otherwise. For inclusion into the analysis of clinical laboratory values, vital signs, and ECG data, subjects also must have had a baseline and at least 1 postbaseline measurement.

There were no deaths reported in this study. A serious adverse event was reported for a 6-year-old male subject assigned to atomoxetine treatment; the subject discontinued from the study due to a focal motor convulsion. This event was considered by the investigator to be possibly related to study medication or procedures. Anorexia, nausea, somnolence, dizziness, and vomiting were reported statistically significantly more often among atomoxetine-treated subjects than in methylphenidate-treated subjects. Most TEAEs for the two groups (88.6%) were reported to be mild or moderate in severity.

Table LYBR.7 contains a summary of TEAEs reported in $\geq 5\%$ of randomized subjects who had taken at least one dose of study drug.

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**Table LYBR.7. Summary of Treatment-Emergent Adverse Events
with ≥5% Incidence
Randomized Subjects Who Took at Least
One Dose of Study Drug**

Preferred Term	ATOMOX (N=164) n (%)	Methyl. (N=166) n (%)	TOTAL (N=330) n (%)	Fisher's Exact p-value
SUBJECTS WITH ≥1 TESS	142 (86.6)	112 (67.5)	254 (77.0)	<.001
SUBJECTS WITH NO TESS	22 (13.4)	54 (32.5)	76 (23.0)	<.001
Anorexia	61 (37.2)	42 (25.3)	103 (31.2)	.024
Decreased appetite	46 (28.0)	32 (19.3)	78 (23.6)	.070
Nausea	33 (20.1)	17 (10.2)	50 (15.2)	.014
Somnolence	43 (26.2)	6 (3.6)	49 (14.8)	<.001
Headache	25 (15.2)	16 (9.6)	41 (12.4)	.135
Dizziness	25 (15.2)	12 (7.2)	37 (11.2)	.024
Abdominal pain	15 (9.1)	15 (9.0)	30 (9.1)	1.00
Pyrexia	11 (6.7)	17 (10.2)	28 (8.5)	.324
Vomiting	19 (11.6)	6 (3.6)	25 (7.6)	.007
Cough	11 (6.7)	10 (6.0)	21 (6.4)	.825
Upper respiratory tract infection	9 (5.5)	11 (6.6)	20 (6.1)	.818
Fatigue	13 (7.9)	5 (3.0)	18 (5.5)	.055
Irritability	7 (4.3)	10 (6.0)	17 (5.2)	.620
Rhinorrhoea	7 (4.3)	10 (6.0)	17 (5.2)	.620
Insomnia	5 (3.0)	9 (5.4)	14 (4.2)	.414

Eighteen (11%) subjects in the atomoxetine group and 6 (3.6%) in the methylphenidate group discontinued due to adverse events. This difference was statistically significant ($p=.011$). The most frequently reported AEs that led to study discontinuation for subjects in both treatment groups were anorexia (5 subjects atomoxetine, 1 subject methylphenidate), decreased appetite (2 atomoxetine, 2 methylphenidate), nausea (2 atomoxetine, 1 methylphenidate), and abdominal pain (2 atomoxetine).

Table LYBR.8 presents a summary of the number and percent of subjects who discontinued from the study due to AEs.

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**Table LYBR.8. Summary of Discontinuations Due to Adverse Events
Randomized Subjects Who Took at Least One Dose of Study Drug**

Preferred Term	Atomoxetine (N=164)	Methylphenidate (N=166)	TOTAL (N=330)	FISHERS EXACT P-VALUE
	n (%)	n (%)	n (%)	
SUBJECTS DISCONTINUED	18 (11.0%)	6 (3.6%)	24 (7.3%)	0.011
Anorexia	5 (3.0%)	1 (0.6%)	6 (1.8%)	0.120
Decreased appetite	2 (1.2%)	2 (1.2%)	4 (1.2%)	1.000
Nausea	2 (1.2%)	1 (0.6%)	3 (0.9%)	0.622
Abdominal pain	2 (1.2%)	0 (0.0%)	2 (0.6%)	0.246
Chest pain	1 (0.6%)	0 (0.0%)	1 (0.3%)	0.497
Constipation	1 (0.6%)	0 (0.0%)	1 (0.3%)	0.497
Dermatitis medicamentosa	1 (0.6%)	0 (0.0%)	1 (0.3%)	0.497
Dizziness	0 (0.0%)	1 (0.6%)	1 (0.3%)	1.000
Palpitations	0 (0.0%)	1 (0.6%)	1 (0.3%)	1.000
Rash	1 (0.6%)	0 (0.0%)	1 (0.3%)	0.497
Simple partial seizures	1 (0.6%)	0 (0.0%)	1 (0.3%)	0.497
Somnolence	1 (0.6%)	0 (0.0%)	1 (0.3%)	0.497
Varicella	1 (0.6%)	0 (0.0%)	1 (0.3%)	0.497

Change from baseline to endpoint was computed for each analyte and treatment group differences were assessed using ANOVA with country, investigator (nested within country), and treatment as independent effects in the model.

Table LYBR.9 summarizes the mean change from baseline to endpoint by treatment group for analytes for which there were statistically significant changes during double-blind treatment. Statistically significant treatment differences in mean change scores were observed for alkaline phosphatase (ALP) and creatine phosphokinase.

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Table LYBR.9. Summary of Statistically Significant Laboratory Data
Mean Change from Baseline to Endpoint - Ranked
Randomized Subjects Who Took at Least One Dose of Study Drug

Laboratory Group: Clinical Chemistry								
Lab Test	Lab Unit	Therapy	N	----Baseline----		Change to ----Endpoint----		--P-value -- Therapy*
				Mean	STD	Mean	STD	
ALKALINE PHOSPHATASE	%URL	ATOMOX	142	77.77	22.09	-6.35	10.67	<.001
		Methyl.	154	77.23	20.74	-2.39	10.59	
CREATINE PHOSPHOKINASE	%URL	ATOMOX	142	79.67	38.90	-7.90	39.66	.041
		Methyl.	154	83.61	50.20	7.90	151.16	

Alkaline phosphatase and creatine phosphokinase were normalized.

N = Total number of Subjects in each treatment group having the variable in both baseline and postbaseline visits.

* Type III Sums of Squares from an ANOVA on the ranks: model=Country, Pooled Investigator(nested within Country) and Therapy.

Table LYBR.10 presents the percentage of subjects who had laboratory values that were normal at baseline, but were found to be statistically significantly abnormal (above or below the normal range) at endpoint. Statistically significantly more atomoxetine-treated subjects had high levels of calcium or abnormal urinalysis-protein than methylphenidate-treated subjects. Statistically significantly more methylphenidate-treated subjects had high laboratory values for alkaline phosphatase, high uric acid values, or low values for urinalysis-specific gravity tests.

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Table LYBR.10. Summary of Laboratory Data
Frequency of Subjects with Abnormal Laboratory Values after Baseline
Randomized Subjects Who Took at Least One Dose of Study Drug

Lab Test	Direction	-----ATOMOX			-----Methyl.			P-value*
		N	n	Percent	N	n	Percent	
ALKALINE PHOSPHATASE	High	125	0	0.0	134	9	6.7	.004
	Low	145	0	0.0	155	0	0.0	
CALCIUM	High	133	19	14.3	145	8	5.5	.015
	Low	144	1	0.7	155	0	0.0	
URIC ACID	High	136	6	4.4	139	16	11.5	.044
	Low	145	1	0.7	155	1	0.6	
UA-PROTEIN	Abnormal	125	28	22.4	133	13	9.8	.006
UA-SPECIFIC GRAVITY	High	146	0	0.0	155	0	0.0	.031
	Low	138	0	0.0	153	6	3.9	

* Frequencies are analyzed using Fisher's Exact test.

N = number of at risk subjects with a baseline and postbaseline measurement.

n = number of at risk subjects with the specific lab result (e.g. High).

Table LYBR.11 shows mean change comparisons between the two treatment groups in terms of vital signs and weight, calculated from baseline to endpoint. Subjects in the atomoxetine group experienced a statistically significant ($p < .001$) average weight loss of 1.2 kg compared to weight loss of 0.42 kg in the methylphenidate group during double-blind treatment. No other vital sign measure was statistically significantly different between groups.

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**Table LYBR.11. Summary of Vital Signs and Weight
Mean Change from Baseline to Endpoint
Randomized Subjects Who Took at Least One Dose of Study Drug**

Variable		Baseline		Endpoint		Change		Within Group	Between Group
Treatment	N	Mean	SD	Mean	SD	Mean	SD	p-value (a)	p-value (b)
DIASAVG									
Atomoxetine	162	62.31	8.22	65.63	9.00	3.33	10.08	<.001	0.646
Methylphenidate	164	63.08	8.17	65.90	8.35	2.82	9.61	<.001	—
SYSAVG									
Atomoxetine	162	100.11	10.35	102.15	10.71	2.04	11.08	0.020	0.927
Methylphenidate	164	101.10	9.87	103.35	10.37	2.25	10.75	0.008	—
PULSAVG									
Atomoxetine	162	84.56	10.52	90.40	11.26	5.84	12.77	<.001	0.174
Methylphenidate	164	83.75	11.01	87.61	12.29	3.87	12.85	<.001	—
WEIGHT									
Atomoxetine	162	33.63	9.72	32.43	9.44	-1.20	1.40	<.001	<.001
Methylphenidate	164	35.28	10.57	34.87	10.61	-0.42	1.34	<.001	—
HEIGHT									
Atomoxetine	151	136.81	13.62	137.72	13.50	0.91	1.13	<.001	0.285
Methylphenidate	157	138.23	13.93	139.30	13.82	1.07	1.41	<.001	—
TEMP									
Atomoxetine	162	36.37	0.39	36.35	0.34	-0.02	0.39	0.600	0.222
Methylphenidate	164	36.38	0.34	36.42	0.34	0.04	0.37	0.202	—

DIASAVG=Diastolic Blood Pressure; SYSAVG=Systolic Blood Pressure; PULSAVG=Pulse; WEIGHT=Weight in KG; HEIGHT=Height in CM; TEMP=Temperature in Centigrade.

(a): P-value is from paired t-test.

(b): Type III Sums of Squares from an ANOVA: PROC GLM model= country, investigator(nested within country) and treatment.

Table LYBR.12 summarizes the comparison of change from baseline to endpoint for heart rate and ECG intervals (RR, PR, QRS, QT, and QT corrected using Bazett's, Fridericia's, and data-corrected methods) between atomoxetine and methylphenidate. Both drugs were associated with a statistically significant increase ($p < .001$) in heart rate; the difference between the mean increase in heart rate for atomoxetine (8.51 bpm) and methylphenidate (4.76 bpm) also was statistically significant ($p = .005$). Statistically significant separation also was noted between the two treatment groups in ECG intervals (RR, QRS, PR, and QT). There were no statistically significant differences between treatment groups on QT intervals using QTcF, QTcB, and QTcD correction formulae.

Analyses assessing the percentage of subjects in each treatment group who met the criteria for potentially clinically significant changes in corrected QTc interval and heart rate following baseline indicated no statistically significant differences in categorical changes in QT intervals.

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**Table LYBR.12. Summary of Mean Change to Endpoint for ECG Data
Randomized Subjects Who Took at Least One Dose of Study Drug**

Variable		Baseline		Endpoint		Change		Within Group	Between Group
Treatment	N	Mean	SD	Mean	SD	Mean	SD	p-value (a)	p-value (b)
HR									
Atomoxetine	152	78.24	10.32	86.76	12.57	8.51	11.54	<.001	0.005
Methylphenidate	157	79.00	12.09	83.76	13.17	4.76	11.79	<.001	—
RR									
Atomoxetine	152	780.25	104.45	707.15	109.90	-73.10	106.06	<.001	0.017
Methylphenidate	157	778.02	124.27	734.40	118.22	-43.62	111.58	<.001	—
QRS									
Atomoxetine	152	81.97	9.43	83.66	9.80	1.68	8.06	0.011	0.009
Methylphenidate	157	82.78	10.41	82.26	10.41	-0.52	6.14	0.294	—
PR									
Atomoxetine	152	139.81	18.45	133.92	16.43	-5.89	14.01	<.001	<.001
Methylphenidate	157	136.43	19.39	135.19	19.04	-1.24	10.22	0.132	—
QT									
Atomoxetine	152	366.20	24.86	352.47	24.00	-13.72	21.51	<.001	0.029
Methylphenidate	157	365.73	28.05	357.45	25.35	-8.28	22.77	<.001	—
QTCF									
Atomoxetine	152	398.30	14.62	396.46	13.10	-1.85	12.59	0.073	0.710
Methylphenidate	157	398.42	15.27	397.12	14.28	-1.31	13.57	0.229	—
QTCB									
Atomoxetine	152	414.93	14.52	420.02	14.97	5.09	15.52	<.001	0.191
Methylphenidate	157	415.45	15.34	418.17	16.33	2.73	16.28	0.037	—
QTCD									
Atomoxetine	152	404.11	13.96	404.56	12.85	0.45	12.86	0.666	0.780
Methylphenidate	157	404.37	14.46	404.39	14.10	0.02	13.75	0.985	—

HR=ECG Heart Rate; PR=PR Interval; QRS=QRS Interval; QT=QT Interval; QTCB=Bazett Corrected QT Interval;
QTCF=Fridericia Corrected QT Interval; QTCD=Data Corrected QT Interval; RR=RR Interval.

(a): P-value is from paired t-test.

(b): Type III Sums of Squares from an ANOVA: PROC GLM model= country, investigator(nested within country) and treatment.

Summary ID# 6962

Clinical Study Summary: Study B4Z-BP-LYBS

A Randomized, Controlled, Open-Label Study of the Broader Efficacy of Atomoxetine Hydrochloride in the Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in Children and Adolescents

Date summary approved by Lilly: 02 April 2007

Brief Summary of Results

This was a randomized, controlled, open-label study to test the hypothesis that atomoxetine given for 10 weeks is superior to standard current therapy (SCT) in patients with Attention-Deficit/Hyperactivity Disorder (ADHD) as measured by total mean change in the parent-rated Child Health and Illness Profile (CHIP-CE) score. This study was comprised of a 10-week acute treatment comparison phase (Study Period II), followed by an optional 22-week atomoxetine extension phase (Study Period III) (i.e., a total duration of 32 weeks).

A total of 208 patients were screened for the study and of those patients, 201 meeting the inclusion criteria were enrolled/randomized in the study (104 in the atomoxetine group and 97 in the SCT group). The study population was mainly male (178, 88.6%) and of Caucasian origin (198, 99.0%). The mean $\pm$ SD age was 10.9 $\pm$ 2.2 years with 130 (64.7%) aged 6 to 11 years and 71 (35.3%) aged 12 to 15 years. At baseline 75.3% of the 97 patients in the SCT group received pharmacotherapy only, and 10.3% received pharmacotherapy in combination with simple behavioral counseling. In all but 3 patients with pharmacotherapy, long and/or short acting methylphenidate was part of their medication regimen. Three (3.1%) patients received simple behavioral counseling alone, and 11 (11.3%) of all patients received neither pharmacotherapy nor counseling.

The results of the study are as follows:

- At baseline, the mean±SD of the CHIP-CE total score for the atomoxetine group and SCT group was 23.2±12.2 and 23.9±11.0, respectively. At Week 10 this score Least Squares (LS) mean±SE increased (i.e. improved) to 38.4±1.3 in the atomoxetine group and 30.8±1.3 in the SCT group ($p<0.001$), respectively. At the end of 10weeks the overall treatment difference between atomoxetine and SCT was statistically significant ($p<0.001$).
- The ADHD-Rating Scale (ADHD-RS) total score showed a statistically significant difference between the 2 treatment groups at Week 4 ($p<0.001$) and Week 10 ($p<0.001$). Response rates ($\geq 40\%$ of ADHD-RS improvement) were 65.3% for atomoxetine and 34.8% for the SCT group.
- There was a statistically significant difference between the treatment groups in the Social Acceptance Domain of the child-rated Harter Self-Perception Profile at Week 10 ($p=0.030$). There were no statistically significant differences in the other domains.
- At Week 10 the Clinical Global Impression-ADHD-Severity (CGI-S) scores showed a statistically significant difference between groups. The LSmean±SE scores were 3.4±0.1 and 3.8±0.1 for the atomoxetine and SCT-treated groups, respectively ($p<0.001$).
- At Week 10 the investigator-rated Clinical Global Impression-ADHD-Improvement (CGI-I) scores were statistically significantly different between the two groups. At Week 10 the LSmean±SE scores were 2.6±0.1 and 3.4±0.1 for atomoxetine and SCT, respectively ($p<0.001$, between group comparison).
- There were no deaths reported in the study.
- There were no serious adverse events (SAEs) during the 10 weeks of randomized treatment in Study Period II (SPII). In Study Period III (SPIII) serious adverse events were reported in three patients. All SAEs in SPIII were considered to be related to atomoxetine treatment.
- In SPII, 26 (25.0%) patients in the atomoxetine group and 6 (6.2%) patients in the SCT group discontinued from the study. The most common reason for discontinuation was Subject/Physician/Sponsor/Parent/Caregiver decision in both the groups. Six patients withdrew due to an adverse event. All adverse events leading to discontinuation were considered to be related to study treatment.
- In SPIII 12 (17.4%) patients in the previous atomoxetine group and 37 (48.1%) patients in the previous SCT group discontinued from the study. The most common reason for discontinuation was Subject/ Physician/ Sponsor/ Parent/ Caregiver decision in both the groups. Eight patients withdrew due to an adverse event; of these, 7 were considered to be related to atomoxetine treatment.

- A total of 75 (72.1%) patients in the atomoxetine group and 45 (46.4%) patients in the SCT group reported one or more treatment-emergent adverse events (TEAE); this difference was statistically significant ($p < 0.001$). The following TEAEs occurred statistically significantly more frequently in the atomoxetine group: headache ($p = 0.016$), nausea ($p < 0.001$), somnolence ($p = 0.003$), fatigue ($p = 0.003$), and unexpected therapeutic drug effect ($p = 0.029$).
- A total of 38 (55.1%) patients in the atomoxetine pre-treatment group and 46 (59.7%) patients in the SCT pre-treatment group (all treated with atomoxetine) reported one or more treatment-emergent adverse events during SPIII.

Title of Study: A Randomised, Controlled, Open-Label Study of the Broader Efficacy of atomoxetine Hydrochloride in the Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in Children and Adolescents	
Investigator(s): This multicenter study included 20 principal investigators	
Study Center(s): This study was conducted at 20 study centers in one country.	
Length of Study: 21months Date first patient enrolled: 25 June 2004 Date last patient completed: 05 April 2006	Phase of Development: 3b
Objectives: Primary objective: To test the hypothesis that atomoxetine given for 10 weeks is superior to standard current therapy (SCT) in patients with ADHD as measured by the mean change in the parent-rated Child Health and Illness Profile Total Score (CHIP-CE). Secondary objectives: - To compare atomoxetine with SCT given for 4 weeks in patients with ADHD as measured by mean change in parent-rated CHIP-CE Total score - To compare atomoxetine with SCT at 4 weeks and 10 weeks in patients with ADHD as measured by the change in the CHIP-CE domains (satisfaction, comfort, resilience, risk avoidance, achievement) - To compare atomoxetine with SCT at 4 weeks and 10 weeks in patients with ADHD as measured by the change in the parent-rated Family Burden of Illness Module score - To compare atomoxetine with SCT at 4 weeks and 10 weeks in patients with ADHD as measured by the change in the child-rated Harter Self-Perception Profile - To compare atomoxetine with SCT at 4 weeks and 10 weeks in patients with ADHD as measured by the change in the investigator-rated ADHD-Rating Scale (ADHD-RS); - To compare atomoxetine with SCT at 4 weeks and 10 weeks in patients with ADHD as measured by the change in the investigator-rated Clinical Global Impression (CGI)-Severity and CGI-Improvement scores - To assess whether the changes in the aforementioned rating scales are maintained over the longer term - To assess the long-term safety of atomoxetine	
Number of Patients: Planned: approximately 200 patients Randomized: 201 patients: 104 atomoxetine , 97 SCT Completed Study Period II: 169 patients: 78 atomoxetine , 91 SCT Completed Study Period III: 97 patients: 57 previous atomoxetine group, 40 previous SCT group	
Diagnosis and Main Criteria for Inclusion: Male and female patients aged 7 to 15 with a diagnosis of ADHD based on the investigator's clinical assessment and with DSM-IV diagnostic criteria for ADHD, and scoring at least 1.5 standard deviations above the age norm for their diagnostic subtype using published norms for the ADHD-RS.	
Test Product, Dose, and Mode of Administration: atomoxetine hydrochloride 1.2 mg/kg/day (range 0.5-1.8 mg/kg/day), given orally once daily (or twice, if preferred), with or without food, as capsules to be swallowed whole	

Reference Therapy, Dose, and Mode of Administration: The comparator was Standard Current Therapy (SCT), as determined by their treating physician (investigator). This was defined as any intervention regarded by the investigator that would benefit the patient, including any combination of medications (except for atomoxetine) and/or simple behavioral approaches or no treatment. During the 10 week period (Study Period II), treatments on this SCT arm could be changed or supplemented as deemed necessary by the investigator. A treatment regimen comprising a formal course of structured psychotherapy was excluded as this would have interfered with the study schedule and such services were available to different degrees at the sites. Study Period III was an optional extension phase in which patients on atomoxetine could continue on treatment, and patients on SCT had the option to switch treatment to atomoxetine or continue their existing treatment.

Duration of Treatment: Study Period II (Acute treatment Phase): 10 weeks treatment
Study Period III (Long-term extension Phase): Designated in protocol as being up to 2 years. The protocol was written so that during this period, patients could receive atomoxetine for up to 2 years or until it became commercially available in the United Kingdom (UK). First patient visit was after atomoxetine was licensed and available in the UK; therefore an appropriate duration of 22 weeks for Study Period III (i.e., 32 weeks overall) was agreed with the national ethics committee

Variables:

Efficacy:

- CHIP-CE total score at 10 weeks (Primary efficacy variable)
- CHIP-CE total score at 4 weeks
- CHIP-CE domains (satisfaction, comfort, resilience, risk avoidance, achievement) at 4 and 10 weeks
- Family Burden of Illness Module at 4 and 10 weeks
- Harter Self-Perception Profile at 4 and 10 weeks
- ADHD-RS at 4 and 10 weeks
- CGI-Severity at 4 and 10 weeks
- CGI-Improvement at 4 and 10 weeks

Safety:

- Treatment-emergent adverse events
- Discontinuations
- Blood pressure changes
- Heart rate changes
- Height and weight

Evaluation Methods:

Statistical: A total of 201 patients were randomised between atomoxetine and SCT in a 1:1 ratio. According to the intention-to-treat (ITT) principles, the primary analysis used the full analysis set (patients who had a baseline and at least one post-baseline measurement in Study Period II). Primary and secondary efficacy variables were analyzed using a mixed models repeated measures (MMRM) analysis. The model contained baseline score, treatment, site, visit, treatment-by-visit interaction, and used an unstructured within-patient covariance structure. The primary treatment analysis was the comparison of the least-squares (LS) means ($\pm$ standard error [SE]) between treatment at the final week of period II (i.e. Week 10). Safety data from all patients who entered in the study were reported. All statistical significance tests were two-sided, with a nominal significance level of 5%. Treatment-emergent adverse events and study discontinuations due to adverse events were compared using Fisher's exact test.

Results:

Patient Demographics

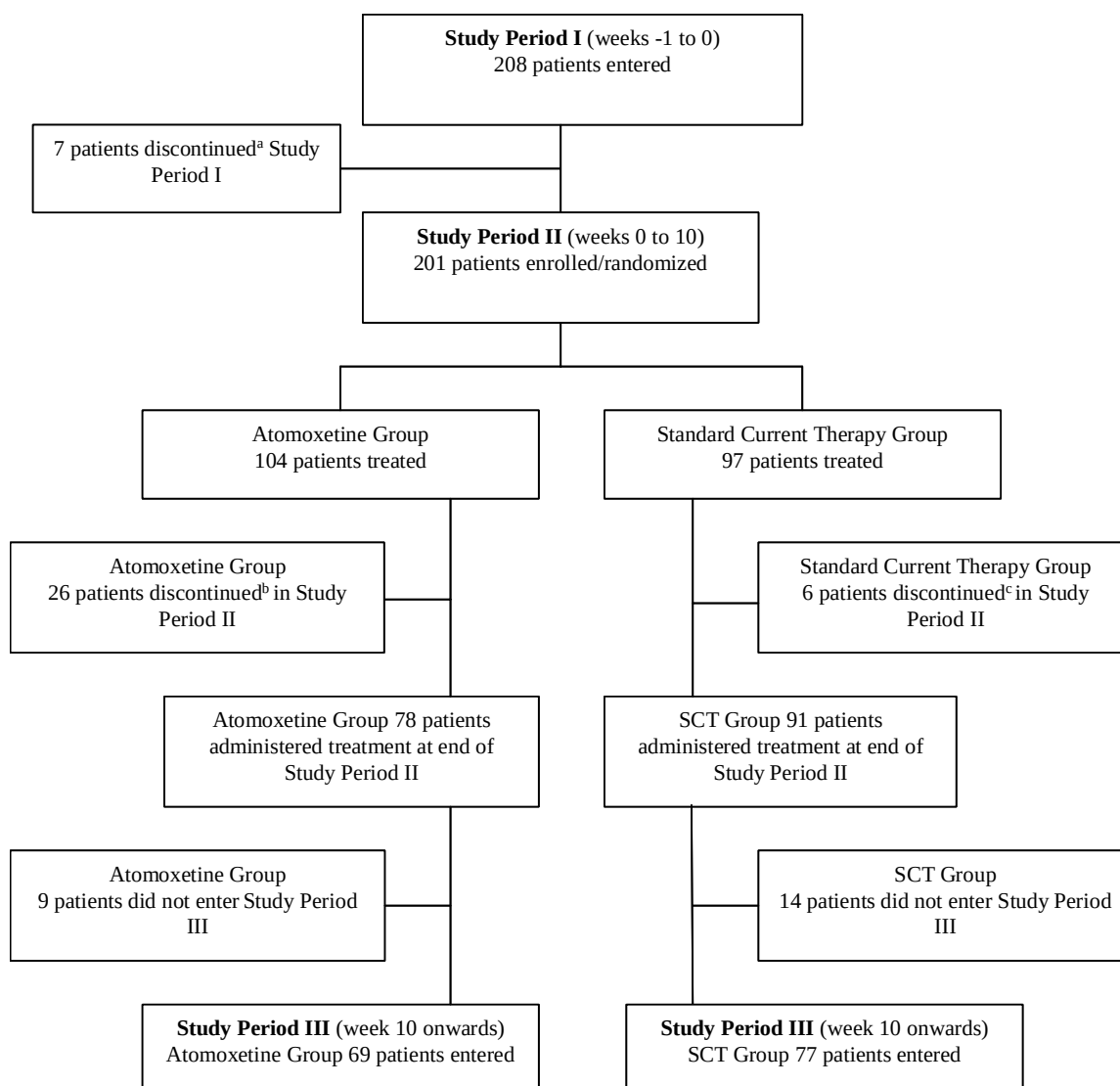
A total of 201 patients were randomized to treatment; 104 patients were assigned to atomoxetine and 97 to SCT. The study population was mainly male (178, 88.6%) and of Caucasian origin (198, 99.0%). The average age (mean±SD) was 10.9 ±2.2 years, with 130 (64.7%) aged 6 to 11 years and 71 (35.3%) 12 to 15 years. Table 1 summarizes the demographics and other baseline characteristics of the patients. There was a statistically significant difference between the groups for BMI (p=0.046). Pre-existing conditions in more than 5% of the total patient population were insomnia (12, 6.0%), asthma (11, 5.5%), eczema (10, 5.0%), and tic (10, 5.0%). Over 90% (181, 90.5%) of patients had the combined ADHD subtype (i.e., suffered from both hyperactivity as well as inattention). Regarding co-morbidities, nearly two-thirds (124, 61.7%) of all patients had a diagnosis of oppositional defiant disorder (ODD) in addition to ADHD at study entry.

Table 1. Patient Demographics and other Baseline Characteristics

	Atomoxetine (N=104)	Standard Current Therapy (N=97)	Total (N=201)	p-value
Gender: No (%)				
Male	92 (88.5)	86 (88.7)	178 (88.6)	>0.999
Female	12 (11.5)	11 (11.3)	23 (11.4)	
Origin: No (%)				
African	1 (1.0)	0 (0.0)	1 (0.5)	0.730
Caucasian	103 (99.0)	95 (99.0)	198 (99.0)	
West Asian (Indian sub-continent)	0 (0.0)	1 (1.0)	1 (0.5)	
Age: years				
Mean (standard deviation)	11.1 (2.4)	10.8 (2.0)	10.9 (2.2)	0.380
Minimum, Maximum	7.1, 15.9	6.9, 15.4	6.9, 15.9	
Age group: No (%)				
6 -11 years	65 (62.5)	65 (67.0)	130 (64.7)	0.555
12 - 15 years	39 (37.5)	32 (33.0)	71 (35.3)	
BMI: Kg/m ²				
Mean (standard deviation)	28.0 (8.2)	26.1 (5.4)	27.1 (7.0)	0.046
Minimum, Maximum	17.1, 65.3	17.4, 43.3	17.1, 65.3	
Weight: Kg				
Mean (Standard deviation)	41.4 (15.7)	37.6 (11.0)	39.6 (13.7)	0.054
Minimum, Maximum	21.0, 109.0	20.5, 73.0	20.5, 109.0	

Patient Disposition

Figure 1 shows patient disposition in this study.



Reasons for discontinuation: a, subject/physician/sponsor/ parent/caregiver decision (3 patients), entry criteria exclusion/ protocol violation (4 patients); b, lack of efficacy (3 patients), subject/ physician/ sponsor/ parent/ caregiver decision (14 patients), adverse event (5 patients), entry criteria exclusion/ protocol violation (4 patients); c, lack of efficacy (1 patient), subject/ physician/ sponsor/ parent/ caregiver decision (2 patients), adverse event (1 patient), lost to follow-up (1 patient) entry criteria exclusion/protocol violation (1 patient).

Figure 1. Patient disposition.

A total of 32 patients in SPII and 49 patients (Table 2) in SPIII (Table 3) discontinued from the study. The most common reasons for early discontinuation in SPII were subject/physician/sponsor/parent/caregiver decision (16 patients) and adverse events (6 patients).

Table 2. Reasons for Discontinuation in Study Period II

	Atomoxetine (N=104)		Standard Current Therapy (N= 97)		Total (N=201)	
	n	%	n	%	N	%
Lack of efficacy	3	2.9	1	1.0	4	2.0
Subject/Physician/Sponsor/Parent/Caregiver decision	14	13.5	2	2.1	16	8.0
Adverse event	5	4.8	1	1.0	6	3.0
Lost to follow-up			1	1.0	1	0.5
Entry criteria exclusion or protocol violation	4	3.8	1	1.0	5	2.5
Total discontinuations	26		6		32	

Abbreviations: N = total number of patients; n = number of patients in the category.

Table 3. Reasons for Discontinuation in Study Period III

	Atomoxetine (N= 69)		Standard Current Therapy (N= 77)		Overall (N=146)	
	n	%	n	%	n	%
Primary Reason for Discontinuation						
Lack of efficacy	1	1.4	7	9.1	8	5.5
Subject/Physician/Sponsor/Parent/Caregiver decision	7	10.1	20	26.0	27	18.5
Adverse event	2	2.9	6	7.8	8	5.5
Lost to follow-up	0	0.0	2	2.6	2	1.4
Entry criteria exclusion or protocol violation	2	2.9	2	2.6	4	2.7
Total discontinuations	12		37			

Abbreviations: N = total number of patients; n = number of patients in the category.

Treatment in the Standard Current Therapy group

In the SCT group at baseline, 75.3% of the patients received pharmacotherapy only, and 10.3% in combination with simple behavioral counseling. Three (3.1%) patients received simple behavioral counseling alone and 11 (11.3%) of all patients received neither pharmacotherapy nor counseling. Apart from 3 patients (3.6%) who received clonidine alone, all 80 other pharmacologically-treated patients (96.4%) received short- or long-acting methylphenidate in mono- or combination therapy. Additional pharmacological

treatments documented in combination with methylphenidate were clonidine, melatonin, nortryptiline, and 'other' agents.

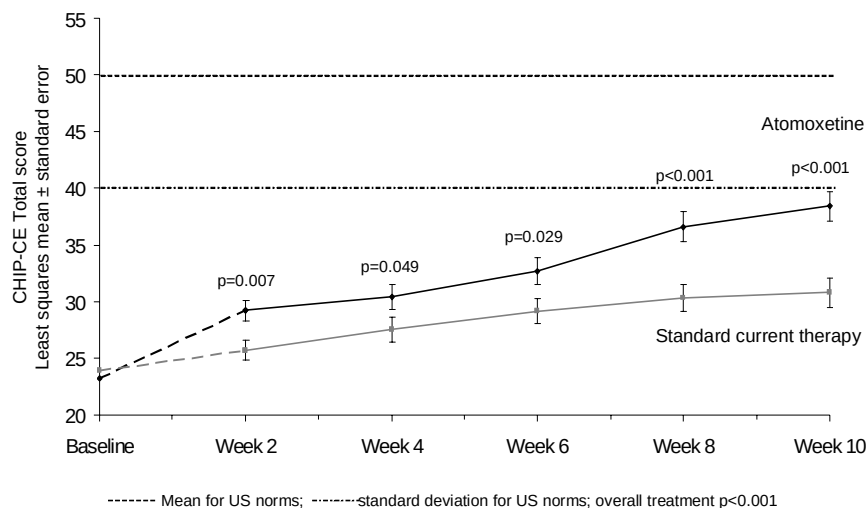
Primary Endpoint

The primary objective of the study was to test the hypothesis that atomoxetine given for 10 weeks was superior to standard current therapy (SCT) in patients with ADHD as measured by mean change in the parent-rated Child Health and Illness Profile Total Score (CHIP-CE). Scores were compared to a mean $\pm$ standard deviation for US norms of 50 ± 10 . The mean baseline score of the CHIP-CE was 23.2 ± 12.2 in the atomoxetine group and 23.9 ± 11.0 in the SCT group. The Least Squares (LS) mean $\pm$ SE scores increased (i.e., improved) to 38.4 ± 1.3 in the atomoxetine and to 30.8 ± 1.3 in the SCT group. This difference was statistically significant for patients treated with atomoxetine compared with those treated with SCT at Week 10 ($p < 0.001$). The overall treatment difference was statistically significantly different ($p < 0.001$). The CHIP-CE total scores (repeated measures least square means) for the atomoxetine and SCT groups over the 10 weeks of treatment in Study Period II are shown in Table 4 and Figure 2.

Table 4. Total Score of the Child Health and Illness Profile (Repeated Measures Least Square Means) – by Treatment Group at Baseline

	Atomoxetine (N=104)	Standard Current Therapy (N=97)	Difference in LSM (95% CI)	p-value
Baseline (mean $\pm$ SD)	23.2 $\pm$ 12.2	23.9 $\pm$ 11.0		
Week 2 (LSM $\pm$ SE)	29.2 $\pm$ 0.9	25.7 $\pm$ 0.9	3.4 (0.9, 5.9)	0.007
Week 4 (LSM $\pm$ SE)	30.4 $\pm$ 1.1	27.5 $\pm$ 1.1	3.0 (0.0, 6.0)	0.049
Week 6 (LSM $\pm$ SE)	32.7 $\pm$ 1.2	29.1 $\pm$ 1.1	3.6 (0.4, 6.8)	0.029
Week 8 (LSM $\pm$ SE)	36.6 $\pm$ 1.3	30.3 $\pm$ 1.2	6.3 (2.9, 9.6)	<0.001
Week 10 (LSM $\pm$ SE)	38.4 $\pm$ 1.3	30.8 $\pm$ 1.3	7.6 (4.1, 11.2)	<0.001

Abbreviations: CI = confidence interval; LSM = least square means; N = total number of patients; SD = standard deviation; SE = standard error;.



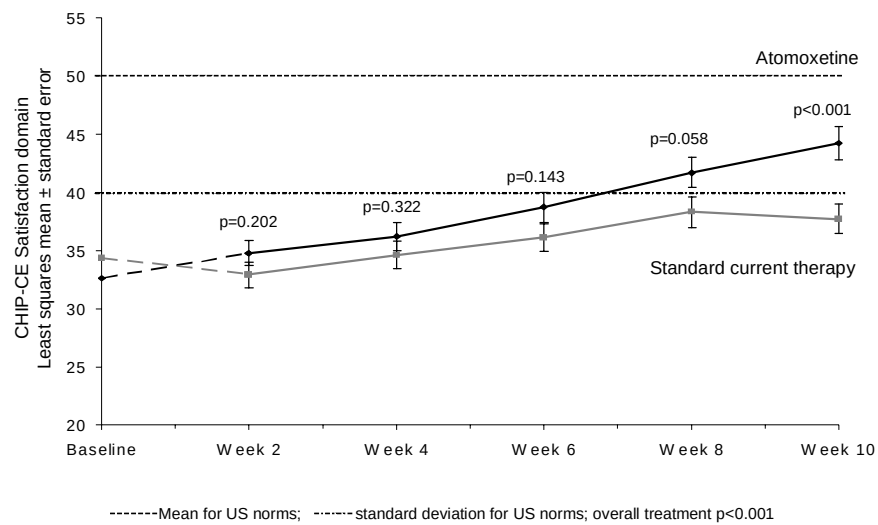
Abbreviation: CHIP-CE = Child Health and Illness Profile; US = United States.

Figure 2. Primary outcome measure: CHIP-CE total score – repeated measures least square means in Study Period II.

Secondary Efficacy Measures

The five CHIP-CE domains were satisfaction, comfort, resilience, risk avoidance, and achievement. Single domain scores enabled identification of the area(s) in which the child was most affected by the illness and its treatment. Scores were compared to a mean $\pm$ standard deviation for US norms of 50 ± 10 . Results of secondary objectives are as follows:

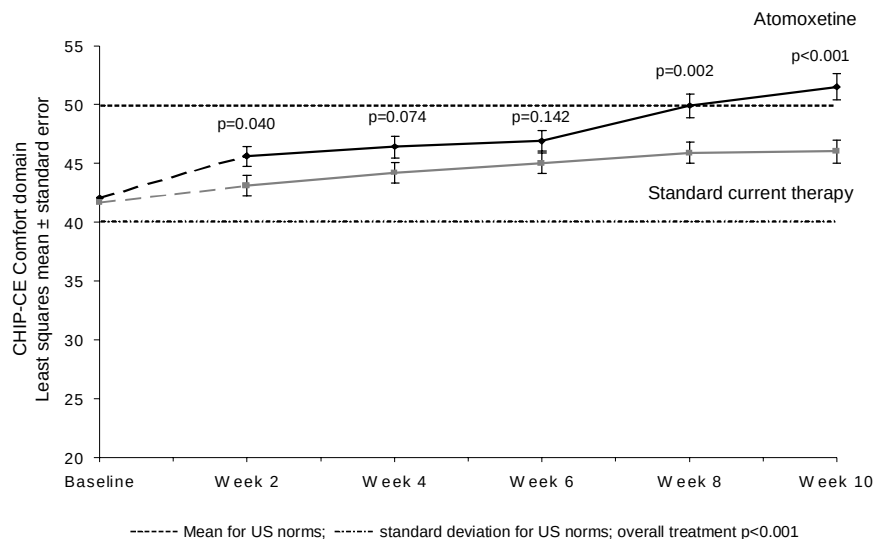
- Satisfaction domain:** The CHIP-CE satisfaction domain (repeated measures least square means) for the atomoxetine and SCT groups over the 10 weeks of treatment in SPII is shown in Figure 3. There was a statistically significant difference in the satisfaction domain for patients treated with atomoxetine compared with those receiving SCT ($p < 0.001$) at Week 10. The overall treatment difference was statistically significant ($p < 0.001$).



Abbreviation: CHIP-CE = Child Health and Illness Profile; US = United States.

Figure 3. CHIP-CE satisfaction domain – repeated measures least square means in Study Period II.

- Comfort domain:** The CHIP-CE comfort domain (repeated measures least square means) for the atomoxetine and SCT groups over the 10 weeks of treatment in SPII is shown in Figure 4. There was a statistically significant difference in the comfort domain for patients treated with atomoxetine compared with those receiving SCT ($p < 0.001$) by the end of the 10-week treatment period. The overall treatment difference was statistically significant ($p < 0.001$).

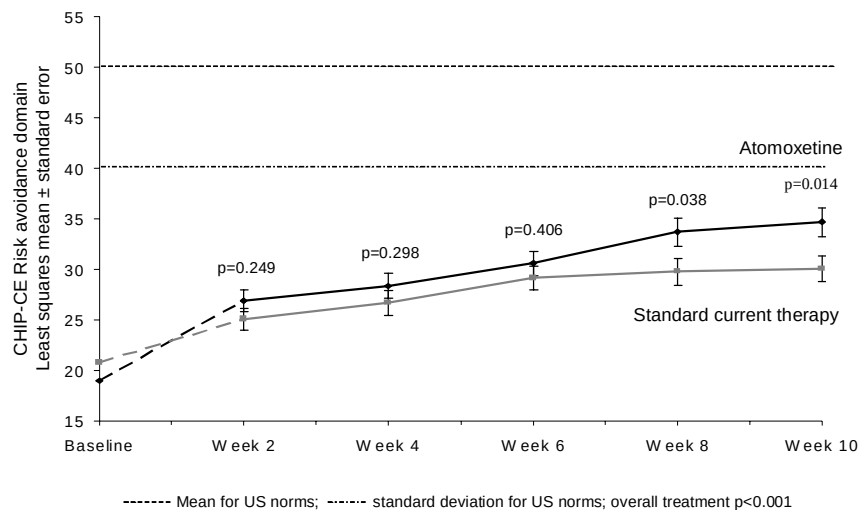


Abbreviation: CHIP-CE = Child Health and Illness Profile; US = United States.

Figure 4.

CHIP-CE comfort domain – repeated measures least square means in Study Period II.

- Risk avoidance domain:** The CHIP-CE risk avoidance domain (repeated measures least square means) for the atomoxetine and SCT groups over the 10 weeks of treatment in SPII is shown in Figure 5. There was a statistically significant difference in the risk avoidance domain for patients treated with atomoxetine compared with those receiving SCT ($p=0.014$) by the end of the 10-week treatment period. The overall treatment difference was statistically significant ($p<0.001$).

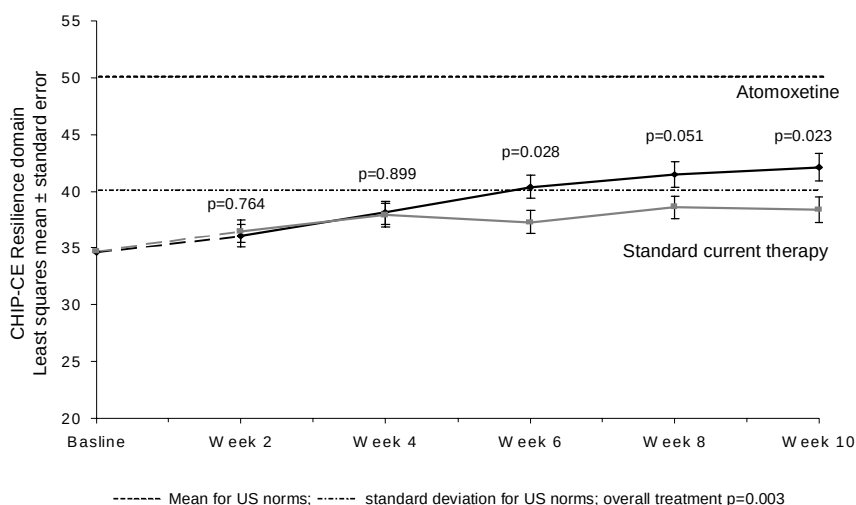


Abbreviation: CHIP-CE = Child Health and Illness Profile; US = United States.

Figure 5.

CHIP-CE risk avoidance domain – repeated measures least square means in Study Period II.

- Resilience domain:** The CHIP-CE resilience domain (repeated measures least square means) for the atomoxetine and SCT groups over the 10 weeks of treatment in SPII is shown in Figure 6. There was a statistically significant difference in the resilience domain for patients treated with atomoxetine compared with those receiving SCT ($p=0.023$) by the end of the 10-week treatment period. The overall treatment difference was statistically significant ($p=0.003$).

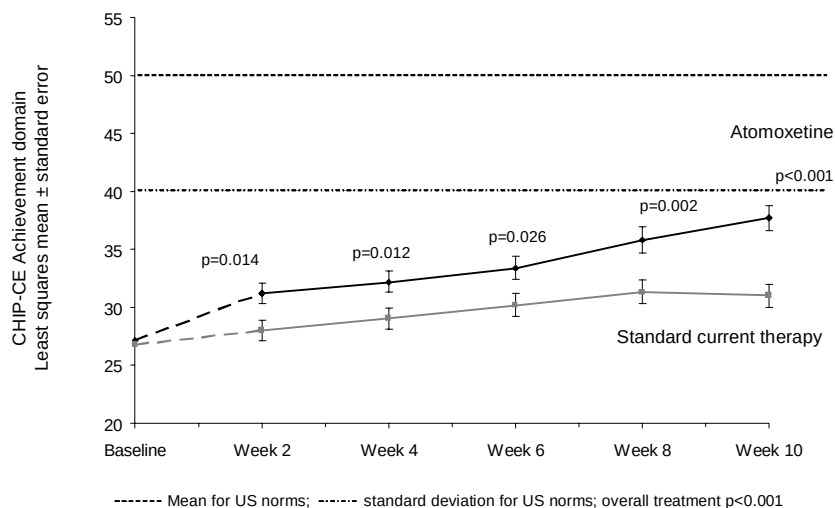


Abbreviation: CHIP-CE = Child Health and Illness Profile; US = United States.

Figure 6.

CHIP-CE resilience domain – repeated measures least square means in Study Period II.

Achievement domain: The CHIP-CE achievement domain (repeated measures least square means) for the atomoxetine and SCT groups over the 10 weeks of treatment in SPII is shown in Figure 7. After 10 weeks of treatment, there was a statistically significant difference in the level of achievement in the atomoxetine group compared with patients receiving with SCT ($p<0.001$). The overall treatment difference was statistically significant ($p<0.001$).



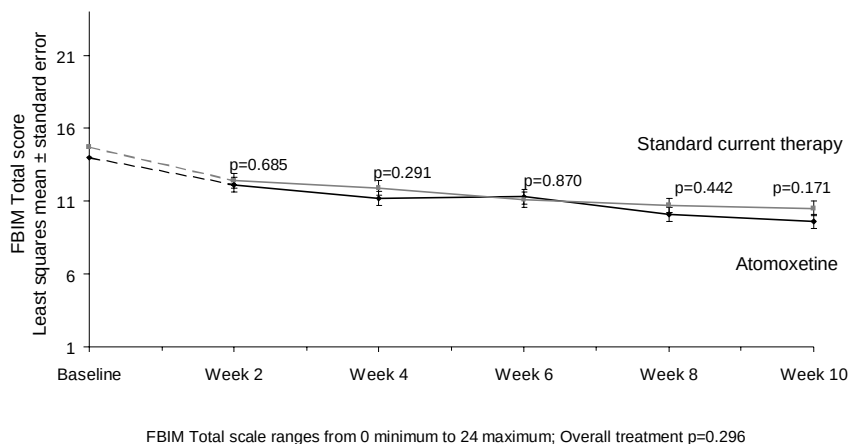
Abbreviation: CHIP-CE = Child Health and Illness Profile; US = United States.

Figure 7.

CHIP-CE achievement domain – repeated measures least square means in Study Period II.

Family Burden of Illness Module (FBIM)

There was no statistically significant difference between the atomoxetine and the SCT groups in the FBIM total score (Figure 8), or in either of the FBIM emotional or restriction domains.



Abbreviation: FBIM = Family Burden of Illness Module.

Figure 8. FBIM total score – repeated measures least square means in Study Period II.

Harter Self-Perception Profile (HSPP)

There are 2 versions of the HSPP, a child version and an adolescent version. The use of the adolescent version was at the investigator's discretion. There are six domains in common for the two versions (scholastic competence, social acceptance, athletic competence, physical appearance, behavioral conduct, and global self-worth) and these can be combined across the two versions. For the adolescent version there are three additional domains, (job competence, romantic appeal, close friendship). In the study, the majority of patients completed the child-version of the HSPP. No formal analyses were carried out on the three domains completed by adolescents only as there were too few patients (11 in the atomoxetine group, 4 in the SCT group). There was a statistically significant difference between the groups in the social acceptance domain at Week 10 ($p=0.030$). There were no other statistically significant differences between the groups in the Week 10 HSPP domain scores.

Figure 9 shows the HSPP LSmeans for the social acceptance score.

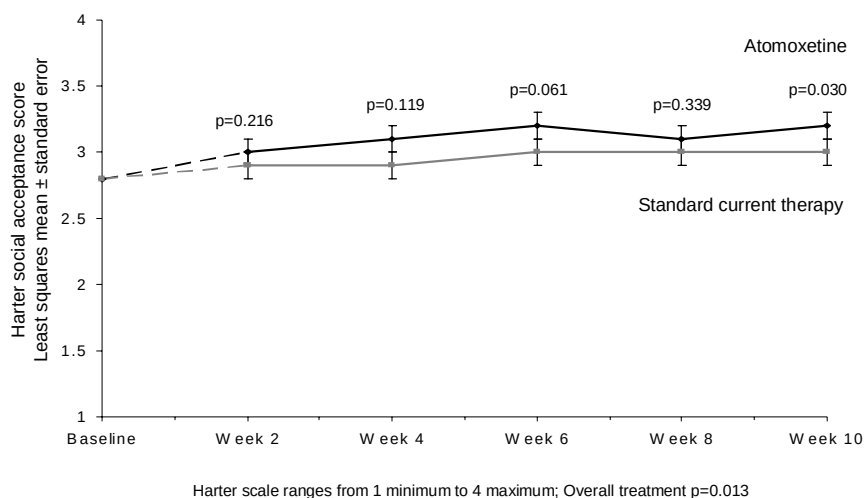
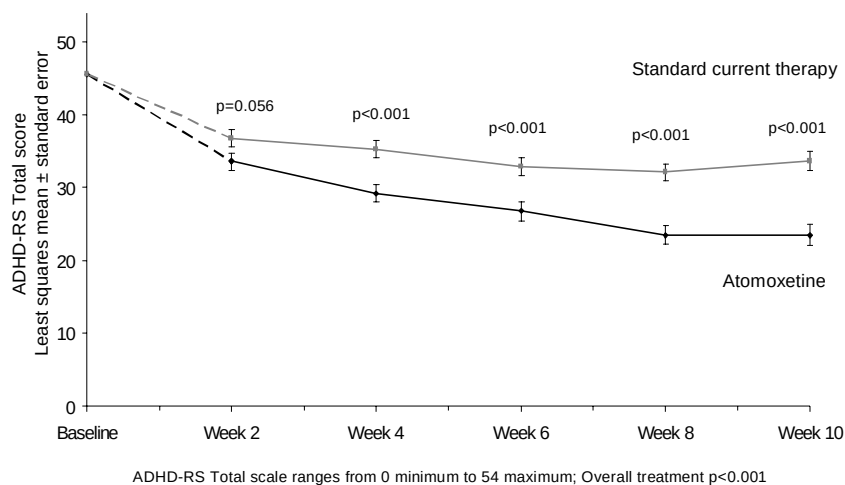


Figure 9. HSPF children and adolescent version combined social acceptance score – repeated measures least square means in Study Period II.

ADHD-Rating Scale

For the ADHD-RS total score the difference between atomoxetine and SCT was statistically significantly different ($p<0.001$) at Week 10. By Week 4 of treatment, there was a statistically significant difference ($p<0.001$) in patients treated with atomoxetine compared with those receiving SCT (Figure 10). Results for the subscales scores (inattentive and the hyperactivity/impulsivity) were similar.



Abbreviations: ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale.

Figure 10. ADHD-RS total score – repeated measures least square means in Study Period II.

There were statistically significant ($p < 0.001$) percentages of responders showing 25% and 40% improvement in the atomoxetine group compared with the SCT group (Table 5).

Table 5. Improvement from Baseline in ADHD-RS Total Score – SPII

	Atomoxetine	Standard Current Therapy	Total	p-value
	N (%)	N (%)	N (%)	
Response rate 25%				
yes	59 (78.7)	43 (48.3)	102 (62.2)	
no	16 (21.3)	46 (51.7)	62 (37.8)	< 0.001
Response rate 40%				
yes	49 (65.3)	31 (34.8)	80 (48.8)	
no	26 (34.7)	58 (65.2)	84 (51.2)	< 0.001

Abbreviations: N = total number of patients.

Clinical Global Impression of Severity (CGI-S)

Table 6 presents the number (percentage) of patients at each severity level at baseline and after 10 weeks of treatment with atomoxetine or SCT.

The CGI-Severity scores (repeated measures least square means) were statistically significantly different between the two groups from Week 4 onwards (Week 4, $p=0.031$; Week 10, $p<0.001$).

Table 6. Number (Percentage) Patients at Each CGI-Severity Level by Treatment Group – Study Period II

	Severity of Illness	Atomoxetine	Standard Current Therapy
		N (%)	N (%)
Baseline	Normal	0 (0)	1 (1.0)
	Borderline ill	0 (0)	0 (0)
	Mildly ill	4 (3.9)	4 (4.2)
	Moderately ill	59 (57.8)	62 (64.6)
	Markedly	24 (23.5)	23 (24.0)
	Severely ill	13 (12.7)	5 (5.2)
	Extreme	2 (2.0)	1 (1.0)
Week 10	Normal	5 (6.6)	3 (3.3)
	Borderline ill	14 (18.4)	10 (11.1)
	Mildly ill	30 (39.5)	16 (17.8)
	Moderately ill	22 (28.9)	49 (54.4)
	Markedly	5 (6.6)	10 (11.1)
	Severely ill	0 (0)	2 (2.2)
	Extreme	0 (0)	0 (0)

Abbreviation: N = number of patients.

Extreme = among the most extremely ill patients.

Clinical Global Impression of Improvement (CGI-I)

Table 7 shows the number (percentage) of patients at each improvement level at week 10.

The CGI-Improvement scores (repeated measures least square means) were statistically significantly different between the two groups at Week 2 ($p=0.022$) and Week 10 ($p<0.001$).

Table 7. Number (Percentage) Patients in Each CGI-Improvement Level by Treatment Group – Study Period II

CGI –Improvement		Atomoxetine	Standard Current Therapy
		N (%)	N (%)
Week 10	Very much improved	14 (18.4)	9 (10.0)
	Much improved	34 (44.7)	16 (17.8)
	Minimally improved	19 (25.0)	17 (18.9)
	No change	7 (9.2)	41 (45.6)
	Minimally worse	1 (1.3)	5 (5.6)
	Much worse	1 (1.3)	2 (2.2)
	Very much worse	0 (0)	0 (0)

Abbreviations: CGI-I = Clinical Global Impression - Improvement; N = number of patients.

Efficacy During Study Period III

The CHIP-CE mean total score for the previously atomoxetine–treated group was maintained over the 22 weeks of Study Period III (Week 10: 36.0 ± 14.6 , Week 32 36.0 ± 15.8). The LOCF endpoint scores were lower than at Week 32 (34.4 ± 15.6). Scores for the previous SCT group showed an improvement compared to the end of Study Period II by Week 32 (Week 10: 30.2 ± 12.3 , Week 32: 34.6 ± 13.1), but did not reach the improvement level of that maintained by the previously atomoxetine-treated group. Similar results were seen for the secondary efficacy parameters.

Safety

Deaths

There were no deaths during the study.

Serious Adverse Events

There were no serious adverse events during the 10 weeks of treatment in SPII. All patients were treated with atomoxetine in Study Period III; results were summarized by the treatment group the patients were on in Study Period II. Serious adverse events during Study Period III were reported in three patients; all were considered to be related to treatment. Depressed mood and suicidal ideation were both considered to be severe and life-threatening and were reported during Study Period III for one patient receiving atomoxetine throughout Study Periods II and III. One patient who had previously received SCT in Study Period II was reported to have severe aggression and self-injurious ideation when being treated with atomoxetine in Study Period III; another patient previously in the SCT group was reported to have had a suicide attempt and intentional self-injury harm, both of moderate severity, when treated with atomoxetine.

Discontinuations Due to Adverse Events

Six patients discontinued from the study due to adverse events in SPII. All six events, five of which occurred in the atomoxetine group, were considered related to study treatment. The events were either gastrointestinal or psychotic in nature (atomoxetine: aggression, nausea, abdominal pain, vomiting, hyperphagia; SCT: depressed mood). All patients were treated with atomoxetine in Study Period III; results were summarized by the treatment group the patients were on in Study Period II. Eight patients discontinued due to adverse events in SPIII. In the group previously treated with atomoxetine, two events occurred in the patients treated with atomoxetine in SPIII; in the previous SCT group six events led to discontinuation in SPIII, five of which were considered related to study treatment.

Treatment-Emergent Adverse Events

Study Period II: A total of 75 patients (72.1%) in the atomoxetine group and 45 patients (46.4%) in the SCT group reported one or more treatment-emergent adverse events (TEAEs), and the difference between the two groups was statistically significant ($p < 0.001$). Table 8 presents treatment-emergent adverse events occurring in $\geq 5\%$ patients in either group. There were also statistically significant differences between the treatment groups in the incidence of headache ($p = 0.016$), nausea ($p < 0.001$), somnolence ($p = 0.003$), fatigue ($p = 0.003$), unexpected therapeutic drug effect ($p = 0.029$), and therapeutic response unexpected ($p = 0.247$).

Note: The MedDRA coding changed during the course of the study resulting in 9 patients recording either unexpected therapeutic drug effect (6, 5.8%) or therapeutic response unexpected (3, 2.9%). No such effects were reported in the SCT group.

Table 8. Summary of Treatment-Emergent Adverse Events by Treatment Group and Preferred Term -- Study Period II (with ≥5% in either Group)

Event Classification	Atomoxetine (N=104)		Standard Current Therapy (N= 97)		Total (N=201)		p-value
	n	%	n	%	n	%	
Headache	22	21.2	8	8.2	30	14.9	0.016
Nausea	18	17.3	3	3.1	21	10.4	<0.001
Weight decreased	8	7.7	8	8.2	16	8.0	>0.999
Decreased appetite	8	7.7	6	6.2	14	7.0	0.784
Vomiting	9	8.7	2	2.1	11	5.5	0.059
Abdominal pain upper	7	6.7	3	3.1	10	5.0	0.334
Cough	6	5.8	4	4.1	10	5.0	0.749
Fatigue	9	8.7	0	0.0	9	4.5	0.003
Somnolence	9	8.7	0	0.0	9	4.5	0.003
Abnormal behavior	6	5.8	2	2.1	8	4.0	0.281
Aggression	6	5.8	2	2.1	8	4.0	0.281
Anorexia	3	2.9	5	5.2	8	4.0	0.486
Rash	6	5.8	1	1.0	7	3.5	0.120
Unexpected therapeutic drug effect	6	5.8	0	0.0	6	3.0	0.029
Therapeutic response unexpected	3	2.9	0	0.0	3	1.5	0.247

Abbreviations: N = total number of patients; n = number of patients in the category.

Study Period III: The number of patients with one or more treatment-emergent adverse events during SPIII were 38 (55.1%) in the atomoxetine pre-treatment group and 46 (59.7%) in the SCT pre-treatment group (p=0.616). Treatment-emergent adverse events occurring in $\geq 5\%$ of patients by any previous treatment group during atomoxetine treatment in Study Period III are presented in Table 9.

Table 9. Treatment-Emergent Adverse Events Occurring in $\geq 5\%$ of Patients in any Previous Treatment Group, Preferred Term – SPIII

Event Classification	Atomoxetine (n=69)		Standard Current Therapy (n=77)		Total (n=146)		p-value
	n	%	N	%	n	%	
Headache	8	11.6	9	11.7	17	11.6	>0.999
Aggression	5	7.2	9	11.7	14	9.6	0.410
Vomiting	6	8.7	7	9.1	13	8.9	>0.999
Nausea	4	5.8	8	10.4	12	8.2	0.376
Abnormal behavior	5	7.2	4	5.2	9	6.2	0.735
Decreased appetite	2	2.9	7	9.1	9	6.2	0.172
Abdominal pain upper	3	4.3	4	5.2	7	4.8	>0.999
Nasopharyngitis	4	5.8	1	1.3	5	3.4	0.189
Insomnia	1	1.4	4	5.2	5	3.4	0.370
Somnolence	0	0.0	4	5.2	4	2.7	0.122

Abbreviation: n = total number of patients.

Other Relevant Safety Results

Blood Pressure: The change from baseline to endpoint for systolic blood pressure was an increase of 2.2 mmHg in the atomoxetine group and 0.7 mmHg in SCT group. Change in diastolic blood pressure was 4.4 mmHg in the atomoxetine group and 1.7 mmHg in the SCT group in SPII. These changes are presented over time in Figure 11.

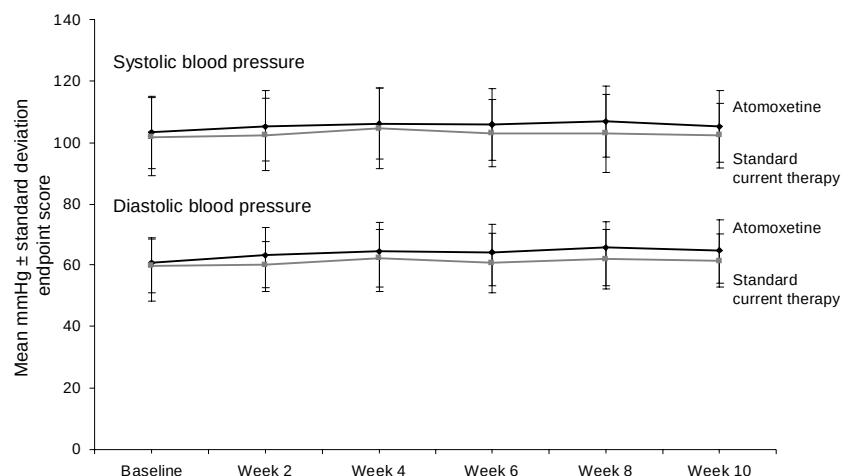


Figure 11. Endpoint scores for systolic and diastolic blood pressure by treatment group in Study Period II.

Heart Rate: Figure 12 shows the change in heart rate from baseline to endpoint. There was an average increase of 5.3 beats per minute in the atomoxetine and 1.1 beats per minute for the SCT group in SPII.

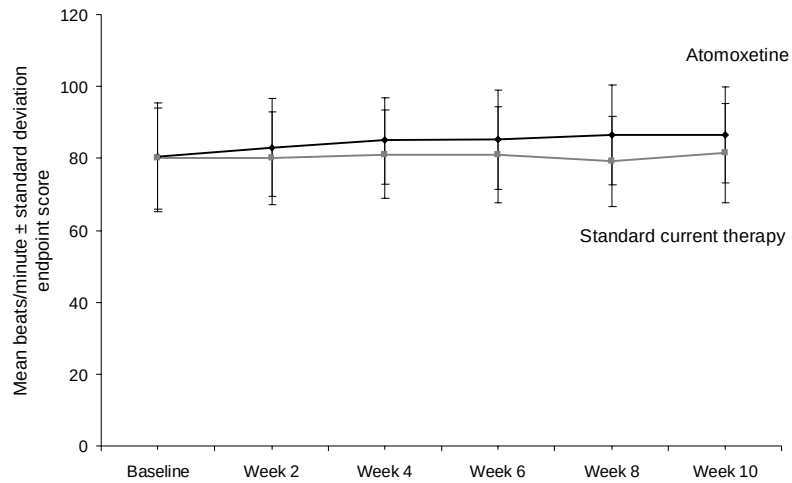


Figure 12. Endpoint scores for heart rate by treatment group in Study Period II.

Weight: Changes from baseline to endpoint scores (percentiles and z scores) in body weight for the atomoxetine and SCT groups are shown in Table 10.

Table 10. Change from Baseline to Endpoint Scores for Weight by Treatment Group – Study Period II

Weight	Baseline			Endpoint		Change	
	N	Mean±SD	Min, Max	Mean±SD	Min, Max	Mean±SD	Min, Max
Percentiles							
Atomoxetine	102	60.8±30.7	0.2, 100	56.0 ± 31.0	0.2, 100	-4.8±7.8	-28.4, 10.7
Standard current therapy	96	56.0±30.5	1.5, 99.8	51.7 ± 31.7	1.0, 99.7	-4.3±7.4	-30.1, 13.0
z scores							
Atomoxetine	102	0.4 ± 1.3	-2.8, 4.2	0.3 ± 1.3	-2.9, 3.6	-0.2 ± 0.2	-0.7, 0.6
Standard current therapy	96	0.2 ± 1.1	-2.2, 2.9	0.1 ± 1.2	-2.3, 2.8	-0.2 ± 0.2	-0.8, 0.4

Abbreviations: Max = maximum; min = minimum; N = number of patients; SD = Standard deviation.

Height: Changes from baseline to endpoint scores (percentiles and z scores) in height of patients in the atomoxetine and SCT groups are shown in Table 11.

Table 11. Change from Baseline to Endpoint Scores for Height by Treatment Group – Study Period II

Height	N	Baseline		Endpoint		Change	
		Mean±SD	Min, Max	Mean±SD	Min, Max	Mean±SD	Min, Max
Percentiles							
Atomoxetine	69	51.8 ± 29.1	2.9, 99.2	52.4 ± 29.3	1.5, 98.4	0.5 ± 6.9	-42.8, 19.2
Standard current therapy	77	46.8 ± 31.4	0.2, 100.0	46.6 ± 30.7	0.2, 100.0	-0.2 ± 5.3	-14.8, 16.2
z scores							
Atomoxetine	69	0.1 ± 1.0	-1.9, 2.4	0.1 ± 1.0	-2.2, 2.2	-0.0 ± 0.3	-2.0, 0.5
Standard current therapy	77	-0.1 ± 1.2	-2.9, 3.6	-0.1 ± 1.2	-2.8, 3.7	-0.0 ± 0.2	-0.9, 0.6

Abbreviations: Max = maximum; min = minimum; N = number of patients; SD = Standard deviation.

Summary ID# 7065

Clinical Study Summary: Study B4Z-MC-LYBU

A Randomized, Double-Blind Comparison of Atomoxetine Hydrochloride Augmented with Either Extended-Release Methylphenidate Hydrochloride (Concerta®) or Placebo in Children with Attention-Deficit/Hyperactivity Disorder (ADHD) Who Have Not Responded to Stimulant Mono Therapy

Date summary approved by Lilly: 13 July 2006

Brief Summary of Results

Study B4Z-MC-LYBU was a 10-week study in children aged 6-12 years with ADHD, and retrospectively identified in other well-documented clinical trials as non-responsive to stimulant therapy (nonremitter). The primary objective of the study was to assess the safety of up to 1.4 mg/kg/day of atomoxetine plus placebo administered once daily (QD), compared with up to 1.4 mg/kg/day of atomoxetine plus up to 1.1 mg/kg/day of Concerta® administered QD, in stimulant nonremitter patients exposed to acute treatment with atomoxetine. Safety was measured by categorical changes in blood pressure or pulse.

Secondary objectives were to assess the safety of atomoxetine+placebo compared with atomoxetine+Concerta as measured by electrocardiograms (ECGs), clinical laboratory tests, and adverse events (AEs); and to compare efficacy as measured by the Attention-Deficit/ Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv), Weekly Parent Ratings of Evening and Morning Behavior-Revised (WPREMB-Revised), Life Participation Scale-Parent Version (LPS-P), Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S), and the Conners' Global Index-Teacher Version (Conners' GI-T).

Study LYBU consisted of two study periods: Study Period I, the screening and washout phase (5-28 days); and Study Period II, the double-blind treatment phase. During Study Period IIa (4 weeks), eligible patients were titrated to a target dose of up to 1.4 mg/kg/day atomoxetine+placebo. During Study Period IIb (6 weeks), patients who had a marked response (remitter group) in Study Period IIa continued atomoxetine+placebo, but patients who did not have a marked response were randomized to receive up to 1.4 mg/kg/day atomoxetine+placebo (atomoxetine+placebo treatment group) or up to 1.1 mg/kg/day Concerta (atomoxetine+Concerta treatment group).

Enrollment was stopped due to lower than expected enrollment rates (25 patients; 50 patients were planned).

Results of the study were as follows:

- In Study Period IIb, 3 patients from the atomoxetine+Concerta treatment group, 1 patient from the atomoxetine+placebo treatment group, and 1 patient from the remitter group had one or more categorical changes in vital signs. There were no statistically significant differences across randomized groups in categorical changes in vital signs.
- There were no statistically significant changes in vital signs or weight across treatment groups in either study period. Statistically significant decreases from baseline in body mass index ($p=.014$) and orthostatic diastolic blood pressure ($p=.006$) were noted at LOCF endpoint in the atomoxetine+Concerta treatment group, and increases in standing systolic blood pressure ($p=.036$) in the remitter group.
- In Study Period IIa, statistically significant decreases from baseline to LOCF endpoint ($p<.001$) were noted for ADHDRS-IV-Parent:Inv, Total, Inattention, and Hyperactivity-Impulsivity Subscale scores; CGI-ADHD-S; WPREMB-Revised-Parent, total score; and CPRS-R:S, total score.
- In Study Period IIa, a statistically significant increase from baseline to endpoint (LOCF) was noted for LPS-P ($p<.001$).
- In Study Period IIb, there were no statistically significant differences across randomized groups among the secondary objective measures. Within the atomoxetine+placebo treatment group, statistically significant decreases from baseline to LOCF endpoint were noted for CGI-ADHD-S ($p=.011$) and ADHDRS-IV-Parent:Inv, Inattention ($p=.031$) Subscale scores.
- No patients died or experienced serious adverse events (SAEs) during this study.

Title of Study: A Randomized, Double-Blind Comparison of Atomoxetine Hydrochloride Augmented with Either Extended-Release Methylphenidate Hydrochloride (Concerta®) or Placebo in Children with Attention-Deficit/Hyperactivity Disorder (ADHD) Who Have Not Responded to Stimulant Mono Therapy	
Investigator(s): This multicenter study included 5 principal investigators.	
Study Center(s): This study was conducted at 5 study centers in 1 country.	
Length of Study: 14 months Date first patient enrolled: 06 January 2004 Date last patient completed: 10 March 2005	Phase of Development: 3
Objectives: The primary objective was to assess the safety of up to 1.4 mg/kg/day of atomoxetine plus placebo administered QD, compared with up to 1.4 mg/kg/day of atomoxetine plus up to 1.1 mg/kg/day of Concerta® administered QD, in children (aged 6 to 12 years) with ADHD who were retrospectively identified as stimulant nonremitters and who were exposed to acute treatment with atomoxetine. Safety was measured by categorical changes in blood pressure or pulse. Secondary objectives were to assess the safety of atomoxetine+placebo compared with atomoxetine+Concerta as measured by ECGs, clinical laboratory tests, and AEs; and to compare efficacy as measured by the ADHDRS-IV-Parent:Inv, WPREMB-Revised, LPS-P, Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity and -Improvement (CGI-ADHD-S and CGI-ADHD-I) scales, CPRS-R:S, and the Conners' GI-T.	
Study Design: Study LYBU was a multicenter, Phase 3, randomized, parallel, double-blind pilot study of atomoxetine+ either Concerta or placebo in children aged 6 through 12 years who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition™ (DSM-IV™) criteria for ADHD and who were previously identified as stimulant nonremitters. Following a screening and washout period (Study Period I; 5-28 days), eligible patients were titrated to a target dose of up to 1.4 mg/kg/day atomoxetine+placebo (Study Period IIa). Patients who had a marked response after 4 weeks (remitter group; defined as clinical remission of their symptoms, as measured by a CGI-ADHD-S score of 1 or 2) continued atomoxetine+placebo for an additional 6 weeks (Study Period IIb). Patients who did not have a marked response after 4 weeks (nonremitter group) were randomized to receive up to 1.4 mg/kg/day atomoxetine+ either placebo (atomoxetine+placebo treatment group) or up to 1.1 mg/kg/day Concerta (atomoxetine+Concerta treatment group) during Study Period IIb.	
Number of Patients: <u>Planned:</u> Up to 85 patients entered with approximately 50 nonremitting patients randomized (25 to atomoxetine+placebo and 25 to atomoxetine+Concerta). Screened: 30 patients. <u>Study Period IIa:</u> Enrolled: 25 patients (enrollment was stopped due to lower-than-expected enrollment rates). <u>Study Period IIb:</u> Remitters: 4 patients. Nonremitters: 17 patients (randomized: 9 to atomoxetine+Concerta, 8 to atomoxetine+placebo). <u>Completed:</u> Remitters: 4 patients. Nonremitters: 13 patients (7 atomoxetine+Concerta, 6 atomoxetine+placebo).	
Diagnosis and Main Criteria for Inclusion: Male and female children aged 6 through 12 years who met DSM-IV™ criteria for ADHD as confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children—Present and Lifetime, Behavioral Disorders Supplement (K-SADS-PL). Patients had a severity rating at least 1.5 standard deviations (SD) above their age and gender norms on the ADHDRS-IV-Parent:Inv, as well as a CGI-ADHD-S score ≥ 4 (at Visit 1 and Visit 2). Patients met criteria for a stimulant nonremitter (for example, the patient did not demonstrate clinically significant improvement during a well-documented clinical trial with adequate therapy in approximately the 12 months prior to study enrollment, such that in the clinical opinion of the treating physician a change in therapy was indicated).	

Study Drug, Dose, and Mode of Administration: Atomoxetine up to 1.4 mg/kg/day (exact dose could vary slightly to correspond to available capsule strengths, but was not to exceed 1.8 mg/kg/day), given orally QD. The exact dose was based on the patient's weight. Atomoxetine was provided as 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, and 40 mg capsules.

Reference Therapy, Dose, and Mode of Administration: Concerta up to 1.1 mg/kg/day, given orally QD. The exact dose was based on the patient's weight but was not to exceed 54 mg/day. Concerta was provided as 18 mg capsules. Placebo capsules, identical in appearance to atomoxetine or Concerta, given orally QD.

Duration of Treatment: Study Period IIa (Visit 2 until Visit 5) was approximately 4 weeks; Study Period IIb (Visit 5 through Visit 8) was approximately 6 weeks.

Variables:

Efficacy: ADHDRS-IV-Parent:Inv, Total and subscale scores; WPREMB-Revised, total score; Life Participation Scale, total score; CGI-ADHD-S score; CGI-ADHD-Improvement (CGI-ADHD-I) score; CPRS-R:S, total score; and Conners' GI-T, total score.

Safety: AEs, vital sign measurements, laboratory test results, and ECGs.

Evaluation Methods:

Statistical: Analyses were performed on an intent-to-treat basis, unless otherwise specified. Safety analyses included data from all patients who took at least one dose of Study Period II medication. All tests of hypotheses were considered statistically significant if the two-sided p-value was less than 0.05, unless otherwise stated. No adjustments for multiple comparisons were made. An LOCF endpoint approach was used to impute missing post-baseline data. For Study Period IIa, baseline was defined as the last measurement obtained on, or prior to Visit 2 (start of Study Period IIa); and endpoint as the last measurement obtained after Visit 2 but on, or before Visit 5 (the time of randomization). For Study Period IIb, baseline was defined as the last measurement obtained on, or prior to Visit 5; and endpoint as the last measurement obtained after Visit 5 but on, or before Visit 8 (final visit).

Safety Analyses:

Study Period IIa: The incidences of treatment-emergent adverse events (TEAEs) and SAEs were tabulated for all treated patients. Changes from baseline to endpoint values were summarized for vital signs, laboratory measures, and ECG parameters. Within-treatment group changes were assessed using a Wilcoxon's signed-rank test for laboratory parameters and a paired t-test for vital signs and ECG intervals. Categorical analyses of vital signs and ECG intervals were summarized.

Study Period IIb: The primary analysis was a Fisher's exact test of the proportion of patients experiencing one or more categorical changes in vital signs. Criteria for categorical changes were: for diastolic and systolic blood pressure, an increase of at least 5 mmHg to above the 95th percentile based on age, gender, and height-adjusted National Institute of Health norms and; for pulse, an increase of at least 25 bpm to a value of at least 110 bpm. The incidences of TEAEs and SAEs were tabulated for all remitter patients and for randomized patients by treatment group. Treatment group differences were analyzed using Fisher's exact test. Changes from baseline to endpoint values were summarized for vital signs, laboratory measures, and ECG parameters. Within-treatment group changes were assessed using a Wilcoxon signed-rank test for laboratory parameters and a paired t-test for vital signs and ECG intervals. Categorical analyses of vital signs and ECG intervals were summarized. Treatment comparisons were assessed using an analysis of covariance (ANCOVA).

Efficacy Analyses:

Study Period IIa: For CGI-ADHD-I scores, mean values at endpoint were provided and proportions in each category were summarized. For other efficacy variables, changes from baseline to endpoint were summarized for all treated patients. A paired t-test was used to assess whether mean changes from baseline to endpoint were statistically significant.

Efficacy Analyses (concluded):

Study Period IIb: For CGI-ADHD-I scores, mean values at endpoint were provided and proportions in each category were summarized. For other efficacy variables, changes from baseline to endpoint were summarized for all remitter patients and for randomized patients by treatment group. Changes from baseline to endpoint were analyzed using an ANCOVA model with treatment and investigator as factors and baseline as a covariate. A paired t-test test was used to assess whether mean changes within treatment groups from baseline to endpoint were statistically significant.

Results:

Patient Demographics

Table LYBU.1 summarizes baseline characteristics for enrolled patients. Enrollment rates were lower than expected; therefore, enrollment was closed after 25 patients had enrolled in Study Period IIa. Of these patients, 24 received double-blind treatment with atomoxetine+placebo. Most treated patients were Caucasian (83.3%), male (83.3%), and met the criteria for the combined ADHD subtype (79.2%). The mean (SD) age was 9.6 (1.8) years.

Except for Life Participation Scale-Parent-rated (LPS-P) total score, randomized groups were comparable across demographic and baseline characteristics. The least square mean LPS-P total score in the atomoxetine+Concerta treatment group was 21.5 at baseline compared with 28.4 in the atomoxetine+placebo treatment group ($p=.015$).

**Table LYBU.1. Summary of Patient Characteristics at Baseline
Enrolled Patients Receiving Treatment**

Characteristic	Study Period IIa		Study Period IIb ^b	
	Atomoxetine ^a (N=24)	Remitters (N=4)	Atx+Cnc (N=9)	Atx+Pla (N=8)
Age, years: mean (SD)	9.6 (1.8)	10.5 (1.3)	10 (1.9)	9 (1.9)
Sex: n (%)				
Male	20 (83.3)	4 (100.0)	8 (88.9)	6 (75.0)
Female	4 (16.7)	0 (0.0)	1 (11.1)	2 (25.0)
Race Origin: n (%)				
Caucasian	20 (83.3)	2 (50.0)	8 (88.9)	7 (87.5)
African descent	2 (8.3)	1 (25.0)	0 (0.0)	1 (12.5)
Other	2 (8.3)	1 (25.0)	1 (11.1)	0 (0.0)
ADHD Subtype: n (%)				
Combined	20 (83.3)	3 (75.0)	7 (77.8)	7 (87.5)
Inattentive	4 (16.7)	1 (25.0)	2 (22.2)	1 (12.5)
Hyperactive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CYP2D6 Phenotype: n (%)				
Extensive	21 (87.5)	4 (100.0)	8 (88.9)	8 (100.0)
Poor	3 (12.5)	0 (0.0)	1 (11.1)	0 (0.0)
LPS-P:				
LS Mean	N/A	N/A	21.5	28.4

Abbreviations: ADHD = Attention-Deficit/Hyperactivity Disorder; Atx = atomoxetine; Cnc = Concerta; CYP2D6 = cytochrome P450 2D6; LPS-P = Life Participation Scale-Parent Rated Total Score; LS = least square; N = number of enrolled patients; n = number of patients with specific characteristic; N/A = not applicable; Pla = placebo; SD = standard deviation.

a One enrolled patient did not receive treatment.

b Three patients discontinued during Study Period IIa and did not get randomized into Study Period IIb: two patients due to adverse events and one patient due to lack of efficacy.

Patient Disposition

A total of 30 patients entered the screening phase (Figure LYBU.1). Of the 25 patients who enrolled in Phase IIa of the study, 24 patients received double-blind treatment with atomoxetine+placebo. Twenty-one patients continued into Study Period IIb: 4 patients met the double-blind criteria for remission (remitters) and continued double-blind treatment with atomoxetine+placebo; 17 patients were nonremitters and were randomized to acute, double-blind treatment with either atomoxetine+Concerta (9 patients) or atomoxetine+placebo (8 patients).

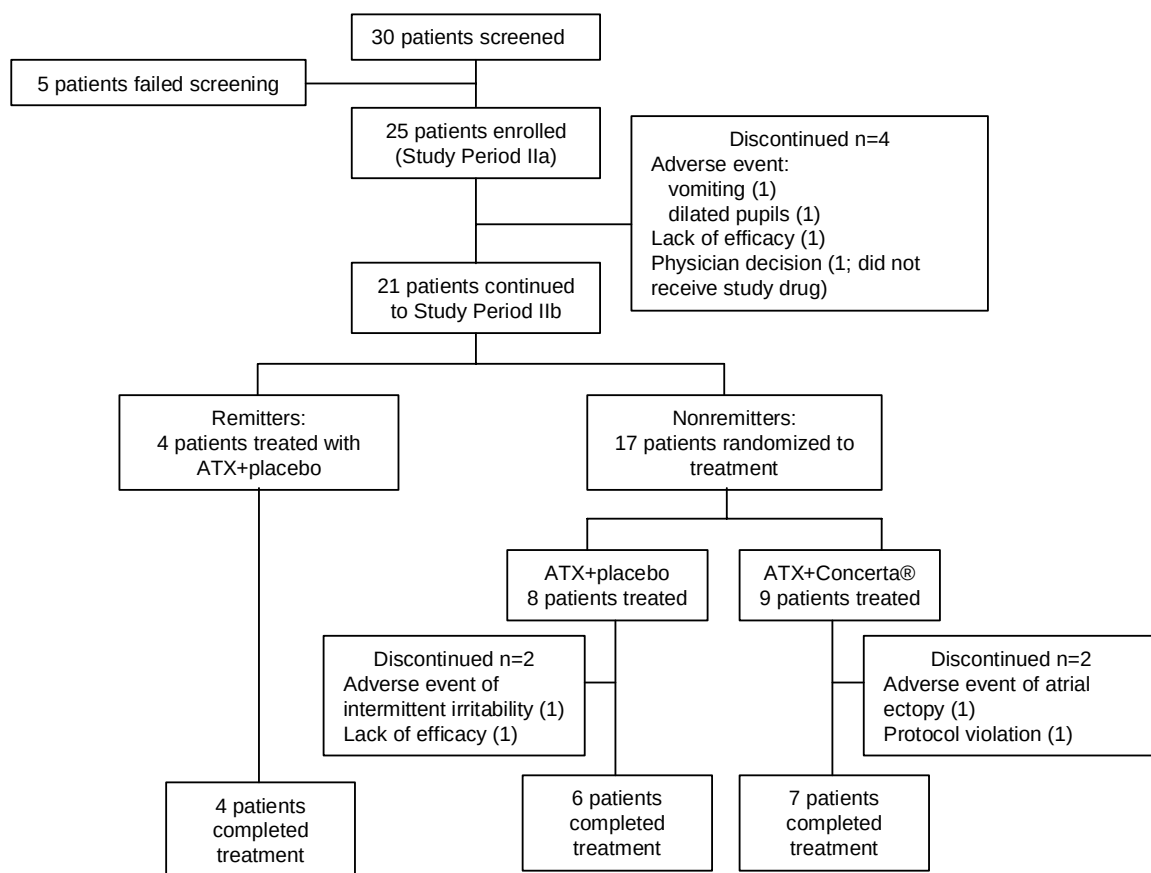


Figure LYBU.1. Patient disposition.

Primary Objective

The primary objective of this study was to assess the safety of up to 1.4 mg/kg/day of atomoxetine and placebo administered QD, compared to 1.4 mg/kg/day of atomoxetine and 1.1 mg/kg/day of Concerta administered QD. Safety was measured by categorical changes in blood pressure or pulse.

In Study Period IIb, 3 patients in the atomoxetine+Concerta treatment group had one or more categorical changes in vital signs (diastolic blood pressure in 1 patient; systolic blood pressure in 1 patient; and both diastolic blood pressure and pulse in 1 patient). In addition, 1 patient from the atomoxetine+placebo treatment group had a categorical change in pulse; and 1 patient in the remitter group had a categorical change in diastolic blood pressure. There were no significant differences across randomized treatment groups in categorical changes in vital signs.

Table LYBU.2 presents a summary of patients with one or more categorical changes in vital signs within Study Period IIb.

**Table LYBU.2. Patients With Categorical Changes in Vital Signs
Study Period IIb**

Treatment Group	Diastolic BP^a n (%)	Systolic BP^a n (%)	Pulse^b n (%)
Remitters (N=4)	1 (25.0)	-	-
Atomoxetine + Concerta (N=9)	2 (22.2) ^c	1 (11.1)	1 (11.1)
Atomoxetine + Placebo (N=8)	-	-	1 (12.5)

Abbreviations: BP = blood pressure, bpm = beats per minute.

^a Blood pressure categorical change: ≥ 5 mmHg increase and above 95th percentile.

^b Pulse categorical change: ≥ 25 bpm increase to ≥ 110 bpm.

^c One patient had a categorical change in both diastolic BP and pulse.

Secondary Objectives

The secondary objectives of this study were as follows:

- To assess the safety, as measured by ECGs, of 1.4 mg/kg/day of atomoxetine and placebo administered QD as compared to 1.4 mg/kg/day of atomoxetine and 1.1 mg/kg/day of Concerta administered QD
- To assess the safety, as measured by clinical laboratory tests, of 1.4 mg/kg/day of atomoxetine and placebo administered QD as compared to 1.4 mg/kg/day of atomoxetine and 1.1 mg/kg/day of Concerta administered QD
- To assess the tolerability, as measured by spontaneously reported AEs, of 1.4 mg/kg/day of atomoxetine and placebo administered QD as compared to 1.4 mg/kg/day of atomoxetine and 1.1 mg/kg/day of Concerta administered QD
- To compare the efficacy of 1.4 mg/kg/day of atomoxetine and placebo administered QD as compared to 1.4 mg/kg/day of atomoxetine and 1.1 mg/kg/day of Concerta administered QD as measured by the ADHDRS-IV-Parent:Inv, the WPREMB-Revised, the LPS-P, the CPRS-R:S, and the Conners' GI-T.

In Study Period IIa, statistically significant decreases from baseline to LOCF endpoint ($p < .001$) were noted for ADHDRS-IV-Parent:Inv, Total, Inattention, and Hyperactivity-Impulsivity Subscale scores; CGI-ADHD-S; WPREMB-Revised, total score; and CPRS-R:S, total score. A statistically significant increase was noted for LPS-P ($p < 0.001$). Mean changes from baseline at LOCF endpoint are summarized below (Table LYBU.3).

In Study Period IIb, statistically significant decreases from baseline were noted at LOCF endpoint for CGI-ADHD-S ($p = .011$) and ADHDRS-IV-Parent:Inv, Inattention ($p = .031$) scores in the atomoxetine+placebo treatment group. No statistically significant changes from baseline—either within or across randomized treatment groups—were noted for any other efficacy parameter. Mean changes from baseline are summarized below (Table LYBU.4).

Table LYBU.3. Secondary Objective
Study Period IIa
Mean Change from Baseline to LOCF Endpoint
Enrolled Patients

Parameter, Mean (SD)	Atomoxetine (N=24)^a	p-Value^b
ADHDRS-IV-Parent:Inv, total		
Baseline	44.9 (6.6)	
Change at endpoint (LOCF)	-17.8 (9.2)	<0.001
ADHDRS-IV-Parent:Inv, Inattention		
Baseline	23.4 (3.3)	
Change at endpoint (LOCF)	-8.0 (5.8)	<0.001
ADHDRS-IV-Parent:Inv, Hyperactivity-Impulsivity		
Baseline	21.5 (5.4)	
Change at endpoint (LOCF)	-9.8 (5.9)	<0.001
WPREMB-Revised, total		
Baseline	21.4 (6.3)	
Change at endpoint (LOCF)	-6.7 (6.5)	<0.001
LPS-P, total		
Baseline	25.4 (7.9)	
Change at endpoint (LOCF)	8.2 (7.9)	<0.001
CGI-ADHD-S		
Baseline	5.3 (0.7)	
Change at endpoint (LOCF)	-1.5 (0.9)	<0.001
CPRS-R:S, total		
Baseline	59.5 (13.4)	
Change at endpoint (LOCF)	-17.1 (11.0)	<0.001
Conners' GI-T, total		
Baseline	17.4 (6.8) (n=14)	
Change at endpoint (LOCF)	-0.5 (4.1)	0.653

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored, CGI-ADHD-S = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity, Conners' GI-T = Conners' Global Index-Teacher, CPRS-R:S = Conners' Parent Rating Scale-Revised: Short Form, LPS-P = Life Participation Scale-Parent Version, WPREMB-Revised-Parent = Weekly Parent Ratings of Evening and Morning Behavior-Revised

^a Treatment included double-blind atomoxetine+placebo.

^b Within-treatment group changes were assessed using a paired t-test.

Baseline: last measurement obtained on or prior to Visit 2.

Endpoint: last measurement after Visit 2 but on, or before Visit 5 (time of randomization).

Table LYBU.4. Secondary Objective
Study Period IIb
Mean Change from Baseline to LOCF Endpoint
Enrolled Patients

Parameter, Mean (SD)	Atomoxetine+Concerta (N=9)	Atomoxetine+Placebo (N=8)	p-Value ^b
ADHDRS-IV-Parent:Inv, total			
Baseline	28.7 (12.1)	31.9 (10.9)	
Change at endpoint (LOCF)	-3.3 (20.9)	-4.3 (5.2)	0.909
p-value ^a	0.645	0.053	
ADHDRS-IV- Parent:Inv, Inattention			
Baseline	18.1 (5.8)	16.3 (5.1)	
Change at endpoint (LOCF)	-4.0 (10.0)	-1.8 (1.8)	0.662
p-value ^a	0.265	0.031	
ADHDRS-IV- Parent:Inv, Hyperactivity-Impulsivity			
Baseline	10.6 (7.9)	15.6 (6.5)	
Change at endpoint (LOCF)	0.7 (11.5)	-2.5 (4.2)	0.657
p-value ^a	0.866	0.140	
WPREMB-Revised-Parent, total			
Baseline	15.4 (7.7)	17.4 (6.9)	
Change at endpoint (LOCF)	1.9 (9.4)	-2.1 (4.8)	0.419
p-value ^a	0.562	0.253	
LPS-P, total			
Baseline	31.2 (10.3)	35.4 (6.6)	
Change at endpoint (LOCF)	3.3 (15.7)	-1.3 (9.0)	0.601
p-value ^a	0.541	0.707	
CGI-ADHD-S			
Baseline	4.1 (1.1)	4.3 (1.2)	
Change at endpoint (LOCF)	-0.7 (1.8)	-0.6 (0.5)	0.953
p-value ^a	0.299	0.011	
CGI-ADHD-I			
Baseline	2.78 (0.83)	3.5 (0.93)	
Change at endpoint (LOCF)	0.11 (1.54)	-0.63 (1.30)	0.433
CPRS-R:S, total			
Baseline	40.9 (19.4)	45.6 (18.3)	
Change at endpoint (LOCF)	-4.7 (24.5)	-2.9 (5.6)	0.771
p-value ^a	0.584	0.187	
Conners' GI-T, total			
Baseline	13.7 (5.9) (n=6)	17.4 (6.4) (n=7)	
Change at endpoint (LOCF)	-1.3 (1.4) (n=6)	-0.2 (2.7) (n=5)	0.339
p-value ^a	0.062	0.876	

(Abbreviations and footnotes continues)

Table LYBU.4. Secondary Objective
Study Period IIb
Mean Change from Baseline to LOCF Endpoint
Enrolled Patients (concluded)

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored, CGI-ADHD-I = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Improvement, CGI-ADHD-S = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity, Conners' GI-T = Conners' Global Index-Teacher, CPRS-R:S = Conners' Parent Rating Scale-Revised: Short Form, LOCF = last observation carried forward, LPS-P = Life Participation Scale-Parent Version, N = number of patients, SD = standard deviation, WPREMB-Revised-Parent = Weekly Parent Ratings of Evening and Morning Behavior-Revised.

^a Within-treatment group changes were assessed using a paired t-test.

^b Treatment comparisons were assessed using an ANCOVA.

Baseline: last measurement obtained on or prior to Visit 5.

Endpoint: last measurement after Visit 5 but on, or before Visit 8 (final visit).

Safety

There were no deaths or SAEs in this study.

Table LYBU.5 lists the treatment-emergent adverse events that occurred in $\geq 2\%$ of patients. Treatment-emergent adverse events (TEAEs) were reported by 16 of the 24 patients treated in Study Period IIa. Events reported by 14 of the 16 patients were considered possibly related to study drug. The most frequently reported events were vomiting (5 patients); headache (4 patients); decreased appetite, nausea, pyrexia, and somnolence (each in 3 patients); and irritability and rash (each in 2 patients). One TEAE (headache) was considered severe. Two patients discontinued due to AEs (mydriasis/dilated pupils and vomiting).

In Study Period IIb, TEAEs were reported for 2 of 4 patients in the remitter group, 5 of 9 patients in the atomoxetine+Concerta treatment group, and 6 of 8 patients in the atomoxetine+placebo treatment group. Of the 13 patients randomized across all three treatment groups, 9 patients had events that were considered possibly related to study drug. Adverse events reported by more than 1 patient included nausea, vomiting, and initial insomnia (each in 3 patients); and headache and rhinitis (each in 2 patients). There were no significant differences in the incidence of TEAEs across the randomized groups. Only one TEAE (irritability in an atomoxetine+placebo patient) was considered severe. Two patients discontinued due to an AE: 1 patient due to intermittent irritability (atomoxetine+placebo treatment group), and 1 patient due to atrial ectopy (atomoxetine+Concerta treatment group).

**Table LYBU.5. Summary of Treatment-Emergent Adverse Events
Incidence Greater than or Equal to 2 Percent
All Study Periods, Enrolled Patients**

	Study Period IIa (N=24)	Study Period IIb (N=21)			
MedDRA Preferred Term ^a	Atx + Pla (N=24) n (%)	Atx + Pla Remitters (N=4) n (%)	Atx + Cnc Nonremitters (N=9) n (%)	Atx + Pla Nonremitters (N=8) n (%)	Total SPIIb (N=21) n (%)
Patients with no TEAE	8 (33.3)	2 (50.0)	4 (44.4)	3 (37.5)	9 (42.9)
Patients with ≥1 TEAE	16 (66.7)	2 (50.0)	5 (55.6)	5 (62.5)	12 (57.1)
Vomiting	5 (20.8)	1 (25.0)	1 (11.1)	1 (12.5)	3 (14.3)
Headache	4 (16.7) ^b		1 (11.1)	1 (12.5)	2 (9.5)
Nausea	3 (12.5)			1 (12.5)	1 (4.8)
Pyrexia	3 (12.5)				
Decreased appetite	3 (12.5)	-	-	-	-
Somnolence	3 (12.5)				
Irritability	2 (8.3)			1 (12.5) ^c	1 (4.8)
Rash	2 (8.3)		1 (11.1)		1 (4.8)
Mydriasis	1 (4.2)				
Diarrhoea	1 (4.2)				
Fatigue	1 (4.2)				
Therapeutic response unexpected	1 (4.2)				
Influenza	1 (4.2)				
Hand fracture	1 (4.2)				
Blood pressure increased	1 (4.2)				
Dizziness	1 (4.2)				
Initial insomnia	1 (4.2)		1 (11.1)	2 (25.0)	3 (14.3)
Mood altered	1 (4.2)				
Rhinorrhoea	1 (4.2)				
Rhinitis		1 (25.0)		1 (12.5)	2 (9.5)
Supraventricular extrasystoles			1 (11.1)		1 (4.8)
Stomach discomfort			1 (11.1)		1 (4.8)
Toothache			1 (11.1)		1 (4.8)
Abdominal pain, upper				1 (12.5)	1 (4.8)

(abbreviations and footnotes continues)

**Table LYBU.5. Summary of Treatment-Emergent Adverse Events
Incidence Greater than or Equal to 2 Percent
All Study Periods
Enrolled Patients (concluded)**

Abbreviations: Atx = atomoxetine, Cnc = Concerta, N = number of patients who took at least one dose of study drug, n = number of patients with treatment-emergent adverse event, Pla = placebo, TEAE = treatment-emergent adverse event.

- ^a Based on MedDRA coding dictionary version 8.0.
- ^b Reported as “severe” by 1 patient.
- ^c Reported as “severe” by 1 patient.

Note: Study Period IIa: Baseline defined as Visits 1-2, and endpoint as Visits 3-5. Study Period IIb: Baseline defined as Visit 5, and endpoint as Visits 6-8.

Laboratory Values

No ECG changes were statistically significant in either Study Period IIa or IIb. In Study Period IIa, statistically significant laboratory changes were seen in non-fasting glucose ($p=.022$) and alkaline phosphate ($p<.001$). In Study Period IIb, statistically significant laboratory changes were seen only in the atomoxetine+Concerta treatment group. These laboratory changes included: alkaline phosphate ($p=.004$), GGT ($p=.016$), leukocyte count ($p=.016$), and neutrophils ($p=.039$). However, none of the changes in ECGs or laboratory analytes in either Study Period IIa or Study Period IIb were considered by study physician review to be clinically meaningful. No patient discontinued from the study due to an abnormal lab value. Table LYBU.6 presents a summary of ECG results.

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**Table LYBU.6. Summary of Mean Change in Electrocardiogram from Baseline to Endpoint
Study Periods IIa and IIb**

ECG Assessment	Study Period IIa ^a		Study Period IIb ^b			
	Atx (n=24)	p-value	Remitters (n=4)	Atx + Cnc (n=9)	Atx + Plc (n=8)	p-value ^c
Heart rate (bpm)						
Mean baseline (SD)	87.5 (13.0)	.674	89.5 (5.7)	84.6 (16.6)	87.5 (16.1)	.650
Mean change (SD)	-1.3 (14.7)		2.0 (4.1)	2.2 (16.8)	1.0 (13.1)	
RR interval (msec)						
Mean baseline (SD)	699.9 (101.4) ^d	.642	672.8 (44.2)	738.2 (172.6)	704.6 (118.5)	.774
Mean change (SD)	11.5 (117.2) ^e		-15.8 (33.1)	-29.8 (126.7)	-13.5 (98.8)	
PR interval (msec)						
Mean baseline (SD)	133.8 (18.1) ^d	.903	137.5 (12.6)	132.2 (13.9)	131.3 (21.0)	.873
Mean change (SD)	-0.4 (16.9) ^e		-12.0 (14.2)	0.0 (15.0)	0.0 (20.7)	
QRS interval (msec)						
Mean baseline (SD)	80.4 (6.2) ^d	.648	80.0 (8.2)	77.8 (6.7)	81.3 (8.3)	.455
Mean change (SD)	-0.9 (9.0) ^e		2.5 (5.0)	5.6 (7.3)	1.3 (6.4)	
QT interval (msec)						
Mean baseline (SD)	350.0 (24.0) ^d	.763	347.5 (9.6)	353.3 (22.9)	353.8 (32.9)	.162
Mean change (SD)	-1.3 (20.5) ^e		-12.5 (9.6)	0.0 (24.5)	-10.0 (23.3)	
Data-corrected QT interval (msec)						
Mean baseline (SD)	403.3 (16.9) ^d	.354	406.0 (15.9)	400.8 (19.9)	406.4 (18.2)	.208
Mean change (SD)	-3.5 (17.6) ^e		-11.0 (18.2)	5.3 (19.6)	-8.6 (17.3)	
QTcB interval (msec)						
Mean baseline (SD)	420.0 (19.2) ^d	.380	424.3 (19.0)	415.6 (27.2)	422.9 (18.5)	.331
Mean change (SD)	-4.3 (22.8) ^e		-10.8 (20.9)	7.0 (25.3)	-7.9 (20.5)	
QTcF interval (msec)						
Mean baseline (SD)	395.0 (16.7) ^d	.369	397.0 (14.6)	393.6 (17.3)	398.1 (19.5)	.187
Mean change (SD)	-3.0 (15.9) ^e		-11.3 (16.6)	4.2 (18.2)	-8.9 (17.1)	

(continues)

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**Table LYBU.6. Summary of Mean Change in Electrocardiogram from Baseline to Endpoint
Study Periods IIa and IIb (Concluded)**

ECG Assessment	Study Period IIa ^a		Study Period IIb ^b			
	Atx (n=24)	p-value	Remitters (n=4)	Atx + Cnc (n=9)	Atx + Plc (n=8)	p-value ^c
QTcR interval (msec)						
Mean baseline (SD)	400.4 (16.8) ^d	.341	403.0 (15.1)	398.0 (19.0)	403.4 (18.6)	.203
Mean change (SD)	-3.4 (16.9) ^e		-11.5 (16.9)	5.2 (19.1)	-8.5 (17.3)	

Abbreviations: Atx = atomoxetine, bpm = beats per minute, Cnc = Concerta®, ECG = electrocardiogram; msec = milliseconds; n = number of patients with nonmissing data, Plc = placebo, PR interval = the time elapsing between the beginning of the P wave and the beginning of the next QRS complex; QRS = deflections in an electrocardiographic tracing that represent ventricular activity of the heart; QTc = corrected QT interval; QTcB = corrected QT interval using Bazett's correction; QTcF = corrected QT interval using Fridericia's correction; QTcR = corrected QT interval using Regression correction; RR = The time elapsing between two consecutive R waves; SD = standard deviation.

Analyzed using paired t-test.

^a Baseline was last observation taken before or on Visit 2. Endpoint was last observation taken after Visit 2.

^b Baseline was last observation taken before or on Visit 5. Endpoint was last observation taken after Visit 5.

^c Analyzed using analysis of covariance with effects for treatment and investigator with baseline value as covariate. Remitters were excluded from this analysis.

^d n=24

^e n=23

Vital Signs and Weight

There were no statistically significant changes in vital signs or weight across treatment groups during either of the Study Periods. In Study Period IIb, statistically significant decreases from baseline in body mass index ($p=.014$) and orthostatic diastolic blood pressure ($p=.006$) were noted at LOCF endpoint in the atomoxetine+Concerta treatment group, and increases in standing systolic blood pressure ($p=.036$) in the remitter group. There were no other significant changes from baseline to LOCF endpoint either within or across randomized groups in other vital sign parameters or body weight. Table LYBU.7 presents a summary of mean change in vital signs and weight from baseline to endpoint.

Table LYBU.7. Summary of Mean Change in Vital Signs and Weight from Baseline to Endpoint Study Periods IIa and IIb Enrolled Patients

	Study Period IIa ^a	Study Period IIb ^b			
Variable	Atx + Plc n=24	Remitters n=4	Atx + Cnc n=9	Atx + Plc n=8	p-value ^c
Diastolic blood pressure (mmHg); sitting					
Mean baseline (SD)	69.1 (9.7)	69.0 (10.4)	62.7 (7.6)	71.0 (9.5)	.502
Mean change (SD)	-0.6 (12.8)	0.0 (5.4)	7.1 (9.8)	-2.5 (8.7)	
p-value ^d	.825	1.000	.062	.445	
Diastolic blood pressure (mmHg); standing					
Mean baseline (SD)	70.0 (8.2)	68.5 (15.0)	62.8 (8.5)	71.6 (8.7)	.903
Mean change (SD)	-1.9 (10.3)	-1.0 (5.0)	3.6 (8.4)	-3.1 (9.1)	
p-value ^d	.373	.718	.240	.365	
Diastolic blood pressure (mmHg); orthstatic					
Mean baseline (SD)	0.9 (4.8)	-0.5 (9.0)	0.1 (3.6)	0.6 (6.5)	.062
Mean change (SD)	-1.3 (8.4)	-1.0 (4.8)	-3.6 (2.8)	-0.6 (3.5)	
p-value ^d	.443	.703	.006	.629	
Systolic blood pressure (mmHg); sitting					
Mean baseline (SD)	106.2 (11.5)	104.5 (9.3)	99.9 (15.0)	108.8 (11.3)	.269
Mean change (SD)	0.5 (11.8)	-1.5 (14.1)	5.0 (10.0)	-5.8 (12.5)	
p-value ^d	.850	.845	.171	.234	
Systolic blood pressure (mmHg); standing					
Mean baseline (SD)	104.3 (10.3)	99.5 (9.6)	99.2 (14.4)	109.3 (13.7)	.681
Mean change (SD)	0.3 (11.2)	7.5 (4.1)	3.2 (11.5)	-4.4 (11.7)	
p-value ^d	.886	.036	.424	.326	

(continues)

**Table LYBU.7. Summary of Mean Change in Vital Signs and Weight from Baseline to Endpoint
Study Periods IIa and IIb
Enrolled Patients (concluded)**

	Study Period IIa ^a	Study Period IIb ^b			
Variable	Atx + Plc n=24	Remitters n=4	Atx + Cnc n=9	Atx + Plc n=8	p-value ^c
Systolic blood pressure (mmHg); orthstatic					
Mean baseline (SD)	-1.9 (7.3)	-5.0 (7.4)	-0.7 (4.7)	0.5 (5.0)	.120
Mean change (SD)	-0.1 (7.9)	9.0 (10.1)	-1.8 (5.2)	1.4 (5.2)	
p-value ^d	.939	.174	.332	.480	
Heart rate (bpm); sitting					
Mean baseline (SD)	92.0 (13.2)	101.5 (13.0)	85.7 (11.1)	94.0 (14.0)	.901
Mean change (SD)	0.4 (14.2)	-9.5 (9.1)	5.0 (13.0)	-5.5 (18.0)	
p-value ^d	.887	.129	.281	.415	
Heart rate (bpm); standing					
Mean baseline (SD)	93.8 (13.4)	105.5 (15.8)	89.7 (12.7)	93.8 (14.2)	.988
Mean change (SD)	0.9 (15.0)	-6.5 (7.2)	5.0 (12.6)	1.0 (13.4)	
p-value ^d	.767	.168	.268	.838	
Heart rate (bpm); orthstatic					
Mean baseline (SD)	1.8 (10.9)	4.0 (5.7)	4.0 (3.0)	-0.3 (5.4)	.751
Mean change (SD)	0.5 (12.3)	3.0 (6.2)	0.0 (4.6)	6.5 (12.1)	
p-value ^d	.844	.406	1.000	.172	
Body Mass Index (kg/m ²)					
Mean baseline (SD)	17.8 (3.3)	21.4 (6.1)	17.6 (2.1)	16.4 (1.6)	.168
Mean change (SD)	0.0 (0.6)	0.5 (1.4)	-0.9 (0.8)	-0.2 (0.5)	
p-value ^d	.847	.492	.014	.392	
Weight (kg)					
Mean baseline (SD)	35.5 (12.2)	45.0 (17.8)	37.8 (11.9)	29.7 (6.9)	.189
Mean change (SD)	0.0 (1.3)	2.6 (4.1)	-1.0 (1.9)	0.0 (0.6)	
p-value ^d	.988	.288	.146	.956	
Body Temperature (°C)					
Mean baseline (SD)	36.4 (0.7)	36.5 (0.2)	36.3 (0.5)	36.0 (0.7)	.882
Mean change (SD)	-0.1 (0.5)	0.0 (0.5)	-0.1 (0.4)	0.1 (0.7)	
p-value ^d	.372	.929	.601	.677	

Abbreviations: bpm = beats per minute, C = Celsius; Cnc = Concerta®, kg = kilogram; n = number of patients with non-missing data, Plc = placebo, SD = standard deviation.

Population: Enrolled patients with at least one baseline and endpoint observation.

^a Baseline was last observation taken before or on Visit 2. Endpoint was last observation taken after Visit 2.

^b Baseline was last observation taken before or on Visit 5. Endpoint was last observation taken after Visit 5.

^c Analyzed using analysis of covariance with effects for treatment and investigator with baseline value as covariate. Remitters were excluded from this analysis.

^d Within group changes analyzed using a paired t-test.

Summary ID# 7066

Clinical Study Summary: Study B4Z-MC-LYBV

A Double-Blind Study of Functional Outcomes with Atomoxetine-Hydrochloride and Placebo in Adult Outpatients with DSM-IV Attention-Deficit/Hyperactivity Disorder

Date summary approved by Lilly: 08 June 2006

Brief Summary of Results:

The primary objective of this double-blind, randomized trial was to test the hypothesis that, compared with placebo, administration of atomoxetine at total daily doses of 40 to 100 mg for approximately 6 months will result in an improved work productivity, as measured on the Endicott Work Productivity Scale (EWPS), during Study Period II.

- 532 patients entered the study, 410 patients were randomized, 238 patients (58%) discontinued and 172 (42%) completed Study Period II and continued into Study Period III, 56 patients discontinued from Study Period III, and 116 patients completed the study.
- There were no statistically significant differences between treatment groups for the primary or secondary gatekeeper efficacy measures (EWPS total score and CAARS-Inv:SV), except for the EWPS repeated measures analysis at Visit 3, which showed a statistically significant ($p=.003$) decrease (improvement) for the atomoxetine-treated group compared with the placebo-treated group.
- Two SAEs (pneumonia and pregnancy) and no deaths were reported during this study.
- In Study Period II, increases in systolic blood pressure and pulse in atomoxetine-treated patients were statistically significant ($p=.020$ and $p<.001$, respectively) compared with placebo-treated patients. Weight decreases in atomoxetine-treated patients were statistically significant ($p<.001$) compared with placebo-treated patients.

Title of Study: A Double-Blind Study of Functional Outcomes with Atomoxetine-Hydrochloride and Placebo in Adult Outpatients with DSM-IV Attention-Deficit/Hyperactivity Disorder	
Investigators: This multicenter study included 22 principal investigators.	
Study Centers: This study was conducted at 23 study centers in one country. Note: One investigator was responsible for two separate sites.	
Length of Study: 1 year, 7 months Date first patient enrolled (assigned to therapy): 01 December 2003 Date last patient completed: 07 July 2005	Phase of Development: 4
Objectives: <u>Primary Objective:</u> To test the hypothesis that, compared with placebo, administration of atomoxetine at total daily doses of 40 to 100 mg for approximately 6 months will result in improved work productivity, as measured on the Endicott Work Productivity Scale (EWPS), during Study Period II. <u>Secondary Gatekeeper Objective:</u> To assess the efficacy of atomoxetine in treating core symptoms in adults during Study Period II in the Conners' Adult Attention-Deficit/Hyperactivity Disorder Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV). <u>Additional Secondary Objectives:</u> 1) To assess the efficacy of atomoxetine therapy in treating core symptoms in adults with Attention-Deficit/Hyperactivity Disorder (ADHD) during Study Period II using the Conners' Adult ADHD Rating Scale-Self Report: Screening Version (CAARS-S:SV) and the Conners' Adult ADHD Rating Scale-Observer: Screening Version (CAARS-O:SV); 2) To assess changes in the health outcomes measures; 3) To compare safety of atomoxetine with placebo in a population of adult patients who meet Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision™ (DSM-IV-TR™) criteria for ADHD.	
Study Design: Study B4Z-MC-LYBV was a multicenter, randomized, approximately 6-month double-blind study comparing atomoxetine with placebo in adult outpatients with ADHD. A 4-month open-label extension followed the acute period. (See Figure 1 for study design.)	
Number of Patients: Planned: Approximately 400 randomized patients Randomized: 271 atomoxetine, 139 placebo: 410 total Completed Study Period II (double-blind): 104 atomoxetine, 68 placebo: 172 total Completed Study Period III (open-label): 74 atomoxetine, 42 placebo: 116 total	
Diagnosis and Main Criteria for Inclusion: Patients had to be at least 18 and less than 50 years old at the time of entry; had to meet DSM-IV-TR™ and CAARS-Inv:SV criteria for ADHD; had to have a Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity (CGI-ADHD-S) score of 4 (moderate symptoms) or greater at Visit 1 and Visit 2; and had to be employed 20 hours or more per week and be in their current place of employment for 6 months or more.	
Test Product, Dose, and Mode of Administration: <u>Study Period I:</u> No study drug administered. <u>Study Period II:</u> Atomoxetine 40 mg/day or placebo, given orally once daily for approximately 9 days; atomoxetine 80 mg/day or placebo, given orally once daily as two 40-mg capsules for approximately 19 days; atomoxetine 40 to 100 mg/day, based on clinical response or tolerability, or placebo, given orally once or twice daily (as a split dose) for approximately 5 months. <u>Study Period III:</u> Atomoxetine 40 mg/day, given orally once daily for approximately 9 days; atomoxetine 80 mg/day, given orally once daily as two 40-mg capsules for approximately 19 days; atomoxetine 40 to 100 mg/day, based on clinical response or tolerability, given orally once or twice daily (as a split dose) for approximately 3 months.	

Duration of Treatment: Approximately 10 months (222 days).

Variables:

Efficacy: Primary: EWPS total score; secondary gatekeeper: CAARS-Inv:SV; additional secondary: Adult ADHD Self-Report Scale Symptom Checklist (ASRS), CAARS-O:SV, CAARS-S:SV, CGI-ADHD-S, Global Assessment of Functioning (GAF), Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Improvement (CGI-ADHD-I).

Safety: Serious adverse events (SAEs) and AEs, laboratory tests, electrocardiograms (ECGs), vital signs.

Health Outcomes: Adult ADHD Quality of Life Measure (AAQOL), Driving Behavior Surveys (Self and Other Reports), Habits Questionnaires, Quality of Life Enjoyment & Satisfaction Questionnaire Short Form (Q-LES-Q-SF), Resource Utilization, Medical Outcomes Study (MOS) 36-Item Short Form Health Survey (SF-36), and Work Productivity and Activity Impairment Questionnaire (WPAI).

Evaluation Methods: Note: Study Period II consisted of Visits 3 through 6 (four visits total); Study Period III consisted of Visits 7 and 8 (two visits total).

Statistical: The primary efficacy analysis was an analysis of covariance (ANCOVA) on the last observation carried forward (LOCF) change from baseline to endpoint observation during Study Period II. The independent effects in the ANCOVA model were investigator, treatment, and baseline EWPS total score. Secondary severity variables included the ASRS, CAARS-O:SV, CAARS-S:SV, and CGI-ADHD-S. These variables were analyzed using ANCOVA on the LOCF change from baseline to endpoint observation. The independent effects in the ANCOVA model were investigator, treatment, and baseline score. The CAARS-S:SV Total score, Inattention subscale score, and Hyperactivity-Impulsivity subscale score were also analyzed using a repeated measures analysis based on a restricted maximum likelihood algorithm and assuming an unstructured covariance matrix. The Satterthwaite approximation was used for the estimated denominator degrees of freedom in t-tests at each visit. The independent effects in the model were investigator, treatment, visit, baseline score, and treatment-by-visit interaction. Binary outcome response variables (functional and symptomatic response) were analyzed by Fisher's exact test.

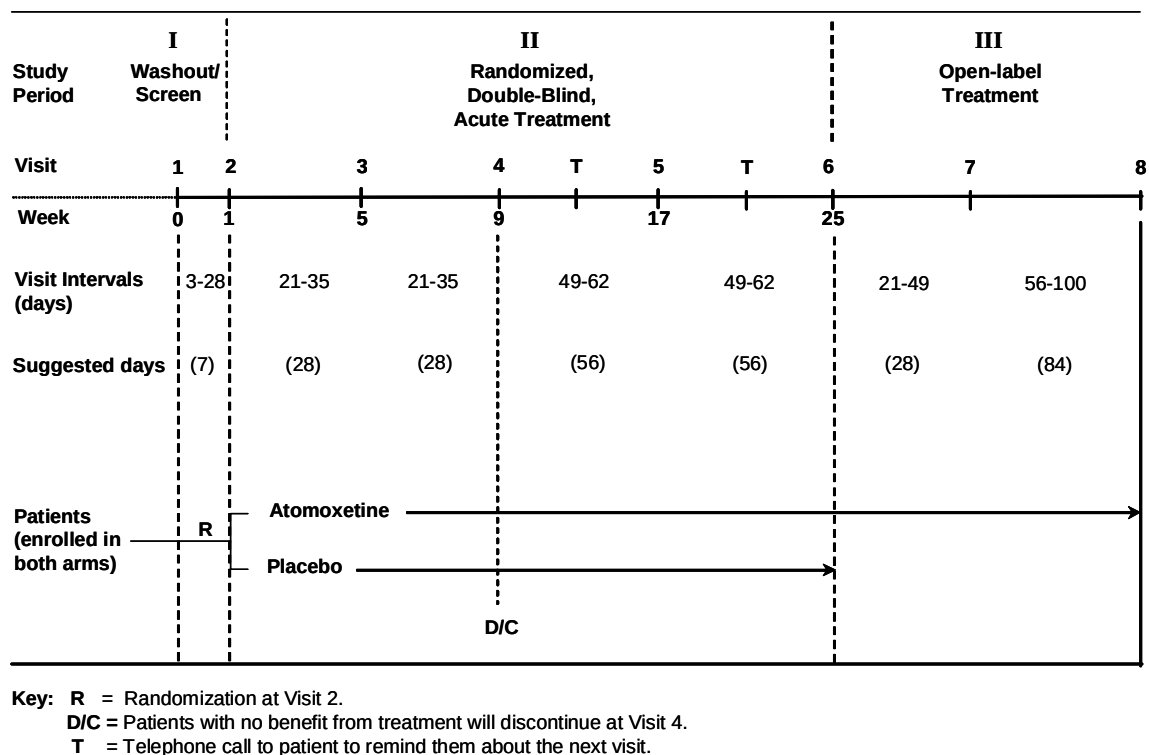


Figure 1. Study design for B4Z-MC-LYBV.

Results:

Patient Demographics

Table LYBV.1 summarizes patient characteristics at baseline for all randomized patients. Of the 410 randomized patients, 59% were male; 82% were Caucasian. The mean age was 36.8 years (range of 18.5 to 50.0 years). The majority of patients reported no previous stimulant use and no family history of ADHD, although the number of atomoxetine-treated patients with an unknown paternal history of ADHD was statistically higher ($p=.046$) compared with placebo-treated patients. The most common current and lifetime ADHD subtype, regardless of treatment assignment, was the Combined type (68%). Regarding disease severity, there were no statistically significant differences observed between treatment groups.

**Table LYBV.1. Summary of Patient Characteristics at Baseline
All Randomized Patients**

Characteristic	Atomoxetine (N=271)	Placebo (N=139)	Total (N=410)
Age, years: mean (SD)	37.1 (8.3)	36.0 (8.4)	36.8 (8.3)
Sex: n (%)			
Male	152 (56.1)	88 (63.3)	240 (58.5)
Female	119 (43.9)	51 (36.7)	170 (41.5)
Race Origin: n (%)			
Caucasian	223 (82.3)	113 (81.30)	336 (82.0)
African descent	14 (5.2)	10 (7.2)	24 (5.9)
Hispanic	21 (7.8)	13 (9.4)	34 (8.3)
ADHD Subtype: n (%)			
Combined	185 (68.3)	95 (68.4)	280 (68.3)
Inattentive	84 (31.0)	43 (30.9)	127 (31.0)
Hyperactive-Impulsive	2 (0.7)	0 (0.0)	2 (0.5)
Missing	0 (0.0)	1 (0.7)	1 (0.2)

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; N = number of randomized subjects;
n = number of subjects; SD = standard deviation.

Patient Disposition

Figure 2 presents a summary of patient disposition for Study Period I and Study Period II. Of the 532 patients who entered the study, 271 patients were randomized to treatment with atomoxetine, 139 patients were randomized to treatment with placebo, and 122 patients were not assigned to treatment. Of the 410 patients randomized, 172 (42%) completed Study Period II and continued into Study Period III, and 238 patients discontinued.

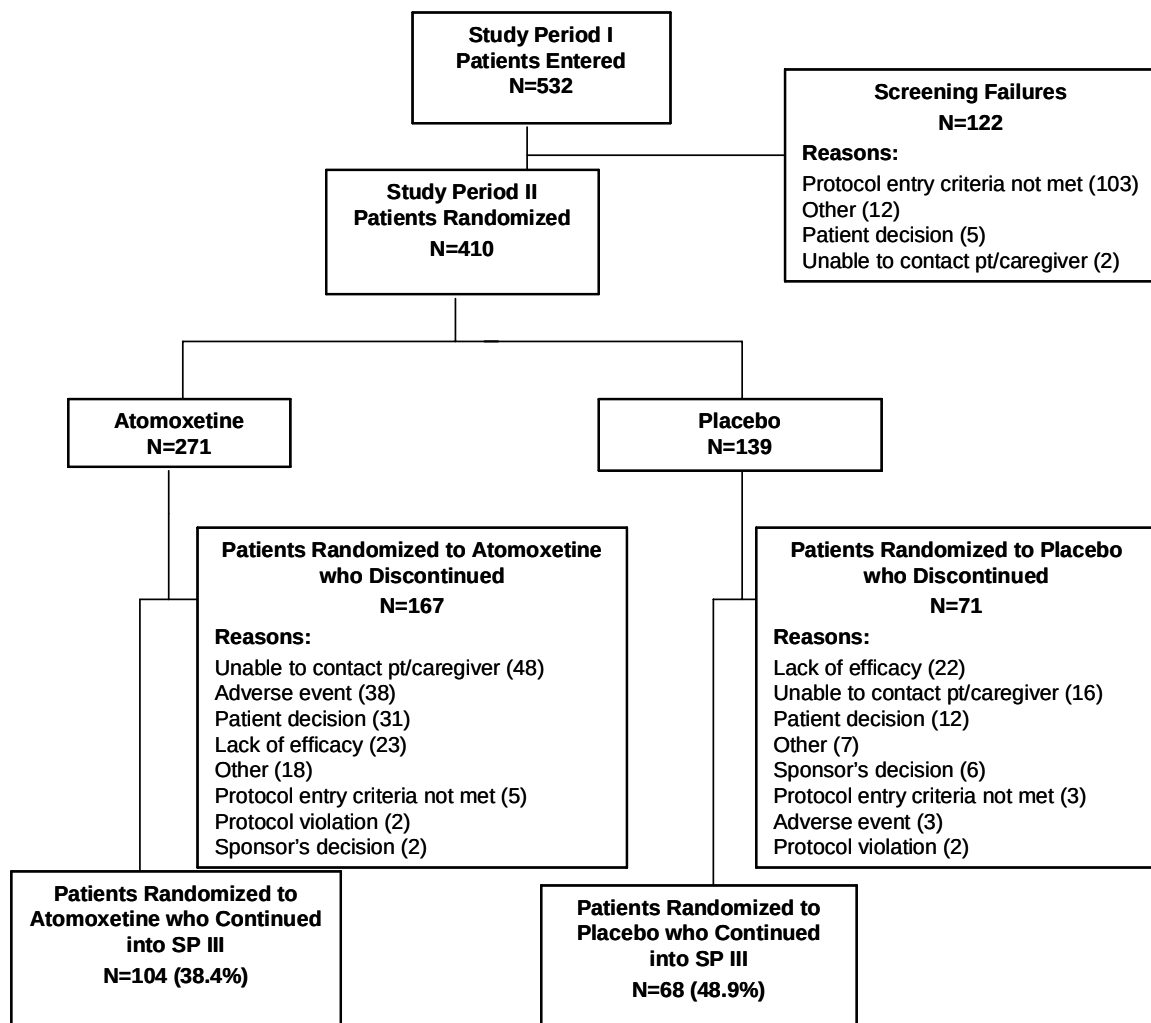


Figure 2. Patient disposition Study Periods I and II.

Figure 3 presents a summary of patient disposition for Study Period III. Of the 172 patients who continued into Study Period III, 104 patients had been randomized to atomoxetine and 68 had been randomized to placebo, and 56 patients discontinued. The total number of patients who completed the study was 116.

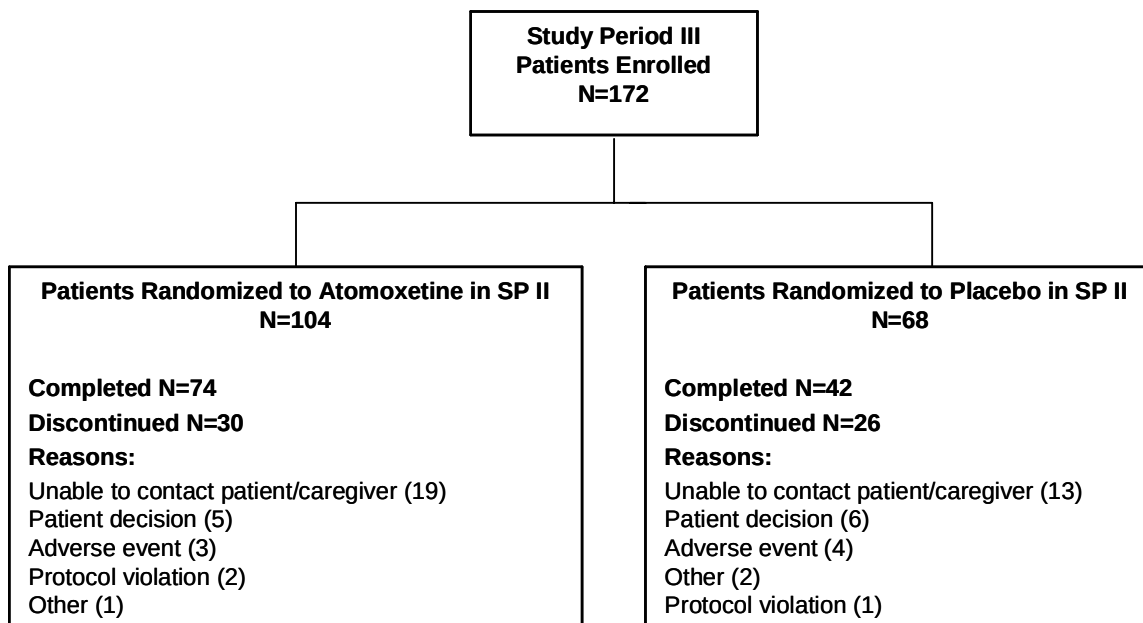


Figure 3. Patient disposition Study Period III.

The most common reasons for early discontinuation from Study Period II were “unable to contact patient/caregiver” for atomoxetine-treated patients and “lack of efficacy” for placebo-treated patients. The most common reason for discontinuation in Study Period III for both treatment groups was “unable to contact patient/caregiver.”

Primary Efficacy Measure

The primary efficacy measure was the EWPS total score, a self-rated work productivity scale. Table LYBV.2 and Table LYBV.3 summarize the results of the primary analysis of mean change in the EWPS from baseline to endpoint at 6 months and repeated measures for Study Period II. There were no statistically significant differences between treatment groups, except that at Visit 3, the EWPS repeated measures analysis did show a statistically significant ($p=.003$) decrease (improvement) for the atomoxetine-treated group compared with the placebo-treated group (Table LYBV.3).

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Table LYBV.2. Endicott Work Productivity Scale (EWPS) Total Score
Mean Change from Baseline to Endpoint
Randomized Patients Who Have Taken at Least One Dose of Study Drug
Six-Month Analysis

Treatment	N	Baseline		Endpoint		Change		Within Group	Between Group
		Mean	SD	Mean	SD	Mean	SD	p-value (a)	p-value (b)
ATOMOX	248	48.79	16.71	32.58	19.44	-16.22	18.42	<.001	.406
PLACEBO	134	50.75	15.46	35.14	19.29	-15.60	15.96	<.001	—
95% Confidence Interval for Treatment Difference: (-4.94 , 2.00)									

SD=standard deviation

(a): P-value is from paired t-test.

(b): P-value is based on an ANCOVA on change from baseline scores with terms for baseline, treatment and investigator.

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Table LYBV.3. Endicott Work Productivity Scale (EWPS) Total Score
Repeated Measures Analysis
Randomized Patients Who Have Taken at Least One Dose of Study Drug
Study Period II

VISIT	-----ATOMOX-----			-----PLACEBO-----			----- DIFFERENCE -----		
	LS MEAN	SE	P-VAL A	LS MEAN	SE	P-VAL A	LS MEAN	SE	P-VAL B
3	36.17	0.92	<.001	40.67	1.24	<.001	4.50	1.51	.003
4	33.28	1.08	<.001	33.46	1.42	<.001	0.18	1.76	.919
5	30.95	1.16	<.001	32.73	1.50	<.001	1.78	1.86	.339
6	29.12	1.32	<.001	31.70	1.67	<.001	2.58	2.09	.220

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Table LYBV.3. Endicott Work Productivity Scale (EWPS) Total Score
Repeated Measures Analysis
Randomized Patients Who Have Taken at Least One Dose of Study Drug
Study Period II (Concluded)

SUMMARY OF MODEL PARAMETERS		
Effect	F-VALUE	P-VAL C
INVP	1.34	0.1443
TRT	2.51	0.1144
VISIT	21.85	<.0001
BASELINE	237.66	<.0001
TRT*VISIT	2.33	0.0750

MODEL: Score = Imputed Baseline Score, Treatment, Pooled Investigator, Visit and Interaction of Treatment By Visit.

COVARIANCE STRUCTURE = UNSTRUCTURED, VISITS: 3-6

SE = Standard Error

A P-VALUES ARE FROM TESTS FOR A NONZERO LEAST SQUARES MEAN AT THE GIVEN VISIT

B P-VALUES ARE FROM TESTS FOR A TREATMENT DIFFERENCE IN LEAST SQUARES MEAN AT THE GIVEN VISIT

C P-VALUES ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE

Secondary Efficacy Measures

Secondary Gatekeeper Efficacy Measure

The secondary gatekeeper efficacy measure was the Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV) Total and Subscales mean change from baseline to endpoint at 6 months. There were no statistically significant differences between treatment groups for the CAARS-Inv:SV.

Additional Secondary Efficacy Measures

Table LYBV.4 and Table LYBV.5 show Study Period II results for secondary efficacy measure Conners' Adult ADHD Rating Scale-Self Report: Screening Version (CAARS-S:SV). The CAARS-S:SV Total and Subscales at 6 months was statistically significant in the mean change from baseline to endpoint for the total ADHD score ($p=.027$) and the inattention subscale ($p=.027$) for atomoxetine-treated patients compared with placebo-treated patients (Table LYBV.4). For repeated measures of the CAARS-S:SV Total ADHD score, differences between treatment groups were statistically significant at Visits 3, 4, and 5 but not at Visit 6 (Table LYBV.5).

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Table LYBV.4. CAARS-S:SV Total and Subscales
Mean Change from Baseline to Endpoint
Randomized Patients Who Have Taken at Least One Dose of Study Drug
Six-Month Analysis

Variable		Baseline		Endpoint		Change		Within Group	Between Group
Treatment	N	Mean	SD	Mean	SD	Mean	SD	p-value (a)	p-value (b)
Total ADHD Score - Imputed									
ATOMOX	251	34.67	8.50	23.20	10.20	-11.47	11.27	<.001	.027
PLACEBO	134	35.91	7.74	25.98	10.32	-9.92	10.67	<.001	—
95% Confidence Interval for Treatment Difference: (-4.39 , -0.2)									
Inattention Subscale - Imputed									
ATOMOX	251	19.35	4.53	12.71	5.90	-6.64	6.24	<.001	.027
PLACEBO	134	20.21	3.99	14.42	6.05	-5.79	6.34	<.001	—
95% Confidence Interval for Treatment Difference: (-2.54 , -0.1)									
Hyper/Impulsive Subscale - Imputed									
ATOMOX	251	15.32	5.66	10.49	5.36	-4.83	5.76	<.001	.075
PLACEBO	134	15.69	5.35	11.57	5.49	-4.13	5.19	<.001	—
95% Confidence Interval for Treatment Difference: (-1.92 , 0.09)									
ADHD Index Subscale - Imputed									
ATOMOX	251	21.65	5.11	14.83	6.65	-6.82	6.79	<.001	.248
PLACEBO	134	22.21	5.10	15.84	6.49	-6.37	6.88	<.001	—
95% Confidence Interval for Treatment Difference: (-2.08 , 0.54)									

SD=standard deviation

(a): P-value is from paired t-test.

(b): P-value is based on an ANCOVA on change from baseline scores with terms for baseline, treatment and investigator.

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Table LYBV.5. CAARS-S:SV Total ADHD Score
Repeated Measures Analysis
Randomized Patients Who Have Taken at Least One Dose of Study Drug
Study Period II

VISIT	-----ATOMOX-----			-----PLACEBO-----			----- DIFFERENCE -----		
	LS MEAN	SE	P-VAL A	LS MEAN	SE	P-VAL A	LS MEAN	SE	P-VAL B
3	25.89	0.56	<.001	29.98	0.76	<.001	4.09	0.92	<.001
4	24.10	0.62	<.001	27.00	0.82	<.001	2.90	1.01	.004
5	22.19	0.71	<.001	24.62	0.93	<.001	2.43	1.15	.036
6	20.27	0.82	<.001	21.98	1.02	<.001	1.71	1.28	.183

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Table LYBV.5. CAARS-S:SV Total ADHD Score
Repeated Measures Analysis
Randomized Patients Who Have Taken at Least One Dose of Study Drug
Study Period II (Concluded)

SUMMARY OF MODEL PARAMETERS		
Effect	F-VALUE	P-VAL C
INVP	1.22	0.2328
TRT	11.03	0.0010
VISIT	43.27	<.0001
BASELINE	31.97	<.0001
TRT*VISIT	1.54	0.2043

MODEL: Score = Imputed Baseline Score, Treatment, Pooled Investigator, Visit and Interaction of Treatment By Visit.

COVARIANCE STRUCTURE = UNSTRUCTURED, VISITS: 3-6

SE = Standard Error

A P-VALUES ARE FROM TESTS FOR A NONZERO LEAST SQUARES MEAN AT THE GIVEN VISIT

B P-VALUES ARE FROM TESTS FOR A TREATMENT DIFFERENCE IN LEAST SQUARES MEAN AT THE GIVEN VISIT

C P-VALUES ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE

Table LYBV.6 shows Study Period II results for secondary efficacy measure Conners' Adult ADHD Rating Scale-Observer Report: Screening Version (CAARS-O:SV). The CAARS-O:SV Inattentive Subscale at 6 months was statistically significant in the mean change from baseline to endpoint for the inattention subscale ($p=.022$) for atomoxetine-treated patients compared with placebo-treated patients.

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Table LYBV.6. CAARS-O:SV Total and Subscales
Mean Change from Baseline to Endpoint
Randomized Patients Who Have Taken at Least One Dose of Study Drug
Six-Month Analysis

Variable		Baseline		Endpoint		Change		Within Group	Between Group
Treatment	N	Mean	SD	Mean	SD	Mean	SD	p-value (a)	p-value (b)
Total ADHD Score - Imputed									
ATOMOX	77	30.59	10.50	19.91	9.98	-10.68	11.25	<.001	.083
PLACEBO	47	28.07	10.35	22.22	9.10	-5.84	9.07	<.001	—
95% Confidence Interval for Treatment Difference: (-6.65 , 0.41)									
Inattention Subscale - Imputed									
ATOMOX	77	16.79	6.13	10.58	5.92	-6.21	6.43	<.001	.022
PLACEBO	47	16.35	6.55	12.94	4.69	-3.41	6.03	<.001	—
95% Confidence Interval for Treatment Difference: (-4.35 , -0.3)									
Hyper/Impulsive Subscale - Imputed									
ATOMOX	77	13.79	6.39	9.33	5.23	-4.47	5.62	<.001	.272
PLACEBO	47	11.72	5.66	9.29	5.66	-2.43	4.05	<.001	—
95% Confidence Interval for Treatment Difference: (-2.69 , 0.77)									
ADHD Index Subscale - Imputed									
ATOMOX	77	20.18	7.24	13.40	6.91	-6.78	7.35	<.001	.190
PLACEBO	47	18.66	6.58	14.75	5.85	-3.91	5.47	<.001	—
95% Confidence Interval for Treatment Difference: (-3.70 , 0.74)									

SD=standard deviation

(a): P-value is from paired t-test.

(b): P-value is based on an ANCOVA on change from baseline scores with terms for baseline, treatment and investigator.

Health Outcome Measures

Adult ADHD Quality of Life Measure (AAQOL): The Life Outlook Subscale of the QOL measure showed a statistically significant improvement ($p=.024$) for the atomoxetine-treated group compared with the placebo-treated group (Table LYBV.7). The other three subscales and 29-item total showed no statistically significant differences.

Driving Behavior Survey (Self Report): No statistically significant differences between treatment groups were observed.

Driving Behavior Survey (Other Report): The Total of Items 2 through 27 showed a statistically significant improvement ($p=.011$) for the atomoxetine-treated group compared with the placebo-treated group (Table LYBV.8). Overall Driving Performance showed no statistically significant differences.

Quality of Life Enjoyment & Satisfaction Questionnaire Short Form (Q-LES-Q-SF): No statistically significant differences between treatment groups were observed.

Medical Outcomes Study (MOS) 36-Item Short Form Health Survey (SF-36): No statistically significant differences between treatment groups were observed.

Work Productivity and Activity Impairment Questionnaire (WPAI): No statistically significant differences between treatment groups were observed.

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Table LYBV.7. AAQOL
Mean Change from Baseline to Endpoint
Randomized Patients Who Have Taken at Least One Dose of Study Drug
Six Month Analysis

Variable		Baseline		Endpoint		Change		Within Group	Between Group
Treatment	N	Mean	SD	Mean	SD	Mean	SD	p-value (a)	p-value (b)
Productivity Subscale - Imputed									
ATOMOX	225	43.17	16.09	60.45	19.31	17.28	20.35	<.001	.080
PLACEBO	127	41.68	17.02	56.41	19.51	14.72	19.85	<.001	—
95% Confidence Interval for Treatment Difference: (-0.41 , 7.32)									
Psychological Health Subscale - Imputed									
ATOMOX	225	49.06	18.41	61.93	20.07	12.87	20.79	<.001	.236
PLACEBO	128	51.07	20.05	60.84	20.29	9.77	17.06	<.001	—
95% Confidence Interval for Treatment Difference: (-1.51 , 6.09)									
Life Outlook Subscale - Imputed									
ATOMOX	225	51.05	13.74	61.44	17.49	10.39	17.13	<.001	.024
PLACEBO	128	50.53	13.60	57.29	17.70	6.77	15.27	<.001	—
95% Confidence Interval for Treatment Difference: (0.50 , 7.20)									

SD=standard deviation

(a): P-value is from paired t-test.

(b): P-value is based on an ANCOVA on change from baseline scores with terms for baseline, treatment and investigator.

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Table LYBV.7. AAQOL
Mean Change from Baseline to Endpoint
Randomized Patients Who Have Taken at Least One Dose of Study Drug
Six Month Analysis (Concluded)

Variable		Baseline		Endpoint		Change		Within Group	Between Group
Treatment	N	Mean	SD	Mean	SD	Mean	SD	p-value (a)	p-value (b)
Relationships Subscale - Imputed									
ATOMOX	226	52.91	18.12	65.14	19.50	12.23	20.50	<.001	.425
PLACEBO	128	51.05	19.17	62.90	19.60	11.85	17.44	<.001	—
95% Confidence Interval for Treatment Difference: (-2.23 , 5.28)									
29 Item Total - Imputed									
ATOMOX	225	47.95	12.29	61.85	16.45	13.90	16.20	<.001	.052
PLACEBO	128	47.39	13.31	58.57	15.68	11.18	13.51	<.001	—
95% Confidence Interval for Treatment Difference: (-0.03 , 6.14)									

SD=standard deviation

(a): P-value is from paired t-test.

(b): P-value is based on an ANCOVA on change from baseline scores with terms for baseline, treatment and investigator.

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Table LYBV.8. Driving Behavior Survey (Other Report)
Mean Change from Baseline to Endpoint
Randomized Patients Who Have Taken at Least One Dose of Study Drug
Six Month Analysis

Variable		Baseline		Endpoint		Change		Within Group	Between Group
Treatment	N	Mean	SD	Mean	SD	Mean	SD	p-value (a)	p-value (b)
Total of 2-27 - Imputed									
ATOMOX	156	75.65	15.31	81.73	13.50	6.08	13.78	<.001	.011
PLACEBO	96	76.08	13.83	78.04	13.16	1.96	11.14	.088	—
95% Confidence Interval for Treatment Difference: (0.86 , 6.56)									
Overall Driving Performance									
ATOMOX	156	6.63	1.95	7.11	1.64	0.47	1.57	<.001	.818
PLACEBO	97	6.72	1.76	7.11	1.71	0.39	1.39	.007	—
95% Confidence Interval for Treatment Difference: (-0.29 , 0.36)									

SD=standard deviation

(a): P-value is from paired t-test.

(b): P-value is based on an ANCOVA on change from baseline scores with terms for baseline, treatment and investigator.

Safety

There were no patient deaths during this study. Two serious adverse events (SAEs) were reported, pneumonia and pregnancy. Although both patients were randomized to atomoxetine, neither SAE was considered to be related to study drug.

A summary of discontinuations due to AEs is shown in Table LYBV.9 and Table LYBV.10. Forty-eight patients discontinued their participation in this study due to AEs. Of the 41 patients who discontinued due to AEs during Study Period II, 38 were atomoxetine-treated patients and 3 were placebo-treated patients. The two most frequent AEs leading to discontinuation during Study Period II were nausea and fatigue, occurring in 4 (2%) and 3 (1%) of atomoxetine-treated patients, respectively (Table LYBV.9).

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**Table LYBV.9. Summary of Discontinuations due to Adverse Events
Randomized Patients Who Have Taken at Least One Dose of Study Drug
Study Period II**

Reason for Discontinuation: Adverse Event

Preferred Term	ATOMOX (N=271)		PLACEBO (N=139)		TOTAL (N=410)		FISHERS EXACT P-VALUE
	n	(%)	n	(%)	n	(%)	
SUBJECTS DISCONTINUED	38	(14.0%)	3	(2.2%)	41	(10.0%)	<.001
Nausea	4	(1.5%)	0	(0.0%)	4	(1.0%)	0.305
Fatigue	3	(1.1%)	0	(0.0%)	3	(0.7%)	0.554
Chest pain	2	(0.7%)	0	(0.0%)	2	(0.5%)	0.551
Insomnia	2	(0.7%)	0	(0.0%)	2	(0.5%)	0.551
Mood swings	2	(0.7%)	0	(0.0%)	2	(0.5%)	0.551
Nervousness	2	(0.7%)	0	(0.0%)	2	(0.5%)	0.551
Abdominal pain upper	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Aggression	0	(0.0%)	1	(0.7%)	1	(0.2%)	0.339
Anorgasmia	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Anxiety	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Constipation	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Depressive symptom	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Dizziness	0	(0.0%)	1	(0.7%)	1	(0.2%)	0.339
Ejaculation disorder	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Erectile dysfunction	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Headache	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Hyperhidrosis	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Irritability	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Lethargy	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Micturition urgency	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Mood altered	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Penis disorder	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Pollakiuria	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Rash pruritic	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Sedation	0	(0.0%)	1	(0.7%)	1	(0.2%)	0.339
Sensory disturbance	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Tachycardia	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Testicular retraction	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000

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Table LYBV.9. Summary of Discontinuations due to Adverse Events
Randomized Patients Who Have Taken at Least One Dose of Study Drug
Study Period II (Concluded)

Reason for Discontinuation: Adverse Event

Preferred Term	ATOMOX (N=271)		PLACEBO (N=139)		TOTAL (N=410)		FISHERS EXACT P-VALUE
	n	(%)	n	(%)	n	(%)	
Tic	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Tremor	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Urinary hesitation	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000
Urine flow decreased	1	(0.4%)	0	(0.0%)	1	(0.2%)	1.000

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**Table LYBV.10. Summary of Discontinuations due to Adverse Events
Enrolled Patients
Study Period III**

Reason for Discontinuation: Adverse Event

Preferred Term	ATOMOX-ATOMOX (N=104)	PLACEBO-ATOMOX (N=68)	TOTAL (N=172)
	n (%)	n (%)	n (%)
SUBJECTS DISCONTINUED	3 (2.9)	4 (5.9)	7 (4.1)
Anxiety	0 (0.0)	1 (1.5)	1 (0.6)
Dizziness	0 (0.0)	1 (1.5)	1 (0.6)
Ejaculation disorder**	1 (1.8)	0 (0.0)	1 (1.0)
Erectile dysfunction**	1 (1.8)	0 (0.0)	1 (1.0)
Nausea	1 (1.0)	0 (0.0)	1 (0.6)
Urinary hesitation	0 (0.0)	1 (1.5)	1 (0.6)
Vomiting	0 (0.0)	1 (1.5)	1 (0.6)

*Denominator based on females only :ATOMOX-ATOMOX (N = 47)

:PLACEBO-ATOMOX (N = 26)

**Denominator based on males only :ATOMOX-ATOMOX (N = 57)

:PLACEBO-ATOMOX (N = 42)

Table LYBV.11 and Table LYBV.12 summarize the treatment-emergent adverse events (TEAEs) with $\geq 5\%$ incidence for either treatment or total in Study Periods II and III. The most commonly reported TEAEs in Study Period II were nausea, occurring in 77 (28%) atomoxetine-treated patients and 8 (6%) placebo-treated patients; and dry mouth, occurring in 59 (22%) atomoxetine-treated patients and 10 (7%) placebo-treated patients.

Table LYBV.11. Summary of TEAEs with $\geq 5\%$ Incidence Using MedDRA Preferred Terms Randomized Patients Who Have Taken at Least One Dose of Study Drug Study Period II

Preferred Term	Atomoxetine (N=271) n (%)	Placebo (N=139) n (%)	Total (N=410) n (%)	Fisher's Exact p-value
Overall with ≥ 1 TEAE	222 (81.9)	82 (59.0)	304 (74.1)	<.001
Overall with no TEAE	49 (18.1)	57 (41.0)	106 (25.9)	<.001
Nausea	77 (28.4)	8 (5.8)	85 (20.7)	<.001
Dry mouth	59 (21.8)	10 (7.2)	69 (16.8)	<.001
Headache	33 (12.2)	24 (17.3)	57 (13.9)	0.176
Fatigue	35 (12.9)	7 (5.0)	42 (10.2)	0.015
Insomnia	32 (11.8)	5 (3.6)	37 (9.0)	0.006
Decreased appetite	30 (11.1)	1 (0.7)	31 (7.6)	<.001
Constipation	24 (8.9)	3 (2.2)	27 (6.6)	0.010
Dizziness	14 (5.2)	10 (7.2)	24 (5.9)	0.505
Urinary hesitation	21 (7.7)	1 (0.7)	22 (5.4)	0.002

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; MedDRA = Medical Dictionary for Regulatory Activities; N = number of randomized subjects; n = number of subjects; TEAE = treatment-emergent adverse event.

Table LYBV.12. Summary of TEAEs with $\geq 5\%$ Incidence Using MedDRA Preferred Terms Enrolled Patients Study Period III

Preferred Term	Atomoxetine-Atomoxetine (N=104) n (%)	Placebo-Atomoxetine (N=68) n (%)	Total (N=172) n (%)
Overall with ≥ 1 TEAE	42 (40.4)	42 (61.8)	84 (48.8)
Overall with no TEAE	62 (59.6)	26 (38.2)	88 (51.2)
Dry mouth	4 (3.8)	9 (13.2)	13 (7.6)
Nausea	5 (4.8)	5 (7.4)	10 (5.8)
Headache	5 (4.8)	5 (7.4)	10 (5.8)
Fatigue	3 (2.9)	6 (8.8)	9 (5.2)
Dizziness	3 (2.9)	5 (7.4)	8 (4.7)
Insomnia	3 (2.9)	4 (5.9)	7 (4.1)
Anxiety	1 (1.0)	5 (7.4)	6 (3.5)
Decreased appetite	0 (0.0)	4 (5.9)	4 (2.3)

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; MedDRA = Medical Dictionary for Regulatory Activities; N = number of randomized subjects; n = number of subjects; TEAE = treatment-emergent adverse event.

Table LYBV.13 and Table LYBV.14 summarize mean changes from baseline to endpoint in vital signs (blood pressure, pulse, and weight) for Study Periods II and III. In Study Period II, increases in systolic blood pressure and pulse in atomoxetine-treated patients were statistically significant compared with placebo-treated patients ($p=.020$ and $p<.001$, respectively). Mean change in systolic blood pressure from baseline to endpoint was 1.3 (10.1 SD) for atomoxetine-treated patients and -0.8 (8.6 SD) for placebo-treated patients. Mean change in pulse from baseline to endpoint was 4.6 (10.7 SD) for atomoxetine-treated patients and -0.3 (9.9 SD) for placebo-treated patients. Weight decreases in atomoxetine-treated patients were statistically significant ($p<.001$) compared with placebo-treated patients. Mean change in weight from baseline to endpoint was -1.7 (3.1 SD) for atomoxetine-treated patients and 0.1 (3.6 SD) for placebo-treated patients (Table LYBV.13).

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**Table LYBV.13. Summary of Vital Signs
Mean Change from Baseline to Endpoint
Randomized Patients Who Have Taken at Least One Dose of Study Drug
Study Period II**

Variable		Baseline		Endpoint		Change		Within Group	Between Group
Treatment	N	Mean	SD	Mean	SD	Mean	SD	p-value (a)	p-value (b)
Diastolic Blood Pressure									
ATOMOX	252	75.34	8.42	76.41	8.49	1.07	7.79	.031	.078
PLACEBO	135	74.77	7.28	74.97	7.14	0.20	6.20	.714	—
95% Confidence Interval for Treatment Difference: (-0.14 , 2.58)									
Systolic Blood Pressure									
ATOMOX	252	118.04	11.26	119.33	13.72	1.29	10.08	.044	.020
PLACEBO	135	118.16	11.63	117.33	11.99	-0.83	8.59	.264	—
95% Confidence Interval for Treatment Difference: (0.36 , 4.20)									
Pulse									
ATOMOX	252	72.80	9.67	77.44	10.94	4.64	10.67	<.001	<.001
PLACEBO	135	73.16	9.73	72.88	8.99	-0.28	9.93	.742	—
95% Confidence Interval for Treatment Difference: (2.79 , 6.58)									

SD=standard deviation

(a): P-value is from paired t-test.

(b): P-value is based on an ANCOVA on change from baseline scores with terms for baseline, treatment and investigator.

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Table LYBV.13. Summary of Vital Signs
Mean Change from Baseline to Endpoint
Randomized Patients Who Have Taken at Least One Dose of Study Drug
Study Period II (Concluded)

Variable		Baseline		Endpoint		Change		Within Group	Between Group
Treatment	N	Mean	SD	Mean	SD	Mean	SD	p-value (a)	p-value (b)
Weight in KG									
ATOMOX	252	84.18	18.53	82.50	18.17	-1.68	3.09	<.001	<.001
PLACEBO	134	86.17	19.76	86.30	19.51	0.14	3.57	.655	—
95% Confidence Interval for Treatment Difference: (-2.59 , -1.2)									

SD=standard deviation

(a): P-value is from paired t-test.

(b): P-value is based on an ANCOVA on change from baseline scores with terms for baseline, treatment and investigator.

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Table LYBV.14. **Summary of Vital Signs**
Mean Change from Baseline to Endpoint
Enrolled Patients
Study Period III

Variable		Baseline		Endpoint		Change		Within Group
Treatment	N	Mean	SD	Mean	SD	Mean	SD	p-value (a)
Diastolic Blood Pressure								
ATOMOX-ATOMOX	95	76.94	8.21	77.74	9.32	0.80	7.77	.318
PLACEBO-ATOMOX	61	74.27	7.33	76.98	8.19	2.71	7.77	.008
Systolic Blood Pressure								
ATOMOX-ATOMOX	95	119.81	13.30	120.72	13.84	0.91	9.45	.350
PLACEBO-ATOMOX	61	116.44	12.01	118.60	12.58	2.16	9.86	.093
Pulse								
ATOMOX-ATOMOX	95	77.93	11.60	78.22	10.77	0.28	10.66	.795
PLACEBO-ATOMOX	61	72.62	8.46	76.66	9.70	4.03	11.39	.008
Weight in KG								
ATOMOX-ATOMOX	95	82.05	18.23	82.38	18.48	0.34	2.47	.189
PLACEBO-ATOMOX	61	86.06	21.33	85.43	20.96	-0.63	3.55	.168

SD=standard deviation

(a): P-value is from paired t-test.

Summary ID# 7068

Clinical Study Summary: Study B4Z-MC-LYBX

A Randomized, Double-Blind Comparison of Atomoxetine Hydrochloride and Placebo in Child and Adolescent Outpatients with Attention- Deficit/Hyperactivity Disorder and Comorbid Oppositional Defiant Disorder

Date summary approved by Lilly: 17 September 2008

Title of Study: A Randomized, Double-Blind Comparison of Atomoxetine Hydrochloride and Placebo in Child and Adolescent Outpatients with Attention-Deficit/Hyperactivity Disorder and Comorbid Oppositional Defiant Disorder	
Investigator(s): This multicenter study included 17 principal investigators.	
Study Center(s): This study was conducted at 17 study centers in the European Union and Australia.	
Length of Study: Date of first patient entered: (acute phase: 22 December 2003; 06 April 2004 for the open-label phase) Date of last patient completed: (acute phase: 02 June 2005; 16 November 2007 for the open-label phase)	Phase of Development: 3
Objectives: Primary: The primary objective of this study was to test the hypothesis that atomoxetine hydrochloride (hereafter referred to as atomoxetine [ATX]), given once daily at a dose of 1.2 mg/kg/day for approximately 8 weeks, is superior to placebo in the treatment of children and adolescents with attention-deficit/hyperactivity disorder (ADHD) and comorbid oppositional defiant disorder (ODD). Symptom change was measured by mean reduction in ODD symptoms on the investigator-rated ODD subscale score of the Swanson, Nolan, and Pelham Rating Scale-Revised (SNAP-IV). Secondary: - To test the hypothesis that ATX given once daily at a dose of 1.2 mg/kg/day is superior to placebo in reducing symptoms of ADHD as measured by mean change in the investigator-rated ADHD subscale score of the SNAP-IV. - To compare the efficacy of ATX given at a dose of 2.4 mg/kg/day with ATX given at a dose of 1.2 mg/kg/day in reducing symptoms of ODD (in patients with peak plasma ATX concentrations of <800 ng/mL during once-daily dosing), as measured by mean change in ratings on the ODD subscale of the SNAP-IV. - To compare the efficacy of ATX given at a dose of 2.4 mg/kg/day with ATX given at a dose of 1.2 mg/kg/day in reducing symptoms of ADHD (in patients with peak plasma ATX concentrations of <800 ng/mL during once-daily dosing), as measured by mean change in ratings on the ADHD subscale of the SNAP-IV. - To test the hypothesis that ATX is superior to placebo in reducing symptoms of ADHD and ODD, as measured by mean change in ratings on the Clinical Global Impressions-Severity (CGI-S). - To test the hypothesis that ATX is superior to placebo in improving psychosocial functioning, as measured by the total score on the ADHD Impact Module (AIM). - To investigate the role of environmental stress, as measured by the Social Readjustment Rating Scale (SRRS), in the exacerbation of ODD symptoms. - To assess the safety and tolerability of ATX compared with placebo, as assessed by adverse events (AEs) elicited during open-ended questioning. The purpose of the open-label phase (Study Periods IV to VI) of Study B4Z-MC-LYBX (hereafter referred to as Study LYBX) was to assess long-term safety and tolerability in children and adolescent patients who had completed the earlier acute phase (Study Periods I to III). Also assessed were selected primary and secondary efficacy and health outcome measures collected during the acute phase (Study Periods I to III).	
Study Design: Study LYBX was a multicenter, randomized, double-blind, placebo-controlled, parallel group comparison of outpatients with ADHD and comorbid ODD. Patients were aged 6 to 12 years. This study consisted of 6 study periods: Study Period I: Screening, assessment, and washout. Study Period II; Primary Objective Placebo-Controlled Phase: This phase consisted of randomized, double-blind, placebo-controlled, acute treatment; it was an approximately 8-week treatment comparison of ATX 1.2 mg/kg/day or placebo in a 2:1 ratio and administered once daily or optional twice daily.	

Study Period III; Dose-Comparison Phase: This phase consisted of a randomized, double-blind, acute dose comparison of ATX-treated patients who did not achieve a peak plasma concentration of at least 800 ng/mL and who did not demonstrate adequate ODD symptom reduction during Study Period II. These patients were re-randomized in a 1:1 ratio to either a higher dose (ATX 2.4 mg/kg/day) or the same dose (ATX 1.2 mg/kg/day) of continued ATX treatment for approximately 4 weeks. All other Study Period II completers were eligible to continue into Study Period III and were not re-randomized. Study Period II ATX remitter patients continued at ATX 1.2 mg/kg/day and Study Period II placebo patients were titrated to ATX 1.2 mg/kg/day.

The open-label phase consisted of Study Period IV (Visits 7 to 13) and Study Periods V to VI (Visits 14 to 25). These extension phases allowed eligible patients to receive continued ATX treatment for up to 4 years' duration.

Number of Patients:

Planned: Approximately 220 patients

Entered: 257

Enrolled/Randomized: 226

Study Period II: acute, double-blind, placebo-controlled

Randomized: 2:1; 226 patients (156 ATX, 70 placebo)

Completed: 197 patients (132 ATX, 65 placebo)

Study Period III: Total patients entered: 197

Total patients completed: 179

All patients who entered Study Period III were in one of the following 3 ATX treatment groups:

Group 1: Patients who were nonremitters and who had an ATX peak plasma concentration of less than 800 ng/mL in Study Period II were re-randomized 1:1 to a higher dose of ATX treatment (ATX 2.4 mg/kg/day) or the same dose administered in Study Period II (ATX 1.2 mg/kg/day).

Patients entered: 92 (46 high dose, ATX 2.4 mg/kg/day; 46 low dose, ATX 1.2 mg/kg/day)

Patients completed: 82 (41 high dose; 41 low dose)

Group 2: Patients who were remitters or who had an ATX peak plasma concentration of at least 800 ng/mL in Study Period II remained at their ATX treatment dose (ATX 1.2 mg/kg/day).

Patients entered: 40

Patients completed: 38

Group 3: Patients who were treated with placebo in Study Period II were titrated to an ATX dose (ATX 1.2 mg/kg/day).

Patients entered: 65

Patients completed: 59

Entered Open-Label Phase (Study Period IV): 173 patients

Completed Study Period IV: 102 patients

Completed Study Period V: 52 patients

Completed Study Period VI: 17 patients

Diagnosis and Main Criteria for Inclusion: Patients who were at least 6 years of age and not more than 12 years of age at Visit 1, and met the disease diagnostic criteria for ADHD and comorbid ODD as determined by a physician investigator's clinical assessment using the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), the K-SADS-PL, the SNAP-IV ADHD subscale score, the CGI-S score, and the SNAP-IV ODD subscale score. Patients who completed the acute phase of the study were given the option to enter the open-label extension phase of the study.

Test Product/Study Drug, Dose, and Mode of Administration: The dose administered was ATX 1.2 mg/kg/day given orally once daily. Patients randomly assigned to a higher dose during the dose comparison phase were administered ATX 2.4 mg/kg/day orally as a once-daily or twice-daily dose. The doses of ATX were administered as hydrochloride salt with doses expressed as ATX free base in capsules

supplied in blister cards. The dose was weight-based and was given once daily or twice daily as a divided dose (equally or unequally) in the morning and late afternoon/evening. During the open-label phase, the maximum dose was not to exceed ATX 1.4 mg/kg/day but could have been increased to a maximum of ATX 1.8 mg/kg/day, provided the total daily dose did not exceed ATX 150 mg. Doses could be adjusted at any time during the open-label phase based on weight and tolerability.

Reference Therapy, Dose, and Mode of Administration: Placebo was administered during Study Period II only and was identical in appearance to ATX.

Duration of Treatment:

Study Period II: Approximately 8 weeks

Study Period III: Approximately 4 weeks

Open-label phase (Study Periods IV to VI): 1 to 3.25 years

Variables:

Efficacy:

Primary: SNAP-IV ODD subscale total score (8 items)

Secondary: SNAP-IV subscale scores of 18 ADHD items (including inattention and hyperactivity/impulsivity, and 8 ODD items), as well as CGI-S (ADHD/ODD), Clinical Global Impressions-Improvement (CGI-I [ADHD/ODD]), Connors' Global Index-Parent Version (CGI-P), and the SRRS

Safety: Treatment-emergent adverse events (TEAEs), vital signs, height, weight, laboratory analyses, and electrocardiograms (ECGs)

Pharmacokinetic: Peak plasma ATX concentration

Health Outcomes: AIM

Evaluation Methods:

Statistical: The primary efficacy analysis was a mixed-effects model repeated measures (MMRM) analysis of the SNAP-IV ODD subscale score. The independent effects in the model were investigator, treatment, visit, baseline SNAP-IV ODD subscale score, and treatment-by-visit interaction. Secondary analyses using analysis of covariance (ANCOVA) on the last observation carried forward (LOCF) change from baseline to endpoint were conducted on secondary efficacy variables. Study Period II baseline was defined as Visit 1 or Visit 2, and endpoint was defined as the final visit or Visit 5. Study Period III baseline was defined as Visit 5, and endpoint was defined as the final visit with nonmissing data. Separate analyses were conducted, one using Visits 1 and 2 as baseline and another using Visit 7 as baseline (for the open-label phase). If more than 1 item of an efficacy subscale was missing, the score for the subscale was considered missing. If a single item of a subscale was missing, the mean score of all other items in the subscale was imputed as the score for the missing item when computing totals (imputed data).

The frequency of serious adverse events (SAEs), discontinuations due to TEAEs, overall rate of TEAEs, categorical changes in abnormal laboratory analytes, and changes in QT intervals were computed. Changes in vital signs from baseline to endpoint were compared using the Wilcoxon signed-rank test.

Bioanalytical: Plasma samples were assayed for ATX concentration using a validated Atmospheric Pressure Chemical Ionization (APCI) Liquid Chromatography/Mass Spectrometry/Mass Spectrometry (LC/MS/MS) analytical method.

Pharmacokinetic: ATX concentration data were summarized by treatment, response category, and/or CYP2D6 status.

Summary:

Patient Demographics and Baseline Illness Characteristics

Of the 257 patients entering Study Period I, 31 patients did not meet inclusion criteria; therefore, 226 patients were enrolled in the Study Period II treatment phase. Patients were randomly assigned to treatment with either ATX (n=156) or placebo (n=70). Of the total enrolled patients, the mean age was 9.6 years, the majority (n=211, 93.4%) were male, and 69.0% had prior stimulant exposure. There were no statistically significant differences between treatment groups for any parameter except weight (p=.024); the placebo group weighed more at baseline.

All patients had a present diagnosis of ADHD/ODD as per the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL). The other common present comorbid disorders noted were behavior conduct disorder current (12.0%), followed by anxiety (2.2%). Overall, 30.1% of ATX-treated patients and 27.1% of placebo-treated patients had at least 1 historical disorder.

For the open-label phase (Study Periods IV to VI), the mean age was 9.65 years. Most of the patients were Caucasian males (n=165, 95.4%), and had combined hyperactive and inattentive ADHD (n=144, 83.2%). The majority of patients (n=119, 68.8%) had previously used stimulants prior to treatment with ATX.

Severity of Illness

For both Study Period II and Study Period III, baseline score symptom severity of ADHD and ODD did not show a statistically significant difference between any treatment groups.

Patient Disposition

Study Period II: Of the 257 patients who entered the study, 226 were randomized (156 ATX, 70 placebo). In all, 197 patients completed Study Period II, in which the primary objective was evaluated as ADHD and comorbid ODD symptom improvement in patients treated with 1.2 mg/kg/day ATX versus patients treated with placebo.

Study Period III: Of the 156 patients randomly assigned to ATX treatment in Study Period II, 132 (84.6%) patients continued into Study Period III. Of the 70 patients randomly assigned to placebo treatment in Study Period II, 65 (92.9%) patients continued into Study Period III.

Open-label phase: A total of 173 patients received at least 1 dose of ATX 1.2 mg/kg/day. A total of 102 patients completed Study Period IV, 52 patients completed Study Period V, and 17 patients completed Study Period VI.

Patient Discontinuation

Study Period II (n=226): The most frequent reasons for discontinuation in this study period were protocol violation (n=8; 3.5%) and adverse event (n=6; 2.6%). No statistically significant differences were observed between treatment groups for reasons of discontinuation during Study Period II.

Study Period III (n=197): The most frequent reasons for discontinuation in this study period were lack of efficacy as perceived by the patient and physician (n=10; 5.1%), unable to contact patient/caregiver (n=3; 1.5%), and adverse event (n=3; 1.5%). No statistically significant differences were observed between treatment groups regarding reasons for discontinuation during Study Period III.

Open-label phase (n=173): The most frequent reasons for discontinuation in this study period were lack of efficacy as perceived by the patient and physician (n=33; 19.1%), and lack of efficacy as perceived by the patient (n=19; 11.0%).

Efficacy (Acute Phase: Study Periods II and III)

The primary efficacy analysis was performed during Study Period II only. Additionally, there was a comparison between the ATX and placebo treatment groups at the final week of Study Period II (Visit 5). Baseline was defined as scores obtained for Visit 1 or Visit 2.

Study Period III was included to evaluate the effectiveness of an increased ATX dose of up to 2.4 mg/kg/day for patients who had not reached ATX plasma level concentrations of at least 800 ng/mL or who did not demonstrate symptom improvement at the 1.2 mg/kg/day ATX dose administered during Study Period II. All patients who completed Study Period II were allowed to continue into Study Period III.

Primary efficacy

Study Period II: Results of the MMRM analysis of the SNAP-IV ODD subscale score demonstrated that overall treatment effect of ATX was statistically significantly greater than that of placebo ($p=.01$). Looking at each visit using MMRM analysis of least-squares mean (LS Mean) demonstrated statistically significantly greater ODD symptom improvement on the SNAP-IV ODD subscale score in the ATX treatment group compared to the placebo treatment group at Visit 3 ($p=.003$) and Visit 4 ($p=.043$), but not at Visit 5 ($p=.209$).

Secondary Efficacy Derived from SNAP-IV ODD and ADHD Subscale Scores

Study Period II: The mean change from baseline to LOCF in SNAP-IV ODD subscale scores did not demonstrate statistical significance between placebo and ATX treatment groups. A statistically significantly greater ADHD symptom improvement was observed in ATX-treated patients compared to placebo-treated patients in mean change from baseline to LOCF for all SNAP-IV ADHD subscale scores, including combined subtype ($p<.001$), inattentive subtype ($p<.001$), and hyperactive/impulsive subtype ($p=.003$).

Study Period III: Patients who had been non-remitters in Study Period II demonstrated no statistically significant differences on any of the Imputed subscale scores between treatment groups treated with 1.2 mg/kg/day ATX or treated with 2.4 mg/kg/day ATX.

Response

Response was defined as a reduction of 1 standard deviation (SD) on the SNAP-IV ODD subscale and an improvement of 1 point on the ADHD/ODD score of the CGI-S.

Remission was defined as a score <9 on the SNAP-IV ODD subscale and a score of 1 or 2 on the ADHD/ODD score of the Clinical Global Impressions-Improvement (CGI-I).

Study Period II: A statistically significantly greater percentage of ATX-treated patients met the protocol-defined criteria for both response ($p=.011$) and remission ($p=.041$) in ODD symptom improvement compared to placebo-treated patients.

Study period III: Results did not demonstrate a statistically significant difference in the percentage of responders ($p=.266$) or in the percentage of remitters ($p=.485$) in patients treated with 1.2 mg/kg/day ATX or in patients treated with 2.4 mg/kg/day ATX.

Clinical Global Impressions–Severity (ADHD and ODD)

Study Period II: Results of the CGI-S scale demonstrated a statistically significantly greater mean score reduction from baseline to LOCF endpoint ($p=.013$) in the severity of ADHD with comorbid ODD symptoms in ATX-treated patients compared to placebo-treated patients.

Study Period III: No statistically significant differences were observed in mean change from baseline to LOCF endpoint scores between patients treated with 1.2 mg/kg/day ATX or patients treated with 2.4 mg/kg/day ATX ($p=.464$).

Clinical Global Impressions–Improvement (ADHD and ODD)

Study Period II: Patients treated with ATX were assessed by the clinician as having statistically significantly symptom improvement compared to placebo-treated patients ($p=.037$).

Conners' Global Index-Parent

Study Period II: The CGI-P total score and the Restless/Impulsive subscore demonstrated a statistically significant mean score reduction from baseline to endpoint ($p=.002$ and $p<.001$, respectively) in the ATX treatment group compared to the placebo treatment group.

Study Period III: No statistically significant differences were observed on the CGI-P total score, Emotional Liability subscore or the Restless/Impulsive subscore, between the group treated with 1.2 mg/kg/day ATX and the group treated with 2.4 mg/kg/day ATX.

Social Readjustment Rating Scale

Study Period II: No statistically significant difference was observed between ATX-treated patients and placebo-treated patients in the mean change from baseline to LOCF endpoint on the SRRS ($p=.636$).

Study Period III: The within-group mean reduction from baseline to LOCF endpoint SRRS scores for the 2.4 mg/kg/day ATX treatment group was statistically significant ($p=.010$), but the between-group comparison with the 1.2 mg/kg/day ATX treatment group was not statistically significant ($p=.072$).

Health Outcome

Attention-Deficit/Hyperactivity Disorder Impact Module

Study Period II: A statistically significant improvement (score increase) in mean change from baseline to LOCF endpoint was demonstrated in the ATX treatment group compared to patients in the placebo-treatment group on both summary subscale scores, the Child Scale ($p=.002$) and the Parent-Home Scale ($p=.018$). No statistically significant difference between treatment groups was observed on the single-item Child Self-Control subscale score; however, there was no decrease in mean change from baseline to endpoint score observed in either group.

Study Period III: The mean change from baseline to LOCF endpoint for the AIM summary scores (Child Scale and Parent-Home Scale) and the single-item Child Self-Control subscale score for Study Period III did not demonstrate a statistically significant difference between patients treated with 1.2 mg/kg/day or 2.4 mg/kg/day ATX.

Efficacy (Open-Label Phase)

For the LOCF analysis of mean change from baseline (Visit 7) to endpoint of the SNAP-IV subscale scores for patients who took at least 1 dose of ATX during the open-label phase, some minor fluctuation of scores (increase or decrease) was observed in the SNAP-IV ODD and ADHD subscales. However, there was a statistically significant decrease (improvement) in the ATX group ($p=.019$) and in the all-treatments-combined group ($p=.013$) for the Hyperactivity/Impulsivity subscale scores.

For the LOCF analysis of mean change of scores from baseline (Visit 7) to endpoint for other efficacy and health outcome measures for patients who took at least 1 dose of ATX during the open-label phase, there were no statistically significant changes observed for any measure other than the SRRS ($p<.001$), which demonstrated a worsening (increase) in score compared to Visit 7.

The ODD remitters were defined as those patients who had a score of <9 on the SNAP-IV ODD subscale and a score of 1 or 2 on the CGI-I. Of the 173 patients who entered the open-label phase, 38 (22%) patients were remitters. This percentage is higher than that observed in Study Period III, during which 3 (6.5%) patients in the ATX 1.2 mg/kg/day group and 6 (13%) patients in the ATX 2.4 mg/kg/day group were remitters.

Pharmacokinetics

A blood sample for the measurement of plasma ATX was collected for all patients at both Visit 3 (Study Period II; placebo and ATX 1.2 mg/kg/day doses) and Visit 7 (Study Period III; ATX 1.2 mg/kg/day and ATX 2.4 mg/kg/day doses). Samples were intended to capture peak ATX plasma concentration and were to be drawn between 30 and 90 minutes postdose. The samples collected at Visit 3 served to determine eligibility for double-blinded re-randomization into Study Period III. Overall, mean concentrations in nonremitters (both nonresponders and responders) and remitters were comparable after the initial dosing with ATX 1.2 mg/kg/day. As expected at Visit 7, concentrations were higher in the ATX 2.4 mg/kg/day group compared with the ATX 1.2 mg/kg/day group.

Safety

Extent of Exposure

Study Period II: The mean final prescribed dose and mean maximum prescribed dose were ATX 1.14 mg/kg/day and ATX 1.17 mg/kg/day, respectively, and the mean of the total days on therapy was similar between treatment groups (ATX, 79 days; placebo, 84 days).

Study Period III: The mean of the total days on therapy (87 days) was the same for ATX 1.2 mg/kg/day (low dose) and ATX 2.4 mg/kg/day (high dose) of ATX treatment groups.

Open-label phase: The mean final prescribed daily dose was ATX 1.33 mg/kg and the mean daily maximum dose was ATX 1.64 mg/kg. The mean duration of therapy was 435.11 days.

Adverse Events

Deaths and Serious Adverse Events

No deaths were reported during any period of the study.

Study Period II: One placebo-treated patient experienced the SAE of self-injurious ideation. Three ATX-treated patients experienced the following SAEs: 1 report each of obsessive compulsive disorder, tic, and fatigue.

Study Period III: One patient (1.2 mg/kg/day of ATX) experienced aggression reported as an SAE.

Open-label phase: A total of 15 (8.7%) patients experienced 1 or more SAEs. The most frequently-reported SAEs were appendicitis (n=3, 1.7%) and oppositional defiant disorder (n=2, 1.2%).

Patient Discontinuation due to Adverse Events

Study Period II: Of the 156 ATX-treated patients, 6 (3.8%) patients discontinued due to an adverse event (AE; 1 report each of upper abdominal pain, aggression, fatigue, headache, irritability, and nausea). No placebo-treated patients discontinued due to an AE.

Study Period III: A total of 3 (1.5%) of the 197 patients enrolled in Study Period III who took at least 1 dose of study drug discontinued the study due to an AE. One patient (ATX 1.2 mg/kg/day) discontinued due to rash, and 2 patients (ATX 2.4 mg/kg/day) discontinued due to an AE (1 report each of tic and elevated AST).

Open-label phase: Of the 173 patients who took at least 1 dose of study medication, 13 (7.5%) patients discontinued due to an AE. Those AEs were oppositional defiant disorder (n=2, 1.2%), weight decreased (n=2, 1.2%), abdominal pain upper, anxiety, blood bilirubin increased, disturbance in attention, electrocardiogram QT corrected interval prolonged, hepatic enzyme increased, somnolence, syncope, and vomiting (n=1 in each, 0.6%).

Treatment-Emergent Adverse Events

Study Period II: Of the 226 randomized patients who took at least 1 dose of study drug, 126 (80.8%) ATX-treated patients and 43 (61.4%) placebo-treated patients reported at least 1 TEAE. The most commonly reported TEAEs (reported in $\geq 10\%$ of patients) for ATX-treated patients were headache (n=54, 34.6%), decreased appetite (n=38, 24.4%; $p < .001$ versus placebo), nausea (n=32, 20.5%; $p = .033$ versus placebo), fatigue (n=27, 17.3%; $p = .021$ versus placebo), vomiting (n=19, 12.2%), abdominal pain upper (n=19, 12.2%), and nasopharyngitis (n=17, 10.9%). The most commonly reported AE in placebo-treated patients was headache in 18 patients (25.7%).

Study Period III: Of the 197 patients who entered this study period, 83 (55.0%) patients treated with ATX 1.2 mg/kg/day (low dose) and 27 (58.7%) patients treated with ATX 2.4 mg/kg/day (high dose) reported at least 1 TEAE. No statistically significant differences between low- or high-dose ATX treatment groups were seen for any AE in $\geq 5\%$ of patients. The most common AE (reported in $\geq 10\%$ of patients) was fatigue (low dose, 18 patients [11.9%]; high dose, 4 patients [8.7%]). One of the 10 female patients in the low-dose group reported a hot flush.

Open-label phase: Of the 173 patients who entered this phase, 150 (86.7%) patients experienced 1 or more TEAEs. The most frequently reported TEAEs ($> 10\%$) were headache (n=112, 64.7%), nasopharyngitis (n=52, 30.1%), vomiting (n=41, 23.7%), nausea (n=31, 17.9%), cough (n=27, 15.6%), upper abdominal pain (n=25, 14.5%), diarrhea (n=20, 11.6%), and fatigue (n=19, 11.0%).

Clinical Laboratory Evaluation

Study Period II: Statistically significant between-group changes from baseline to LOCF endpoint were observed in alkaline phosphatase ($p=.002$), creatine phosphokinase ($p=.008$), total protein ($p=.040$), erythrocyte count ($p=.031$), and uric acid ($p<.001$). The ATX-treated patients showed a mean decrease in alkaline phosphatase and uric acid. Both ATX- and placebo-treated patients showed a mean increase in creatine phosphokinase and erythrocyte count. The ATX-treated patients showed a mean increase in total protein, whereas a decrease in total protein was observed in placebo-treated patients.

Study Period III: No statistically significant differences were observed between treatment groups (low- or high-dose ATX treatment) in the change to LOCF endpoint for any laboratory analyte.

Open-label phase: Increased levels above the normal range (observed in $\geq 5\%$ of patients) were creatinine ($n=23$, 18.1%), platelet count ($n=12$, 10.7%), calcium ($n=13$, 10.6%), urine specific gravity ($n=11$, 8.4%), eosinophils ($n=8$, 7.2%), and creatinine phosphokinase ($n=7$, 5.4%). The number of patients with levels of creatinine elevated above normal ranges in the open-label phase was relatively large compared to Study Period II (5 [3.6%] patients in the ATX 1.2 mg/kg/day group, and 3 [4.7%] patients in the placebo group) and Study Period III (8 [6.0%] patients in the ATX 1.2 mg/kg/day group, and 3 [6.7%] patients in the ATX 2.4 mg/kg/day group). The only decrease in laboratory analytes that occurred at a frequency of $\geq 5\%$ was observed in the leukocyte count ($n=8$, 7%).

Vital Signs

Study Period II: A statistically significant difference was observed in the ATX treatment group compared to the placebo-treated group in the percentage of patients who met the criterion for increases in diastolic blood pressure ($p=.042$). No patient discontinued due to an increase in diastolic blood pressure or due to weight loss concerns. A statistically significant ($p<.001$) number of ATX-treated patients showed a decrease (at least 3.5%) in weight compared to placebo-treated patients.

Study Period III: No statistically significant differences in mean change from baseline to LOCF endpoint were observed for any vital sign or weight between the low-dose and high-dose ATX treatment groups.

Open-label phase: There was a statistically significant increase ($p<.001$) in height and weight from baseline to endpoint in this phase; this was not unexpected in the patient population studied. There were no statistically significant changes observed in other vital signs from baseline to endpoint.

Electrocardiogram

Study Period II: Statistically significant differences were observed between the ATX-treatment group compared to the placebo treatment group in mean change from baseline to LOCF endpoint for ECG parameters, with a statistically significant increase in ECG heart rate (8.19 bpm, $p<.001$), and decreases in RR interval (-77.36 msec, $p<.001$), QT interval (-15.76 msec, $p<.001$), and QT interval corrected by both Fridericia (-3.78 msec, $p<.001$) and Data correction (-1.50 msec, $p=.015$) methods.

Study Period III: No statistically significant differences were observed between ATX low-dose and high-dose treatment groups in mean change from baseline to LOCF endpoint for the ECG parameters.

Open-label phase: No patient demonstrated a postbaseline QT interval increase ≥ 60 msec or had an endpoint QT interval value ≥ 500 msec, whether corrected by the Fridericia, Bazett, or Data methods. Additionally, no increases from normal to prolonged QT intervals were observed.

Summary ID# 7069

Clinical Study Summary: Study B4Z-MC-LYBY

Atomoxetine Treatment of Adults with ADHD and Comorbid Alcohol Abuse: A Randomized, Placebo-Controlled Trial

Date summary approved by Lilly: 07 June 2007

Brief Summary of Results

Study B4Z-MC-LYBY (LYBY) was a multicenter, randomized, double-blind, parallel, placebo-controlled trial with 3 study periods in adult patients with Attention-Deficit Hyperactivity Disorder (ADHD) and comorbid alcohol abuse or dependence disorder. Study Period I was a washout, screening, and assessment period. Study Period II was a 12-week, double-blind, treatment period with either atomoxetine or placebo. Study Period III was a 12-week, open-label, treatment period with atomoxetine. The primary objectives of the study were to test the hypotheses that atomoxetine given in doses of 25-100 mg/day was superior to placebo in reducing the symptoms of ADHD, as assessed by mean reduction in scores on the Adult ADHD Investigator Symptom Rating Scale (AISRS), and was superior to placebo in the prevention of relapse of alcohol abuse, as defined by time to relapse, in patients with ADHD and comorbid alcohol abuse disorder.

Results for the primary objectives are as follows:

- For the first primary objective, severity of ADHD symptoms as measured by mean change in AISRS scores from baseline to endpoint, the mean change was statistically significantly lower (indicating improvement) in the atomoxetine group compared to the placebo group ($p=0.007$).

- For the second primary objective, atomoxetine was not statistically significantly different than placebo in the prevention of relapse of alcohol abuse as measured by time to relapse using the Timeline Followback method (as analyzed by the log-rank test based on Kaplan-Meier estimates). Furthermore, a high percentage of patients in both treatment groups relapsed (94.1% in the atomoxetine group and 95.8% in the placebo group).

The analysis of secondary efficacy measures demonstrated that:

- Atomoxetine resulted in statistically significant improvements when compared to placebo (as measured by mean change from baseline to endpoint) in:
 - ◇ social and occupational functioning, as measured by the Endicott Work Productivity Scale (EWPS) ($p=0.007$), and global functioning, as measured by the Clinical Global Impressions-Overall-Severity (CGI-Overall-S) ($p=0.048$),
 - ◇ clinical assessments, as measured by the Clinical Global Impressions-Improvement ($p=0.006$),
 - ◇ self-reported ADHD symptoms, as measured by the Adult ADHD Self-Report Scale v1.1 (ASRS) ($p=0.029$),
 - ◇ self-reported awareness of alcohol cravings, as assessed by mean changes in the Obsessive Compulsive Drinking Scale (OCDS) ($p=0.025$), and
 - ◇ work and social functioning, as measured by the Sheehan Disability Scale ($p<0.001$ and $p=0.024$, respectively).
- Atomoxetine, when compared to placebo, produced no statistically significant differences in total alcohol consumption, proportion of drinking days, number of drinks per drinking day, abuse of substances other than alcohol, depressive symptoms, anxiety symptoms, and general quality of life issues.
- There were no deaths or serious adverse events (SAEs) reported during this study. Nine patients discontinued due to an adverse event (AE) (atomoxetine $n=7$, 10.4%; placebo $n=2$, 2.7%) during Study Period II. Eight patients in Study Period III discontinued due to an AE (continued on atomoxetine $n=1$, 3.2%; switched from placebo to atomoxetine $n=7$, 15.2%). Except for neck pain and pregnancy, all events during Study Periods II and III were considered related to study drug.

Title of Study: Atomoxetine Treatment of Adults with ADHD and Comorbid Alcohol Abuse: A Randomized, Placebo-Controlled Trial	
Investigator(s): This multicenter study included 14 principal investigator(s).	
Study Center(s): This study was conducted at 14 study center(s) in two countries.	
Length of Study: 17 months Date of first patient enrolled: 31 August 2004 Date of last patient completed: 20 January 2006	Phase of Development: IV
Objectives: <u>Primary Objective:</u> To test the hypotheses that atomoxetine given in doses of 25-100 mg daily, as either a single daily dose or a divided twice daily dose, for approximately 12 weeks is superior to placebo in reducing the symptoms of ADHD, as assessed by mean reduction in scores on the AISRS, and is superior to placebo in the prevention of relapse of alcohol abuse, as defined by time to relapse, in patients with ADHD and comorbid alcohol abuse disorder. The definition of relapse for the primary objective is 4 (for females) or 5 (for males) or more standard alcoholic drinks within 24 hours, or at least 3 standard alcoholic drinks/day for at least 1 week. For the purposes of this protocol, a standard alcoholic drink is defined by the Dietary Guidelines for Americans, published by the United States (US) Departments of Agriculture and Health and Human Services: 1 drink is equal to 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of 80-proof distilled spirits. <u>Secondary Objectives:</u> To test the following hypotheses: ◇ That total alcohol consumption (mean drinks/day) during the final week of treatment is lower in patients treated with atomoxetine than in patients receiving placebo. ◇ That the proportion of drinking days is smaller for atomoxetine-treated patients compared with those in the placebo group during Study Period II. A drinking day is defined as any day on which an alcoholic drink is consumed. ◇ That time to relapse of alcohol abuse (as defined in the primary objective) is longer for atomoxetine-treated patients compared with those in the placebo group. ◇ That the number of drinks per drinking day is smaller for patients treated with atomoxetine compared with placebo. ◇ That the proportion of substance use days, for substances other than alcohol, is smaller among patients treated with atomoxetine as compared with those treated with placebo. ◇ That, after approximately 12 weeks of treatment, patients who receive atomoxetine have superior social and occupational functioning compared with those who receive placebo, as assessed by changes in the EWPS. ◇ That global functioning, as assessed by the CGI-Overall-S scale, and clinical improvement, as assessed by the CGI-I scale, is superior in patients treated with atomoxetine as compared with those treated with placebo. ◇ That atomoxetine improves depressive symptoms in patients with ADHD and alcohol abuse, as assessed by mean changes in the Hamilton Depression Rating Scale (HAMD-17) and several HAMD-17 subscales, including the anxiety/somatization, retardation, sleep, core, and Maier-Phillips subscales. ◇ That atomoxetine improves anxiety symptoms in patients with ADHD and alcohol abuse, as assessed by mean changes in the Hamilton Anxiety Rating Scale (HAM-A) total score and several HAM-A factor scores and individual items, including the psychic anxiety factor score, somatic anxiety factor score, anxious mood item, and tension item. ◇ That atomoxetine improves self-reported ADHD symptoms, as assessed by changes in the ASRS. ◇ That atomoxetine improves self-rated symptoms of alcohol craving, as assessed by changes in the OCDS. ◇ That atomoxetine improves specific symptoms of ADHD, as assessed by changes in the	

Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS). ◊ That atomoxetine improves self-rated adaptive functioning, as assessed by changes in the Adult Self-Report Form (ASR). ◊ That atomoxetine improves informant-related adaptive functioning, as assessed by changes in the Adult Behavior Checklist (ABCL). ◊ That atomoxetine improves work, social, and home life functioning, as assessed by changes in the Sheehan Disability Scale. ◊ That atomoxetine improves general quality of life, as assessed by changes in the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and by changes in the Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF).
Study Design: Study B4Z-MC-LYBY was a multicenter, randomized, double-blind, parallel, placebo-controlled trial with 3 study periods. Study Period I was a washout, screening, and assessment period of 4 to 28 days. After informed consent was obtained and eligibility was confirmed, patient numbers were assigned, and patients were randomized to receive either atomoxetine or placebo. Study Period II was a 12-week double-blind acute treatment period, when patients were seen weekly. Study Period III was a 12-week, open-label, treatment period to provide further information about safety and efficacy, and to follow the course of response during longer-term treatment. All patients were treated as outpatients.
Number of Patients: <u>Planned:</u> 140 enrolled: 134 patients with post-baseline information (67 atomoxetine, 67 placebo) <u>Entered Study Period II:</u> 215 Randomized: 147 (72 atomoxetine, 75 placebo) <u>Completed Study Period II:</u> 80 (32 atomoxetine, 48 placebo) <u>Entered Study Period III:</u> 77 (31 atomoxetine, 46 placebo) <u>Completed:</u> 50 (24 atomoxetine, 26 placebo)
Diagnosis and Main Criteria for Inclusion: Patients were eligible to be included in the study if they were males or females aged at least 18 years or the minimum drinking age, whichever was older, when the informed consent document was obtained; met the ADHD disease diagnostic criteria based on the <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised™ (DSM-IV-TR™)</i>, and had comorbid alcohol abuse or dependence as defined by the DSM-IV; had no significant laboratory or electrocardiogram (ECG) abnormalities at screening; and were deemed by the investigator to be capable of keeping their study appointments and communicating suitably with the study staff.
Test Product, Dose, and Mode of Administration: <u>Study Period I:</u> No study drug administered. <u>Study Period II:</u> Atomoxetine 25 mg/day or placebo, given orally once daily (QD) for approximately 7 days; atomoxetine 40 mg/day or placebo, given orally QD for approximately 7 days; atomoxetine 80 mg/day or placebo, given orally QD or twice daily (BID) for approximately 14 days; atomoxetine 80 or 100 mg/day or placebo, given orally QD or BID for approximately 8 weeks, using 20 or 25 mg capsules. <u>Study Period III:</u> Atomoxetine 25 mg/day, given orally QD for approximately 7 days; atomoxetine 40 mg/day, given orally QD for approximately 7 days; atomoxetine 80 mg/day, given orally QD or BID for approximately 28 days; atomoxetine 80 or 100 mg/day, given orally QD or BID for approximately 6 weeks, using 20 or 25 mg capsules.
Reference Therapy, Dose, and Mode of Administration: <u>Study Period II:</u> Placebo given orally QD or BID in capsules matching atomoxetine capsules. <u>Study Period III:</u> There was no reference therapy.
Duration of Treatment: <u>Study Period II:</u> Approximately 12 weeks, with atomoxetine or placebo taken daily. <u>Study Period III:</u> Approximately 12 weeks, with atomoxetine taken daily.

Variables:

Efficacy: Primary efficacy outcome measures were ADHD severity, as measured by the AISRS total score, and alcohol abuse, as measured by time to relapse using the Timeline Followback method. Secondary efficacy included other summaries of alcohol consumption and substance abuse (using the Timeline Followback method), and other secondary efficacy outcome measures (AISRS subscales; ASRS total and subscale scores; HAM-D-17 total score; HAM-A total score; CGI-Overall-S; CGI-I; WRAADDS total score; OCDS total score; ASR total score; and ABCL total score).

Safety: Safety measures included AEs, vital signs, laboratory tests, and ECGs.

Health Outcomes: Health outcomes and quality of life measures were EWPS total score; Sheehan Disability Scale; SF-36 Physical Component Summary (PCS) score and Mental Component Summary (MCS) score; and Q-LES-Q-SF total score.

Evaluation Methods:

Statistical: The two primary efficacy endpoints were ADHD severity and time to relapse of alcohol abuse, compared by treatment groups. ADHD severity analysis included mean change from baseline to last-observation-carried-forward (LOCF) endpoint total score values compared between treatment groups, using an analysis of covariance (ANCOVA) model with effects for treatment group, investigator, and baseline score. Time to relapse of alcohol abuse, as measured by the Timeline Followback method, was defined as the amount of time (in days) from first dose of study drug to first occurrence of relapse, and was analyzed using log-rank tests based on Kaplan-Meier estimates. Patients who dropped out of the study as lost-to-follow-up were also counted as relapsed. All analyses were conducted separately for the double-blind treatment period (Study Period II) and the open-label treatment period (Study Period III). Secondary efficacy analyses included AISRS, ASRS, HAM-D-17, HAM-A, CGI-Overall-S, CGI-I, OCDS, WRAADDS, ASR, and ABCL. For AISRS and ASRS questionnaires, if more than one item of a subscale was missing, the score for that subscale was also considered missing. If a single item was missing, the mean score calculated from all other items in the subscale was imputed as the score for the missing item when computing totals. Safety analyses were conducted on all randomized patients taking at least one dose of study drug, according to treatment actually received. Categorical laboratory data, vital signs, and ECGs, and the percentage of patients reporting treatment-emergent adverse events (TEAEs) were tabulated by treatment group separately for Study Periods II and III, using Fisher's exact test. Treatment comparisons of changes from baseline to endpoint for laboratory data, vital signs, weight, and ECGs were done using an ANCOVA model. Within-group changes were assessed using Wilcoxon's signed-rank test for laboratory data, and the paired t-test for vital signs, weight, and ECGs.

Results:

Patient Demographics

Most patients were Caucasian (87.8% overall) males (85.0% overall; 84.7% atomoxetine; 85.3% placebo), with an overall average age of 34.6 years (standard deviation [SD]=10.02; Table LYBY.1). There were no statistically significant baseline differences between treatment groups in mean age, race, gender, body mass index (BMI), family history of ADHD, or number of drinking days.

Overall, 98.6% of patients had a childhood history of inattention criteria on the Adult ADHD Clinician Diagnostic Scale (ACDS), and 99.3% had an adult history. Overall, 86.4% of patients had a childhood history of hyperactive/impulsive criterion on the ACDS, and 91.8% had an adult history. Baseline ACDS scores were comparable between the treatment groups. The most common ADHD subtype was the Combined

type. Overall, 83.7% of patients had a childhood history of Combined type, and 85.0% had an adult history.

Baseline ADHD severity was assessed for all randomized patients and between treatment groups, using the CGI-Overall-S scale and the AISRS. Results were consistent across patients and between groups, indicating no statistically significant differences in baseline illness.

Table LYBY.1. Demographics and Baseline Characteristics for Atomoxetine and Placebo Groups Study Period II

	Atomoxetine	Placebo	p Value
Age (years), mean (SD)	34.3 (10.23)	34.8 (9.9)	.710
Race, n (%)			.746
Caucasian	64 (88.9)	65 (86.7)	
African descent	3 (4.2)	3 (4.0)	
Asian	1 (1.4)	0	
Hispanic	4 (5.6)	5 (6.7)	
Other	0	2 (2.7)	
Sex, n (%)			1.000
Female	11 (15.3)	11 (14.7)	
Male	61 (84.7)	64 (85.3)	
CGI-Overall-S, mean (SD)	4.8 (0.75)	4.8 (0.64)	.992
AISRS Total Score, mean (SD)	40.6 (7.75)	40.1 (7.88)	.633
ADHD family history, n (%)			
Mother	8 (11.1)	8 (10.7)	.97
Father	6 (8.3)	9 (12.0)	.53
Grandparents	1 (1.4)	0	.79
Siblings	17 (23.6)	14 (18.7)	.50

Abbreviations: ADHD = Attention-Deficit Hyperactivity Disorder; AISRS = Adult ADHD Investigator Symptom Rating Scale; CGI-Overall-S = Clinical Global Impressions-Overall –Severity; n = number of patients; SD = standard deviation.

Patient Disposition

A total of 215 patients were enrolled in the study. Of these, 147 were randomly assigned to the 12-week double-blind acute treatment phase in Study Period II (atomoxetine n=72, placebo n=75). Seven patients were not treated (atomoxetine n=5, placebo n=2), and 60 patients discontinued (atomoxetine n=35, placebo n=25). The most common reason for study discontinuation in both groups was “unable to contact patient/caregiver” (atomoxetine, 19 of 35 patients [54.3%]; placebo, 18 of 25 patients [72.0%]). Eighty patients completed Study Period II (atomoxetine n=32, placebo n=48; p=0.021).

A total of 77 patients began the open-label Study Period III. Twenty-seven patients discontinued (continued on atomoxetine n=7, switched from placebo to atomoxetine n=20). The most common reason for study discontinuation in the continued on

atomoxetine group was “unable to contact patient/caregiver” (3 of 7 patients [42.9%]), while in the patients who were switched from placebo to atomoxetine, the most common reasons for discontinuation were “adverse event” (7 of 20 patients [35.0%]) and “unable to contact patient/caregiver” (7 of 20 patients [35.0%]). Fifty patients completed Study Period III (atomoxetine n=24, placebo n=26).

Patient disposition is shown in Figure LYBY.1, and summarized for Study Period II in Table LYBY.2 and Study Period III in Table LYBY.3.

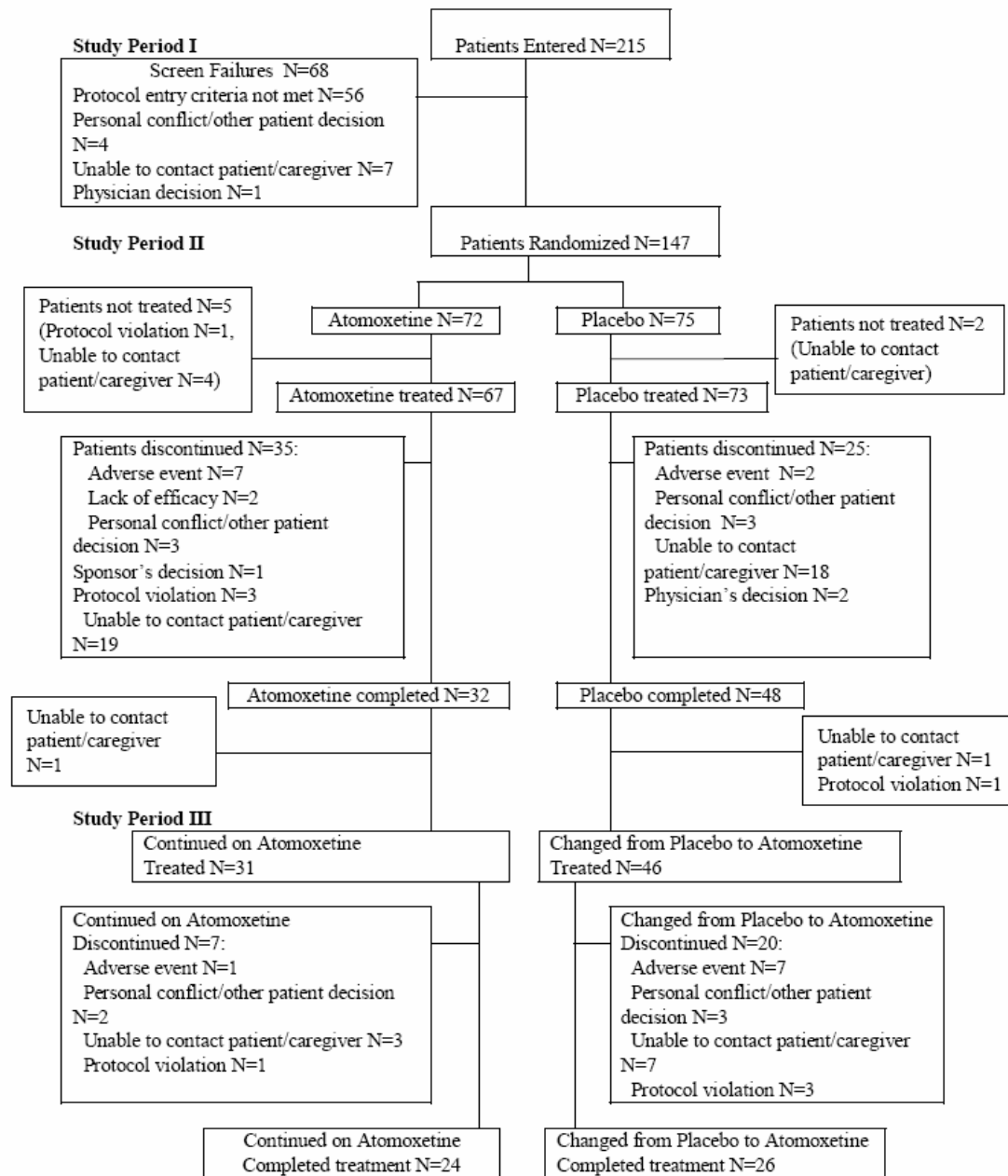


Figure LYBY.1. Patient Disposition

**Table LYBY.2. Reasons for Discontinuation
Study Period II**

	Atomoxetine n (%)	Placebo n (%)	p-Value ^a
Number of patients randomized	72 (100)	75 (100)	
Number of patients who completed study phase	32 (44.4)	48 (64.0)	0.021
Patients not entered study phase III ^b	1 (1.4)	2 (2.7)	
Number of patients prematurely discontinued	40 (55.6)	27 (36.0)	
Patients randomized but no treatment documented	5 (6.9)	2 (2.7)	
Primary reason for discontinuation:			
Adverse event	7 (9.7)	2 (2.7)	0.093
Lack of efficacy	2 (2.8)	0	0.238
Personal conflict or other patient decision	3 (4.2)	3 (4.0)	1.000
Unable to contact patient/caregiver	23 (31.9)	20 (26.7)	0.587
Sponsor's decision	1 (1.4)	0	0.490
Physician's decision	0	2 (2.7)	0.497
Protocol violation	4 (5.6)	0	0.055

a Frequencies analyzed using Fisher's exact test. Treatment group comparisons for Study Period II only.

b Two patients unable to contact; one patient with protocol violation.

Note: Denominator for calculating the percentages is the total number of patients randomized/enrolled for each treatment.

Abbreviations: n = number of patients in the category.

**Table LYBY.3. Reasons for Discontinuation
Study Period III**

	Atomoxetine n (%)	Placebo n (%)
Number of patients entered/enrolled ^a	31 (100)	46 (100)
Number of patients who completed study phase	24 (77.4)	26 (56.5)
Number of patients prematurely discontinued	7 (22.6)	20 (43.5)
Primary reason for discontinuation:		
Adverse event	1 (3.2)	7 (15.2)
Personal conflict or other patient decision	2 (6.5)	3 (6.5)
Unable to contact patient/caregiver	3 (9.7)	7 (15.2)
Protocol violation	1 (3.2)	3 (6.5)

a A patient is counted to be enrolled in Study Period III (open-label treatment) if treatment was assigned at Visit 14.

Note: Denominator for calculating the percentages is the total number of patients randomized/enrolled for each treatment.

Abbreviations: n = number of patients in the category.

Primary Efficacy Results: Study Period II

The primary objectives of the LYBY study were to test the hypotheses that atomoxetine, given in doses of 25-100 mg daily as either a single daily dose or a divided twice daily dose for approximately 12 weeks, was superior to placebo in reducing the symptoms of

ADHD, as assessed by mean reduction in scores on the AISRS, and was superior to placebo in the prevention of relapse of alcohol abuse, as defined by time to relapse, in patients with ADHD and comorbid alcohol abuse disorder.

The first hypothesis was met, as the analysis demonstrated statistically significant differences between the treatment groups (atomoxetine versus placebo, $p=0.007$) in reduction of the severity of ADHD symptoms as measured by the mean change from baseline to LOCF endpoint on the AISRS Total Score (Table LYBY.4).

**Table LYBY.4. Primary Efficacy Analysis: ADHD Severity
AISRS Total Score
Mean Change from Baseline to LOCF Endpoint**

Primary Analysis	Atomoxetine (n=72)		Placebo (n=75)		p-Value
	Baseline mean (SD)	Change from Baseline mean (SD)	Baseline mean (SD)	Change from Baseline mean (SD)	
AISRS Total score	40.63 (7.75)	-13.63 (11.35)	40.05 (7.88)	-8.31 (11.44)	.007

Abbreviations: AISRS = Adult ADHD Investigator Symptom Rating Scale; LOCF = last observation carried forward; n = number of patients in the category; SD = standard deviation.

As shown in Table LYBY.5, the second hypothesis was not met using the Kaplan-Meier method of estimating the time to first event, as the analysis indicated that atomoxetine was not statistically significantly different from placebo in the time to first relapse of alcohol abuse. Table LYBY.6 shows this analysis with patients lost to follow-up included as relapse.

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**Table LYBY.5. Summary of Kaplan-Meier Estimates and Log-rank Test for Times to Relapse of Alcohol Abuse
Full Analysis Set
Study Period II**

Statistic	Atomoxetine (N=72)	Placebo (N=75)
Total number of patient with followback information	68	72
Number (%) with relapse	64 (94.1%)	69 (95.8%)
Number (%) censored	4 (5.9%)	3 (4.2%)
25% quantile of relapse-free time (days)	1.0	1.0
50% quantile of relapse-free time (days)	2.0	3.0
Estimates of relapse-free survival probability at:		
4 weeks after randomization	0.065	0.057
8 weeks after randomization	0.049	0.019
12 weeks after randomization	0.049	0.019
Log-rank test		0.934

Note: Summary statistics for quantiles are based on the Kaplan-Meier estimate of the distribution of survival time.
Abbreviations: N = total number of patients.

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**Table LYBY.6. Summary of Kaplan-Meier Estimates and Log-rank Test for Times to Relapse of Alcohol Abuse
Full Analysis Set
Lost to Follow-up included as Relapse
Study Period II**

Statistic	Atomoxetine (N=72)	Placebo (N=75)
Total number of patient with followback information	68	72
Number (%) with relapse	64 (94.1%)	70 (97.2%)
Number (%) censored	4 (5.9%)	2 (2.8%)
25% quantile of relapse-free time (days)	1.0	1.0
50% quantile of relapse-free time (days)	2.0	3.0
Estimates of relapse-free survival probability at:		
4 weeks after randomization	0.065	0.057
8 weeks after randomization	0.049	0.014
12 weeks after randomization	0.049	0.014
Log-rank test		0.986

Note: Summary statistics for quantiles are based on the Kaplan-Meier estimate of the distribution of survival time
Abbreviations: N = total number of patients.

As shown in Table LYBY.7, there was a statistically significantly greater decrease (improvement) from baseline in the atomoxetine group compared to the placebo group for the AISRS hyperactive-impulsive and inattentive subscales ($p=0.009$ and $p=0.013$, respectively), ASRS total score ($p=0.029$) and hyperactive-impulsive and inattentive subscales ($p=0.034$ and $p=0.032$, respectively), OCDS total score ($p=0.025$) and obsessive subscale ($p=0.023$), and CGI-Overall-S ($p=0.048$). There also was a statistically significant difference between groups with respect to CGI-I ($p=0.006$).

There were no statistically significant differences ($p>0.050$) between groups for total alcohol consumption, proportion of drinking days, time to relapse, number of drinks per drinking day, abuse of substances other than alcohol, depressive symptoms (as assessed by HAM-D-17), anxiety symptoms (as assessed by HAM-A), and general quality of life (as assessed by the SF-36 Health Survey and the Q-LES-Q-SF).

Total ABCL scores were assessed only at baseline, at Visit 15, and at the end of Study Period III (LOCF). At Visit 15, there was a statistically significantly greater mean decrease from baseline in ABCL score within each treatment group (atomoxetine, -29.4, $p=0.002$; placebo, for ages 18 to 59, overall, -25.8 [$p<0.011$]).

Total WRAADS scores were assessed only at baseline and at Visit 15, and at the end of Study Period III (LOCF). At the end of the entire study, there were no statistically significant differences between treatment groups in WRAADDs scores. There was, however, a statistically significant reduction (improvement) in scores for each group (atomoxetine, -9.9; placebo, -9.0; $p<0.001$).

**Table LYBY.7. Secondary Efficacy Results
Study Period II**

	Atomoxetine (n=72)		Placebo (n=75)		
Measure	Baseline mean (SD)	Change from Baseline mean (SD)	Baseline mean (SD)	Change from Baseline mean (SD)	p-Value
ADHD-related measures					
AISRS					
Hyperactive/impulsive subscale	18.97 (4.99)	-6.48 (5.97)	18.69 (5.16)	-3.90 (5.61)	0.009
Inattentive subscale	21.65 (3.88)	-7.15 (6.15)	21.36 (4.06)	-4.41 (6.72)	0.013
ASRS					
Total Score	48.52 (10.11)	-12.85 (12.81)	51.27 (9.31)	-8.28 (12.87)	0.029
Hyperactive/impulsive subscale	23.64 (6.07)	-6.36 (6.99)	24.56 (5.98)	-4.08 (6.58)	0.034
Inattentive subscale	24.88 (5.52)	-6.49 (6.67)	26.71 (5.56)	-4.19 (7.09)	0.032
Drinking-related measures					
Mean drinks per day	2.02 (1.53)	1.01 (3.17)	2.01 (1.75)	1.47 (2.63)	0.353
Proportion of drinking days	0.33 (0.20)	0.20 (0.32)	0.31 (0.18)	0.28 (0.34)	0.258
Drinks per drinking day	6.45 (2.91)	-1.08 (3.10)	6.69 (3.50)	-0.58 (2.41)	0.144
OCDS					
Total score	20.3 (8.46)	-6.0 (5.49)	21.9 (8.34)	-3.4 (7.04)	0.025
Obsessive subscale	6.6 (4.38)	-2.6 (3.29)	7.4 (4.12)	-1.5 (2.82)	0.023
Compulsive subscale	13.7 (4.85)	-3.3 (3.22)	14.4 (4.92)	-1.9 (5.35)	0.097
Other measures					
CGI-Overall-S	4.8 (0.75)	-1.0 (1.16)	4.8 (0.64)	-0.7 (1.05)	0.048
CGI-I ^a	--	2.9 (1.05)	--	3.4 (1.17)	0.006
HAMD-17	8.0 (3.62)	-1.0 (4.31)	8.0 (3.67)	-1.1 (5.83)	0.885
HAM-A Total Score	9.7 (3.45)	-1.5 (4.25)	9.5 (3.75)	-1.2 (6.31)	0.836

a There is no baseline measure for this variable. P-value is based on an ANCOVA with only treatment baseline value and investigator included in the model.

b Abbreviations: ADHD = Attention-Deficit/Hyperactivity Disorder; AISRS = ADHD Investigator Symptom Rating Scale; ASRS = Adult ADHD Self-Report scale; CGI-I = Clinical Global Impressions-Improvement; CGI-Overall-S = Clinical Global Impressions-Overall-Severity; HAM-A = Hamilton Anxiety Scale; HAMD-17 = Hamilton Depression Rating Scale; OCDS = Obsessive Compulsive Drinking Scale; SD = standard deviation.

Safety

Adverse Events

There were no deaths or SAEs reported during this study. Nine patients discontinued due to an AE (atomoxetine n=7, 10.4%; placebo n=2, 2.7%) during Study Period II. Eight patients in Study Period III discontinued due to an AE (continued on atomoxetine n=1, 3.2%; switched from placebo to atomoxetine n=7, 15.2%). Except for neck pain and pregnancy, all events during Study Periods II and III were considered related to study drug.

Table LYBY.8 presents those AEs by Preferred Term (Medical Dictionary for Regulatory Activities [MedDRA] version 8.0) leading to discontinuation in Study Period II, while Table LYBY.9 presents AEs (by Preferred Term) leading to patient discontinuation during Study Period III.

Table LYBY.8. Adverse Events (Preferred Term, MedDRA version 8.0) Leading to Discontinuation, Incidence by Decreasing Frequency within the Atomoxetine Treatment Group Study Period II

System Organ Class Preferred Term ^a	Atomoxetine (N=67) n (%)	Placebo (N=73) n (%)	p-Value ^b
Any Adverse Event	7 (10.4%)	2 (2.7%)	0.087
Gastrointestinal Disorders	2 (3.0%)	0 (0.0%)	0.227
Nausea	2 (3.0%)	0 (0.0%)	0.227
Renal and Urinary Disorders	2 (3.0%)	0 (0.0%)	0.227
Dysuria	1 (1.5%)	0 (0.0%)	0.479
Urinary Hesitation	1 (1.5%)	0 (0.0%)	0.479
Musculoskeletal and Connective Tissue Disorders	1 (1.5%)	1 (1.4%)	1.000
Muscle Tightness	0 (0.0%)	1 (1.4%)	1.000
Neck Pain	1 (1.5%)	0 (0.0%)	0.479
Investigations	1 (1.5%)	0 (0.0%)	0.479
Red Blood Cells Semen	1 (1.5%)	0 (0.0%)	0.479
Pregnancy, Puerperium and Perinatal Conditions	1 (1.5%)	0 (0.0%)	0.479
Pregnancy	1 (1.5%)	0 (0.0%)	0.479
General Disorders and Administrative Site Conditions	0 (0.0%)	1 (1.4%)	1.000
Chest Discomfort	0 (0.0%)	1 (1.4%)	1.000

a MedDRA version 8.0.

b Analyzed using Fisher's exact test.

Note: Patients reporting more than one adverse event within the table row are counted only once within that row.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients; n = number of patients in the category.

Table LYBY.9. Adverse Events (Preferred Term, MedDRA version 8.0) Leading to Discontinuation, Incidence by Decreasing Frequency Within the Atomoxetine Treatment Group Study Period III

System Organ Class Preferred Term ^a	Overall (N=77) n (%)	Continued on Atomoxetine (N=31) n (%)	Changed from Placebo to Atomoxetine (N=46) n (%)	p-Value ^b
Any Adverse Event	8 (10.4%)	1 (3.2%)	7 (15.2%)	0.134
Psychiatric Disorders	3 (3.9%)	1 (3.2%)	2 (4.3%)	1.000
Anorgasmia	1 (1.3%)	0 (0.0%)	1 (2.2%)	1.000
Apathy	1 (1.3%)	1 (3.2%)	0 (0.0%)	0.403
Orgasm Abnormal	1 (1.3%)	0 (0.0%)	1 (2.2%)	1.000
Renal and Urinary Disorders	2 (2.6%)	0 (0.0%)	2 (4.3%)	0.513
Urinary Hesitation	1 (1.3%)	0 (0.0%)	1 (2.2%)	1.000
Urinary Retention	1 (1.3%)	0 (0.0%)	1 (2.2%)	1.000
Gastrointestinal Disorders	1 (1.3%)	0 (0.0%)	1 (2.2%)	1.000
Nausea	1 (1.3%)	0 (0.0%)	1 (2.2%)	1.000
Investigations	1 (1.3%)	0 (0.0%)	1 (2.2%)	1.000
Weight Decreased	1 (1.3%)	0 (0.0%)	1 (2.2%)	1.000
Skin and Subcutaneous Tissue Disorders	1 (1.3%)	0 (0.0%)	1 (2.2%)	1.000
Hyperhidrosis	1 (1.3%)	0 (0.0%)	1 (2.2%)	1.000

a MedDRA version 8.0.

b Analyzed using Fisher's exact test.

Note: Patients reporting more than one adverse event within the table row are counted only once within that row.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients; n = number of patients in the category.

Treatment-emergent AEs (TEAEs) were analyzed for the safety set in Study Period II. Nausea was the most frequent TEAE in the atomoxetine group, at 43.3% (9.6% of placebo patients), followed by dry mouth (26.9% atomoxetine, 11.0% placebo), and headache (22.4% atomoxetine, 21.9% placebo). Overall, there was a statistically significantly higher proportion of TEAEs in the atomoxetine group (92.5%) than in the placebo group (79.5%) (p=0.031). A summary of TEAEs reported for at least 5% of patients in either treatment group during Study Period II is provided in Table LYBY.10.

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Table LYBY.10. Summary of Treatment-Emergent Adverse Events, Greater than or Equal to 5% Incidence, Using MedDRA (version 8.0) Preferred Terms Study Period II

Preferred Term ^a	Atomoxetine N=67 n (%)	Placebo N=73 n (%)	p-Value ^b
Any Adverse Event	62 (92.5)	58 (79.5)	0.031
Nausea	29 (43.3)	7 (9.6)	<0.001
Dry Mouth	18 (26.9)	8 (11.0)	0.018
Headache	15 (22.4)	16 (21.9)	1.000
Decreased Appetite	12 (17.9)	2 (2.7)	0.004
Insomnia	11 (16.4)	10 (13.7)	0.813
Dizziness	10 (14.9)	2 (2.7)	0.014
Nasopharyngitis	9 (13.4)	3 (4.1)	0.069
Fatigue	9 (13.4)	2 (2.7)	0.026
Constipation	8 (11.9)	1 (1.4)	0.014
Upper Respiratory Tract Infection	8 (11.9)	11 (15.1)	0.630
Abdominal Pain, Upper	6 (9.0)	3 (4.1)	0.311
Abnormal Dreams	6 (9.0)	4 (5.5)	0.520
Irritability	6 (9.0)	3 (4.1)	0.311
Heart Rate Increased	6 (9.0)	1 (1.4)	0.054
Erectile Dysfunction	6 (9.0)	1 (1.4)	0.054
Vomiting	5 (7.5)	2 (2.7)	0.259
Urinary Hesitation	5 (7.5)	0	0.023
Dyspepsia	4 (6.0)	1 (1.4)	0.193
Stomach Discomfort	4 (6.0)	1 (1.4)	0.193
Somnolence	4 (6.0)	4 (5.5)	1.000
Paresthesia	4 (6.0)	0	0.050
Pharyngolaryngeal Pain	4 (6.0)	3 (4.1)	0.710
Pollakiuria	4 (6.0)	1 (1.4)	0.193
Hyperhidrosis	4 (6.0)	3 (4.1)	0.710
Hot Flush	4 (6.0)	0	0.050

(continued)

Atomoxetine hydrochloride

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Table LYBY.10. Summary of Treatment-Emergent Adverse Events, Greater than or Equal to 5% Incidence, Using MedDRA (version 8.0) Preferred Terms Study Period II, Concluded

Preferred Term ^a	Atomoxetine N=67 n (%)	Placebo N=73 n (%)	p-Value ^b
Diarrhea	3 (4.5)	5 (6.8)	0.721
Anxiety	3 (4.5)	4 (5.5)	1.000
Nasal Congestion	3 (4.5)	6 (8.2)	0.497
Cough	2 (3.0)	5 (6.8)	0.444
Influenza	1 (1.5)	5 (6.8)	0.211
Blood Pressure Increased	3 (4.5)	4 (5.5)	1.000
Back Pain	2 (3.0)	4 (5.5)	0.682

Population: Enrolled patients who took at least 1 dose of study drug.

a MedDRA version 8.0.

b Analyzed using Fisher's exact test.

Note: Patients reporting more than one adverse event within the table row are counted only once within that row.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients; n = number of patients in the category.

In Study Period III, the most frequently reported TEAEs overall were dry mouth (19.5%), nausea (18.2%), and insomnia (15.6%). Dry mouth occurred statistically significantly more frequently in the patients who were switched from placebo to atomoxetine than in the patients who continued on atomoxetine (28.3% versus 6.5%; $p=0.020$). A summary of TEAEs reported for at least 5% of patients in either treatment group during Study Period III is provided in Table LYBY.11.

Table LYBY.11. Summary of Treatment-Emergent Adverse Events, Greater than or Equal to 5% Incidence in Either Treatment Group, Using MedDRA (version 8.0) Preferred Terms Study Period III

Preferred Term ^a	Overall N=77 n (%)	Continued on Atomoxetine N=31 n (%)	Changed from Placebo to Atomoxetine N=46 n (%)	p-Value ^b
Any Adverse Event	64 (83.1)	23 (74.2)	41 (89.1)	0.122
Dry mouth	15 (19.5)	2 (6.5)	13 (28.3)	0.020
Nausea	14 (18.2)	6 (19.4)	8 (17.4)	1.000
Constipation	5 (6.5)	0	5 (10.9)	0.078
Dyspepsia	5 (6.5)	3 (9.7)	2 (4.3)	0.387
Stomach discomfort	4 (5.2)	1 (3.2)	3 (6.5)	0.644
Insomnia	12 (15.6)	2 (6.5)	10 (21.7)	0.109
Anxiety	4 (5.2)	1 (3.2)	3 (6.5)	0.644
Irritability	4 (5.2)	0	4 (8.7)	0.144
Libido decreased	3 (3.9)	0	3 (6.5)	0.269
Headache	7 (9.1)	2 (6.5)	5 (10.9)	0.695
Dizziness	5 (6.5)	2 (6.5)	3 (6.5)	1.000
Fatigue	7 (9.1)	4 (12.9)	3 (6.5)	0.430
Influenza	3 (3.9)	2 (6.5)	1 (2.2)	0.561
Blood pressure increased	4 (5.2)	0	4 (8.7)	0.144
Urinary hesitation	4 (5.2)	0	4 (8.7)	0.144
Dysuria	3 (3.9)	0	3 (6.5)	0.269
Ejaculation disorder	3 (3.9)	0	3 (6.5)	0.269
Decreased appetite	6 (7.8)	0	6 (13.0)	0.076
Hyperhidrosis	4 (5.2)	1 (3.2)	3 (6.5)	0.644
Hot flush	4 (5.2)	2 (6.5)	2 (4.3)	1.000

Population: Enrolled patients who took at least 1 dose of study drug.

a MedDRA Version 8.0

b Analyzed using Fisher's exact test.

Note: Patients reporting more than one adverse event within the table row are counted only once within that row.

Frequencies of abnormal laboratory values, vital signs, and ECGs were compared between the two treatment groups, and treatment group differences in laboratory values were assessed with effects for treatment, investigator, and baseline as covariates.

Laboratory Values

Statistically significant mean changes in laboratory values are shown in Table LYBY.12.

Table LYBY.12. Statistically Significant Mean Changes in Laboratory Values Study Periods II and III

	Period II: Atomoxetine Period III: Continued on Atomoxetine N=67/31		Period II: Placebo Period III: Changed to Atomoxetine N=73/46	
	Measured Value	Change	Measured Value	Change
Hematocrit				
Post Study Period III	n=26	n=25	n=37	n=37
Mean	0.451	0.014	0.459	0.002
P-value ^a	--	0.010	--	0.874
Eosinophils (G/L)				
Post Study Period III	n=26	n=25	n=37	n=37
Mean ^b	0.118	-0.046	0.139	-0.004
P-value ^a	--	0.009	--	0.972
Mean cell volume (fL)				
Post Study Period III	n=26	n=25	n=37	n=37
Mean	88.8	1.8	88.2	-0.7
p-value ^a	--	0.005	--	0.185
Creatine phosphokinase (U/L)				
Post Study Period III	n=26	n=26	n=37	n=37
Mean	157.8	-26.8	175.6	-200.0
P-value ^a	--	0.028	--	0.486
Calcium (mmol/L)				
Post Study Period II	n=11	n=10	n=6	n=6
Mean	2.401	-0.064	2.478	-0.030
P-value ^a	--	0.018	--	0.469
Post Study Period III	n=26	n=26	n=37	n=37
Mean	2.470	-0.015	2.456	-0.042
P-value ^a	--	0.427	--	0.031
Sodium (mmol/L)				
Post Study Period II	n=11	n=10	n=6	n=6
Mean	140.6	-1.3	141.0	-1.0
P-value ^a	--	0.029	--	0.313
Post Study Period III	n=25	n=24	n=37	n=37
Mean	139.8	-1.6	139.8	-1.4
P-value ^a	--	0.008	--	0.022

(continued)

Table LYBY.12. Statistically Significant Mean Changes in Laboratory Values Study Periods II and III, Concluded

	Period II: Atomoxetine Period III: Continued on Atomoxetine N=67/31		Period II: Placebo Period III: Changed to Atomoxetine N=73/46	
	Measured Value	Change	Measured Value	Change
Chloride (mmol/L)				
Post Study Period II	n=11	n=10	n=6	n=6
Mean	102.4	-1.7	103.3	-1.3
P-value ^a	--	0.008	--	0.250
Post Study Period III	n=25	n=24	n=37	n=37
Mean	101.4	-1.7	101.5	-0.7
P-value ^a	--	<0.001	--	0.105
Cholesterol (mmol/L)				
Post Study Period III	n=26	n=26	n=37	n=37
Mean ^b	5.627	0.183	5.162	-0.165
P-value ^a	--	0.212	--	0.113
Bicarbonate (mmol/L)				
Post Study Period III	n=25	n=25	n=37	n=37
Mean	26.59	2.33	25.79	1.90
P-value ^a	--	<0.001	--	<0.001
Bilirubin, total (μmol/L)				
Post Study Period III	n=26	n=26	n=37	n=37
Mean	10.0	1.6	9.7	0.6
P-value ^a	--	0.046	--	0.530

a Analyzed using Wilcoxon's signed rank test.

b Statistically significant difference (p<0.05) between treatment groups. Analyzed using analysis of covariance on the ranked change from baseline with effects for treatment, investigator, with baseline value as covariate.

Abbreviations: LOCF = last observation carried forward; N = total number of patients; n = number of patients in the category.

Vital Signs

Statistically significant mean changes in vital signs at the end of Study Period II are shown in Table LYBY.13. There were statistically significant differences between the atomoxetine and placebo groups for mean change from baseline in BMI and weight, with mean decreases in the atomoxetine group and mean increases in the placebo group. In the atomoxetine group, there were statistically significant mean increases in systolic and diastolic blood pressure and heart rate, and decreases in BMI and weight. In the placebo group, there were statistically significant increases in BMI and diastolic blood pressure.

Table LYBY.13. Statistically Significant Mean Changes in Vital Sign Values End of Study Period II (LOCF)

	Atomoxetine N=72	Placebo N=75	p-Value ^a
Body mass index (kg/m ²)	n=66	n=69	
Mean	-0.27	0.16	<0.001
P-value ^b	0.002	0.028	
Weight (kg)	n=68	n=72	
Mean	-0.91	0.42	<0.001
P-value ^b	<0.001	0.068	
Systolic blood pressure (mm Hg)	n=68	n=72	
Mean	2.5	1.1	0.447
P-value ^b	0.023	0.369	
Diastolic blood pressure (mm Hg)	n=68	n=72	
Mean	2.6	2.6	0.825
P-value ^b	0.008	0.014	
Heart rate (bpm)	n=68	n=72	
Mean	6.3	2.3	0.122
P-value ^b	<0.001	0.105	

a Analyzed using analysis of covariance with effects for treatment and investigator with baseline value as covariate.

b Analyzed using paired t-test.

Abbreviations: LOCF = last observation carried forward; N = total number of patients; n = number of patients in the category.

Statistically significant mean changes in vital signs at the end of Study Period III are shown in Table LYBY.14. There was a statistically significant difference between treatment groups with respect to mean change in systolic blood pressure and heart rate, with mean decreases in the atomoxetine/atomoxetine group and mean increases in the placebo/atomoxetine group. Various statistically significant mean changes in vital signs were seen within treatment groups.

Table LYBY.14. Statistically Significant Mean Changes in Vital Sign Values End of Study Period III (LOCF)

	Continued on Atomoxetine N=31		Changed to Atomoxetine N=46		Overall N=77		p- Value ^a
	Change from Baseline	Change from Visit 14	Change from Baseline	Change from Visit 14	Change from Baseline	Change from Visit 14	
Body mass index (kg/m ²)	n=30	n=30	n=45	n=44	n=75	n=74	
Mean	-0.29	0.04	-0.31	-0.39	-0.30	-0.21	0.079
P-value ^b	0.103	0.808	0.033	<0.001	0.007	0.020	
Weight (kg)	n=31	n=31	n=46	n=45	n=77	n=76	
Mean	-0.90	0.17	-0.99	-1.23	-0.95	-0.66	0.070
P-value ^b	0.099	0.705	0.027	<0.001	0.005	0.022	
Systolic BP (mm Hg)	n=31	n=31	n=46	n=46	n=77	n=77	
Mean	0.8	-0.9	4.5	4.8	3.0	2.5	0.048
P-value ^b	0.655	0.666	0.021	0.003	0.029	0.055	
Diastolic BP (mm Hg)	n=31	n=31	n=46	n=46	n=77	n=77	
Mean	3.6	0.5	6.8	4.1	5.5	2.7	0.064
P-value ^b	0.007	0.756	<0.001	0.006	<0.001	0.017	
Heart rate (bpm)	n=31	n=31	n=46	n=46	n=77	n=77	
Mean	6.5	-0.3	8.3	5.9	7.6	3.4	0.028
P-value ^b	<0.001	0.888	<0.001	0.007	<0.001	0.023	

a Analyzed using analysis of covariance for changes from end of Study Period II with effects for treatment and investigator with end of Study Period II value as covariate.

b Analyzed using paired t-test.

Abbreviations: BP = blood pressure; N = total number of patients; n = number of patients in the category.

ECGs

Statistically significant mean changes in ECG values from baseline to the end of Study Period II are shown in Table LYBY.15.

Table LYBY.15. Statistically Significant Mean Changes from Baseline in ECG Values End of Study Period II

	Atomoxetine N=67	Placebo N=73	p-Value^a
Heart rate (bpm)	n=39	n=45	
Mean	7.2	1.5	0.042
P-value ^b	<0.001	0.294	
RR interval (msec)	n=39	n=45	
Mean	-98.8	-16.0	0.044
P-value ^b	<0.001	0.391	
PR interval (msec)	n=39	n=45	
Mean	-7.3	0.0	0.003
P-value ^b	<0.001	1.000	
QT interval (msec)	n=39	n=45	
Mean	-18.3	-4.7	0.035
P-value ^b	<0.001	0.144	

a Analyzed using analysis of covariance on the change from baseline with effects for treatment and investigator, with baseline value as covariate.

b Analyzed using paired t-test.

Abbreviations: N = total number of patients; n = number of patients in the category.

Statistically significant mean changes in ECG values at the end of Study Period III are shown in Table LYBY.16.

Table LYBY.16. Statistically Significant Mean Changes in ECG Values Study Period III

	Continued on Atomoxetine N=31		Changed to Atomoxetine N=46		Overall N=77	
	Change from Baseline	Change from Visit 14	Change from Baseline	Change from Visit 14	Change from Baseline	Change from Visit 14
Heart Rate (bpm)	n=24	n=24	n=31	n=30	n=55	n=54
Mean	4.8	0.5	10.7	7.3	8.1	4.2
P-value ^a	0.017	0.843	<0.001	0.003	<0.001	0.014
RR interval (msec)	n=24	n=24	n=31	n=30	n=55	n=54
Mean	-66.7	-7.2	-112.3	-72.1	-92.4	-43.3
P-value ^a	0.014	0.779	<0.001	0.006	<0.001	0.019
PR Interval (msec)	n=24	n=24	n=31	n=30	n=55	n=54
Mean ^b	-4.5	3.2	-6.9	-7.2	-5.9	-2.6
P-value ^a	0.119	0.166	0.009	0.003	0.002	0.137
QT interval (msec)	n=24	n=24	n=31	n=30	n=55	n=54
Mean ^b	-12.6	2.9	-17.6	-8.5	-15.4	-3.4
P-value ^a	0.025	0.547	<0.001	0.043	<0.001	0.279
QTcB (msec)	n=24	n=24	n=31	n=30	n=55	n=54
Mean	2.0	4.4	9.7	10.4	6.3	7.7
P-value ^a	0.554	0.213	0.037	0.004	0.034	0.002
QTcF (msec)	n=24	n=24	n=31	n=30	n=55	n=54
Mean	-3.3	4.1	-0.2	3.3	-1.5	3.6
P-value ^a	0.312	0.158	0.963	0.181	0.527	0.049
QTcD (msec)	n=24	n=24	n=31	n=30	n=55	n=54
Mean	-1.5	4.4	3.3	5.6	1.2	5.1
P-value ^a	0.618	0.131	0.388	0.040	0.641	0.010
QTcR (msec)	n=24	n=24	n=31	n=30	n=55	n=54
Mean	-2.2	4.4	2.1	4.9	0.2	4.6
P-value ^a	0.489	0.137	0.565	0.059	0.923	0.015

a Analyzed using paired t-test.

b Statistically significant difference ($p < 0.05$) between treatment groups with respect to change from end of Study Period II. Analyzed using analysis of covariance on the change from end of Study Period II with effects for treatment, investigator, with end of Study Period II value as covariate.

Abbreviations: N = total number of patients; n = number of patients in the category; QTcB = QT corrected according to Bazett; QTcD = QT corrected dispersion; QTcF = QT corrected according to Fridericia; QTcR = QT corrected rest.

Health Outcomes

The secondary objectives dealing with health outcomes included the hypotheses that, after approximately 12 weeks of treatment, patients who received atomoxetine would have superior social and occupational functioning compared with those who received placebo, as assessed by changes in the EWPS; that atomoxetine would improve work, social, and home life functioning, as assessed by changes in the Sheehan Disability Scale; and that atomoxetine would improve general quality of life, as assessed by changes in the SF-36 Health Status Survey and by changes in the Q-LES-Q-SF. There were no statistically significant differences between the treatment groups in general quality of life results. However, in analyzing occupational functioning (EWPS total score), and work and social life functioning (Work life and Social life subscales of the Sheehan Disability scale), those patients treated with atomoxetine were seen to have statistically significant improvements ($p \leq 0.024$), compared to those patients treated with placebo. Health outcomes and quality of life results are summarized for Study Period II in Table LYBY.17 and Study Period III in Table LYBY.18.

Table LYBY.17. Summary of Health Outcome Results, Mean Change from Baseline to End of Study Period II Full Analysis Set

Scale	Atomoxetine N=72			Placebo N=75			p- Value ^a
	Baseline (SD)	Endpoint (SD)	Change (SD)	Baseline (SD)	Endpoint (SD)	Change (SD)	
EWPS Total Score	43.21 (15.697)	29.82 (17.171)	-14.32 (14.585)	46.23 (17.815)	38.44 (19.151)	-6.69 (17.539)	0.007
Sheehan Disability Scale							
Family Life Subscale	5.8 (2.86)	3.7 (2.77)	-1.6 (2.73)	5.9 (2.61)	4.7 (2.95)	-0.9 (2.91)	0.097
Work Life Subscale	6.0 (2.79)	3.5 (2.55)	-2.2 (2.19)	5.9 (2.86)	5.0 (3.20)	-0.3 (2.55)	<0.001
Social Life Subscale	5.3 (2.50)	3.3 (2.86)	-1.6 (2.05)	4.9 (2.71)	4.0 (2.64)	-0.4 (2.90)	0.024
SF-36							
PCS Score	53.459 (6.565)	52.544 (5.248)	-0.931 (5.269)	53.540 (6.069)	53.040 (4.330)	-1.013 (5.076)	0.562
MCS Score	44.859 (5.678)	48.260 (6.056)	2.235 (4.581)	44.202 (5.985)	47.388 (4.639)	2.486 (4.890)	0.664
Q-LES-Q-SF Total Score	48.64 (7.797)	51.87 (9.363)	2.54 (7.221)	48.69 (8.658)	52.08 (8.664)	2.44 (7.604)	0.747

Population: All randomized patients, according to treatment received, whether or not drug was actually taken.

a P-value for mean change from baseline to LOCF endpoint for study period II was based on an ANCOVA model with effects for treatment group, investigator and baseline score as a covariate.

Abbreviations: EWPS = Endicott Work Productivity Scale; MCS = Mental Component Summary; N = total number of patients; PCS = Physical Component Summary; SD = standard deviation; SF-36 = SF-36 Health Status Survey; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire Short Form.

Table LYBY.18. Summary of Health Outcome Results, Mean Change from Baseline to End of Study Period III (LOCF) Full Analysis Set

	Continued on Atomoxetine N=31		Changed to Atomoxetine N=46		Overall N=77	
	Change from Baseline	Change from end of Period II	Change from Baseline	Change from end of Period II	Change from Baseline	Change from end of Period II
EWPS total score						
n	25	26	33	34	58	60
Mean	-20.12	-2.54	-15.15	-8.38	-17.29	-5.85
SD	14.131	14.445	22.414	18.961	19.295	17.263
P-value ^a	<0.001	0.379	<0.001	0.015	<0.001	0.011
Sheehan Disability Scale						
Family Life Subscale						
n	27	27	33	33	60	60
Mean	-2.0	-0.2	-2.7	-1.3	-2.4	-0.8
SD	2.47	2.06	3.24	2.84	2.92	2.56
P-value ^a	<0.001	0.580	<0.001	0.013	<0.001	0.016
Work Life Subscale						
n	26	26	31	30	57	56
Mean	-2.3	-0.3	-2.2	-1.8	-2.2	-1.1
SD	2.37	1.95	3.05	3.30	2.73	2.84
P-value ^a	<0.001	0.4730	<0.001	0.005	<0.001	0.004
Social Life Subscale						
n	27	27	33	33	60	60
Mean	-2.1	-0.7	-2.1	1.3	-2.1	-1.0
SD	2.30	2.06	3.00	2.97	2.68	2.60
P-value ^a	<0.001	0.104	<0.001	0.015	<0.001	0.003
36-Item Short Form Health Survey						
PCS						
n	26	25	36	37	62	62
Mean	-1.243	0.484	-2.395	-1.079	-1.912	-0.449
SD	5.8154	6.7622	5.9262	4.8200	5.8600	5.6833
P-value ^a	0.286	0.723	0.021	0.182	0.013	0.536
MCS						
n	26	25	36	37	62	62
Mean	3.148	0.589	5.036	2.219	4.244	1.562
SD	5.1450	5.1614	6.3950	4.6817	5.9327	4.9057
P-value ^a	0.0058	0.574	<0.001	0.007	<0.001	0.015

(continued)

Table LYBY.18. Summary of Health Outcome Results, Mean Change from Baseline to End of Study Period III (LOCF) Full Analysis Set, Concluded

	Continued on Atomoxetine N=31		Changed to Atomoxetine N=46		Overall N=77	
	Change from Baseline	Change from end of Period II	Change from Baseline	Change from end of Period II	Change from Baseline	Change from end of Period II
Q-LES-Q-SF Total Score						
n	26	25	35	35	61	60
Mean	5.49	1.80	5.89	3.46	5.72	2.77
SD	7.315	5.439	8.704	7.205	8.078	6.529
P-value ^a	<0.001	0.111	<0.001	0.008	<0.001	0.002

Population: All randomized patients, according to treatment received, whether or not drug was actually taken.

a Analyzed using paired t-test. LOCF is the last measurement after Visit 14.

Abbreviations: EWPS = Endicott Work Productivity Scale; MCS = Mental Component Summary; N = total number of patients; n = number of patients in the category; PCS = Physical Component Summary; SD = standard deviation; SF-36 = SF-36 Health Status Survey; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire Short Form.

Summary ID# 7233

Clinical Study Summary: Study B4Z-SB-LYDE

An Open-label Study on Effectiveness and Tolerability of Atomoxetine as Perceived by Patients, Parents, and Physicians in Adolescents with Attention-Deficit/Hyperactivity Disorder in Germany

Date summary approved by Lilly: 08 February 2007

Brief Summary of Results

The primary objective of this study was to compare the perception of general effectiveness and tolerability of atomoxetine between adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD), their parents/primary caregivers, and their physicians, as measured by the newly devised Global Impression of Perceived Difficulties (GIPD) instrument.

The Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) Scale and Clinical Global Impression (CGI) Scales were also used to assess the baseline severity of ADHD and to evaluate the effectiveness of atomoxetine. The effect of atomoxetine on evening and morning behavior was assessed with the Weekly Ratings of Evening and Morning Behavior - Revised - Investigator Rated (WREMB-R-Inv) evening and morning scores, and Items 1 (morning) and 4 (evening) of the newly devised GIPD instrument. The Rosenberg Self-Esteem Scale (Rosenberg SES) was used to assess changes in self-esteem.

The results of this open-label study (Screening and Washout [Study Period I], 8-week Treatment Period [Study Period II], followed by a 16-week Extension Period [Study Period III]) were as follows:

- Patients gave the lowest ratings for ADHD-related difficulties, parents higher ratings, and physicians the highest ratings. The mean baseline ratings for the GIPD total score differed statistically significantly as shown by non-overlapping 95% confidence intervals (CIs): patients 12.5 ± 5.8 (95% CI: 11.6;13.5); parents 17.2 ± 6.3 (95% CI: 16.2;18.2); physicians 18.8 ± 6.0 (95% CI: 17.8;19.8).
- The mean scores per rater group for the GIPD total score decreased statistically significantly from baseline to Week 8, and decreases were maintained at Week 24. This improvement was smallest for the patients' rating, greater for the parents' rating, and greatest for the physicians' rating. The mean decrease from baseline to Week 8 for the physician-rated score of -7.8 ± 6.9 (95% CI: -8.9;-6.7) was statistically significantly greater than the corresponding mean change for the patient-rated score of -2.9 ± 5.9 (95% CI: -3.9;-2.0) and the mean change for the parent-rated score of -5.9 ± 6.8 (95% CI: -7.0;-4.8).
- There was a higher degree of agreement between the mean parent- and physician-rated scores than between the mean patient- and parent- or patient- and physician-rated scores (Cohen's kappa [95% CI]: parent-physician 0.53 [0.45;0.62]; patient-parent 0.22 [0.13;0.31]; patient-physician 0.19 [0.11;0.26]).
- All effectiveness scores used, including the ADHDRS-IV-Parent:Inv, CGI-S-ADHD, WREMB-R-Inv, and Rosenberg SES scores, improved consistently and statistically significantly (non-overlapping 95% CIs) from baseline to Week 8. Improvements were maintained at Week 24.
- Evening and morning behavior of ADHD patients both improved consistently during the study, as shown by statistically significant decreases (non-overlapping 95% CIs) in the mean WREMB-R-Inv evening (e.g., from 12.2 ± 5.1 to 4.9 ± 4.5 at Week 8) and morning subscores (e.g., from 3.8 ± 2.5 to 1.4 ± 1.8 at Week 8). All changes from baseline to Week 24 were also statistically significant. Corresponding statistically significant decreases (non-overlapping 95% CIs) were found for the ADHD-related morning and evening difficulties (GIPD Items 1 and 4) at Week 8 and Week 24 as perceived by patients, parents, and physicians.

- No patients died during the study. Serious adverse events were reported in 8 patients and were considered possibly related to study drug in 2 patients (1 patient with severe vomiting; 1 patient with suspected polyendocrine autoimmune syndrome developed peripheral vasoconstriction with dark coloration of extremities and marbled skin, accompanied by abdominal pain, dizziness, lack of concentration, feeling of absence, and tiredness). Adverse events possibly related to study drug were reported in 51.6% of patients overall, with fatigue (26.4%), nausea (13.8%), headache (9.4%), upper abdominal pain and decreased appetite (6.9% each), and dizziness and vomiting (5.7% each) reported most frequently. Treatment-emergent adverse events led to atomoxetine discontinuation in 7 (4.4%) patients.

Title of Study: An Open-label Study on Effectiveness and Tolerability of Atomoxetine as Perceived by Patients, Parents, and Physicians in Adolescents with Attention-Deficit/Hyperactivity Disorder in Germany	
Investigator(s): This multicenter study included 34 principal investigators (1 investigator recruited patients at 2 different sites).	
Study Center(s): This study was conducted at 35 study centers in one country.	
Length of Study: 1 year and 4 months Date first patient entered: 14 October 2004 Date first patient enrolled: 10 November 2004 Date last patient completed: 24 February 2006	Phase of Development: 3
Objectives: The primary objective of this study was to compare the perception of general effectiveness and tolerability of atomoxetine between adolescents with ADHD, their parents/primary caregivers, and their physicians, based on scores on the newly devised GIPD Scale at baseline, Week 8, and Week 24. Secondary objectives : – To assess differences in the perception of ADHD severity (ADHD-related difficulties as assessed by the GIPD Scale) between rater groups at baseline and over the course of atomoxetine treatment. – To assess the effectiveness of atomoxetine in the treatment of adolescents as measured by the ADHDRS-IV-Parent:Inv. – To assess the effectiveness of atomoxetine in the treatment of adolescents as measured by the Clinical Global Impression-Severity-ADHD (CGI-S-ADHD) and Clinical Global Impression-Improvement-ADHD (CGI-I-ADHD). – To assess the effect of atomoxetine on evening and morning behavior of adolescents as measured by the WREMB-R-Inv. – To assess the self-esteem of adolescents treated with atomoxetine based on the Rosenberg Self-Esteem Scale (SES). – To assess the tolerability of atomoxetine in the treatment of adolescents as assessed by treatment-emergent adverse events (TEAEs) elicited by open-ended questioning. – To assess solicited tolerability parameters as rated by the patients, their parents/primary caregivers and physicians, measured by the Pediatric Adverse Events Rating Scale (PAERS). – To assess parameters reflecting attitudes towards ADHD and representing common clinical practice in Germany (e.g., pretreatment, concomitant treatment, treatment by pediatricians or child and adolescent psychiatrists, family setting) and their impact on effectiveness and tolerability of	

atomoxetine (not included in Statistical Analysis Plan; to be reported separately). – To assess specific safety parameters as measured by the PAERS in subgroups (i.e., type of pretreatment) of patients at screening (not included in Statistical Analysis Plan; to be reported separately). – To evaluate effectiveness and tolerability of atomoxetine in the treatment of adolescents and children (accomplished by a pooled analysis of data from the studies B4Z-SB-LYDE [adolescents] and B4Z-SB-LYDD [children; CT#9496]).
Study Design: Single-arm, open-label, phase 3, multicenter study to evaluate the effectiveness and tolerability of atomoxetine (once daily, target dose 1.2 mg/kg/day), as perceived by patients, parents and physicians, in adolescents with ADHD treated as outpatients in Germany (aged 12–17 years). After an initial Screening and Washout Period (Study Period I), there was an 8-week Treatment Period (Study Period II), followed by a 16-week Extension Period (Study Period III). At the end of Study Period II, the physician decided whether the patient was to be continued into Study Period III.
Number of Patients: Planned: 147 Screened: 160 Enrolled: 159 Completed: 111
Diagnosis and Main Criteria for Inclusion: ADHD according to the <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition™</i> (DSM-IV™) criteria, confirmed by the German instrument “Diagnose-Checkliste Hyperkinetische Störungen” (Diagnostic checklist for hyperkinetic disorders) routinely used for ADHD diagnosis in Germany. Patients had to be adolescents aged between 12 and 17 years. They had to be of normal intelligence (likely to achieve an IQ test score of ≥ 70). Patients were to be excluded if they had any significantly abnormal laboratory findings, any acute or unstable medical conditions, cardiovascular diseases, history of seizure disorder, bipolar disorder, psychosis or pervasive developmental disorder, any medical condition that would markedly increase sympathetic nervous system activity, or were likely to need psychotropic medication other than the study drug.
Test Product, Dose, and Mode of Administration: Atomoxetine capsules. Recommended dosing according to German Summary of Product Characteristics (SmPC): initial dose approx. 0.5 mg/kg/day for 7 days, titrated to a target of approx. 1.2 mg/kg/day for the remainder of Study Period II. During Study Period II, dose reductions to a minimum of 0.5 mg/kg were allowed for safety reasons only. During Study Period III, the investigator was allowed to titrate the dose between 0.5 and 1.2 mg/kg/day according to clinical effectiveness and tolerability.
Duration of Treatment: An 8-week treatment period (Study Period II) was followed by a 16-week Extension Period (Study Period III).
Variables: <u>Effectiveness:</u> Primary - comparison of the perception of general effectiveness and tolerability (ADHD-related difficulties) of atomoxetine between patients, parents, and their physicians at baseline, and after 8 and 24 weeks of treatment based on the GIPD Scale completed by all rater groups at each visit. Secondary - application of the ADHDRS-IV-Parent:Inv Scale, CGI-S-ADHD Scale, CGI-I-ADHD Scale, WREMB-R-Inv Scale and Rosenberg SES Scale to observe effectiveness, compare ratings, and assess self-esteem. <u>Safety:</u> Standard adverse event reporting, laboratory safety investigations, and application of the Pediatric Adverse Events Rating Scale (PAERS).
Evaluation Methods: <u>Statistical:</u> Analyses of effectiveness parameters were based on the full analysis set. Different imputation rules for missing values were applied, including “last observation carried forward” (LOCF) and “observed cases” (OC) approaches. For all instruments used, the scores at each visit and the respective changes from baseline were presented using descriptive statistics. In addition, exploratory 95% confidence intervals (CIs) were calculated. For the primary analysis, the agreement between patient, parent, and physician GIPD ratings was assessed using Cohen’s kappa. Subgroup analyses by gender and by type of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis were provided.

Results:

Patient Demographics

Of the 159 patients enrolled, 125 (78.6%) patients were male and 34 (21.4%) were female. Table 1 shows the DSM-IV diagnostic subtypes of ADHD by gender.

**Table 1. Diagnostic Subtypes According to DSM-IV by Gender
Full Analysis Set**

DSM-IV ADHD diagnosis	Number (%) of patients					
	Female		Male		Total	
	N=34 (100%)		N=125 (100%)		N=159 (100%)	
Combined type	13	(38.2)	68	(54.4)	81	(50.9)
Predominantly inattentive type	20	(58.8)	53	(42.4)	73	(45.9)
ADHD not otherwise specified	1	(2.9)	4	(3.2)	5	(3.1)

Abbreviations: ADHD=Attention-Deficit/Hyperactivity Disorder; DSM-IV=*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*TM; N = total number of patients.

Combined type ADHD was the most frequent DSM-IV diagnosis (81, 50.9%), followed by predominantly inattentive type ADHD (73, 45.9%). No patients had predominantly hyperactive-impulsive type ADHD, and in 5 (3.1%) patients the ADHD type was not otherwise specified (not further reported). The proportion of combined type ADHD patients was 54.4% in male patients (68/125) and 38.2% in female patients (13/34), and the proportion of predominantly inattentive type ADHD patients was 58.8% in female patients (20/34) and 42.4% in male patients (53/125).

The patients' mean age ($\pm$ SD) at baseline was 14.1 $\pm$ 1.5 years. Symptoms of ADHD first occurred at a mean age of 4.3 $\pm$ 2.2 years, and ADHD was first diagnosed at a mean age of 9.8 $\pm$ 2.8 years. A mean interval of 5.5 $\pm$ 3.4 years had elapsed between the first occurrence of ADHD symptoms and the first diagnosis of ADHD. Details of age characteristics by gender and DSM-IV diagnostic subtypes can be found in Table 2 and Table 3, respectively.

Table 2. Age of Patients at Baseline, First Occurrence of ADHD Symptoms and First Diagnosis of ADHD, and Time Difference between First Occurrence and Diagnosis by Gender, Full Analysis Set

Variable (years)	Female N=34	Male N=125	Total N=159
Age at baseline			
Median	14.0	14.0	14.0
Mean $\pm$ standard deviation	14.4 $\pm$ 1.7	14.0 $\pm$ 1.5	14.1 $\pm$ 1.5
95% confidence interval	[13.8;15.0]	[13.7;14.2]	[13.8;14.3]
Age at first occurrence			
Median	4.8	4.4	4.4
Mean $\pm$ standard deviation	4.9 $\pm$ 2.5	4.2 $\pm$ 2.1	4.3 $\pm$ 2.2
95% confidence interval	[4.1;5.8]	[3.8;4.6]	[4.0;4.7]
Age at first diagnosis			
Median	10.0	9.0	9.2
Mean $\pm$ standard deviation	10.7 $\pm$ 2.9	9.6 $\pm$ 2.7	9.8 $\pm$ 2.8
95% confidence interval	[9.7;11.7]	[9.1;10.0]	[9.4;10.2]
Time difference			
Median	5.3	5.0	5.0
Mean $\pm$ standard deviation	5.8 $\pm$ 3.6	5.4 $\pm$ 3.4	5.5 $\pm$ 3.4
95% confidence interval	[4.5;7.0]	[4.8;6.0]	[4.9;6.0]

Abbreviations: ADHD=Attention-Deficit/Hyperactivity Disorder; N = total number of patients.

Table 3. Age of Patients at Baseline, First Occurrence of ADHD Symptoms and First Diagnosis of ADHD, and Time Difference between First Occurrence and Diagnosis by DSM-IV Diagnosis, Full Analysis Set

Variable (years)	Combined type ADHD N=81	Predominantly inattentive type ADHD N=73
Age at baseline		
Median	14.0	14.0
Mean $\pm$ standard deviation	13.9 $\pm$ 1.5	14.2 $\pm$ 1.5
95% confidence interval	[13.5;14.2]	[13.9;14.6]
Age at first occurrence		
Median	4.2	4.8
Mean $\pm$ standard deviation	4.1 $\pm$ 2.1	4.5 $\pm$ 2.0
95% confidence interval	[3.6;4.5]	[4.0;5.0]
Age at first diagnosis		
Median	8.9	9.3
Mean $\pm$ standard deviation	9.5 $\pm$ 2.7	10.1 $\pm$ 2.9
95% confidence interval	[8.9;10.1]	[9.4;10.8]
Time difference		
Median	5.3	4.9
Mean $\pm$ standard deviation	5.4 $\pm$ 3.3	5.6 $\pm$ 3.4
95% confidence interval	[4.7;6.1]	[4.8;6.4]

Abbreviations: ADHD=Attention-Deficit/Hyperactivity Disorder; DSM-IV=*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*TM.

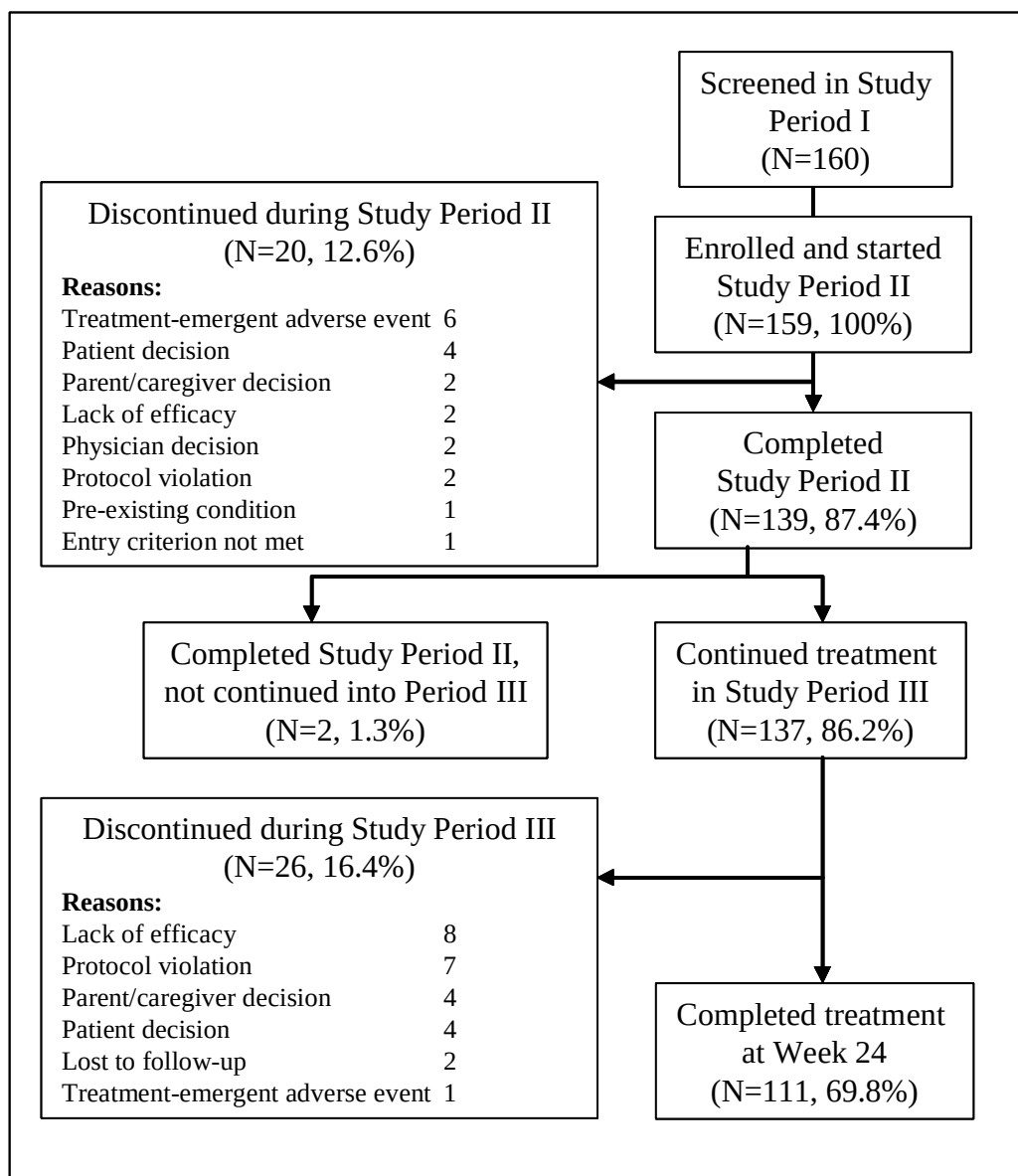
Overall, 137 (86.2%) patients had had previous treatment for ADHD (males 109, 87.2%; females 28, 82.4%). A total of 67 (82.7%) patients with combined type ADHD and 65 (89.0%) patients with predominantly inattentive type ADHD had been treated previously for ADHD.

Overall, 99 (62.3%) patients were given any concomitant therapy, most frequently pharmacological therapy. Concomitant medications used in more than 5% of all patients included paracetamol (13; 8.2%), ibuprofen (12; 7.5%), acetylcysteine (11; 6.9%), and acetylsalicylic acid (10; 6.3%).

The mean daily prescribed dose of atomoxetine remained in the same range of 1.18 or 1.19 mg/kg/day at each visit after the first week of up-titration, respectively, up to the final prescription at Week 16 (for the last visit interval, i.e., Weeks 17–24). The mean final prescribed dose at Week 16 was 1.19 ± 0.13 mg/kg/day. A total of 19 (11.9%) patients were noncompliant with respect to medication at some time during the study.

Patient Disposition

Of the 159 patients enrolled, 137 (86.2%) continued into Study Period III and 111 (69.8%) completed treatment at Week 24. Figure 1 summarizes patient disposition, including the reasons for discontinuation.



Abbreviation: N = total number of patients.

Note: At the end of the Study Period II (Visit 7), it was decided whether the patient should continue into the Extension Period (Study Period III). This decision was at the investigator's discretion, based on the effectiveness and tolerability of treatment as well as parents' and patients' wishes.

Figure 1. Patient disposition and reasons for discontinuation.

For 2 (1.3%) patients who completed Study Period II, the physician decided they should not continue into Study Period III. In addition, 20 (12.6%) patients were withdrawn during Study Period II, and 26 (16.4%) patients were withdrawn during Study Period III. The main reasons for withdrawal were lack of efficacy in 10 (6.3%) patients overall,

protocol violations in 9 (5.7%) patients overall, patient decision in 8 (5.0%) patients and treatment-emergent adverse events in 7 (4.4%) overall.

Primary Effectiveness Measure

The primary objective of this study was to compare the perception of general effectiveness and tolerability (ADHD-related difficulties) of atomoxetine between patients, their parents/primary caregivers, and their physicians. The GIPD Scale was used to assess ADHD-related difficulties, and was completed by all three rater groups. The degree of agreement between the mean scores was also assessed using Cohen's kappa. The primary assessment timepoints were baseline, Week 8, and Week 24.

Table 4 shows details of the GIPD Total Score, the GIPD Score Item 1 (ADHD-related difficulties in the morning), and GIPD Score Item 4 (ADHD-related difficulties in the evening).

**Table 4. GIPD Scores at Baseline, Week 8, and Week 24
Full Analysis Set (LOCF)**

Time-point	Patient			Parent ^a			Physician		
	N	Mean ± SD	95% CI	N	Mean ± SD	95% CI	N	Mean ± SD	95% CI
<i>GIPD Total Score (Sum of Items 1-5)</i>									
BL	156	12.5±5.8	11.6;13.5	155	17.2±6.3	16.2;18.2	155	18.8±6.0	17.8;19.8
Wk 8	158	9.6±5.6	8.7;10.5	150	11.4±5.7	10.5;12.4	158	11.0±5.5	10.2;11.9
Wk 24	158	9.9±6.1	8.9;10.9	153	11.7±6.0	10.7;12.7	158	12.1±6.5	11.0;13.1
<i>GIPD Score Item 1 (ADHD-related difficulties in the morning)</i>									
BL	158	2.5±1.6	2.3;2.8	157	3.1±1.7	2.8;3.4	158	3.3±1.5	3.1;3.5
Wk 8	158	2.0±1.4	1.8;2.2	150	2.1±1.4	1.9;2.3	158	1.9±1.2	1.7;2.1
Wk 24	158	1.9±1.5	1.7;2.2	153	2.1±1.4	1.9;2.4	158	2.2±1.4	2.0;2.4
<i>GIPD Score Item 4 (ADHD-related difficulties in the evening)</i>									
BL	158	2.2±1.5	2.0;2.4	158	3.5±1.6	3.3;3.7	158	3.9±1.6	3.6;4.1
Wk 8	158	1.8±1.3	1.6;2.0	150	2.2±1.3	2.0;2.4	158	2.2±1.3	2.0;2.4
Wk 24	158	1.9±1.3	1.7;2.1	153	2.3±1.4	2.1;2.6	158	2.4±1.6	2.2;2.7

^a LOCF-BR for parent-rated scores, i.e., LOCF for all ratings made by the same parent.

Abbreviations: ADHD=Attention-Deficit/Hyperactivity Disorder; BL=Baseline; CI=Confidence interval; GIPD=Global Impression of Perceived Difficulties; LOCF=Last observation carried forward; LOCF-BR=Last observation carried forward, baseline rater; N = total number of patients; SD=standard deviation; Wk=Week.

At baseline, the mean patient-rated total score (±SD) was the lowest at 12.5±5.8, the parent-rated score was intermediate at 17.2±6.3, and the physician-rated score was highest at 18.8±6.0. The mean patient-rated baseline total score differed statistically significantly (non-overlapping 95% CIs) from the parent-rated and physician-rated scores, but the latter two did not differ statistically significantly. All scores improved statistically significantly up to Week 8 but did not differ statistically significantly between rater groups (Table 4). The improvement was maintained at Week 24.

Morning and evening ADHD-related difficulties both improved statistically significantly from baseline to Week 8 in all three rater groups (non-overlapping 95% CIs). Again, this improvement was maintained at Week 24 (Table 4).

There was no statistically significant difference in the rating of ADHD-related difficulties between combined type ADHD patients and predominantly inattentive type ADHD patients in any of the three rater groups. At baseline, parents and physicians rated ADHD-related difficulties statistically significantly higher than patients in both combined type and predominantly inattentive type ADHD patients (GIPD total score for combined type ADHD patients: physician-rated: 19.6 ± 6.0 , 95% CI [18.3;21.0]; patient-rated: 12.6 ± 5.2 , 95% CI [11.4;13.8]).

Analysis of agreement between rater groups for GIPD scores: The agreement was highest between parent- and physician-rated scores (kappa for agreement at baseline [95% CI]: 0.53 [0.45;0.62]) and low between patient- and physician- (0.19 [0.11;0.26]) and patient- and parent-rated (0.22 [0.13;0.31]) scores. Table 5 shows details of the degree of agreement between each rater group at baseline, Week 8, and Week 24 for the GIPD Total Score, GIPD Item 1 (Morning) Score, and GIPD Item 4 (Evening) Score.

Table 5. Agreement Between Each Rater Group at Baseline, Week 8, and Week 24 for GIPD Total Score, GIPD Item 1 (Morning) Score and GIPD Item 4 (Evening) Score, Weighted Kappa Statistics, Full Analysis Set

Timepoint	Kappa statistic, 95% Confidence interval								
	Patient–Parent			Patient–Physician			Parent–Physician		
	N	K ^a	95% CI	N	K ^a	95% CI	N	K ^a	95% CI
<i>GIPD Total Score</i>									
Baseline	153	0.22	0.13;0.31	154	0.19	0.11;0.26	153	0.53	0.45;0.62
Week 8	111	0.32	0.21;0.43	126	0.38	0.28;0.49	112	0.54	0.44;0.63
Week 24	103	0.36	0.26;0.47	111	0.43	0.32;0.53	104	0.64	0.55;0.73
<i>GIPD Score Item 1 (ADHD-related difficulties in the morning)</i>									
Baseline	157	0.25	0.15;0.35	158	0.30	0.21;0.39	157	0.55	0.47;0.64
Week 8	119	0.40	0.26;0.54	132	0.38	0.26;0.49	119	0.53	0.40;0.67
Week 24	105	0.29	0.11;0.47	112	0.42	0.29;0.55	105	0.59	0.48;0.70
<i>GIPD Score Item 4 (ADHD-related difficulties in the evening)</i>									
Baseline	158	0.10	0.02;0.18	158	0.16	0.09;0.23	158	0.50	0.40;0.60
Week 8	118	0.21	0.09;0.34	131	0.29	0.17;0.41	119	0.45	0.32;0.57
Week 24	104	0.28	0.16;0.41	111	0.37	0.24;0.51	105	0.46	0.34;0.58

^a K: weighted Kappa coefficient; analysis based on OC data for patient- and physician-ratings, and OC-BR for parents.

Abbreviations: ADHD=Attention-Deficit/Hyperactivity Disorder; CI=confidence interval; GIPD=Global Impression of Perceived Difficulties; N = total number of patients; OC=last observed value within a visit interval was taken for this visit interval; OC-BR=values not rated by the baseline rater were deleted and then the last value from the baseline rater within a visit interval was chosen, if present, otherwise the value was dropped.

Changes in GIPD scores over time: Changes in GIPD scores over time are presented in Figures 2–4 (observed cases, vertical bars indicate 95% CIs). Mean GIPD total scores decreased statistically significantly (non-overlapping 95% CIs) in all three rater groups from baseline to Week 8. The smallest improvements were given by patients, greater improvements by parents, and the greatest improvement by physicians (LOCF/LOCF-baseline rater (BR), mean changes in GIPD total scores: patients, LOCF, -2.9 ± 5.9 ; parents, LOCF-BR, -5.9 ± 6.8 ; physicians, LOCF, -7.8 ± 6.9). These improvements were maintained at Week 24 (Figure 2). Morning and evening problems both decreased statistically significantly from baseline to Week 8 in all three rater groups. Again, this improvement was maintained at Week 24 (Figures 3 and 4).

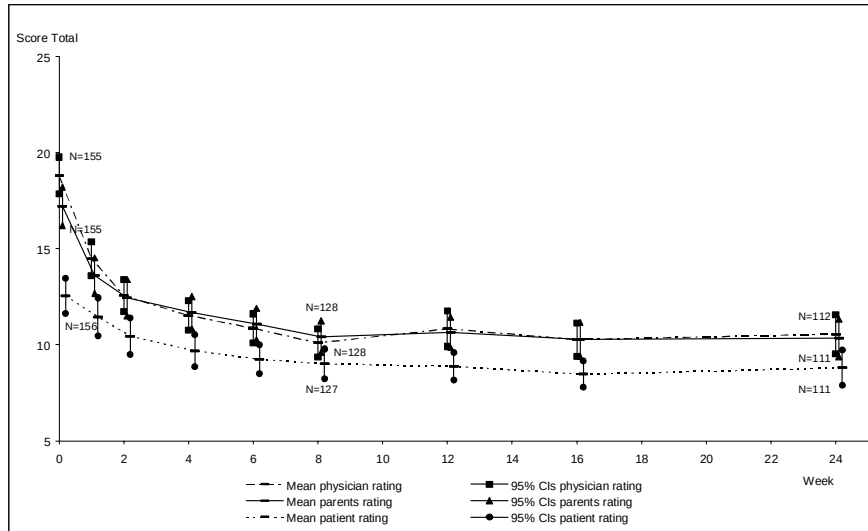


Figure 2. GIPD mean total scores over time for the full analysis set; OC analysis.

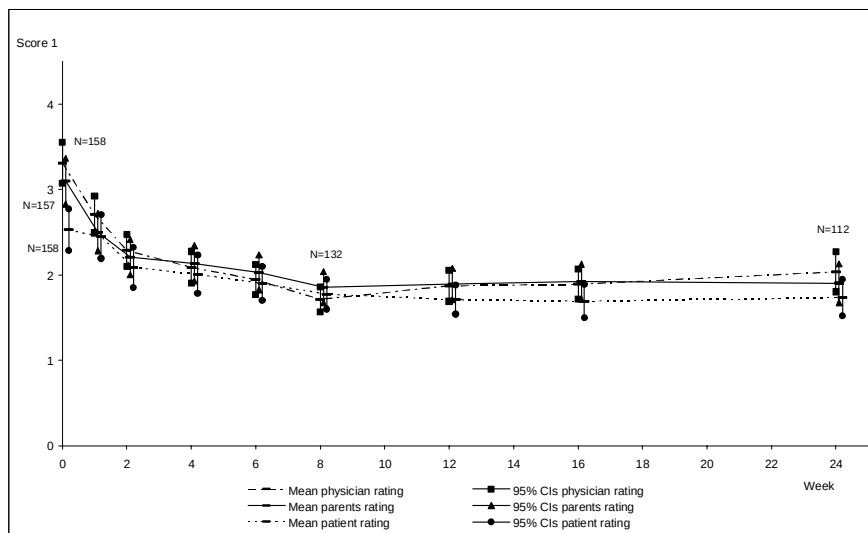


Figure 3. GIPD mean scores for Item 1 (morning) over time for the full analysis set; OC analysis.

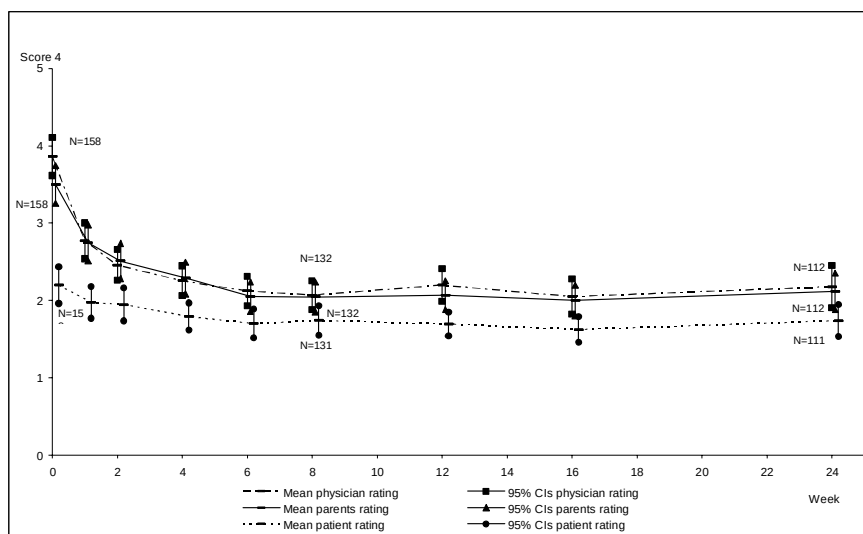


Figure 4. GIPD mean scores for Item 4 (evening) over time for the full analysis set; OC analysis.

Abbreviations in Figures 2–4: CI=confidence interval; GIPD=Global Impression of Perceived Difficulties; N = total number of patients; OC=observed cases, last observed value within a visit interval was taken for this visit interval.

Secondary Effectiveness Measures

The ADHDRS-IV-Parent:Inv, CGI-S-ADHD, WREMB-R-Inv evening and morning scores, and Rosenberg SES scores all improved statistically significantly and consistently from baseline to Week 8 (non-overlapping 95% CIs, Table 6). The improvements were maintained at Week 24. On the CGI-S-ADHD Scale, the proportion of patients rated as at least “markedly ill” decreased from 109 (68.6%) at baseline to 32 (20.1%) at Week 8 and 39 (24.5%) at Week 24. In terms of CGI-I-ADHD, 95 (59.8%) patients were rated as “much or very much improved” at Week 8, and 97 (61.0%) at Week 24.

With all instruments, combined type ADHD patients had numerically higher ratings than predominantly inattentive type ADHD patients at baseline, Week 8 and Week 24 (numerically lower for the Rosenberg SES). The ADHD RS-IV-Parent:Inv Score was statistically significantly higher for combined type patients compared with predominantly inattentive type patients at baseline, Week 8 and Week 24. With all instruments, except the Rosenberg SES, statistically significant improvements were found from baseline to Week 8 in both subgroups. Mean Rosenberg SES scores increased in both subgroups, but the improvement was not statistically significant in the predominantly inattentive type ADHD group (overlapping 95% CIs). In terms of CGI-I-ADHD, 56.8% of combined type and 62.5% of predominantly inattentive type ADHD patients were rated as “much or very much improved” at Week 8 (61.7% and 61.1% at Week 24).

Table 6. ADHDRS-IV-Parent:Inv, CGI-ADHD, WREMB-R-Inv, and Rosenberg SES Scores at Baseline, Week 8 and 24 Full Analysis Set (LOCF)

Time-point	Total			ADHD subtype					
	N	Mean ± SD	95% CI	Combined			Predom. inattentive		
				N	Mean ± SD	95% CI	N	Mean ± SD	95% CI
ADHDRS-IV-Parent:Inv Score									
BL	158	28.4±10.1	26.8;29.9	80	32.4± 9.8	30.2;34.5	73	24.3±8.4	22.4;26.3
Wk 8	158	12.9± 9.5	11.4;14.4	81	15.4±11.1	13.0;17.9	72	10.3±6.5	8.8;11.8
Wk 24	158	13.3±10.3	11.7;15.0	81	15.7±11.3	13.2;18.2	72	11.1±8.6	9.1;13.1
CGI-S-ADHD Score									
BL	158	4.8±0.9	4.7;5.0	80	5.0±0.9	4.8;5.2	73	4.7±0.8	4.5;4.9
Wk 8	159	3.4±1.2	3.2;3.6	81	3.6±1.2	3.3;3.8	73	3.2±1.1	3.0;3.5
Wk 24	159	3.3±1.4	3.1;3.5	81	3.4±1.5	3.1;3.8	73	3.3±1.3	3.0;3.6
CGI-I-ADHD Score									
Wk 8	158	2.6±1.3	2.4;2.8	81	2.7±1.3	2.4;3.0	72	2.4±1.1	2.2;2.7
Wk 24	158	2.6±1.5	2.4;2.8	81	2.6±1.5	2.3;3.0	72	2.5±1.4	2.2;2.9
WREMB-R-Inv – Evening Score (8 items)									
BL	158	12.2±5.1	11.4;13.0	80	13.4±5.0	12.3;14.5	73	11.0±4.9	9.9;12.2
Wk 8	158	4.9±4.5	4.2;5.6	81	5.7±4.9	4.6;6.8	72	4.2±4.1	3.3;5.2
Wk 24	158	5.7±5.1	4.9;6.5	81	6.4±5.3	5.2;7.5	72	5.3±5.0	4.1;6.4
WREMB-R-Inv – Morning Score (3 items)									
BL	158	3.8±2.5	3.4;4.2	80	4.1±2.4	3.5;4.6	73	3.6±2.4	3.0;4.1
Wk 8	158	1.4±1.8	1.1;1.7	81	1.7±1.9	1.3;2.1	72	1.1±1.5	0.7;1.4
Wk 24	158	1.7±2.1	1.4;2.0	81	1.9±2.2	1.4;2.4	72	1.5±1.9	1.0;1.9
Rosenberg SES Score									
BL	154	20.4±5.1	19.6;21.2	78	19.5±5.2	18.3;20.6	71	21.6±5.0	20.4;22.8
Wk 8	158	22.9±5.9	22.0;23.8	81	22.8±5.7	21.6;24.1	72	23.4±6.1	21.9;24.8
Wk 24	158	23.1±5.9	22.2;24.0	81	22.9±6.0	21.5;24.2	72	23.8±5.6	22.5; 25.1

Abbreviations: ADHDRS-IV-Parent:Inv=Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored; BL=Baseline; CGI-I-ADHD=Clinical Global Impression – Improvement – Attention Deficit/Hyperactivity Disorder; CGI-S-ADHD=Clinical Global Impression – Severity – Attention Deficit/Hyperactivity Disorder; CI=confidence interval; LOCF=Last observation carried forward; Rosenberg SES=Rosenberg Self-Esteem Scale; N = total number of patients; Predom = predominantly; SD=standard deviation; Wk=Week; WREMB-R-INV=Weekly Ratings of Evening and Morning Behavior-Revised.

The ADHDRS-IV-Parent:Inv mean score over time by gender is shown in Figure 5.

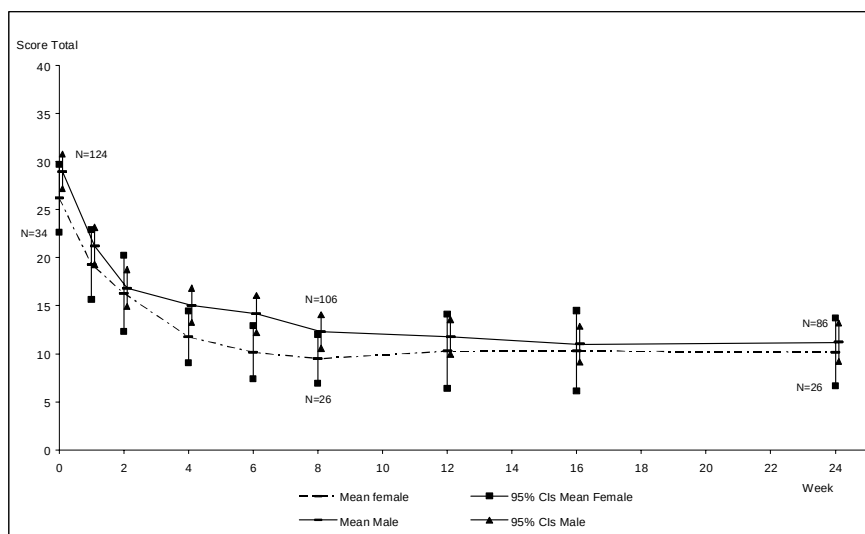


Figure 5. ADHDRS-IV-Parent:Inv mean score over time by gender for the full analysis set; OC analysis.

Note: Vertical bars indicate 95% confidence intervals.

Abbreviations: ADHDRS-IV-Parent:Inv=Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored; CI = confidence interval; N = total number of patients; OC=observed cases, last observed value within a visit interval was taken for this visit interval.

Safety

Treatment-emergent adverse events (TEAEs) were reported in 124/159 (78.0%) patients and were considered as possibly related to study drug in 82/159 (51.6%) patients. Table 7 shows an overview of adverse events reported during the study.

Table 7. Overview of Adverse Events, Full Analysis Set

Type of adverse event	Number (%) of patients N=159 (100%)	
Deaths	0	(0)
Serious adverse events	8	(5.0)
Serious adverse events (possibly, probably, or definitely related to study drug treatment as judged by the investigator)	2	(1.3)
Treatment-emergent adverse events (TEAEs) leading to discontinuation	7	(4.4)
Treatment-emergent adverse events (TEAEs)	124	(78.0)
Adverse reactions (TEAEs possibly, probably, or definitely related to study drug as judged by the investigator)	82	(51.6)

Abbreviation: N = total number of patients.

Serious adverse events were reported in 8 patients and were considered possibly related to study drug in 2 of these patients (1 patient with severe vomiting; 1 patient with suspected polyendocrine autoimmune syndrome developed peripheral vasoconstriction with dark coloration of extremities and marbled skin, accompanied by abdominal pain, dizziness, lack of concentration, feeling of absence, and tiredness). In 7 (4.4%) patients, treatment-emergent adverse events led to discontinuation from the study (alopecia, decreased appetite, drug abuse, fatigue, vasoconstriction, vertigo, and vomiting in 1 [0.6%] patient each). One (0.6%) additional patient was discontinued in Study Period II due to a pre-existing condition (increased blood bilirubin).

Table 8 presents the TEAEs reported in at least 5% of patients.

Table 8. Treatment-Emergent Adverse Events Occurring in ≥5% of Patients by Preferred Term, Full Analysis Set

Adverse Event	Number (%) of patients	
	N=159 (100%)	
Fatigue	45	(28.3)
Headache	38	(23.9)
Nausea	30	(18.9)
Nasopharyngitis	21	(13.2)
Vomiting	21	(13.2)
Abdominal pain upper	12	(7.5)
Decreased appetite	12	(7.5)
Dizziness	12	(7.5)
Diarrhea	9	(5.7)
Abdominal pain	8	(5.0)
Sleep disorder	8	(5.0)
Vertigo	8	(5.0)

Abbreviation: N = total number of patients.

The most common spontaneously reported TEAEs were fatigue (28.3%), headache (23.9%), nausea (18.9%), nasopharyngitis and vomiting (13.2% each), and upper abdominal pain, decreased appetite, and dizziness (7.5% each).

Table 9 shows the TEAEs considered at least as possibly related to study drug by the investigator, reported in at least 3% of patients.

Table 9. Treatment-Emergent Adverse Events Classified as Related to Study Drug Occurring in $\geq 3\%$ of Patients by Preferred Term, Full Analysis Set

Adverse Event	Number (%) of patients	
	N=159 (100%)	
Fatigue	42	(26.4)
Nausea	22	(13.8)
Headache	15	(9.4)
Abdominal pain, upper	11	(6.9)
Decreased appetite	11	(6.9)
Dizziness	9	(5.7)
Vomiting	9	(5.7)
Sleep disorder	7	(4.4)
Abdominal pain	6	(3.8)
Weight decreased	6	(3.8)
Hypersomnia	5	(3.1)
Somnolence	5	(3.1)
Vertigo	5	(3.1)

Abbreviation: N = total number of patients.

The most common TEAEs classified as related to study drug by the investigator were fatigue (26.4%), nausea (13.8%), headache (9.4%), upper abdominal pain and decreased appetite (6.9% each), and dizziness and vomiting (5.7%) each.

Clinical laboratory measurements and changes in vital signs were unremarkable; there were no clinically relevant changes and their evaluation gave no cause for any safety concerns.

PAERS: The PAERS questionnaire assesses the frequency and severity of 48 solicited events frequently observed in pediatric patient populations under treatment with psychotropic medication. Because several items represent symptoms of ADHD, the patient-, physician-, and parent-rated PAERS total scores were high at baseline and decreased over time (e.g., mean total patient-rated score: Baseline, 19.0 ± 14.5 ; Week 8, 11.4 ± 13.4 ; Week 24, 11.2 ± 13.3).

Pooled Analysis of Studies B4Z-SB-LYDD and B4Z-SB-LYDE

Parallel to this study B4Z-SB-LYDE in adolescents, a similarly designed study in children (B4Z-SB-LYDD; CT#9496) was performed. The pooled dataset from Studies LYDE and LYDD comprised a sample of 421 patients aged 6–17 years. In the pooled sample, the mean patient-rated GIPD total score ($\pm$ SD) was the lowest at 13.1 ± 5.8 , the parent-rated score was intermediate at 18.6 ± 6.1 , and the physician-rated score was highest at 20.3 ± 5.9 . All 3 ratings differed statistically significantly at baseline (non-overlapping 95% CIs), but the parent- and physician-rated scores did not differ statistically significantly at Week 8 and Week 24. The analysis of agreement by Cohen kappa statistics also showed that agreement was highest between parent- and physician-

rated scores (Cohen's kappa for agreement at baseline [95% CI]: 0.52 [0.47;0.57]), and low between patient- and parent-rated scores (0.16 [0.12;0.21]) or between patient- and physician-rated scores (0.14 [0.11;0.18]). All effectiveness scores used, including the ADHDRS-IV-Parent:Inv, CGI-S-ADHD and WREMB-R-Inv scores, improved consistently and statistically significantly from baseline to Week 8. Improvements were maintained at Week 24.

In the pooled sample, treatment-emergent adverse events were reported in 331/421 (76.3%) patients, which were considered as possibly related to study drug in 207/421 (49.2%) patients. The most common spontaneously reported adverse events were fatigue (25.2%, related 22.3%), headache (20.4%, related 8.6%), nausea (18.3%, related 13.5%), vomiting (12.4%, related 5.0%), and upper abdominal pain (10.0%, related 7.1%). Laboratory investigations and vital signs were not clinically significant and gave no cause for concern.

Summary ID# 7649

Clinical Study Summary: Study B4Z-CA-LYCS

A Phase IIIb Open-label Trial of Atomoxetine Hydrochloride to Evaluate Academic Outcome in Children Ages 8 to 11 Years with Attention-Deficit/Hyperactivity Disorder

Date summary approved by Lilly: 26 June 2007

Brief Summary of Results

The primary objective of this 1-year, Phase 3b, multicenter, open-label study was to assess, in medication-naïve patients treated with atomoxetine, the correlation between change from baseline (premedicated) to 1 year in attention-deficit/hyperactivity disorder (ADHD) symptoms as measured by the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) total score, and change from baseline to 1 year in academic achievement as measured by the total of the composite scores of the Broad Reading, Broad Math, and Broad Written Language subtests of the Woodcock-Johnson Tests of Achievement® (WJ III®).

- A total of 105 patients were enrolled in the study, of which 83 (79.0%) patients completed Visit 9 (6 months), and 72 (68.6%) patients completed the study (1 year).
- The majority of patients were male (72.4%) and Caucasian (77.1%). The mean age was 9.3 years (95% CI: 9.2, 9.5). A total of 70.5% and 29.5% of patients were diagnosed with Combined and Inattentive subtypes of ADHD respectively.

- The correlation of change from baseline between ADHDRS-IV-Parent:Inv and WJ III for 1-year completers was -.066 and not statistically significant ($p=.600$). A negative correlation indicates agreement between both scales.
- The mean change from baseline in ADHDRS-IV-Parent:Inv for 1-year completers was -21.8 ($n=66$, 95% CI: -24.6, -18.9, $p<.001$), indicating an improvement.
- The mean increase in raw WJ III total composite score at 1 year was 37.6 ($n=66$, 95% CI: 32.3, 42.9, $p<.001$), indicating an improvement. In terms of subtests, improvements were demonstrated on all WJ III subtests in raw scores, with all changes from baseline statistically significant ($p<.001$). For patients completing the 6-month visit, correlation between Letter-Word Identification and ADHDRS-IV-Parent:Inv was -.296 ($p=.011$). Disagreement or nonsignificant correlations were observed for all other subitems.
- Improvements were observed in the raw scores of all Behavior Rating Inventory of Executive Function™ (BRIEF™) scales at 1 year. Correlations of .6 or greater were observed between the ADHDRS-IV-Parent:Inv and Global Executive Composite, Metacognition, and Behavioral Regulation indices. The correlations between ADHDRS-IV-Parent:Inv and each clinical scale were all statistically significant ($p\leq.05$) and ranged from .392 to .645.
- Correlations between the Behavior Assessment System for Children (BASC) raw scores at 1 year and ADHDRS-IV-Parent:Inv were statistically significant ($p\leq.05$) for most scales within the Parent Rating Scale-Child (PRS-C), with the exception of Somatization, Anxiety, and Leadership. For the Self-Report of Personality-Child (SRP-C), correlations with ADHDRS-IV-Parent:Inv were not statistically significant with the following exceptions: Attitude to School ($r = -.329$, $p=.009$), Attitude to Teachers ($r = -.249$, $p=.049$), and Relations with Parents ($r = .283$, $p=.026$).
- The mean change from baseline in the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) for 1-year completers was -0.42 (95% CI: -0.54, -0.31, $p<.001$). The correlation between improvement in ADHDRS-IV-Parent:Inv and improvement in WFIRS-P was .520 ($p<.001$).
- Symptom improvement observed with the ADHDRS-IV-Parent:Inv was in agreement with the Clinical Global Impressions-ADHD-Severity scale (CGI-ADHD-S), where the mean decrease in severity was 2.3 (95% CI: -2.6, -2.0, $p<.001$). The correlation between these two measures was .672 ($p<.001$).

- One serious adverse event, suicidal ideation, occurred at 6 months, which the investigator believed was possibly related to study medication. There were no deaths during this study. The most common treatment-emergent adverse events were decreased appetite, headache, vomiting, nausea, upper abdominal pain, and fatigue.

Title of Study: A Phase IIIb Open-label Trial of Atomoxetine Hydrochloride to Evaluate Academic Outcome in Children Ages 8 to 11 Years with Attention-Deficit/Hyperactivity Disorder.	
Investigators: This multicenter study included 10 principal investigators.	
Study Centers: This study was conducted at 10 study centers in one country.	
Length of Study: 22 months Date of first patient visit: 12 August 2004 Date of last patient visit: 29 June 2006	Phase of Development: 3b
Objectives: The primary objective of this study was to assess the correlation of change from baseline (premedicated) to 1 year in attention-deficit/hyperactivity disorder (ADHD) symptoms as measured by the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) total score (DuPaul et al. 1998; Faries et al. 2001) with change from baseline to 1 year in academic achievement as measured by the total of the Broad Reading, Broad Math, and Broad Written Language subtest composite scores of the Woodcock-Johnson Tests of Achievement® (WJ III®; Woodcock et al. 2000) in medication-naïve patients treated with atomoxetine. The secondary objectives of the study were as follows: • To assess the correlation of change from baseline to 1 year, or study discontinuation, in ADHD symptoms as measured by the ADHDRS-IV-Parent:Inv with change from baseline in each of the academic achievement composite scores of the Broad Reading, Broad Math, and Broad Written Language subtests of the WJ III. • To assess the change from baseline to endpoint in academic achievement of patients treated with atomoxetine as measured by the total of the composite scores of the Broad Reading, Broad Math, and Broad Written Language subtests of the WJ III. • To assess the change from baseline to endpoint in academic achievement of patients treated with atomoxetine as assessed by the composite scores and the items in the composite scores (Broad Reading: letter word identification, reading fluency, passage comprehension; Broad Math: calculation, math fluency, applied problems; Broad Written Language: spelling, writing fluency, writing samples) of the WJ III. • To assess change from baseline to 1 year, or study discontinuation, in executive functioning as assessed by the Behavior Rating Inventory of Executive Function™ (BRIEF™; Gioia et al. 2000). • To assess the change from baseline to 1 year, or study discontinuation, in behavior and emotions as assessed by the Behavior Assessment System for Children (BASC; Reynolds and Kamphaus 1992) rating scales completed by the child's parent and the child. • To assess the efficacy of atomoxetine treatment on the core symptoms of ADHD by the change from baseline to 1 year, or study discontinuation, in the total score of the ADHDRS-IV-Parent:Inv and the Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity scale (CGI-ADHD-S; Guy 1976). • To assess the relationships between change in core ADHD symptoms and change in functional outcome at home, at school, in social interactions, in activities of daily living and health, and in risk-taking and general well-being as assessed by the parent-completed questionnaire: Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) at baseline and at 1 year, or at study discontinuation. • To assess the relationships and inter-relationships between changes in the secondary objective measures and changes in core ADHD symptoms.	
Study Design: This was a Phase 3b, multicenter, single-arm, 1-year, open-label study of atomoxetine in outpatients aged 8 to 11 years diagnosed with ADHD.	

Number of Patients: Planned: 100 Enrolled: 105 Completed: 72
Diagnosis and Main Criteria for Inclusion: Male or female outpatients of at least 8 years of age but less than 11 years of age at Visit 1, who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision™ (DSM-IV-TR™) criteria for ADHD and had a symptom severity threshold of at least 1.5 standard deviations above the age and gender norm for total score on the ADHDRS-IV-Parent:Inv. Patients were naïve to medications used to treat ADHD. Patients with current or past history of bipolar I or II disorder, psychosis, autism, Asperger's syndrome, pervasive developmental disorder, conduct disorder, seizure disorder, or serious medical conditions were excluded.
Test Product, Dose, and Mode of Administration: Atomoxetine was initially administered for 7 days at 0.5 mg/kg/day as a single daily dose, followed by an increase to approximately 1.2 mg/kg/day. Investigators were allowed to adjust the atomoxetine dose between 0.8 mg/kg/day and 1.4 mg/kg/day based on efficacy and tolerability.
Duration of Treatment: 1 year
Variables: Efficacy: Academic achievement was measured by WJ III. ADHD symptoms were assessed using ADHDRS-IV-Parent:Inv. The WJ III combined raw scores of the Broad Reading, Broad Math, and Broad Written Language subtests and the ADHDRS-IV-Parent:Inv total score were the primary outcome variables. The WJ III Broad Reading, Broad Math, and Broad Written Language subscores and the ADHDRS-IV-Parent:Inv Inattention and Hyperactivity-Impulsivity subscale scores were considered secondary outcomes variables. Other secondary outcome variables were: BRIEF total and subscale scores, which measured executive functioning; BASC, which assessed a child's behavior and feelings (both the parent rating scales [PRS-C] and self-report of personality [SRP-C] were used); CGI-ADHD-S, which assessed global severity of ADHD symptoms. WFIRS-P total and subscales measured the child's functioning. In addition, raw scores, T-scores, and percentile rankings of the scales at baseline and endpoint were presented where available. When change from baseline was measured, only raw scores were used. Safety: Assessment of adverse events and vital signs.
Evaluation Methods: Statistical: The primary efficacy analysis utilized the Pearson's correlation coefficient between the change from baseline to 1 year in ADHDRS-IV-Parent:Inv total score and the change from baseline to 1 year of the combined raw scores of the Broad Reading, Broad Math, and Broad Written Language subtests of the WJ III. The primary analysis population was 1-year completers. For secondary analyses, any change from baseline analyses were performed using both 1-year completers and patients completing the 6-month visit who were still on study medication. When the 1-year visit was missing; a last observation carried forward approach was used. Summary statistics were computed on change scores including mean, median, standard deviation, and the two-sided 95% confidence interval. Change from baseline was tested using a paired t-test or Wilcoxon signed rank test at two-sided alpha of 0.05.

Study Design:

The schematic displayed in Figure 1 represents the study design.

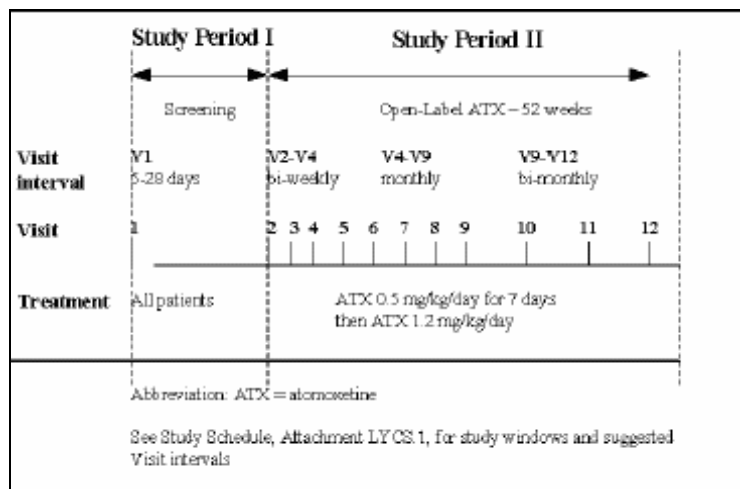


Figure 1. Study design.

Results:

Patient Characteristics

Table 1 summarizes the baseline characteristics of all patients enrolled in this study.

Table 1. Patient Characteristics at Baseline

Variable	N=105
Age (years), mean (95% CI)	9.3 (9.2, 9.5)
Gender [n (%)]	
Male	76 (72.4)
Female	29 (27.6)
Race [n (%)]	
Caucasian	81 (77.1)
African Descent	5 (4.8)
East Asian	4 (3.8)
Western Asian	5 (4.8)
Other	10 (9.5)
Education, current grade [n (%)]	
Grade 2	15 (14.3)
Grade 3	28 (26.7)
Grade 4	39 (37.1)
Grade 5	22 (21.0)
Grade 6	1 (1.0)
ADHD Subtype [n (%)]	
Inattentive	31 (29.5)
Combined	74 (70.5)

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; n = number of patients; N = total number of patients.

Patient Disposition

A total of 105 patients were enrolled in the study. Of these, 72 patients (68.6%) completed the study and 33 patients (31.4%) discontinued early. Table 2 displays a summary of the reasons for discontinuation.

Table 2. Reasons for Discontinuation

Reason for Discontinuation [n (%)]	N=105
Adverse event	6 (5.7)
Lack of efficacy, patient/caregiver perception	3 (2.9)
Lack of efficacy, physician perception	1 (1.0)
Lack of efficacy, patient/caregiver and physician perception	10 (9.5)
Personal conflict or other patient/caregiver decision	4 (3.8)
Protocol violation	6 (5.7)
Lost to follow up	3 (2.9)

Abbreviations: n = number of patients; N = total number of patients.

Primary Outcome Measure

Among 1-year completers, the correlation of change from baseline between the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) and the Woodcock-Johnson Tests of Achievement (WJ III) was -.066 and not statistically significant ($p=.600$; Table 3). An increase in WJ III score indicates an improvement. A negative correlation indicates agreement between both scales.

Atomoxetine

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Table 3. Change in WJ III Total Composite Score and Correlation with Change in ADHDRS-IV-Parent:Inv for Patients who Completed Visit 12 (1 Year)

	Change from Baseline to Endpoint Score												Correlation with Change in ADHDRS-Parent:Inv			
	Baseline Score				Endpoint Score				p-value ¹	95% CI	p-value ²					
	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI								
WJ III @total of the composite scores	66	241.1 (7.90)	81, 393, 241	(225.3, 256.8)	66	278.7 (7.85)	110, 436, 284	(263.0, 294.3)	66	37.6 (2.66)	-14, 92, 41	(32.3, 42.9)	<.0001	-.066	(-0.322, 0.191)	0.6003

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CI = confidence interval; Min = minimum; Max = maximum; N = number of patients; SD = standard deviation of mean; WJ III = Woodcock-Johnson Tests of Achievement.

¹ p-value using paired t-test comparing the mean change in the total of the composite scores of the WJ III to zero for patients completing Visit 12.

² p-value comparing the correlation between the change in ADHDRS-IV-Parent:Inv and the change in the total of the composite scores of the WJ III to zero for patients completing Visit 12.

Secondary Outcome Measures

The correlations of change from baseline to 6 months and 1 year in ADHD symptoms measured by the ADHDRS-IV-Parent:Inv with composite scores of the Broad Reading, Broad Math, and Broad Written Language subtests of the WJ III are summarized in Table 4 and Table 5, respectively.

The changes from baseline to 6 months or later, and 1 year in Behavior Rating Inventory of Executive Function™ (BRIEF™) overall and subscale scores are summarized in Table 6 and Table 7, respectively. A decrease in raw score indicates improvement. See Table 6 and Table 7 for the correlations between change in BRIEF and change in ADHDRS-IV-Parent:Inv.

The changes from baseline to 6 months or later, and 1 year in each of the subscales of the Behavior Assessment System for Children (BASC) are summarized in Table 8 and Table 9, respectively. A decrease on a clinical scale or an increase on an adaptive scale indicates improvement. See Table 8 and Table 9 for the correlations between change in BASC and change in ADHDRS-IV-Parent:Inv.

The changes from baseline to 6 months or later, and 1 year in the ADHDRS-IV-Parent:Inv (Table 10 and Table 11) and the Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity scale (CGI-ADHD-S; Table 12 and Table 13) scores are summarized. A decrease in score indicates an improvement. See Table 12 and Table 13 for the correlations between change in CGI-ADHD-S and change in ADHDRS-IV-Parent:Inv.

The changes from baseline to 6 months or later, and 1 year in total and subscale scores of the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) are summarized in Table 14 and Table 15, respectively. A decrease in score indicates an improvement. The correlations between changes in the WFIRS-P and change in ADHDRS-IV-Parent:Inv total score are summarized in Table 14 and Table 15.

Atomoxetine

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Table 4. Change in WJ III Raw Scores (Subscales and Subtests) and Correlation with Change in ADHDRS-IV-Parent:Inv for Patients who Completed Visit 9 (6 Months) or Later

WJ III ® Subscale or Subtest	Baseline Raw Score				Endpoint Raw Score				Change in Raw Score from Baseline to Endpoint				p-value ¹	Correlation with Change in ADHDRS-IV-Parent:Inv		p-value ²
	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI		Parent:Inv	95% CI	
Broad Reading, total	73	99.9 (3.55)	27, 162, 104	(92.8, 107.0)	73	113.4 (3.24)	27, 184, 118	(106.9, 119.8)	73	13.5 (1.33)	-11, 36, 16	(10.8, 16.1)	<.0001	-.190	(-0.426, 0.047)	0.1083
Letter-Word Identification	73	44.9 (1.27)	18, 65, 46	(42.4, 47.4)	73	49.3 (1.11)	19, 67, 51	(47.0, 51.5)	73	4.3 (0.52)	-6, 15, 4	(3.3, 5.4)	<.0001	-.296	(-0.493, -0.099)	0.0110
Reading Fluency	73	31.0 (1.77)	0, 65, 31	(27.4, 34.5)	73	37.5 (1.80)	0, 88, 37	(33.9, 41.1)	73	6.5 (0.93)	-19, 23, 7	(4.7, 8.4)	<.0001	-.063	(-0.280, 0.154)	0.5952
Passage Comprehension	73	24.0 (0.72)	9, 33, 25	(22.6, 25.4)	73	26.6 (0.61)	8, 35, 28	(25.4, 27.8)	73	2.6 (0.51)	-6, 18, 2	(1.6, 3.6)	<.0001	-.075	(-0.252, 0.103)	0.5306
Broad Math, total	73	80.3 (2.50)	32, 140, 79	(75.4, 85.3)	73	94.4 (2.76)	34, 159, 95	(88.9, 99.9)	73	14.1 (1.23)	-11, 41, 14	(11.6, 16.5)	<.0001	-.030	(-0.296, 0.236)	0.7991
Calculation	73	13.5 (0.44)	4, 21, 14	(12.7, 14.4)	73	15.5 (0.42)	8, 26, 16	(14.7, 16.4)	73	2.0 (0.32)	-5, 8, 2	(1.4, 2.6)	<.0001	0.266	(0.041, 0.492)	0.0227
Math Fluency	73	36.4 (1.77)	6, 80, 35	(32.9, 40.0)	73	44.5 (2.00)	14, 101, 42	(40.5, 48.5)	73	8.0 (1.10)	-19, 33, 7	(5.8, 10.2)	<.0001	-.087	(-0.332, 0.159)	0.4647
Applied Problems	73	30.4 (0.58)	19, 41, 30	(29.2, 31.5)	73	34.4 (0.70)	10, 46, 35	(33.0, 35.8)	73	4.1 (0.49)	-13, 12, 4	(3.1, 5.0)	<.0001	-.055	(-0.289, 0.179)	0.6452
Broad Written Language, total	73	62.2 (2.00)	21, 98, 65	(58.2, 66.2)	73	69.8 (2.09)	22, 110, 71	(65.7, 74.0)	73	7.6 (1.07)	-17, 26, 7	(5.5, 9.8)	<.0001	-.048	(-0.235, 0.139)	0.6866
Spelling	73	27.4 (0.83)	13, 46, 28	(25.8, 29.1)	73	30.2 (0.87)	15, 54, 29	(28.4, 31.9)	73	2.7 (0.43)	-8, 16, 3	(1.9, 3.6)	<.0001	-.052	(-0.253, 0.149)	0.6628
Writing Fluency	73	12.4 (0.68)	1, 31, 13	(11.0, 13.7)	73	14.9 (0.72)	0, 29, 15	(13.4, 16.3)	73	2.5 (0.55)	-24, 10, 3	(1.4, 3.6)	<.0001	-.019	(-0.191, 0.152)	0.8715
Writing Samples	73	22.4 (0.77)	6, 38, 24	(20.8, 23.9)	72	25.1 (0.71)	8, 41, 26	(23.7, 26.6)	72	2.6 (0.58)	-14, 15, 3	(1.5, 3.8)	<.0001	-.085	(-0.298, 0.129)	0.4800

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CI = confidence interval; Min = minimum; Max = maximum; N = number of patients; SD = standard deviation of mean; WJ III = Woodcock-Johnson Tests of Achievement.

- 1 p-value using a paired t-test or Wilcoxon signed rank test comparing the mean change in subscale or subtest score of the WJ III to zero for patients completing Visit 9 or later.
- 2 p-value comparing the correlation between the change in ADHDRS-IV-Parent:Inv and the change in subscale or subtest score of the WJ III to zero for patients completing Visit 9 or later.

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Table 5. Change in WJ III Raw Scores (Subscales and Subtests) and Correlation with Change in ADHDRS-IV-Parent:Inv for Patients who Completed Visit 12 (1 Year)

W J III ® Subscale or Subtest	Change in Raw Score												Correlation with Change in ADHD RS-Parent:Inv			
	Baseline Raw Score				Endpoint Raw Score				from Baseline to Endpoint				p-value ¹	95% CI	p-value ²	
	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI				
Broad Reading, total	66	98.6 (3.77)	27, 162, 101	(91.1, 106.1)	66	113.7 (3.44)	27, 184, 118	(106.8, 120.6)	66	15.1 (1.36)	-10, 38, 16	(12.3, 17.8)	<.0001	-.105	(-0.374, 0.165)	0.4036
Letter-Word Identification	66	44.2 (1.31)	18, 65, 45	(41.6, 46.8)	66	49.2 (1.17)	19, 67, 49	(46.8, 51.5)	66	5.0 (0.54)	-4, 15, 5	(3.9, 6.0)	<.0001	-.221	(-0.435, -0.007)	0.0744
Reading Fluency	66	30.4 (1.91)	0, 65, 30	(26.6, 34.2)	66	37.8 (1.90)	0, 88, 37	(34.0, 41.6)	66	7.4 (0.97)	-19, 23, 8	(5.4, 9.3)	<.0001	0.032	(-0.199, 0.263)	0.7980
Passage Comprehension	66	24.0 (0.77)	9, 33, 25	(22.5, 25.5)	66	26.7 (0.66)	8, 35, 28	(25.4, 28.1)	66	2.7 (0.54)	-6, 18, 2	(1.7, 3.8)	<.0001	-.102	(-0.283, 0.080)	0.4153
Broad Math, total	66	81.0 (2.67)	32, 140, 79	(75.7, 86.3)	66	95.0 (2.80)	52, 159, 95	(89.4, 100.6)	66	14.0 (1.25)	-11, 41, 14	(11.5, 16.6)	<.0001	-.028	(-0.303, 0.247)	0.8230
Calculation	66	13.8 (0.45)	7, 21, 14	(13.0, 14.7)	66	15.5 (0.45)	8, 26, 15	(14.6, 16.4)	66	1.7 (0.31)	-5, 6, 2	(1.0, 2.3)	<.0001	0.155	(-0.083, 0.394)	0.2128
Math Fluency	66	36.7 (1.93)	6, 80, 35	(32.8, 40.5)	66	44.7 (2.09)	17, 101, 42	(40.5, 48.8)	66	8.0 (1.11)	-19, 33, 7	(5.8, 10.2)	<.0001	-.096	(-0.339, 0.147)	0.4415
Applied Problems	66	30.5 (0.60)	19, 41, 30	(29.3, 31.7)	66	34.9 (0.66)	24, 46, 35	(33.6, 36.2)	66	4.4 (0.49)	-4, 12, 4	(3.4, 5.4)	<.0001	0.050	(-0.205, 0.304)	0.6930
Broad W ritten Language, total	66	61.5 (2.13)	21, 98, 64	(57.2, 65.7)	66	70.0 (2.25)	22, 110, 71	(65.5, 74.4)	66	8.5 (1.14)	-17, 26, 9	(6.2, 10.8)	<.0001	0.003	(-0.188, 0.194)	0.9821
Spelling	66	27.1 (0.90)	13, 46, 27	(25.3, 28.9)	66	30.0 (0.96)	15, 54, 29	(28.1, 32.0)	66	2.9 (0.47)	-8, 16, 3	(2.0, 3.8)	<.0001	-.076	(-0.293, 0.141)	0.5428
Writing Fluency	66	12.0 (0.71)	1, 31, 12	(10.6, 13.4)	66	14.8 (0.74)	0, 29, 16	(13.3, 16.3)	66	2.8 (0.59)	-24, 10, 3	(1.7, 4.0)	<.0001	0.017	(-0.178, 0.213)	0.8900
W riting Samples	66	22.3 (0.81)	6, 38, 24	(20.7, 24.0)	65	25.5 (0.76)	8, 41, 26	(23.9, 27.0)	65	3.0 (0.61)	-14, 12, 3	(1.8, 4.2)	<.0001	-.004	(-0.212, 0.204)	0.9743

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CI = confidence interval; Min = minimum; Max = maximum; N = number of patients; SD = standard deviation of mean; WJ III = Woodcock-Johnson Tests of Achievement.

¹ p-value using a paired t-test or Wilcoxon signed rank test comparing the mean change in subscale or subtest score of the WJ III to zero for patients completing Visit 12.

² p-value comparing the correlation between the change in ADHDRS-IV-Parent:Inv and the change subscale or subtest score of the WJ III to zero for patients completing Visit 12.

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Table 6. Change in BRIEF Global Executive Composite and Subscale Scores and Correlation with Change in ADHDRS-IV-Parent:Inv for Patients who Completed Visit 9 (6 Months) or Later

	Baseline Raw Score				Endpoint Raw Score				Endpoint Percentile Score				Change in Raw Score from Baseline to Endpoint				p-value ¹	Correlation with Change in ADHDRS-Parent:Inv	95% CI	p-value ²
	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI				
Overall: Global Executive Composite	73	169.5 (2.34)	130, 213, 168	(164.8, 174.1)	73	140.1 (3.11)	82, 194, 141	(133.9, 146.3)	73	75.0 (2.83)	3, 99, 82	(69.3, 80.6)	73	-29.3 (3.05)	-78, 33, -26	(-35.4, -23.2)	<.0001	0.643	(0.521, 0.766)	<.0001
Behavioral Regulation	73	60.6 (1.29)	39, 83, 60	(58.1, 63.2)	73	50.0 (1.48)	29, 82, 48	(47.0, 52.9)	73	68.4 (3.24)	6, 99, 77	(61.9, 74.9)	73	-10.7 (1.17)	-32, 12, -10	(-13.0, -8.3)	<.0001	0.609	(0.464, 0.754)	<.0001
Metacognition	73	108.8 (1.39)	79, 130, 110	(106.0, 111.6)	73	90.2 (1.90)	50, 122, 93	(86.4, 93.9)	73	76.5 (2.67)	2, 99, 87	(71.2, 81.8)	73	-18.7 (2.11)	-60, 28, -17	(-22.9, -14.4)	<.0001	0.593	(0.460, 0.727)	<.0001
Inhibit	73	22.8 (0.56)	12, 30, 22	(21.6, 23.9)	73	17.6 (0.62)	10, 29, 18	(16.3, 18.8)	73	68.9 (3.04)	14, 99, 75	(62.9, 75.0)	73	-5.2 (0.49)	-14, 5, -5	(-6.2, -4.2)	<.0001	0.603	(0.449, 0.758)	<.0001
Shift	73	16.1 (0.39)	9, 23, 16	(15.3, 16.9)	73	13.8 (0.45)	8, 23, 13	(12.9, 14.7)	73	70.1 (2.97)	9, 99, 74	(64.2, 76.1)	73	-2.3 (0.41)	-10, 6, -2	(-3.1, -1.5)	<.0001	0.373	(0.184, 0.562)	0.0012
Emotional Control	73	21.8 (0.62)	11, 30, 22	(20.6, 23.0)	73	18.6 (0.63)	10, 30, 19	(17.3, 19.9)	73	66.2 (3.46)	5, 99, 73	(59.3, 73.1)	73	-3.2 (0.54)	-16, 6, -3	(-4.3, -2.1)	<.0001	0.483	(0.317, 0.648)	<.0001
Initiate	73	18.0 (0.30)	12, 24, 18	(17.4, 18.6)	73	15.1 (0.35)	9, 23, 15	(14.4, 15.8)	73	74.1 (2.56)	11, 99, 80	(69.0, 79.2)	73	-2.9 (0.36)	-13, 3, -2	(-3.6, -2.2)	<.0001	0.541	(0.389, 0.693)	<.0001
Working Memory	73	25.5 (0.35)	19, 30, 26	(24.8, 26.2)	73	20.3 (0.50)	11, 30, 20	(19.3, 21.3)	73	79.5 (2.14)	13, 99, 83	(75.2, 83.8)	73	-5.2 (0.57)	-16, 6, -4	(-6.3, -4.0)	<.0001	0.582	(0.426, 0.739)	<.0001
Plan/Organize	73	29.8 (0.51)	18, 36, 30	(28.7, 30.8)	73	24.7 (0.59)	12, 35, 25	(23.5, 25.9)	73	78.7 (2.56)	10, 99, 87	(73.6, 83.8)	73	-5.1 (0.73)	-18, 12, -6	(-6.5, -3.6)	<.0001	0.497	(0.357, 0.638)	<.0001
Organization of Materials	73	15.6 (0.28)	9, 18, 16	(15.0, 16.1)	73	13.6 (0.36)	6, 18, 14	(12.9, 14.4)	73	71.3 (2.86)	7, 99, 77	(65.6, 77.0)	73	-1.9 (0.32)	-8, 3, -1	(-2.6, -1.3)	<.0001	0.477	(0.317, 0.636)	<.0001
Monitor	73	20.0 (0.34)	12, 24, 20	(19.3, 20.7)	73	16.4 (0.41)	9, 24, 17	(15.6, 17.2)	73	70.2 (3.31)	5, 99, 79	(63.6, 76.8)	73	-3.6 (0.45)	-12, 7, -4	(-4.5, -2.7)	<.0001	0.455	(0.304, 0.605)	<.0001
Inconsistency (validity)	73	3.0 (0.22)	0, 7, 3	(2.5, 3.4)	73	3.2 (0.19)	0, 7, 3	(2.8, 3.5)					73	0.2 (0.29)	-6, 6, 0	(-0.4, 0.8)	0.5396	-.015	(-0.245, 0.215)	0.9005
Negativity (validity)	73	1.9 (0.24)	0, 9, 1	(1.4, 2.4)	73	0.8 (0.15)	0, 5, 0	(0.6, 1.1)					73	-1.1 (0.22)	-6, 2, -1	(-1.5, -0.6)	<.0001	0.324	(0.107, 0.541)	0.0052

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; BRIEF = Behavior Rating Inventory of Executive Function; CI = confidence interval; Min = minimum; Max = maximum; N = number of patients; SD = standard deviation of mean.

- ¹ p-value using a paired t-test or Wilcoxon signed rank test comparing the mean change in BRIEF Global Executive Composite and subscale scores to zero for patients completing Visit 9 or later.
- ² p-value comparing the correlation between change in ADHDRS-IV-Parent:Inv and change in the BRIEF Global Executive Composite and subscale scores to zero for patients completing Visit 9 or later.

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Table 7. Change in BRIEF Global Executive Composite and Subscale Scores and Correlation with Change in ADHDRS-IV-Parent:Inv for Patients who Completed Visit 12 (1 Year)

		Change in Raw Score from Baseline to Endpoint															p-value ¹	Correlation with Change in ADHDRS-Parent:Inv	95% CI	p-value ²
		Baseline Raw Score			Endpoint Raw Score			Endpoint Percentile Score			Change in Raw Score from Baseline to Endpoint									
		N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median				
Overall: Global Executive Composite	66	168.5 (2.45)	128, 213, 168	(163.6, 173.4)	66	138.1 (3.30)	82, 194, 140	(131.5, 144.7)	66	73.1 (3.18)	3, 99, 82	(66.8, 79.5)	66	-30.4 (3.29)	-79, 33, -27	(-37.0, -23.9)	<.0001	0.664	(0.536, 0.793)	<.0001
Behavioral Regulation	66	60.4 (1.35)	33, 83, 61	(57.7, 63.1)	66	48.9 (1.50)	29, 82, 48	(45.9, 51.9)	66	66.4 (3.48)	6, 99, 72	(59.4, 73.3)	66	-11.5 (1.26)	-32, 12, -12	(-14.1, -9.0)	<.0001	0.607	(0.442, 0.773)	<.0001
Metacognition	66	108.1 (1.45)	79, 130, 110	(105.2, 111.0)	66	89.2 (2.10)	50, 122, 93	(85.0, 93.4)	66	74.9 (3.03)	2, 99, 86	(68.8, 80.9)	66	-18.9 (2.28)	-60, 28, -16	(-23.4, -14.3)	<.0001	0.624	(0.489, 0.760)	<.0001
Inhibit	66	22.5 (0.63)	11, 30, 22	(21.2, 23.8)	66	17.1 (0.64)	10, 29, 17	(15.8, 18.3)	66	66.5 (3.27)	14, 99, 73	(60.0, 73.0)	66	-5.4 (0.55)	-14, 5, -5	(-6.5, -4.3)	<.0001	0.645	(0.487, 0.803)	<.0001
Shift	66	15.8 (0.42)	9, 23, 16	(15.0, 16.6)	66	13.5 (0.45)	8, 23, 13	(12.6, 14.4)	66	68.4 (3.15)	9, 99, 74	(62.1, 74.7)	66	-2.3 (0.41)	-10, 6, -2	(-3.1, -1.5)	<.0001	0.392	(0.186, 0.598)	0.0011
Emotional Control	66	22.1 (0.61)	11, 30, 23	(20.9, 23.3)	66	18.3 (0.63)	10, 30, 19	(17.1, 19.6)	66	65.5 (3.63)	5, 99, 72	(58.3, 72.8)	66	-3.8 (0.58)	-16, 4, -3	(-4.9, -2.6)	<.0001	0.427	(0.235, 0.619)	0.0003
Initiate	66	18.0 (0.32)	12, 24, 18	(17.4, 18.6)	66	15.0 (0.39)	8, 23, 15	(14.2, 15.8)	66	72.5 (2.95)	9, 99, 83	(66.6, 78.4)	66	-3.0 (0.41)	-13, 3, -2	(-3.8, -2.2)	<.0001	0.537	(0.378, 0.695)	<.0001
Working Memory	66	25.5 (0.36)	19, 30, 26	(24.8, 26.2)	66	20.2 (0.55)	11, 30, 20	(19.1, 21.3)	66	78.5 (2.42)	13, 99, 82	(73.7, 83.4)	66	-5.3 (0.60)	-16, 6, -4	(-6.5, -4.1)	<.0001	0.595	(0.437, 0.753)	<.0001
Plan/Organize	66	29.6 (0.52)	18, 36, 30	(28.5, 30.6)	66	24.3 (0.64)	12, 35, 25	(23.0, 25.5)	66	76.9 (2.85)	10, 99, 87	(71.2, 82.6)	66	-5.3 (0.78)	-18, 12, -6	(-6.9, -3.8)	<.0001	0.527	(0.379, 0.675)	<.0001
Organization of Materials	66	15.3 (0.32)	7, 18, 16	(14.7, 16.0)	66	13.6 (0.41)	6, 18, 14	(12.7, 14.4)	66	70.2 (3.23)	7, 99, 77	(63.8, 76.7)	66	-1.8 (0.34)	-8, 3, -1	(-2.4, -1.1)	<.0001	0.512	(0.355, 0.670)	<.0001
Monitor	66	19.7 (0.37)	12, 24, 20	(19.0, 20.4)	66	16.2 (0.44)	9, 24, 17	(15.3, 17.1)	66	69.0 (3.58)	5, 99, 80	(61.8, 76.1)	66	-3.5 (0.50)	-12, 7, -4	(-4.5, -2.5)	<.0001	0.517	(0.357, 0.677)	<.0001
Inconsistency (validity)	66	3.1 (0.24)	0, 7, 3	(2.6, 3.5)	66	3.3 (0.20)	0, 7, 3	(2.9, 3.7)					66	0.2 (0.31)	-6, 6, 0	(-0.4, 0.8)	0.4966	0.104	(-0.139, 0.347)	0.4053
Negativity (validity)	66	1.7 (0.25)	0, 9, 1	(1.2, 2.2)	66	0.8 (0.15)	0, 5, 0	(0.5, 1.1)					66	-0.9 (0.23)	-6, 2, 0	(-1.4, -0.4)	0.0001	0.327	(0.102, 0.552)	0.0075

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; BRIEF = Behavior Rating Inventory of Executive Function; CI = confidence interval; Min = minimum; Max = maximum; N = number of patients; SD = standard deviation of mean.

¹ p-value using a paired t-test or Wilcoxon signed rank test comparing the mean change in BRIEF Global Executive Composite and subscale scores to zero for patients completing Visit 12.

² p-value comparing the correlation between change in ADHDRS-IV-Parent:Inv and change in BRIEF Global Executive Composite and subscale scores to zero for patients completing Visit 12.

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Table 8. Change in BASC (Parent and Child Version) Subscales and Correlation with Change in ADHDRS-IV-Parent:Inv for Patients who Completed Visit 9 (6 Months) or Later

	Change in Raw Score from Baseline to Endpoint																p-value ¹	Correlation with Change in ADHDRS-Parent:Inv	95% CI	p-value ²
	Baseline Raw Score				Endpoint Raw Score				Endpoint T-Score											
	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI				
BASC - Child Self-Report																				
Clinical Scales:																				
Attitude to School	72	4.4 (0.36)	0, 9, 4	(3.7, 5.1)	70	3.3 (0.37)	0, 9, 3	(2.6, 4.0)	70	50.6 (1.38)	38, 72, 48	(47.8, 53.3)	69	-1.0 (0.33)	-8, 6, -1	(-1.7, -0.4)	0.0037	-0.264	(-0.505, -0.023)	0.0283
Attitude to Teachers	72	3.0 (0.33)	0, 10, 2	(2.3, 3.6)	70	2.1 (0.28)	0, 9, 1	(1.5, 2.6)	70	49.1 (1.24)	40, 80, 44	(46.6, 51.6)	69	-0.8 (0.31)	-8, 4, -1	(-1.5, -0.2)	0.0106	-0.078	(-0.355, 0.200)	0.5256
Atypicality	72	6.1 (0.43)	0, 14, 6	(5.2, 6.9)	69	4.7 (0.44)	0, 14, 4	(3.8, 5.5)	69	50.4 (1.26)	37, 77, 48	(47.9, 52.9)	68	-1.3 (0.38)	-8, 6, -2	(-2.1, -0.5)	0.0011	0.010	(-0.247, 0.266)	0.9386
Locus of Control	71	7.0 (0.45)	0, 16, 7	(6.1, 7.9)	70	5.4 (0.50)	0, 16, 5	(4.4, 6.3)	70	48.5 (1.14)	36, 73, 47	(46.3, 50.8)	68	-1.6 (0.45)	-13, 8, -1	(-2.5, -0.7)	0.0004	-0.088	(-0.371, 0.196)	0.4760
Social Stress	72	5.0 (0.37)	0, 12, 5	(4.3, 5.7)	69	3.8 (0.36)	0, 12, 3	(3.0, 4.5)	69	47.2 (1.12)	35, 73, 45	(45.0, 49.4)	68	-1.1 (0.37)	-9, 5, -1	(-1.8, -0.3)	0.0050	0.122	(-0.118, 0.362)	0.3205
Anxiety	72	7.7 (0.59)	0, 17, 8	(6.5, 8.8)	69	5.8 (0.55)	0, 17, 5	(4.7, 6.9)	69	46.2 (1.17)	34, 70, 44	(43.9, 48.6)	68	-1.8 (0.53)	-14, 8, -1	(-2.8, -0.7)	0.0014	-0.052	(-0.282, 0.178)	0.6738
Depression	72	5.4 (0.53)	0, 17, 4	(4.3, 6.4)	70	3.5 (0.49)	0, 17, 2	(2.5, 4.5)	70	49.6 (1.20)	41, 83, 46	(47.2, 52.0)	69	-1.8 (0.42)	-11, 7, -1	(-2.6, -0.9)	<.0001	0.019	(-0.230, 0.268)	0.8754
Sense of Inadequacy	72	4.5 (0.31)	1, 11, 4	(3.9, 5.1)	70	3.0 (0.33)	0, 12, 2	(2.4, 3.7)	70	51.4 (1.29)	40, 86, 47	(48.9, 54.0)	69	-1.3 (0.33)	-6, 6, -2	(-2.0, -0.7)	<.0001	0.095	(-0.134, 0.324)	0.4379
Adaptive Scales:																				
Relations with Parents	72	8.4 (0.24)	1, 10, 9	(7.9, 8.9)	69	8.7 (0.21)	2, 10, 9	(8.3, 9.1)	69	49.4 (1.24)	10, 57, 51	(46.9, 51.9)	68	0.2 (0.28)	-8, 8, 0	(-0.3, 0.8)	0.2510	0.237	(-0.046, 0.520)	0.0517
Interpersonal Relations	72	7.7 (0.34)	0, 10, 9	(7.0, 8.3)	70	8.1 (0.31)	1, 10, 9	(7.5, 8.7)	70	49.4 (1.42)	18, 58, 53	(46.5, 52.2)	69	0.4 (0.34)	-8, 10, 0	(-0.3, 1.1)	0.1499	-0.181	(-0.428, 0.065)	0.1358
Self-Esteem	72	4.8 (0.19)	0, 6, 6	(4.4, 5.2)	70	5.2 (0.18)	0, 6, 6	(4.8, 5.5)	70	52.5 (1.01)	22, 57, 57	(50.5, 54.5)	69	0.4 (0.17)	-6, 4, 0	(0.0, 0.7)	0.0099	0.225	(-0.048, 0.497)	0.0635
Self-Reliance	70	9.6 (0.38)	1, 14, 11	(8.9, 10.4)	69	10.7 (0.33)	1, 14, 11	(10.1, 11.4)	69	49.5 (1.23)	13, 62, 51	(47.0, 52.0)	66	1.0 (0.44)	-7, 9, 1	(0.2, 1.9)	0.0566	0.071	(-0.213, 0.354)	0.5731

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Table 8. Change in BASC (Parent and Child Version) Subscales and Correlation with Change in ADHDRS-IV-Parent:Inv for Patients who Completed Visit 9 (6 Months) or Later (Concluded)

	Baseline and Endpoint Data															p-value ¹	Correlation with Change in ADHDRS-Parent:Inv	95% CI	p-value ²	
	Baseline Raw Score				Endpoint Raw Score				Endpoint T-Score				Change in Raw Score from Baseline to Endpoint							
	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median					95% CI
BASC - Parent Rating																				
Clinical Scales:																				
Hyperactivity	73	14.4 (0.64)	5, 29, 13	(13.1, 15.6)	73	8.2 (0.53)	0, 22, 8	(7.2, 9.3)	73	52.4 (1.43)	30, 89, 52	(49.6, 55.2)	73	-6.2 (0.53)	-18, 2, -6	(-7.2, -5.1)	<.0001	0.649	(0.502, 0.795)	<.0001
Aggression	73	14.0 (0.72)	2, 30, 14	(12.5, 15.4)	73	10.5 (0.65)	1, 24, 10	(9.2, 11.8)	73	54.1 (1.48)	32, 85, 53	(51.1, 57.0)	73	-3.5 (0.52)	-14, 6, -3	(-4.5, -2.5)	<.0001	0.524	(0.375, 0.673)	<.0001
Conduct Problems	73	7.4 (0.53)	0, 17, 7	(6.4, 8.5)	73	5.4 (0.45)	0, 17, 6	(4.5, 6.3)	73	57.7 (1.73)	37, 102, 60	(54.2, 61.1)	73	-2.0 (0.45)	-13, 11, -2	(-2.9, -1.1)	<.0001	0.330	(0.150, 0.509)	0.0044
Anxiety	73	11.9 (0.61)	0, 26, 11	(10.7, 13.1)	73	9.7 (0.63)	1, 26, 9	(8.5, 11.0)	73	47.8 (1.31)	29, 82, 46	(45.2, 50.4)	73	-2.2 (0.55)	-14, 13, -2	(-3.3, -1.1)	0.0001	0.174	(-0.016, 0.364)	0.1411
Depression	73	11.9 (0.75)	0, 34, 11	(10.4, 13.4)	73	8.4 (0.62)	0, 22, 8	(7.1, 9.6)	73	53.7 (1.47)	34, 86, 53	(50.8, 56.7)	73	-3.5 (0.65)	-22, 7, -3	(-4.8, -2.2)	<.0001	0.434	(0.267, 0.600)	0.0001
Somatization	73	4.2 (0.35)	0, 13, 4	(3.5, 4.9)	73	4.0 (0.34)	0, 12, 4	(3.3, 4.7)	73	47.3 (0.99)	36, 71, 47	(45.3, 49.3)	73	-0.1 (0.33)	-9, 8, 0	(-0.8, 0.5)	0.6072	0.052	(-0.175, 0.278)	0.6634
Atypicality	73	5.8 (0.47)	0, 19, 4	(4.9, 6.8)	73	3.2 (0.30)	0, 13, 3	(2.6, 3.8)	73	51.3 (1.25)	38, 93, 50	(48.8, 53.8)	73	-2.6 (0.39)	-13, 3, -2	(-3.4, -1.8)	<.0001	0.396	(0.253, 0.538)	0.0005
Withdrawal	73	5.6 (0.46)	0, 16, 5	(4.7, 6.5)	73	4.6 (0.38)	0, 15, 4	(3.9, 5.4)	73	49.2 (1.19)	35, 82, 47	(46.9, 51.6)	73	-1.0 (0.35)	-9, 8, -1	(-1.7, -0.3)	0.0071	0.409	(0.254, 0.563)	0.0003
Attention Problems	73	15.2 (0.28)	10, 21, 15	(14.7, 15.8)	73	11.5 (0.37)	2, 18, 12	(10.7, 12.2)	73	61.6 (0.97)	37, 79, 63	(59.7, 63.6)	73	-3.8 (0.42)	-13, 4, -3	(-4.6, -2.9)	<.0001	0.609	(0.477, 0.741)	<.0001
Adaptive Scales:																				
Adaptability	73	9.7 (0.37)	1, 20, 9	(8.9, 10.4)	73	11.4 (0.40)	5, 20, 11	(10.6, 12.2)	73	42.7 (1.11)	25, 67, 41	(40.4, 44.9)	73	1.8 (0.32)	-3, 7, 2	(1.1, 2.4)	<.0001	-0.287	(-0.493, -0.082)	0.0137
Social Skills	73	19.6 (0.76)	5, 39, 18	(18.1, 21.1)	73	22.2 (0.80)	6, 38, 23	(20.6, 23.8)	73	44.4 (1.13)	24, 67, 45	(42.1, 46.7)	73	2.6 (0.67)	-11, 23, 2	(1.3, 3.9)	0.0002	-0.502	(-0.625, -0.380)	<.0001
Leadership	73	14.7 (0.49)	7, 27, 14	(13.7, 15.7)	73	15.2 (0.56)	5, 27, 15	(14.1, 16.3)	73	42.9 (1.02)	25, 64, 43	(40.9, 45.0)	73	0.5 (0.52)	-12, 13, 1	(-0.5, 1.5)	0.3439	-0.047	(-0.248, 0.153)	0.6910

Abbreviations: ADHDRS-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; BASC = Behavior Assessment System for Children; CI = confidence interval; Min = minimum; Max = maximum; N = number of patients; SD = standard deviation of mean.

- 1 p-value using a paired t-test or Wilcoxon signed rank test comparing the mean change in BASC (parent and child version) subscale scores to zero for patients completing Visit 9 or later.
- 2 p-value comparing the correlation between change in ADHDRS-IV-Parent:Inv and change in BASC (parent and child version) subscale scores to zero for patients completing Visit 9 or later.

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Table 9. Change in BASC (Parent and Child Version) Subscales and Correlation with Change in ADHDRS-IV-Parent:Inv for Patients who Completed Visit 12 (1 Year)

		Change in Raw Score from Baseline to Endpoint															p-value ¹	Correlation with Change in ADHDRS-Parent:Inv		95% CI	p-value ²
		Baseline Raw Score				Endpoint Raw Score				Endpoint T-Score											
		N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI				
BASC - Child Self-Report	Clinical Scales:																				
	Attitude to School	65	4.1 (0.37)	0, 9, 4	(3.3, 4.8)	64	3.1 (0.37)	0, 9, 2	(2.4, 3.9)	64	49.9 (1.38)	38, 72, 46	(47.1, 52.6)	63	-1.0 (0.34)	-8, 6, -1	(-1.6, -0.3)	0.0081	-0.329	(-0.574, -0.084)	0.0085
	Attitude to Teachers	65	2.8 (0.34)	0, 10, 2	(2.1, 3.5)	64	1.8 (0.27)	0, 9, 1	(1.2, 2.3)	64	47.8 (1.22)	40, 80, 44	(45.4, 50.3)	63	-1.1 (0.30)	-8, 4, -1	(-1.7, -0.5)	0.0006	-0.249	(-0.500, 0.002)	0.0488
	Atypicality	65	6.1 (0.41)	0, 13, 6	(5.3, 6.9)	63	4.4 (0.44)	0, 14, 4	(3.5, 5.3)	63	49.7 (1.26)	37, 77, 48	(47.2, 52.2)	62	-1.6 (0.39)	-8, 6, -2	(-2.4, -0.8)	<.0001	-0.084	(-0.330, 0.161)	0.5150
	Locus of Control	64	6.7 (0.45)	0, 16, 7	(5.8, 7.6)	64	5.0 (0.52)	0, 16, 4	(3.9, 6.0)	64	47.7 (1.19)	36, 73, 45	(45.3, 50.0)	62	-1.9 (0.47)	-13, 8, -1	(-2.8, -0.9)	<.0001	-0.116	(-0.383, 0.151)	0.3677
	Social Stress	65	5.0 (0.37)	0, 12, 5	(4.2, 5.7)	63	3.4 (0.35)	0, 12, 3	(2.7, 4.1)	63	46.3 (1.09)	35, 73, 45	(44.1, 48.4)	62	-1.4 (0.38)	-9, 5, -2	(-2.2, -0.7)	0.0004	-0.016	(-0.266, 0.233)	0.8998
	Anxiety	65	7.9 (0.58)	0, 17, 8	(6.7, 9.0)	63	5.6 (0.57)	0, 17, 5	(4.4, 6.7)	63	45.7 (1.22)	34, 70, 44	(43.2, 48.1)	62	-2.1 (0.52)	-12, 8, -2	(-3.1, -1.0)	0.0002	-0.131	(-0.369, 0.107)	0.3098
	Depression	65	5.1 (0.55)	0, 17, 4	(4.0, 6.2)	64	3.1 (0.48)	0, 16, 2	(2.2, 4.1)	64	48.6 (1.19)	41, 80, 46	(46.3, 51.0)	63	-1.9 (0.45)	-11, 7, -1	(-2.8, -1.0)	<.0001	-0.053	(-0.312, 0.206)	0.6789
	Sense of Inadequacy	65	4.4 (0.31)	1, 11, 4	(3.7, 5.0)	64	2.8 (0.33)	0, 10, 2	(2.1, 3.4)	64	50.4 (1.27)	40, 78, 47	(47.9, 52.9)	63	-1.6 (0.34)	-6, 6, -2	(-2.2, -0.9)	<.0001	-0.094	(-0.326, 0.138)	0.4622
	Adaptive Scales:																				
	Relations with Parents	65	8.6 (0.24)	1, 10, 9	(8.1, 9.0)	63	8.8 (0.22)	2, 10, 9	(8.4, 9.2)	63	49.9 (1.26)	10, 57, 51	(47.3, 52.4)	62	0.2 (0.28)	-8, 8, 0	(-0.3, 0.8)	0.2501	0.283	(0.009, 0.556)	0.0259
	Interpersonal Relations	65	7.6 (0.35)	0, 10, 9	(7.0, 8.3)	64	8.5 (0.30)	2, 10, 10	(7.9, 9.1)	64	51.0 (1.37)	22, 58, 58	(48.2, 53.7)	63	0.8 (0.33)	-8, 10, 1	(0.1, 1.4)	0.0093	-0.212	(-0.464, 0.040)	0.0952
Self-Esteem	65	4.8 (0.20)	0, 6, 6	(4.4, 5.2)	64	5.2 (0.17)	0, 6, 6	(4.9, 5.6)	64	52.8 (0.99)	22, 57, 57	(50.8, 54.7)	63	0.4 (0.18)	-6, 4, 0	(0.0, 0.7)	0.0136	0.207	(-0.072, 0.486)	0.1035	
Self-Reliance	63	9.8 (0.38)	1, 14, 11	(9.0, 10.5)	63	10.9 (0.32)	1, 14, 11	(10.3, 11.5)	63	50.2 (1.18)	13, 62, 51	(47.9, 52.6)	60	1.2 (0.44)	-7, 9, 1	(0.3, 2.1)	0.0129	0.164	(-0.117, 0.446)	0.2099	

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Table 9. Change in BASC (Parent and Child Version) Subscales and Correlation with Change in ADHDRS-IV-Parent:Inv for Patients who Completed Visit 12 (1 Year) (Concluded)

	Baseline Raw Score				Endpoint Raw Score				Endpoint T-Score				Change in Raw Score from Baseline to Endpoint				p-value ¹	Correlation with Change in ADHDRS-Parent:Inv	95% CI	p-value ²
	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI				
BASC - Parent Rating																				
Clinical Scales:																				
Hyperactivity	66	14.3 (0.68)	3, 29, 13	(12.9, 15.6)	66	8.1 (0.58)	0, 22, 7	(6.9, 9.2)	66	52.0 (1.57)	30, 89, 49	(48.9, 55.2)	66	-6.2 (0.62)	-19, 8, -6	(-7.4, -5.0)	<.0001	0.682	(0.550, 0.814)	<.0001
Aggression	66	13.6 (0.79)	2, 30, 14	(12.1, 15.2)	66	10.2 (0.67)	1, 24, 9	(8.9, 11.5)	66	53.5 (1.53)	32, 85, 51	(50.4, 56.5)	66	-3.4 (0.55)	-14, 6, -3	(-4.5, -2.3)	<.0001	0.521	(0.367, 0.674)	<.0001
Conduct Problems	66	7.3 (0.54)	0, 17, 7	(6.2, 8.4)	66	5.2 (0.46)	0, 14, 6	(4.2, 6.1)	66	56.8 (1.75)	37, 91, 58	(53.3, 60.3)	66	-2.1 (0.42)	-13, 4, -2	(-3.0, -1.3)	<.0001	0.416	(0.257, 0.575)	0.0005
Anxiety	66	11.9 (0.66)	0, 26, 11	(10.5, 13.2)	66	9.7 (0.65)	1, 26, 9	(8.4, 11.0)	66	47.8 (1.36)	29, 82, 46	(45.1, 50.5)	66	-2.1 (0.59)	-14, 13, -2	(-3.3, -0.9)	0.0006	0.221	(0.009, 0.434)	0.0739
Depression	66	12.1 (0.81)	0, 34, 12	(10.5, 13.7)	66	8.2 (0.63)	0, 22, 8	(6.9, 9.4)	66	53.3 (1.47)	34, 86, 53	(50.4, 56.3)	66	-3.9 (0.74)	-22, 7, -3	(-5.4, -2.5)	<.0001	0.463	(0.281, 0.645)	<.0001
Somatization	66	4.2 (0.40)	0, 13, 4	(3.4, 5.0)	66	4.0 (0.34)	0, 12, 4	(3.3, 4.7)	66	47.3 (0.99)	36, 71, 47	(45.3, 49.3)	66	-0.2 (0.35)	-9, 8, 0	(-0.9, 0.6)	0.6697	0.104	(-0.152, 0.359)	0.4081
Atypicality	66	6.2 (0.50)	0, 19, 6	(5.2, 7.2)	66	3.5 (0.33)	0, 13, 3	(2.8, 4.2)	66	52.5 (1.41)	38, 93, 50	(49.6, 55.3)	66	-2.7 (0.41)	-13, 7, -2	(-3.5, -1.9)	<.0001	0.432	(0.260, 0.604)	0.0003
Withdrawal	66	5.6 (0.46)	0, 16, 5	(4.7, 6.5)	66	4.5 (0.36)	0, 15, 4	(3.8, 5.2)	66	48.9 (1.14)	35, 82, 47	(46.6, 51.2)	66	-1.1 (0.35)	-9, 5, -1	(-1.8, -0.4)	0.0040	0.357	(0.188, 0.527)	0.0032
Attention Problems	66	15.3 (0.30)	10, 21, 16	(14.7, 15.9)	66	11.2 (0.40)	2, 18, 12	(10.4, 12.0)	66	61.0 (1.04)	37, 79, 62	(59.0, 63.1)	66	-4.1 (0.46)	-14, 4, -4	(-5.0, -3.2)	<.0001	0.638	(0.503, 0.772)	<.0001
Adaptive Scales:																				
Adaptability	66	9.6 (0.38)	1, 20, 10	(8.8, 10.4)	66	11.4 (0.40)	5, 20, 11	(10.6, 12.2)	66	42.5 (1.12)	25, 67, 41	(40.2, 44.7)	66	1.8 (0.34)	-4, 7, 2	(1.1, 2.4)	<.0001	-.300	(-0.498, -0.102)	0.0145
Social Skills	66	19.7 (0.79)	5, 39, 18	(18.1, 21.2)	66	22.7 (0.81)	11, 38, 23	(21.0, 24.3)	66	45.2 (1.16)	28, 67, 45	(42.8, 47.5)	66	3.0 (0.71)	-11, 23, 2	(1.6, 4.4)	<.0001	-.536	(-0.659, -0.412)	<.0001
Leadership	66	15.0 (0.50)	7, 27, 15	(14.1, 16.0)	66	15.5 (0.57)	5, 27, 16	(14.4, 16.6)	66	43.5 (1.03)	25, 64, 44	(41.4, 45.6)	66	0.5 (0.55)	-12, 13, 1	(-0.7, 1.6)	0.4149	-.076	(-0.285, 0.133)	0.5429

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; BASC = Behavior Assessment System for Children; CI = confidence interval; Min = minimum; Max = maximum; N = number of patients; SD = standard deviation of mean.

- ¹ p-value using a paired t-test or Wilcoxon signed rank test comparing the mean change in BASC (parent and child version) subscale scores to zero for patients completing Visit 12.
- ² p-value comparing the correlation between change in ADHDRS-IV-Parent:Inv and change in BASC (parent and child version) subscale scores to zero for patients completing Visit 12.

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Table 10. Change in ADHDRS-IV-Parent:Inv Scores for Patients who Completed Visit 9 (6 Months) or Later

	Baseline N	Baseline Score, Mean (SD), Median, Min, Max, 95% CI	Change N	Change, Mean (SD), Median, Min, Max, 95% CI	p-value ¹
ADHD Rating Scale-IV: Parent Version - Investigator Scored:					
Total Score	75	37.9 (0.88), 38, 16, 54, (36.2, 39.7)	75	-20.9 (1.27), -22, -45, 3, (-23.5, -18.4)	<.0001
Subscale Scores:					
Inattention	75	21.3 (0.42), 21, 11, 27, (20.4, 22.1)	75	-11.0 (0.73), -11, -26, 5, (-12.5, -9.6)	<.0001
Hyperactive/Impulsive	75	16.6 (0.70), 17, 5, 27, (15.2, 18.0)	75	-9.9 (0.71), -9, -25, 3, (-11.3, -8.5)	<.0001

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CI = confidence interval; Min = minimum; Max = maximum; N = number of patients; SD = standard deviation of mean.

¹ p-value using a paired t-test comparing the mean change in ADHDRS-IV-Parent:Inv score to zero for patients completing Visit 9 or later.

Table 11. Change in ADHDRS-IV-Parent:Inv Scores for Patients who Completed Visit 12 (1 Year)

	Baseline N	Baseline Score, Mean (SD), Median, Min, Max, 95% CI	Change N	Change, Mean (SD), Median, Min, Max, 95% CI	p-value ¹
ADHD Rating Scale-IV: Parent Version - Investigator Scored:					
Total Score	66	37.6 (1.01), 38, 15, 54, (35.6, 39.6)	66	-21.8 (1.43), -22, -47, 4, (-24.6, -18.9)	<.0001
Subscale Scores:					
Inattention	66	21.0 (0.49), 21, 10, 27, (20.1, 22.0)	66	-11.4 (0.79), -12, -26, 3, (-13.0, -9.8)	<.0001
Hyperactive/Impulsive	66	16.6 (0.78), 17, 5, 27, (15.0, 18.1)	66	-10.4 (0.82), -9, -26, 3, (-12.0, -8.8)	<.0001

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CI = confidence interval; Min = minimum; Max = maximum; N = number of patients; SD = standard deviation of mean.

¹ p-value using a paired t-test comparing the mean change in ADHDRS-IV-Parent:Inv score to zero for patients completing Visit 12.

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Table 12. Change in CGI-ADHD-S and Correlation with Change in ADHDRS-IV-Parent:Inv for Patients who Completed Visit 9 (6 Months) or Later

																	Correlation with Change in ADHD RS- Parent:Inv			p- value ²
	Baseline Score				Endpoint Score				Change from Baseline to Endpoint				p- value ¹	95% CI						
	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI								
CGI-ADHD-S	75	4.6 (0.09)	3, 7, 4	(4.4, 4.8)	75	2.4 (0.13)	1, 5, 2	(2.1, 2.7)	75	-2.2 (0.15)	-5, 0, -2	(-2.5, - 1.9)	<.0001	0.667	(0.532, 0.802)	<.0001				

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CGI-ADHD-S = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity scale; CI = confidence interval; Min = minimum; Max = maximum; N = number of patients; SD = standard deviation of mean.

¹ p-value using a Wilcoxon signed rank test comparing the mean change in CGI-ADHD-S score to zero for patients completing Visit 9 or later.

² p-value comparing the correlation between change in ADHDRS-IV-Parent:Inv and change in CGI-ADHD-S score to zero for patients completing Visit 9 or later.

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Table 13. Change in CGI-ADHD-S and Correlation with Change in ADHDRS-IV-Parent:Inv for Patients who Completed Visit 12 (1 Year)

													Correlation with Change in ADHD RS-Parent:Inv			
	Baseline Score				Endpoint Score				Change from Baseline to Endpoint				p-value ¹	95% CI	p-value ²	
	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI				
CGI-ADHD-S	66	4.6 (0.10)	3, 7, 4	(4.4, 4.8)	66	2.3 (0.13)	1, 4, 2	(2.0, 2.5)	66	-2.3 (0.16)	-5, 0, -2	(-2.6, - 2.0)	<.0001	0.672	(0.536, 0.808)	<.0001

Abbreviations: ADHDRS-IV-Parent: Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CGI-ADHD-S= Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity scale; CI = confidence interval; Min = minimum; Max = maximum; N = number of patients; SD = standard deviation of mean.

¹ p-value using a Wilcoxon signed rank test comparing the mean change in CGI-ADHD-S score to zero for patients completing Visit 12.

² p-value comparing the correlation between change in ADHDRS-IV-Parent:Inv and change in CGI-ADHD-S score to zero for patients completing Visit 12.

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Table 14. Change in WFIRS-P Total and Subscale Scores and Correlation with Change in ADHDRS-IV-Parent:Inv for Patients who Completed Visit 9 (6 Months) or Later

	Change from Baseline												Correlation with Change in ADHDRS- Parent:Inv	95% CI	p-value ²	
	Baseline Score				Endpoint Score				to Endpoint							p-value ¹
	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI				
Total	72	0.996 (0.052)	0.3, 2.4, 1.0	(0.892, 1.100)	72	0.586 (0.045)	0.0, 1.7, 0.5	(0.496, 0.677)	72	-0.410 (0.053)	-1.6, 0.9, -0.4	(-0.515, -0.304)	<.0001	0.510	(0.321, 0.699)	<.0001
Things at home	72	1.104 (0.070)	0.2, 2.7, 1.0	(0.964, 1.244)	72	0.763 (0.078)	0.0, 2.7, 0.7	(0.607, 0.919)	72	-0.340 (0.079)	-1.8, 1.6, -0.3	(-0.497, -0.184)	<.0001	0.353	(0.131, 0.576)	0.0023
Self-concept	72	1.171 (0.097)	0.0, 3.0, 1.0	(0.978, 1.365)	72	0.856 (0.092)	0.0, 3.0, 0.7	(0.674, 1.039)	72	-0.315 (0.105)	-3.0, 2.7, -0.3	(-0.525, -0.105)	0.0008	0.335	(0.155, 0.514)	0.0041
Things at school	72	1.380 (0.078)	0.2, 2.9, 1.3	(1.225, 1.536)	72	0.673 (0.059)	0.0, 2.4, 0.6	(0.554, 0.791)	72	-0.708 (0.089)	-2.3, 1.1, -0.7	(-0.885, -0.530)	<.0001	0.434	(0.220, 0.649)	0.0001
Social activities	72	1.118 (0.087)	0.0, 3.0, 1.0	(0.945, 1.291)	72	0.589 (0.075)	0.0, 2.3, 0.4	(0.441, 0.738)	72	-0.529 (0.082)	-2.3, 1.1, -0.4	(-0.692, -0.365)	<.0001	0.498	(0.298, 0.698)	<.0001
Activities of daily living	72	0.905 (0.059)	0.0, 2.4, 0.9	(0.786, 1.023)	72	0.577 (0.048)	0.0, 1.8, 0.5	(0.482, 0.672)	72	-0.328 (0.057)	-1.5, 1.0, -0.3	(-0.441, -0.215)	<.0001	0.229	(0.002, 0.457)	0.0519
Risky activities	72	0.437 (0.048)	0.0, 1.7, 0.4	(0.341, 0.533)	72	0.260 (0.029)	0.0, 0.9, 0.2	(0.202, 0.318)	72	-0.177 (0.040)	-1.2, 0.7, -0.1	(-0.258, -0.097)	<.0001	0.367	(0.183, 0.552)	0.0015

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CI = confidence interval; Min = minimum; Max = maximum; N = number of patients; SD = standard deviation of mean; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

¹ p-value using a paired t-test comparing the mean change in total and subscale scores of the WFIRS-P to zero for patients completing Visit 9 or later.

² p-value comparing the correlation between change in ADHDRS-IV-Parent:Inv and change in total and subscale scores of the WFIRS-P to zero for patients completing Visit 9 or later.

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Table 15. Change in WFIRS-P Total and Subscale Scores and Correlation with Change in ADHDRS-IV-Parent:Inv for Patients who Completed Visit 12 (1 Year)

	Change from Baseline												Correlation with Change in ADHDRS- Parent:Inv	95% CI	p-value ²	
	Baseline Score				Endpoint Score				to Endpoint							p-value ¹
	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI				
Total	65	0.990 (0.057)	0.3, 2.4, 0.9	(0.876, 1.104)	65	0.568 (0.048)	0.0, 1.7, 0.5	(0.471, 0.664)	65	-0.422 (0.057)	-1.6, 0.9, -0.4	(-0.537, -0.308)	<.0001	0.520	(0.332, 0.707)	<.0001
Things at home	65	1.091 (0.071)	0.2, 2.7, 1.0	(0.950, 1.232)	65	0.743 (0.081)	0.0, 2.7, 0.6	(0.581, 0.904)	65	-0.349 (0.083)	-1.8, 1.6, -0.3	(-0.515, -0.183)	<.0001	0.394	(0.167, 0.621)	0.0012
Self-concept	65	1.267 (0.105)	0.0, 3.0, 1.0	(1.057, 1.476)	65	0.836 (0.097)	0.0, 3.0, 0.7	(0.642, 1.030)	65	-0.431 (0.118)	-3.0, 2.7, -0.3	(-0.667, -0.194)	<.0001	0.258	(0.020, 0.496)	0.0382
Things at school	65	1.380 (0.085)	0.0, 2.9, 1.3	(1.210, 1.551)	65	0.644 (0.064)	0.0, 2.4, 0.5	(0.517, 0.771)	65	-0.737 (0.092)	-2.3, 1.1, -0.7	(-0.920, -0.553)	<.0001	0.392	(0.170, 0.614)	0.0012
Social activities	65	1.081 (0.093)	0.0, 3.0, 1.0	(0.895, 1.267)	65	0.503 (0.075)	0.0, 2.3, 0.3	(0.354, 0.652)	65	-0.578 (0.082)	-2.3, 1.1, -0.4	(-0.741, -0.415)	<.0001	0.454	(0.243, 0.664)	0.0001
Activities of daily living	65	0.923 (0.067)	0.0, 2.4, 0.9	(0.788, 1.057)	65	0.615 (0.052)	0.0, 1.8, 0.5	(0.511, 0.718)	65	-0.308 (0.067)	-1.5, 1.0, -0.3	(-0.442, -0.173)	<.0001	0.347	(0.115, 0.579)	0.0044
Risky activities	65	0.412 (0.053)	0.0, 1.7, 0.3	(0.305, 0.518)	65	0.254 (0.031)	0.0, 0.9, 0.2	(0.191, 0.316)	65	-0.158 (0.046)	-1.2, 0.7, -0.1	(-0.250, -0.066)	0.0010	0.376	(0.192, 0.561)	0.0020

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CI = confidence interval; Min = minimum; Max = maximum; N = number of patients; SD = standard deviation of mean; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

- 1 p-value using a paired t-test comparing the mean change in total and subscale scores of the WFIRS-P to zero for patients completing Visit 12.
- 2 p-value comparing the correlation between change in ADHDRS-IV-Parent:Inv and change in total and subscale scores of the WFIRS-P to zero for patients completing Visit 12.

Safety

All enrolled patients (N=105) received at least one dose of study drug. No deaths occurred during this study. One serious adverse events was reported, suicidal ideation, which occurred at Month 6 and which the investigator believed was possibly related to study drug. This event led to study discontinuation. Table 16 summarizes the treatment-emergent adverse events with $\geq 5\%$ incidence rate. Table 17 summarizes the change from baseline to endpoint in vital signs, height, and weight.

Table 16. Treatment-Emergent Adverse Events with $\geq 5\%$ Incidence Rate

	N=105
Patients reporting at least one TEAE	99 (94.3)
Preferred Term [n (%)]	
Decreased appetite	46 (43.8)
Headache	41 (39.0)
Vomiting	40 (38.1)
Nausea	28 (26.7)
Abdominal pain upper	26 (24.8)
Fatigue	26 (24.8)
Somnolence	21 (20.0)
Nasopharyngitis	20 (19.0)
Cough	17 (16.2)
Influenza	17 (16.2)
Pyrexia	13 (12.4)
Irritability	12 (11.4)
Weight decreased	12 (11.4)
Pharyngolaryngeal pain	11 (10.5)
Upper respiratory tract infection	10 (9.5)
Rash	9 (8.6)
Dizziness	9 (8.6)
Affect lability	7 (6.7)
Insomnia	7 (6.7)
Anorexia	6 (5.7)
Pharyngitis streptococcal	6 (5.7)

Abbreviations: n = number of patients; N = total number of patients; TEAE = treatment-emergent adverse event.

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Table 17. Mean Change in Vital Signs from Baseline to Endpoint

	Baseline				Endpoint				Change				p-value*
	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	N	Mean (SD)	Min, Max, Median	95% CI	
Diastolic BP (mm Hg)	105	66.4 (0.78)	37, 83, 66	(64.9, 68.0)	104	67.7 (0.64)	56, 83, 67	(66.4, 69.0)	104	1.3 (0.84)	-20, 21, 1.3	(-0.4, 2.9)	0.1353
Systolic BP (mm Hg)	105	102.1 (0.91)	81, 121, 101	(100.3, 103.9)	104	102.3 (0.85)	80, 125, 102	(100.7, 104.0)	104	0.3 (1.03)	-37, 24, 0.5	(-1.7, 2.4)	0.7383
Height (cm)	102	137.0 (0.70)	119, 152, 137	(135.6, 138.4)	95	141.6 (0.76)	124, 159, 141	(140.1, 143.1)	92	4.3 (0.24)	0, 11, 4.0	(3.9, 4.8)	<.0001
Weight (kg)	105	35.5 (0.78)	24, 65, 35	(33.9, 37.0)	104	35.1 (0.76)	23, 69, 34	(33.6, 36.7)	104	-0.3 (0.27)	-11, 6, 0.0	(-0.8, 0.2)	0.3965

Abbreviations: BP = blood pressure; CI = confidence interval; Min = minimum; Max = maximum; N = total number of patients; SD = standard deviation of mean.

* p-value using a paired t-test or Wilcoxon signed rank test comparing the mean change to zero.

References:

DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. 1998. ADHD Rating Scale IV. Checklist, norms, and clinical interpretations. New York: The Guilford Press.

Faries DE, Yalcin D, Harder D, Heiligenstein JH. 2001. Validation of the ADHD Rating Scale as a clinician-administered and scored instrument. J Atten Disord 5(2):107-111.

Gioia GA, Isquith PK, Guy SC, Kenworthy L. 2000. Behavior Rating Inventory of Executive Function™ (BRIEF™). Odessa, FL: Psychological Assessment Resources.

Guy W. 1976. ECDEU assessment manual for psychopharmacology, revised. Bethesda, MD: US Department of Health, Education, and Welfare.

Reynolds CR, Kamphaus RW. 1992. Behavior Assessment System for Children (BASC). Circle Pines, MN: AGS Publishing.

Woodcock RW, McGrew KS, Mather N. 2000. Woodcock-Johnson III Tests of Achievement® (WJ III®). Itasca, IL: Riverside Publishing.

Summary ID# 7951

Clinical Study Summary: Study B4Z-MC-LYCG

Atomoxetine Augmentation of Cholinesterase Inhibitor Therapy in Patients with Alzheimer's Disease

Date summary approved by Lilly: 08 May 2007

Brief Summary of Results

Study B4Z-MC-LYCG (LYCG) was a multicenter, randomized, double-blind, parallel trial with 2 study periods. Study Period I was a 5- to 33-day evaluation and screening period and Study Period II was an approximately 6-month, acute treatment period. Alzheimer's disease (AD) involves perturbation of the cholinergic neurotransmitter system, which forms the basis for the use of cholinesterase inhibitors (CIs), medications that block acetylcholine breakdown. Dysfunction of other neurotransmitters has been implicated as well.

The study's primary objective was to test the hypothesis that patients with AD already receiving stable pharmacologic and other treatments consistent with the current standard of care who were randomly assigned to 6 months of atomoxetine (ATX) treatment would have improved cognitive performance compared with similar patients (on stable treatments) randomly assigned to receive placebo (PLA). Atomoxetine is a selective norepinephrine reuptake inhibitor, which has beneficial effects in Attention-Deficit/Hyperactivity Disorder, and was thought to have some potential for benefiting Alzheimer's patients. Cognitive performance was measured by the Alzheimer's Disease Assessment Scale - Cognitive Portion (ADAS-Cog).

This study was terminated following a futility analysis involving the ADAS – Cog score before the planned number of patients had been fully enrolled.

The study's secondary objectives were:

- To test the hypothesis that in patients with AD who had been treated with a CI, adding ATX would be superior to continued therapy with CI alone in improving overall clinical function as assessed by the mean Clinician's Interview-Based Impression of Change (CIBIC+) score at endpoint.
- To test the hypothesis that patients with AD who had taken both a CI and ATX would display fewer comorbid psychological symptoms as assessed by total score on the Neuropsychiatric Inventory (NPI).
- To determine the efficacy of CI plus ATX compared to CI plus PLA in preserving function or slowing functional decline as measured by Alzheimer's Disease Cooperative Study Inventory-Activities of Daily Living Inventory (ADCS-ADL) total score.
- To demonstrate that CIs and ATX could be taken together without significant side effects.

Results of the study did not demonstrate a statistically significant difference between ATX + CI treatment and PLA + CI treatment in reducing symptoms of AD in patients treated concurrently with CIs. There was no statistically significant evidence showing that ATX has an effect on neuropsychiatric symptoms or clinician's global ratings.

The key results of the study are as follows:

- The primary efficacy measure of mean change from baseline to endpoint in the ADAS-Cog total score did not demonstrate a statistically significant difference between the treatment groups.
- There were no statistically significant improvements between treatment groups in the secondary efficacy measures of change from baseline to endpoint of the CIBIC+, Mini Mental State Examination (MMSE), Clinical Global Impressions – Severity of Illness (CGI-S), and NPI scores.
- The ATX + CI group showed statistically significantly less functional decline over the treatment period compared with the PLA + CI group as measured by ADCS-ADL total score.
- There were no statistically significant differences between treatment groups with respect to treatment-emergent adverse events (TEAEs).
- There was no statistically significant difference between treatment groups in the proportions of patients with abnormal laboratory values.

- There was no statistically significant difference between treatment groups in the proportions of patients who met categorical criteria in vital signs, weight, and adjusted QTc values. Mean change from baseline to endpoint, last-observation-carried-forward (LOCF) analysis found there were statistically significant differences between treatment groups in the following measures: diastolic blood pressure, pulse, weight, heart rate, RR, and QT intervals.
- There were no deaths during the study.

Title of Study: Atomoxetine Augmentation of Cholinesterase Inhibitor Therapy in Patients with Alzheimer's Disease	
Investigator(s): This multicenter study included 7 principal investigators.	
Study Center(s): This study was conducted at 8 study centers in 1 country (1 investigator had 2 sites).	
Length of Study: 28 months Date first patient enrolled: 01 Oct 2003 Date last patient completed: 31 Jan 2006	Phase of Development: 2/3
Objectives: The primary objective of this study was to test the hypothesis that patients with AD receiving stable pharmacologic and other treatments consistent with the current standard of care, randomly assigned to receive ATX (25 to 80 mg) for approximately 6 months had improved cognitive performance as measured by the ADAS-Cog compared with similar patients on stable treatments randomly assigned to receive PLA. The secondary objectives of the study were: • To test the hypothesis that in patients with AD who had been treated with a CI, the addition of ATX 25 to 80 mg for approximately 6 months was superior to continued therapy with CI alone in improving overall clinical function as assessed by the mean CIBIC+ score at endpoint. • To test the hypothesis that patients with AD who had taken both a CI and ATX would display less comorbid psychological symptoms, such as depression, as assessed by the total score on the NPI. • To determine the efficacy of CI plus ATX compared to CI plus placebo in preservation of function or slowing of functional decline as measured by ADCS-ADL total score. • To demonstrate that CIs and ATX could be taken together without significant side effects.	
Study Design: Study LYCG was a multicenter, randomized, double-blind, parallel trial with 2 study periods. Study Period I was a 5- to 33-day evaluation and screening period and Study Period II was an approximately 6-month, acute treatment period.	
Number of Patients: Planned: 124 Randomized: 47 ATX + CI treatment group, 45 PLA + CI treatment group. Completed: 38 ATX + CI treatment group, 35 PLA + CI treatment group	
Diagnosis and Main Criteria for Inclusion: Patients were males or nonfertile females, 55 years of age or older. For inclusion, patients must have met the AD criteria as defined by an MMSE score between 10 and 26 (inclusive) at Visits 1 and 2 and presented with AD based on clinical history, defined by National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) guidelines. Patients must have been currently treated with an adequate dose of a CI for at least 3 months, with the dose unchanged in the last month prior to Visit 1. Patients were to have an electrocardiogram (ECG) performed at Visits 1 and 6.	
Test Product, Dose, and Mode of Administration: At Visit 2, ATX was given as a single, daily, oral dose of 40 mg/day. After 2 weeks, if this dose was well tolerated, the dose was increased to 60 mg/day	

at Visit 4. After 6 weeks, if in the opinion of the investigator the 60 mg/day was well tolerated, a further dose increase to 80 mg/day was instituted at Visit 6.
Reference Therapy, Dose, and Mode of Administration: Placebo tablets, given orally, once a day. All patients were being treated pharmacologically in accordance with current standards of clinical care. All patients received CI within the approved dosage range and had been stable on that dose for a minimum of 3 months prior to randomization. Eleven patients receiving memantine were randomized according to the same stability and prior treatment.
Duration of Treatment: 6 months
Variables: <u>Efficacy:</u> The primary efficacy measure was the mean change from baseline to endpoint in the ADAS-Cog total score. Secondary efficacy measures included: CIBIC+, MMSE, NPI, and CGI-S scores. <u>Safety:</u> Adverse events (AEs), laboratory tests, and ECGs. <u>Health Outcomes:</u> ADCS-ADL total score.
Methods: <u>Statistical:</u> All efficacy evaluations were performed according to an intent-to-treat (ITT) analysis. The efficacy analyses used a last-observation-carried-forward (LOCF) approach for all randomized patients with at least 1 baseline and 1 postbaseline measurement. For the ADAS-Cog and NPI scales, the total scores were treated as missing when more than 20% of the items were missing or scored “not applicable.” When 1 or more items (but not more than 20%) were missing, the total score was adjusted in order to maintain the full range of the scale. For example, ADAS-Cog is a 0 to 70 scale. If the first item, word recall, which ranges from 0 to 10, was missing, then the remaining 10 items were summed and multiplied by 7/6 (that is, 70/[70-10]). If 3 or more items were missing, then the total score on the ADAS-Cog was not computed. For the remaining measures, if any of the individual scale items were missing, then the associated total score was treated as missing. Scores and subscale scores were summarized by the change from baseline and the treatment effects were tested using analysis of covariance (ANCOVA) model with prespecified independent effects. A 2-sided, 0.05 significance level was used for all statistical tests, unless otherwise specified. Safety evaluations were performed for all randomized patients who took at least 1 dose of study drug. Treatment-emergent adverse events (TEAEs), discontinuation due to AE, and other categorical variables were summarized and compared between treatment groups using Fisher’s exact test. The analysis of variance (ANOVA) model was used to test for treatment differences in laboratory values, continuous ECG parameters, and vital signs.

Results:

Patient Demographics

In the ATX + CI group, 93.6% of patients were Caucasian; in the PLA + CI group, 91.1% were Caucasian. Their mean age was 76.6 years in the ATX + CI group and 78.4 years in the PLA + CI group. In the ATX + CI group, 22 (46.8%) patients were female and 25 patients (53.2%) were male. In the PLA + CI group, 28 (62.2%) patients were female and 17 (37.8%) patients were male (Table 1).

Table 1. Patient Demographic Characteristics at Baseline for All Randomized Patients

Variable	n	ATX + CI	n	PLA + CI	p-Value
Gender	47		45		
Female		22 (46.8%)		28 (62.2%)	.150 ^a
Male		25 (53.2%)		17 (37.8%)	
Origin	47		45		
African Descent		2 (4.3%)		2 (4.4%)	.851 ^a
Caucasian		44 (93.6%)		41 (91.1%)	
Hispanic		1 (2.1%)		2 (4.4%)	
Age in Years	47		45		
Mean		76.6		78.4	.246 ^b
Minimum		57.1		55.3	
Maximum		90.4		90.3	

Abbreviations: ATX + CI = atomoxetine hydrochloride plus cholinesterase inhibitor; n = number of patients; PLA + CI = placebo plus cholinesterase inhibitor.

^a Frequencies are analyzed using a Fisher's exact test.

^b Means are analyzed using Type III sum of squares analysis of variance (ANOVA).

Patient Disposition

A total of 92 patients were enrolled in the approximately 6-month LYCG study. The most frequent reason for discontinuation was an AE; (5 patients; 10.6%) in the ATX + CI treatment group and (4 patients; 8.9%) in the PLA + CI treatment group. There were no statistically significant differences between the 2 treatment groups for any discontinuation reason (see Table 2).

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**Table 2. Summary of Primary Reason for Study Discontinuation
All Randomized Patients**

Primary Reason for Discontinuation	ATX + CI N=47 n (%)	PLA + CI N=45 n (%)	Total N=92 n (%)	Fisher's Exact p-Value
Protocol Complete	38 (80.9)	35 (77.8)	73 (79.3)	.799
Adverse event	5 (10.6)	4 (8.9)	9 (9.8)	1.00
Personal conflict or other patient caregiver decision	1 (2.1)	3 (6.7)	4 (4.3)	.356
Physician decision	1 (2.1)	1 (2.2)	2 (2.2)	1.00
Sponsor decision	1 (2.1)	1 (2.2)	2 (2.2)	1.00
Lack of efficacy, patient caregiver perception	1 (2.1)	0 (0.0)	1 (1.1)	1.00
Protocol violation	0 (0.0)	1 (2.2)	1 (1.1)	.489

ATX + CI: Atomoxetine Plus Cholinesterase Inhibitor; PLA + CI: Placebo Plus Cholinesterase Inhibitor

Primary Efficacy Measures

Results of the primary efficacy analysis of mean change from baseline to endpoint on the ADAS-Cog total score did not demonstrate a statistically significant difference between the 2 treatment groups (see Table 3).

**Table 3. Alzheimer's Disease Assessment Scale
Cognitive Subscale Total Score
Change from Baseline to Endpoint**

Treatment Group	n	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	Between Group p-Value
ATX + CI	46	21.72 (10.7)	22.48 (12.8)	0.76 (5.94)	0.484 ^a
PLA + CI	44	21.25 (10.4)	21.13 (10.8)	-0.12 (4.96)	--

Abbreviations: ATX + CI = atomoxetine hydrochloride plus cholinesterase inhibitor; n = number of patients; PLA + CI = placebo plus cholinesterase inhibitor; SD = standard deviation.

^a p-Value is based on an analysis of covariance (ANCOVA) model on change from baseline scores with terms for baseline, treatment, pooled investigator and Mini Mental State Exam (MMSE) stratum.

Secondary Efficacy Measures

Table 4 summarizes the mean change from baseline to endpoint of the CIBIC+ score. There was no statistically significant difference between treatment groups based on CIBIC+ scores. The results of mean change from baseline to endpoint analyses in MMSE, CGI-S, and NPI scores (Tables 5 through 7) did not show statistically significant differences between the treatment groups.

**Table 4. Clinician Interview-Based Impression of Severity Score
Change from Baseline to Endpoint**

Variable	ATX + CI	PLA + CI	p-Value	95% CI
CIBIC+ Score at Endpoint	N=47	N=45	.853b	(-0.32, 0.39)
Mean	4.4	4.3		
SD	0.9	0.9		
CIBIC + Score at Baseline	N=46	N=45	.426a	(-0.36, 0.15)
Mean	3.6	3.7		
SD	0.6	0.6		

Abbreviations: 95% CI = 95% confidence interval; ATX + CI = atomoxetine hydrochloride plus cholinesterase inhibitor; CIBIC+ = Clinician's Interview-Based Impression of Change; N = number of patients; PLA + CI = placebo plus cholinesterase inhibitor; SD = standard deviation.

^a p-Value is based on an analysis of variance (ANOVA) model with the term treatment.

^b p-Value is based on an analysis of variance (ANOVA) model with terms of treatment, pooled investigator and Mini Mental State Exam (MMSE) stratum.

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**Table 5. Mini-Mental State Exam Total Score
Mean Change from Baseline to Endpoint
All Randomized Patients Who Took at Least 1 Dose of Study Drug**

Variable		Baseline		Endpoint		Change		Within Group	Between Group
Treatment	N	Mean	SD	Mean	SD	Mean	SD	p-value (a)	p-value (b)
ATX + CI	46	20.26	4.48	21.41	5.96	1.15	2.95	0.011	0.317
PLA + CI	45	20.27	4.21	20.84	5.30	0.58	2.77	0.168	—

95% Confidence Interval for Treatment Difference: (-0.59 , 1.80)

ATX + CI: Atomoxetine Plus Cholinesterase Inhibitor; PLA + CI: Placebo Plus Cholinesterase Inhibitor

(a): P-value is from paired t-test.

(b): P-value is based on an ANCOVA on change from baseline scores with terms for baseline, treatment and pooled investigator.

**Table 6. Clinical Global Impression – Severity of Alzheimer's Disease
Mean Change from Baseline to Endpoint
All Randomized Patients Who Took at Least 1 Dose of Study Drug**

Variable		Baseline		Endpoint		Change		Within Group	Between Group
Treatment	N	Mean	SD	Mean	SD	Mean	SD	p-value (a)	p-value (b)
ATX + CI	46	3.48	0.69	3.46	0.75	-0.02	0.49	0.767	0.970
PLA + CI	44	3.68	0.60	3.59	0.62	-0.09	0.52	0.253	—

95% Confidence Interval for Treatment Difference: (-0.20 , 0.20)

ATX + CI: Atomoxetine Plus Cholinesterase Inhibitor; PLA + CI: Placebo Plus Cholinesterase Inhibitor

(a): P-value is from paired t-test.

(b): P-value is based on an ANCOVA on change from baseline scores with terms for baseline, treatment, pooled investigator and Mini-Mental State Exam Stratum.

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**Table 7. Summary of Neuropsychiatric Inventory Distress Subscales and Totals
Imputed Mean Change from Baseline to Endpoint
All Randomized Patients Who Took at Least 1 Dose of Study Drug**

Variable		Baseline		Endpoint		Change		Within Group	Between Group
Treatment	N	Mean	SD	Mean	SD	Mean	SD	p-value (a)	p-value (b)
NPI item A-J total imputed									
ATX + CI	46	5.59	11.37	8.15	16.13	2.57	7.74	0.029	0.733
PLA + CI	45	6.93	7.44	9.02	11.85	2.09	10.94	0.207	—
95% Confidence Interval for Treatment Difference: (-3.08 , 4.36)									
NPI item A-J distress subscale imputed									
ATX + CI	46	3.41	5.23	5.07	6.55	1.65	4.42	0.015	0.318
PLA + CI	45	4.31	4.48	4.78	6.02	0.47	5.76	0.589	—
95% Confidence Interval for Treatment Difference: (-0.99 , 3.02)									
NPI item A-L total imputed									
ATX + CI	46	6.76	14.06	10.59	18.17	3.83	8.91	0.006	0.500
PLA + CI	45	8.42	8.66	10.91	13.99	2.49	12.30	0.182	—
95% Confidence Interval for Treatment Difference: (-2.71 , 5.52)									
NPI item A-L distress subscale imputed									
ATX + CI	46	3.72	5.41	5.91	7.23	2.20	4.82	0.003	0.219
PLA + CI	45	4.80	4.71	5.56	7.01	0.76	6.20	0.418	—
95% Confidence Interval for Treatment Difference: (-0.82 , 3.53)									
ATX + CI: Atomoxetine Plus Cholinesterase Inhibitor; PLA + CI: Placebo Plus Cholinesterase Inhibitor									

(a): P-value is from paired t-test.

(b): P-value is based on an ANCOVA on change from baseline scores with terms for baseline, treatment, pooled investigator and Mini-Mental State Exam Stratum.

Safety

The final prescribed mean daily dose of ATX (for the ATX + CI treatment group) was 63.91 mg/day with a minimum dose of 25 mg/day and a maximum dose of 80 mg/day. There were no deaths during this study.

Six patients had serious adverse events (SAEs) during the study (see Table 8). Two of the SAEs were determined by the investigator to be related or possibly related to study drug (1 ATX + CI patient, syncope, possibly related to study drug, and 1 PLA + CI patient, myocardial infarction, related to study drug).

**Table 8. Serious Adverse Events
All Randomized Patients**

Patient Number	Treatment Group	Visit at Discontinuation	Reason (Preferred Term)	Related to Study Drug
A	ATX + CI	5	Physician decision (Syncope)	Possibly Related
B	PLA + CI	6	Adverse Event (Myocardial infarction)	Related
C	ATX + CI	8	Personal Conflict (Pneumonia)	Not Related
D	PLA + CI	11	Protocol Completed (Vertigo)	Not Related
E	PLA + CI	10	Personal Conflict (Hypertension)	Not Related
F	PLA + CI	10	Personal Conflict (Head Injury)	Not Related

Abbreviations: ATX + CI = atomoxetine hydrochloride plus cholinesterase inhibitor; PLA + CI = placebo plus cholinesterase inhibitor.

Treatment-emergent adverse events (TEAEs) with $\geq 5\%$ incidence are summarized in Table 9. In the ATX + CI group, the most commonly reported TEAEs were nausea (7 patients; 15.2%) and decreased appetite (5 patients; 10.9%). The most commonly reported TEAE in the PLA + CI group was agitation (5 patients; 11.1%). All other AEs occurred in ≤ 4 patients for both groups.

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**Table 9. Summary of Treatment-Emergent Adverse Events with ≥5% Incidence
All Randomized Patients Who Took at Least 1 Dose of Study Drug**

Preferred Term	ATX + CI (N=46) n (%)	PLA + CI (N=45) n (%)	TOTAL (N=91) n (%)	Fisher's Exact p-Value
SUBJECTS WITH ≥1 TESS	35 (76.1)	29 (64.4)	64 (70.3)	0.257
SUBJECTS WITH NO TESS	11 (23.9)	16 (35.6)	27 (29.7)	0.257
Nausea	7 (15.2)	3 (6.7)	10 (11.0)	0.315
Insomnia	4 (8.7)	4 (8.9)	8 (8.8)	1.000
Dizziness	4 (8.7)	3 (6.7)	7 (7.7)	1.000
Agitation	1 (2.2)	5 (11.1)	6 (6.6)	0.111
Constipation	2 (4.3)	3 (6.7)	5 (5.5)	0.677
Contusion	4 (8.7)	1 (2.2)	5 (5.5)	0.361
Decreased appetite	5 (10.9)	0	5 (5.5)	0.056
Depression	4 (8.7)	1 (2.2)	5 (5.5)	0.361
Headache	2 (4.3)	3 (6.7)	5 (5.5)	0.677
Nasopharyngitis	1 (2.2)	4 (8.9)	5 (5.5)	0.203
Vomiting	3 (6.5)	2 (4.4)	5 (5.5)	1.000
Anorexia	3 (6.5)	0	3 (3.3)	0.242
Hyperhidrosis	3 (6.5)	0	3 (3.3)	0.242
Irritability	0	3 (6.7)	3 (3.3)	0.117

ATX + CI: Atomoxetine Plus Cholinesterase Inhibitor; PLA + CI: Placebo Plus Cholinesterase Inhibitor
MedDRA VERSION: 9.0

There were no statistically significant differences between treatment groups in the proportions of patients with abnormal laboratory values (above or below the normal range at anytime during the treatment period) (Table 10).

There were no statistically significant differences between treatment groups in the proportions of patients with abnormally high or low blood pressure, pulse, and weight based on prespecified criteria (Table 11). Following is the detailed criteria for each vital sign measure:

- Pulse:
 - High: Increase from baseline ≥ 15 to a value > 120
 - Low: Decrease from baseline ≥ 15 to a value < 50
- Systolic Blood Pressure:
 - High: Increase from baseline ≥ 20 to a value > 180
 - Low: Decrease from baseline ≥ 20 to a value ≤ 90
- Diastolic Blood Pressure:
 - High: Increase from baseline ≥ 15 to a value ≥ 105
 - Low: Decrease from baseline ≥ 15 to a value ≤ 50
- Weight (Kg):
 - High: Increase from baseline $> 7\%$
 - Low: Decrease from baseline $> 7\%$

There were statistically significant differences between treatment groups (Table 12) for mean change from baseline-to-endpoint analysis in: diastolic blood pressure (3.67 mm Hg in the ATX + CI group versus -1.16 mm Hg in PLA + CI group; $p=.019$); pulse (5.13 beats per minute [bpm] in the ATX + CI group versus -1.50 bpm in PLA + CI group; $p=.002$); and weight (-2.07 kg in the ATX + CI group versus 0.72 kg in PLA + CI group; $p<.001$). The difference between treatment groups for mean change in systolic blood pressure was not statistically significant (4.00 mm Hg in the ATX + CI group versus 2.58 mm Hg in PLA + CI group; $p=.681$). There were no statistically significant differences in other vital sign measures.

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Table 10. Summary of Laboratory Data
Frequency of Patients with Abnormal Laboratory Values after Baseline
All Randomized Patients Who Took at Least 1 Dose of Study Drug

Laboratory Group: Clinical Chemistry

Lab Test	Direction	-----ATX + CI-----			-----PLA + CI-----			p-Value*
		N	n	Percent	N	n	Percent	
Alanine transaminase (ALT/SGPT)	High	45	1	2.2	43	0	0.0	1.00
	Low	45	0	0.0	43	0	0.0	
Albumin	High	43	1	2.3	41	0	0.0	1.00
	Low	45	0	0.0	43	0	0.0	
Alkaline phosphatase	High	45	1	2.2	42	0	0.0	1.00
	Low	45	0	0.0	43	0	0.0	
Aspartate transaminase (AST/SGOT)	High	45	0	0.0	41	3	7.3	.104
	Low	45	0	0.0	41	0	0.0	
Blood urea nitrogen (BUN)	High	41	1	2.4	41	1	2.4	1.00
	Low	45	0	0.0	43	1	2.3	
Calcium	High	44	0	0.0	43	1	2.3	.494
	Low	45	0	0.0	43	0	0.0	
Cholesterol	High	44	0	0.0	42	0	0.0	1.00
	Low	25	4	16.0	29	5	17.2	
Creatine kinase (CK)	High	43	0	0.0	39	2	5.1	.223
	Low	45	0	0.0	43	0	0.0	
Gamma-glutamyl transferase (GGT)	High	42	0	0.0	42	0	0.0	

(continued)

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Table 10. Summary of Laboratory Data
Frequency of Patients with Abnormal Laboratory Values after Baseline
All Randomized Patients Who Took at Least 1 Dose of Study Drug (Continued)

Laboratory Group: Clinical Chemistry								
Lab Test	Direction	-----ATX + CI-----			-----PLA + CI-----			p-Value*
		N	n	Percent	N	n	Percent	
Gamma-glutamyl transferase (GGT)	Low	43	1	2.3	43	0	0.0	1.00
Glucose, nonfasting	High	44	1	2.3	43	0	0.0	1.00
	Low	44	3	6.8	43	4	9.3	.713
Phosphorus	High	45	0	0.0	43	0	0.0	
	Low	45	0	0.0	43	0	0.0	
Total bilirubin	High	43	0	0.0	43	0	0.0	
	Low	44	0	0.0	43	0	0.0	
Total protein	High	43	0	0.0	41	0	0.0	
	Low	45	0	0.0	43	0	0.0	
Uric acid	High	43	0	0.0	41	1	2.4	.488
	Low	44	0	0.0	43	1	2.3	.494

(continued)

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Table 10. Summary of Laboratory Data
Frequency of Patients with Abnormal Laboratory Values after Baseline
All Randomized Patients Who Took at Least 1 Dose of Study Drug (Continued)

Laboratory Group: Hematology								
Lab Test	Direction	-----ATX + CI-----			-----PLA + CI-----			p-Value*
		N	n	Percent	N	n	Percent	
Basophils	High	45	0	0.0	40	0	0.0	
	Low	45	0	0.0	40	0	0.0	
Cell morphology	Abnormal	39	0	0.0	35	0	0.0	
Eosinophils	High	45	2	4.4	40	0	0.0	.496
	Low	45	0	0.0	40	0	0.0	
Erythrocyte count (RBC)	High	45	0	0.0	40	0	0.0	1.00
	Low	40	3	7.5	40	2	5.0	
Hematocrit	High	44	0	0.0	39	0	0.0	1.00
	Low	44	2	4.5	40	2	5.0	
Hemoglobin	High	45	0	0.0	40	0	0.0	.675
	Low	41	2	4.9	40	3	7.5	
Lymphocytes	High	43	0	0.0	34	0	0.0	
	Low	44	0	0.0	38	0	0.0	
Mean cell volume (MCV)	High	44	1	2.3	39	0	0.0	1.00
	Low	45	1	2.2	38	1	2.6	1.00
Monocytes	High	45	0	0.0	39	1	2.6	.464
	Low	45	0	0.0	40	1	2.5	.471

(continued)

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Table 10. Summary of Laboratory Data
Frequency of Patients with Abnormal Laboratory Values after Baseline
All Randomized Patients Who Took at Least 1 Dose of Study Drug (Concluded)

Laboratory Group: Hematology								
Lab Test	Direction	-----ATX + CI-----			-----PLA + CI-----			p-Value*
		N	n	Percent	N	n	Percent	
Platelets	High	43	1	2.3	38	0	0.0	1.00
	Low	45	0	0.0	39	0	0.0	
Laboratory Group: Urinalysis								
Lab Test	Direction	-----ATX + CI-----			-----PLA + CI-----			p-Value*
		N	n	Percent	N	n	Percent	
Glucose	Abnormal	42	1	2.4	40	1	2.5	1.00
Leucocyte Esterase	Abnormal	39	2	5.1	37	5	13.5	.256
Microscopic Exam	Abnormal	19	0	0.0	11	0	0.0	
Nitrites	Abnormal	44	2	4.5	40	1	2.5	1.00
Occult Blood	Abnormal	45	1	2.2	38	1	2.6	1.00
Protein	Abnormal	44	1	2.3	37	1	2.7	1.00
RBC	Abnormal	0	0		2	1	50.0	
Specific Gravity	High	41	2	4.9	39	0	0.0	.494
	Low	45	0	0.0	41	2	4.9	.224
WBC	Abnormal	5	1	20.0	2	0	0.0	1.00

ATX + CI: Atomoxetine Plus Cholinesterase Inhibitor; PLA + CI: Placebo Plus Cholinesterase Inhibitor

* Frequencies are analyzed using Fisher's Exact test.

N = number of at risk patients with a baseline and postbaseline measurement.

n = number of at risk patients with the specific lab result (e.g. High).

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Table 11. Summary of Vital Sign Data
Frequency of Patients with Abnormal Vital Sign Values after Baseline
All Randomized Patients Who Took at Least 1 Dose of Study Drug

Vitals	Direction	-----ATX + CI-----			-----PLA + CI-----			P-value*
		N	n	Percent	N	n	Percent	
Pulse	High	46	0	(0.0)	45	0	(0.0)	1.00
	Low	46	0	(0.0)	45	1	(2.2)	.495
Systolic BP	High	46	0	(0.0)	45	0	(0.0)	1.00
	Low	46	0	(0.0)	45	0	(0.0)	1.00
Diastolic BP	High	46	0	(0.0)	45	0	(0.0)	1.00
	Low	46	0	(0.0)	45	0	(0.0)	1.00
Weight (KG)	High	46	1	(2.2)	45	3	(6.7)	.361
	Low	46	4	(8.7)	45	0	(0.0)	.117

 ATX + CI: Atomoxetine Plus Cholinesterase Inhibitor; PLA + CI: Placebo Plus Cholinesterase Inhibitor

*p-values were calculated using a Fisher's Exact Test

Pulse Average:HIGH-Increase from baseline >=15 and >120

:LOW-Decrease from baseline >=15 and < 50

Systolic BP Average:HIGH-Increase from baseline >=20 and >180

:LOW-Decrease from baseline >=20 and <=90

Diastolic Blood Pressure AVG:HIGH-Increase from baseline >=15 and >=105

:LOW-Decrease from baseline >=15 and <=50

Weight (KG):HIGH-Increase from baseline > 7%

:LOW-Decrease from baseline > 7%

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Table 12. **Summary of Vital Sign Data**
Mean Change from Baseline to Endpoint
All Randomized Patients Who Took at Least 1 Dose of Study Drug

Variable		Baseline		Endpoint		Change		Between
		Mean	SD	Mean	SD	Mean	SD	Group
Treatment	N							p-Value (a)
DIASAVG								
ATX + CI	46	69.96	10.52	73.63	8.89	3.67	7.99	0.019
PLA + CI	45	71.82	10.05	70.67	10.28	-1.16	10.71	—
SYSAVG								
ATX + CI	46	129.34	15.16	133.34	15.34	4.00	11.82	0.681
PLA + CI	45	130.01	14.32	132.59	16.32	2.58	14.81	—
PULSAVG								
ATX + CI	46	68.79	9.53	73.92	9.05	5.13	9.36	0.002
PLA + CI	45	66.60	7.40	65.10	9.48	-1.50	9.55	—
WEIGHT								
ATX + CI	46	72.16	13.38	70.09	12.46	-2.07	3.73	<.001
PLA + CI	45	71.14	15.69	71.86	16.24	0.72	2.85	—

ATX + CI: Atomoxetine Plus Cholinesterase Inhibitor; PLA + CI: Placebo Plus Cholinesterase Inhibitor

DIASAVG=Diastolic Blood Pressure; SYSAVG=Systolic Blood Pressure; PULSAVG=Pulse; WEIGHT=Weight in KG.
(a): Type III Sums of Squares from an ANOVA: PROC GLM model= treatment and pooled investigator.

The categorical analysis of changes in QT intervals using the Committee for Proprietary Medicinal Products (CPMP) criteria for potentially clinically significant changes in corrected QT intervals following baseline found that there were no statistically significant differences between treatment groups in the proportion of patients who met any one of the CPMP categorical criteria for QTc at any time during treatment period (Table 13).

The following are detailed CPMP criteria:

- Increase of at least 30 from baseline
- Increase of at least 60 from baseline
- Increase from normal to borderline (males >430 to ≤ 450 , females >450 to ≤ 470)
- Increase from normal to prolonged (males >450 , females >470)
- Value of at least 500

Mean change from baseline-to-endpoint analysis found that there were statistically significant differences ($p \leq .001$) in heart rate (9.09 bpm in ATX + CI group versus 0.87 bpm in PLA + CI group); RR interval (-121.9 ms in ATX + CI group versus -12.05 ms in PLA + CI group); and QT interval (-23.48 ms in ATX + CI group versus -3.56 ms in PLA + CI group). There were no statistically significant differences in mean change from baseline-to-endpoint analysis in any other ECG measures (Table 14).

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Table 13. Summary of ECG Data
Frequency of Patients with Abnormal QTc Values after Baseline
All Randomized Patients Who Took at Least 1 Dose of Study Drug

Criteria(a)	ATX + CI		PLA + CI		Total		Fishers Exact
	N	n (%)	N	n (%)	N	n (%)	p-Value
QTcF Increase >= 30	46	3 (6.5%)	45	3 (6.7%)	91	6 (6.6%)	1.00
QTcF Increase >= 60	46	0 (0.0%)	45	0 (0.0%)	91	0 (0.0%)	
QTcF Inc from Normal to Borderline	35	0 (0.0%)	37	3 (8.1%)	72	3 (4.2%)	0.240
QTcF Inc from Normal to Prolonged	35	0 (0.0%)	37	1 (2.7%)	72	1 (1.4%)	1.00
QTcF Increase to >=500 (b)	45	0 (0.0%)	45	0 (0.0%)	90	0 (0.0%)	
QTcG Increase >= 30	46	3 (6.5%)	45	4 (8.9%)	91	7 (7.7%)	0.714
QTcG Increase >= 60	46	0 (0.0%)	45	0 (0.0%)	91	0 (0.0%)	
QTcG Inc from Normal to Borderline	35	5 (14.3%)	36	3 (8.3%)	71	8 (11.3%)	0.478
QTcG Inc from Normal to Prolonged	35	0 (0.0%)	36	1 (2.8%)	71	1 (1.4%)	1.00
QTcG Increase to >=500 (b)	46	0 (0.0%)	45	0 (0.0%)	91	0 (0.0%)	
QTcB Increase >= 30	46	5 (10.9%)	45	4 (8.9%)	91	9 (9.9%)	1.00
QTcB Increase >= 60	46	1 (2.2%)	45	0 (0.0%)	91	1 (1.1%)	1.00
QTcB Inc from Normal to Borderline	38	10 (26.3%)	36	3 (8.3%)	74	13 (17.6%)	0.065
QTcB Inc from Normal to Prolonged	38	2 (5.3%)	36	1 (2.8%)	74	3 (4.1%)	1.00
QTcB Increase to >=500 (b)	46	0 (0.0%)	45	0 (0.0%)	91	0 (0.0%)	

ATX + CI: Atomoxetine Plus Cholinesterase Inhibitor; PLA + CI: Placebo Plus Cholinesterase Inhibitor
 QTcG = QT interval data correction; QTcF = QT interval Fridericia correa correction; QTcB = QT interval Bazett Correction.

(a) Increase >= 30 : Increase of at least 30 from baseline (visits 1-2)at any endpoint visit.

Increase >= 60 : Increase of at least 60 from baseline (visits 1-2)at any endpoint visit.

Increase from Normal to Borderline(males >430 to <=450, females >450 to <=470).

Increase from Normal to Prolonged(males >450, females >470).

Value >=500 : Endpoint value of at least 500.

(b) Patients with baseline values >=500 excluded

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Table 14. **Summary of ECG Data**
Mean Change from Baseline to Endpoint
All Randomized Patients Who Took at Least 1 Dose of Study Drug

Variable		Baseline		Endpoint		Change		Within Group	Between Group
Treatment	N	Mean	SD	Mean	SD	Mean	SD	p-value (a)	p-value (b)
HR									
ATX + CI	46	62.13	9.21	71.22	11.61	9.09	9.75	<.001	<.001
PLA + CI	45	59.98	6.65	60.84	7.51	0.87	7.42	0.437	—
RR									
ATX + CI	46	987.29	151.84	865.41	147.39	-121.9	135.05	<.001	<.001
PLA + CI	45	1011.9	107.58	999.88	115.72	-12.05	120.36	0.505	—
QRS									
ATX + CI	46	90.00	17.76	92.83	21.57	2.83	19.05	0.320	0.293
PLA + CI	45	92.67	21.15	92.22	21.52	-0.44	8.78	0.736	—
PR									
ATX + CI	46	169.37	37.47	163.13	32.94	-6.24	17.38	0.019	0.127
PLA + CI	44	172.05	27.16	171.36	29.85	-0.68	16.34	0.783	—
QT									
ATX + CI	46	418.70	41.45	395.22	31.88	-23.48	28.69	<.001	<.001
PLA + CI	45	428.00	24.08	424.44	27.10	-3.56	25.24	0.350	—
QTCF									
ATX + CI	46	420.75	24.07	415.74	18.76	-5.01	18.96	0.080	0.420
PLA + CI	45	426.76	16.59	424.97	18.78	-1.80	17.90	0.505	—
QTCB									
ATX + CI	46	422.11	18.80	426.80	20.42	4.70	21.41	0.144	0.187
PLA + CI	45	426.27	17.31	425.40	19.36	-0.87	19.63	0.769	—
QTCG									
ATX + CI	46	421.49	20.75	421.64	18.72	0.16	19.57	0.957	0.697
PLA + CI	45	426.52	16.55	425.22	18.60	-1.31	18.35	0.635	—

ATX + CI: Atomoxetine Plus Cholinesterase Inhibitor; PLA + CI: Placebo Plus Cholinesterase Inhibitor
HR = ECG Heart Rate; RR = RR Interval; QRS = QRS Interval; PR = PR Interval; QT = QT Interval; QTCB = Bazett Corrected QT Interval;
QTCF = Fridericia Corrected QT Interval; QTCG = Data-corrected QT Interval.

(a): P-value is from paired t-test.

(b): Type III Sums of Squares from an ANOVA: PROC GLM model = treatment and pooled investigator.

Health Outcomes

The ADCS-ADL score was used as a health outcomes measure (functional status) during this study. Table 15 presents the mean change from baseline to endpoint for the ADCS-ADL. There was a statistically significant difference between treatment groups for ADCS-ADL scores. Patients in the ATX + CI group showed less decline in functional status over the treatment period than patients in the PLA + CI group.

Table 15. Alzheimer's Disease Cooperative Study Inventory-Activities of Daily Living Inventory Scores Change from Baseline to Endpoint

Treatment Group	n	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	Between Group p-Value ^a
ATX + CI	43	65.1 (6.8)	64.2 (8.5)	-0.86 (5.49)	0.026
PLA + CI	44	58.1 (14.2)	54.9 (15.1)	-3.20 (9.15)	--

Abbreviations: ATX + CI = atomoxetine hydrochloride plus cholinesterase inhibitor; n = number of patients; PLA + CI = placebo plus cholinesterase inhibitor; SD = standard deviation.

^a p-Value is based on an analysis of covariance (ANCOVA) model on change from baseline scores with terms for baseline, treatment, pooled investigator and Mini Mental State Exam (MMSE) stratum.

Summary ID# 7953

Clinical Study Summary: Study B4Z-MC-LYCI

An Open-Label, Multicenter, Pilot Study of the Safety and Efficacy of Transitioning from a Stimulant Medication to Atomoxetine in Pediatric and Adolescent Outpatients with DSM-IV Attention-Deficit/Hyperactivity Disorder (ADHD)

Date summary approved by Lilly: 28 March 2006

Brief Summary of Results

Study B4Z-MC-LYCI was an 8-week pilot study. The primary objective of this study was to assess the change in Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms when switching from stimulant medication to atomoxetine hydrochloride (hereafter referred to as atomoxetine) among subjects who could not tolerate or did not respond to stimulants and required a medication change, as measured by the mean change in the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) Total score at Visit 2 (full-dose stimulant alone) compared with Visit 6 (atomoxetine alone). Secondary objectives included safety and efficacy assessments of atomoxetine when switching from a stimulant medication. The results were as follows:

- Subjects demonstrated a statistically significant mean improvement in ADHDRS-IV-Parent:Inv Total score at endpoint.
- Subjects demonstrated statistically significant improvement in overall ADHD symptoms after changing from a stimulant medication to atomoxetine at each visit, as measured by mean change in the Clinical Global Impressions–Attention-Deficit/Hyperactivity Disorder–Improvement (CGI-ADHD-I) score.

- Forty-seven percent of subjects reported that their reason for switching treatment from a stimulant to atomoxetine was due to adverse events. While receiving both stimulant and atomoxetine treatment, 29% of subjects reported one or more treatment-emergent adverse events. While receiving atomoxetine alone, 44% of subjects reported one or more treatment-emergent adverse events.
- Mean scores on the parent-rated Treatment Satisfaction Survey showed statistically significantly improved satisfaction during treatment with atomoxetine (endpoint) compared with stimulant treatment (baseline) on each domain that was measured ($p < .001$). Atomoxetine treatment was preferred by 66% of subjects, compared with stimulant treatment.
- There was a statistically significant improvement in problem behaviors related to ADHD after switching from stimulant medication to atomoxetine, as measured by the Conners' Parent Rating Scale—Revised: Short Form (CPRS-R:S).
- There was a statistically significant improvement in inattentive and hyperactive symptoms, from baseline to endpoint, as measured by the ADHDRS-IV-Parent:Inv Inattention and Hyperactivity-Impulsivity Subscale scores.
- No subjects died or experienced serious adverse events during this study.

Title of Study: An Open-Label, Multicenter, Pilot Study of the Safety and Efficacy of Transitioning from a Stimulant Medication to Atomoxetine in Pediatric and Adolescent Outpatients with DSM-IV Attention-Deficit/Hyperactivity Disorder (ADHD)	
Investigator(s): This multicenter study included 6 principal investigators.	
Study Center(s): This study was conducted at 6 study centers in 1 country.	
Length of Study: 6 months. Date first subject enrolled: 06 July 2004. Date last subject completed: 11 January 2005.	Phase of Development: 4

Objectives: The primary objective of this pilot study was to assess the change in ADHD symptoms when switching from stimulant medication to atomoxetine among subjects who could not tolerate or did not respond to stimulants and required a medication change, as measured by the mean change in the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) Total score at Visit 2 (full dose stimulant alone) compared with Visit 6 (atomoxetine alone).

The secondary objectives of the study were as follows:

- to assess whether there were statistically significant differences in ADHD symptom measures after a subject changed from a stimulant medication to atomoxetine, as measured by the mean change in the Clinical Global Impressions–Attention-Deficit/Hyperactivity Disorder-Improvement (CGI-ADHD-I) score.
- to assess the safety and tolerability of atomoxetine alone compared with stimulant medications alone and during the time of switch (stimulant plus atomoxetine), as assessed by adverse events elicited during open-ended questioning.
- to compare atomoxetine and stimulant medications on other secondary measures, including parent preference.
- to assess whether there was a significant change in problem behaviors related to ADHD after switching from stimulant medication to atomoxetine, as measured by the Conners' Parent Rating Scale–Revised: Short Form (CPRS-R:S).
- to assess the change in inattentive and hyperactive symptoms among those same subjects, as measured by the ADHDRS-IV-Parent:Inv Inattention and Hyperactivity-Impulsivity Subscale scores.

Study Design: A Phase 4, 8-week, open-label, multicenter, pilot study of the safety and efficacy of transitioning pediatric and adolescent outpatients with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[™] (DSM-IV[™], APA 1994) ADHD from a stimulant medication to atomoxetine. The study consisted of three study periods. Study Period I was an approximate 1-week period during which subjects continued treatment with a stimulant (methylphenidate or amphetamine) at a dose within the United States' (US) product label dosage for the stimulant medication. Study Period II was an approximate 2-week transition period. During the first week of transition, subjects continued to take stimulant medication and also received atomoxetine (approximately 0.5 mg/kg/day). During the second week of transition, subjects took approximately a half dose of stimulant medication and also received atomoxetine (approximately 1.2 mg/kg/day). Study Period III was an approximate 5-week period in which subjects received atomoxetine alone, at approximately 1.2 mg/kg/day.

Number of Subjects:

Planned: 60 subjects.

Study Period II

Enrolled: 62 subjects; Completed: 59 subjects.

Study Period III

Enrolled: 59 subjects; Completed: 53 subjects.

Diagnosis and Main Criteria for Inclusion: Only subjects with unsatisfactory symptom response to stimulant therapy such that the treating physician desired to change the subject's therapy, or subjects experiencing adverse events while on stimulant therapy, were eligible for inclusion in the study. The study enrolled both male and female outpatients who were at least 6 years of age and who had not yet reached 18 years of age at the completion of Visit 6. Subjects had to meet the diagnostic criteria for ADHD (any subtype) as defined in the DSM-IV. For the purposes of the study, the diagnosis of ADHD was confirmed by administration of the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children–Present and Lifetime Version (K-SADS-PL) structured interview.

Test Product, Dose, and Mode of Administration: The exact dose in each study period was based on the subject's weight. Study Period I: Atomoxetine was not given during this study period. Study Period II: Atomoxetine started at approximately 0.5 mg/kg/day and transitioned to approximately 1.2 mg/kg/day, given orally once or twice a day in 10-, 18-, 25-, 40-, and 60-mg capsules. Study Period III: Atomoxetine at approximately 1.2 mg/kg/day (maximum dose of 1.4 mg/kg/day), given orally once or twice a day in 10-, 18-, 25-, 40-, and 60-mg capsules.
Reference Therapy, Dose, and Mode of Administration: Study Period I: Subjects took their full, single oral dose of a stimulant that conformed to that particular stimulant's US product label. Study Period II: This was a drug-transitioning phase. Subjects began the Study Period while taking a full, single oral dose of a stimulant that conformed to that particular stimulant's US product label, then transitioned to a half dose of the stimulant formulation. Study Period III: No stimulant medication was given during this study period.
Duration of Treatment: Study Period I: No treatment with atomoxetine. Study Period II: Approximately 18 days. Study Period III: Approximately 5 weeks.
Variables: <u>Efficacy:</u> ADHDRS-IV-Parent:Inv, CGI-ADHD-I, CPRS-R:S, Treatment Satisfaction Survey, and Treatment Preference Question. <u>Safety:</u> Adverse events, concomitant medications, laboratory data, vital signs and weight, and electrocardiograms (ECGs).
Statistical Methods: Efficacy measures were analyzed using repeated measures and analysis of covariance (ANCOVA). Repeated measures models included Visit 1 efficacy score, visit, stimulant type, primary reason for switching, and an interaction term of visit-by-reason-for-switching. The model assumed an unstructured covariance matrix with a Satterthwaite approximation for the degrees of freedom. Least-square means for Visit 3 through Visit 5 were estimated and compared with the least-square mean estimated at Visit 2. The dependent variable in the ANCOVA model was the change in efficacy score from baseline (Visit 2) to endpoint (the last observation from Visit 5 or 6), and the independent variables included the Visit 1 efficacy score, stimulant type, and primary reason for switching. The p-values in the ANCOVA analyses were based on the estimate of the intercept at the mean value of the Visit 1 efficacy score.

Results:

Subject Demographics

Figure LYCI.1 shows the study design for Study LYCI.

Table LYCI.1 summarizes baseline characteristics for enrolled subjects. Of all 62 enrolled subjects, 74% were Caucasian, and 76% were male. The mean age was 11 years, and 63% of the subjects met the criteria for the Combined ADHD subtype. Types of previous stimulant used by subjects were amphetamine (48%) and methylphenidate (52%). Subjects reported "inadequate response" (53%) and "adverse event" (47%) as their reasons for wanting to switch from a stimulant medication to atomoxetine.

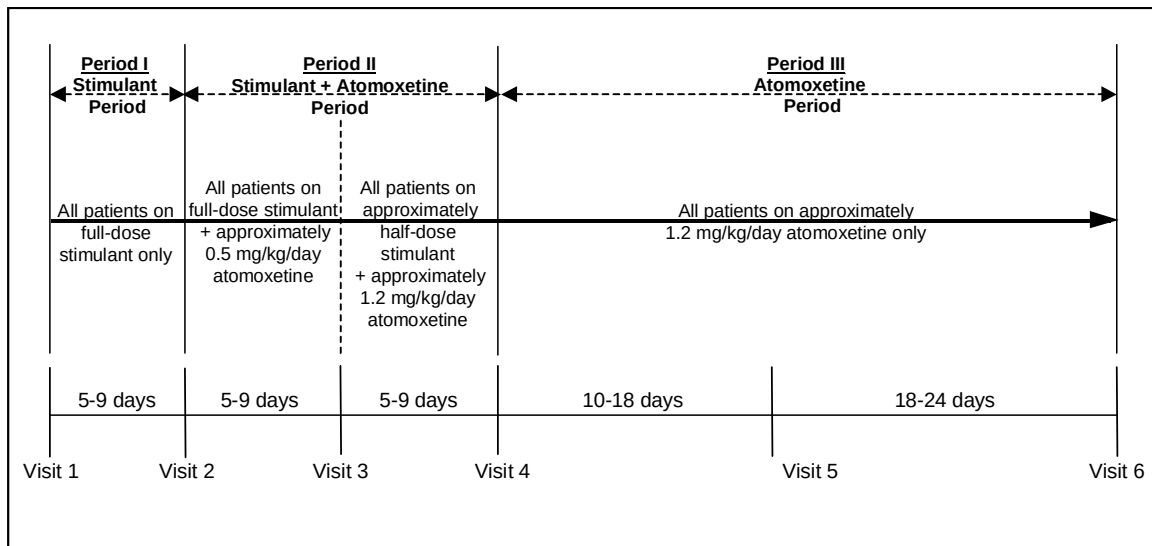


Figure LYCI.1. Study design for LYCI.

Table LYCI.1. Summary of Subject Characteristics at Baseline Enrolled Subjects

Characteristic	Value (N=62)
Age, years: mean (SD)	11.0 (2.7)
Sex: n (%)	
Male	47 (75.8)
Female	15 (24.2)
Race Origin: n (%)	
Caucasian	46 (74.2)
African descent	6 (9.7)
Hispanic	10 (16.1)
ADHD Subtype: n (%)	
Combined	39 (62.9)
Inattentive	22 (35.5)
Hyperactive-Impulsive	1 (1.6)
CYP2D6 Phenotype: n (%)	
Extensive	56 (90.3)
Poor	4 (6.5)
Unknown	2 (3.2)
Previous Stimulant: n (%)	
Amphetamine	30 (48.4)
Methylphenidate	32 (51.6)
Reason for Switching: n (%)	
Inadequate Response	33 (53.2)
Adverse Event	29 (46.8)

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CYP2D6 = cytochrome P450 2D6,
N = number of enrolled subjects with nonmissing data, n = number of subjects, SD = standard deviation.

Subject Disposition

Figure LYCI.2 shows that a total of 71 subjects entered the screening phase (Study Period I). Sixty-two of these subjects enrolled in the 2-week transition phase (Study Period II) and received approximately 0.5 mg/kg/day atomoxetine plus full-dose stimulant for 1 week, followed by 1 week of approximately 1.2 mg/kg/day atomoxetine plus half-dose stimulant. Fifty-nine subjects continued into the final study phase (Study Period III) and received approximately 1.2 mg/kg/day atomoxetine alone for approximately 5 weeks.

A total of 9 subjects discontinued the study (3 during Study Period II, and 6 during Study Period III). One subject discontinued during Study Period II due to an adverse event (fatigue). During Study Period III, 1 subject discontinued due to an adverse event (hypertension), and 1 subject discontinued due to lack of efficacy.

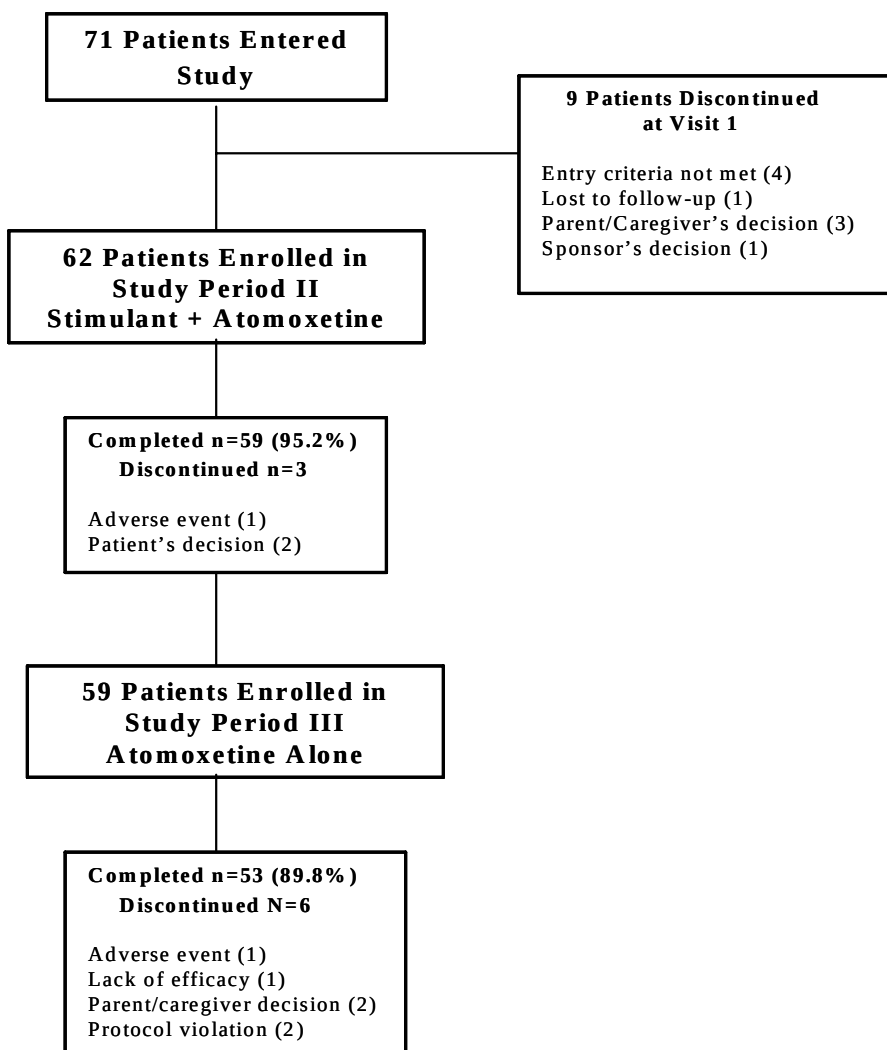


Figure LYCI.2. Subject disposition for all subjects entered into Study LYCI.

Primary Objective

The primary objective of this study was to assess the change in ADHD symptoms when switching from stimulant medication to atomoxetine among pediatric and adolescent subjects who could not tolerate or did not respond to stimulants and required a medication change, as measured by the mean change in the ADHDRS-IV-Parent:Inv Total score at baseline (full-dose stimulant alone) compared with endpoint (atomoxetine alone). Table LYCI.2 is the LOCF analysis using ANCOVA model, controlling for visit 1 value (of the ADHDRS Total Score), stimulant type, and reason for switching. Enrolled subjects who had both a baseline and a postbaseline score were included in the analysis. Table LYCI.2 shows that subjects demonstrated a statistically significant mean improvement in ADHDRS-IV-Parent:Inv Total score from baseline to endpoint ($p < .0001$).

Table LYCI.3 displays the least square means and standard error from the repeated measures analysis. The primary comparison was the analysis of the change in mean ADHDRS-IV-Parent:Inv Total score from Visit 2 to Visit 6 using contrasts from the repeated measures model. A statistically significant ($p < .001$) mean improvement in ADHDRS-IV-Parent:Inv Total score was demonstrated at endpoint.

Table LYCI.2. Primary Objective
Mean Change from Baseline to LOCF Endpoint
ADHDRS-Parent:Inv Total Score
Enrolled Subjects

Measure	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	p-value
ADHDRS-IV- Parent:Inv Total Score	59	32.1 (10.5)	22.6 (14.0)	-9.5 (12.0)	<.0001

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored, LOCF = last observation carried forward;

N = number of subjects enrolled who had both a baseline and a postbaseline, SD = standard deviation.

Population: Enrolled subjects who had taken at least one dose of atomoxetine.

Baseline: Visit 2; Endpoint: Visit 5-6. ANCOVA model – change in total score imputed.

p-Value based on testing the hypothesis that the least-squares mean intercept evaluated at the mean Visit 1 ADHDRS total score (imputed) is equal to zero.

**Table LYCI.3. ADHDRS-IV-Parent:Inv Total and Subscale Scores
Least-Square Means from Repeated Measures Analysis
Enrolled Patients**

Treatment	n	Visit	Total Score* Mean (SE)	Inattention Subscale* Mean (SE)	Hyperact-Impuls Subscale* Mean (SE)
Full-dose stimulant only	61	2	32.1 (±0.9)	18.9 (±0.5)	13.2 (±0.5)
Full-dose stimulant plus 0.5 mg/kg/day ATX	61	3	24.4 (±1.3)	14.2 (±0.7)	10.2 (±0.7)
Half-dose stimulant plus 1.2 mg/kg/day ATX	60	4	20.8 (±1.4)	12.5 (±0.8)	8.3 (±0.7)
Atomoxetine alone	59	5	22.6 (±1.7)	13.3 (±0.9)	9.2 (±0.8)
Atomoxetine alone	56	6	22.5 (±1.6)	13.5 (±0.9)	9.1 (±0.8)

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored, ATX = atomoxetine, Hyperact-Impuls = Hyperactivity-Impulsivity, n = number of patients with non-missing data at the specified visit, SE = standard error.

Population: Enrolled patients who have taken at least one-half dose of atomoxetine.

* Relative to baseline (Visit 2), repeated measures least-squares mean scores were significantly reduced for the ADHDRS-IV-Parent:Inv Total score and both subscale scores at all postbaseline visits ($p < .001$) in the repeated measures model that included terms for Visit 1 ADHDRS-IV-Parent:Inv score, visit, stimulant type, primary reason for switching, and an interaction term (visit-by-reason-for-switching).

Secondary Objectives

Secondary analyses indicated that subjects demonstrated statistically significant improvement ($p < .001$) in overall ADHD symptoms after changing from a stimulant medication to atomoxetine, as measured by the mean change in the CGI-ADHD-I score (Table LYCI.4).

Forty-seven percent of subjects reported that their reason for switching treatment was due to adverse events while being treated with stimulants (Table LYCI.1). Table LYCI.9 shows that 29% of subjects reported one or more treatment-emergent adverse events during Study Period II (stimulant plus atomoxetine). During Study Period III (atomoxetine alone), 44% of subjects reported one or more treatment-emergent adverse events.

Mean scores on the parent-rated Treatment Satisfaction Survey showed statistically significantly improved satisfaction during treatment with atomoxetine compared with stimulant treatment on each domain that was measured ($p < .001$; Table LYCI.5). A majority of subjects reported a treatment preference for atomoxetine (65.5%) compared with stimulants (34.5%) on the Treatment Preference Question (Table LYCI.6).

After transitioning from a stimulant to atomoxetine, improvement in problem behaviors related to ADHD was observed on each subscale (ADHD Index, Cognitive Problems/Inattention, Hyperactivity, and Oppositional Scale) of the CPRS-R:S, with

higher mean change and statistical significance ($<.0001$) seen on the ADHD Index and Cognitive Problems/Inattentive subscales (Table LYCI.7).

There was a statistically significant improvement in inattentive ($p<.0001$) and hyperactive-impulsive ($p<.0001$) symptoms, from baseline to endpoint, as measured by the ADHDRS-IV-Parent:Inv Inattention and Hyperactivity-Impulsivity Subscale scores (Table LYCI.8).

**Table LYCI.4. Secondary Objective
CGI-ADHD-I
Repeated Measures Analysis of CGI Improvement
Enrolled Subjects**

Visit	N	LS Mean	Standard Error	*Pr > /t/
2	61	4.03	0.08	
3	61	3.20	0.13	<.001
4	60	2.76	0.14	<.001
5	59	2.96	0.19	<.001
6	56	2.93	0.19	<.001

Abbreviations: CGI-ADHD-I = Clinical Global Impressions–Attention-Deficit/Hyperactivity Disorder-Improvement; N = number of subjects with nonmissing data at the specified visit.

Population: Enrolled subjects who have taken at least one half dose of atomoxetine.

MODEL: CGI-Improvement = visit, stimulant type, primary reason for switching, interaction of visit by switching reason.

Covariance Structure = unstructured.

* Visit-wise p-value compared to Visit 2.

Baseline: Visit 2; Comparison: Visits 3-6.

**Table LYCI.5. Secondary Objective
Summary of Treatment Satisfaction
Enrolled Subjects**

Observation Name	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	p-value ^a	p-value ^b
Likely to recommend treatment received	58	1.47 (1.03)	0.93 (1.11)	-0.53 (1.47)	<.001	<.001
Overall treatment satisfaction	58	1.91 (1.05)	1.41 (1.40)	-0.50 (1.51)	<.001	<.001
Satisfaction with morning effectiveness	58	1.62 (0.97)	1.19 (1.30)	-0.43 (1.48)	<.001	<.001
Satisfaction with evening effectiveness	58	2.41 (1.04)	1.76 (1.51)	-0.66 (1.76)	<.001	<.001
Treatment satisfaction last 2 weeks	58	1.98 (1.00)	1.12 (1.40)	-0.86 (1.85)	<.001	<.001

Note: Lower scores mean increased satisfaction.

Abbreviations: N = number of subjects, SD = standard deviation.

^a Within-group p-values are based on paired t-test on differences in mean change from baseline to endpoint values.

^b Within-group p-values are based on Wilcoxon's Signed-Rank Test.

Baseline: Visit 2; Endpoint: Visit 5 or 6.

Table LYCI.6. Secondary Objective
Summary of Treatment Preference
Enrolled Subjects

Observation Name	Visit	N	Atomoxetine N (%)	Stimulant N (%)
Preference	5 or 6	58	38 (65.5)	20 (34.5)

Abbreviation: N = number of subjects.

Table LYCI.7. Secondary Objective
Summary of Connor's Parent Rating Scale
Visits 2 and 6
Enrolled Subjects

Observation Name	Visit	N	Mean (SD)	Mean Change* (SD)	p-value
CPRS T-Scores for ADHD Index	2	61	72.82 (9.88)	-9.20	<.0001
	6	55	64.35 (12.96)	(11.77)	
Cognitive Problems/Inattentive	2	61	72.30 (10.44)	-3.52	<.0001
	6	55	64.83 (12.90)	(5.29)	
Hyperactivity	2	61	73.68 (17.58)	-2.39	.0002
	6	55	65.20 (17.67)	(4.33)	
Oppositional Scales	2	61	64.27 (13.22)	-1.56	.0286
	6	55	60.52 (15.06)	(5.08)	

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder, CPRS = Connor's Parent Rating Scale,
N = number of subjects with nonmissing data at the specified visit, SD = standard deviation.

* Mean change calculation based on patients having both a baseline and postbaseline score (N=54).

Table LYCI.8. Secondary Objective
Mean Change from Baseline to LOCF Endpoint
ADHDRS-Parent:Inv Subscale Scores
Enrolled Subjects

Measure	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	p-value
ADHDRS-IV-Parent:Inv Inattention Subscale Score	59	18.9 (5.0)	13.5 (7.3)	-5.4 (6.5)	<.0001
ADHDRS-IV-Parent:Inv Hyperactivity-Impulsivity Subscale Score	59	13.3 (7.1)	9.2 (7.8)	-4.1 (6.7)	<.0001

Abbreviations: ADHDRS-IV-Parent:Inv = Attention Deficit Hyperactivity Disorder Rating Scale-IV-
Parent Version: Investigator-Administered and Scored, LOCF = last observation carried forward;
N = number of subjects with nonmissing data, SD = standard deviation.

Safety

Adverse Events

There were no deaths or serious adverse events in this study. Two subjects discontinued due to an adverse event: 1 subject discontinued during Study Period II due to fatigue, and 1 subject discontinued during Study Period III due to hypertension.

Table LYCI.9 shows treatment-emergent adverse events reported during the study periods in which subjects were treated with atomoxetine. Within Study Period II (stimulant plus atomoxetine), 18 subjects (29% of the 62 enrolled subjects) reported one or more treatment-emergent adverse events. Within Study Period III (atomoxetine alone), 26 subjects (44% of the 59 enrolled subjects) reported one or more treatment-emergent adverse events.

The treatment-emergent adverse events that occurred in $\geq 2\%$ of subjects were nausea, fatigue, and headache for subjects in Study Period II (stimulant plus atomoxetine); and somnolence, cough, decreased appetite, fatigue, headache, and dermatitis contact for subjects in Study Period III (atomoxetine alone).

**Table LYCI.9. Summary of Treatment-Emergent Adverse Events
Incidence Greater than or Equal to 2 Percent
All Study Periods
Enrolled Subjects**

Study Period II (N=62)		Study Period III (N=59)	
Preferred Term ^a	Stimulant + Atomoxetine n (%)	Preferred Term ^a	Atomoxetine Alone n (%)
Subjects with no TEAE	44 (71.0)	Subjects with no TEAE	33 (55.9)
Subjects with ≥ 1 TEAE	18 (29.0)	Subjects with ≥ 1 TEAE	26 (44.1)
Nausea	5 (8.1)	Somnolence	4 (6.8)
Fatigue	3 (4.8)	Cough	3 (5.1)
Headache	3 (4.8)	Decreased appetite	3 (5.1)
-	-	Fatigue	3 (5.1)
-	-	Headache	3 (5.1)
-	-	Dermatitis contact	2 (3.4)

Abbreviations: N = number of patients who took at least one dose of study drug, n = number of patients with treatment-emergent adverse event, TEAE = treatment-emergent adverse event.

^a Based on MedDRA coding dictionary version 7.0.

Study Period II: Baseline defined as Visits 1-2, and endpoint as Visits 3-4.

Study Period III: Baseline defined as Visits 1-2, and endpoint as Visits 5-6.

Laboratory Values

There was a statistically significant decrease within normal range from baseline to endpoint for mean change in albumin ($p < .001$), ALT/SGPT ($p = .008$), calcium ($p = .004$), cholesterol ($p < .001$), GGT ($p < .001$), total protein ($p < .001$), erythrocyte count ($p = .027$), hematocrit ($p < .001$), and mean cell volume ($p < .001$; Table LYCI.10). No subject discontinued from the study due to an abnormal lab value.

Atomoxetine hydrochloride

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Table LYCI.10. Laboratory Analysis
Analyte with Statistically Significant Mean Change from Baseline to Endpoint Value
Enrolled Subjects

Lab Procedure	Lab Test Name	SIU	Reference Range	N	Baseline			Endpoint			Change			p- value
					Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	
Clinical Chemistry	Albumin	g/L	29-47	58	46.03	46.00	2.30	44.33	44.00	2.77	-1.71	-1.00	3.07	<.001
	ALT/SGPT	U/L	6-43	58	17.84	16.00	7.76	15.76	15.00	4.65	-2.09	-1.00	6.26	.008
	Calcium	mmol/L	2.1-2.57	58	2.53	2.54	0.06	2.49	2.5	0.08	-0.04	-0.05	0.10	.004
	Cholesterol	mmol/L	3.36-5.28	58	4.24	4.22	0.72	3.97	4.01	0.62	-0.27	-0.23	0.51	<.001
	GGT (GGPT/SGGT /YGGT)	U/L	0-51	58	12.71	12.00	5.26	11.57	11.00	4.04	-1.14	-1.00	2.34	<.001
	Total Protein	g/L	61-84	58	75.31	75.00	4.00	73.43	73.50	4.02	-1.88	-2.00	3.64	<.001
Hematology	Erythrocyte Count	TI/L	4.5-6.4	58	4.87	4.90	0.32	4.80	4.70	0.29	-0.07	-0.05	0.26	.027
	Hematocrit	l	0.39-0.54	58	0.41	0.41	0.03	0.39	0.39	0.03	-0.01	-0.01	0.02	<.001
	Mean Cell Volume (MCV)	fL	79-96	58	84.05	84.00	4.37	82.26	81.50	4.67	-1.79	-1.00	3.09	<.001

Abbreviations: N = number of subjects with non-missing data, SD = standard deviation, SIU = standard international unit of measure

Wilcoxon's Signed-Rank test.

Baseline: Visit 1; Endpoint: Visit 5-6.

Vital Signs and Weight

Table LYCI.11 shows a statistically significant increase in diastolic blood pressure ($p=.012$) in Study Period II and in diastolic ($p=.031$) and systolic ($p=.029$) blood pressure in Study Period III. One subject developed treatment-emergent hypertension as an adverse event in Study Period III.

Table LYCI.12 shows a statistically significant ($p<.001$) increase in heart rate in Study Periods II and III, and a corresponding statistically significant ($p<.001$) decrease in QT interval and in RR interval in Study Periods II and III. Correcting the QT interval for heart rate resulted in a statistically significant increase in QTc interval using Bazett's correction and no statistically significant changes in QTc using Fridericia's correction (QTcF) or data-derived correction. Bazett's QT correction is known to overcorrect the QT interval in cases where there is an increase in heart rate (Funck-Brentano and Jaillon 1993).

Table LYCI.11. Summary of Mean Change in Vital Signs and Weight from Baseline to Endpoint Study Periods II and III Enrolled Subjects

Variable	Study Period II ^a	p-value	Study Period III ^b	p-value
Diastolic blood pressure (mmHg)	n=57		n=53	
Mean baseline (SD)	66.3 (7.78)		66.26 (7.93)	
Mean change (SD)	2.76 (8.00)	.012	2.37 (7.79)	.031
Systolic blood pressure (mmHg)	n=57		n=53	
Mean baseline (SD)	105.5 (10.7)		105.65 (11.06)	
Mean change (SD)	1.12 (7.53)	.265	2.43 (7.90)	.029
Heart rate average (bpm)	n=57		n=53	
Mean baseline (SD)	83.49 (13.45)		84.34 (13.04)	
Mean change (SD)	2.68 (12.97)	.124	3.01 (14.71)	.142
Temperature (°C)	n=57		n=53	
Mean baseline (SD)	36.44 (0.50)		36.43 (0.50)	
Mean change (SD)	0.01 (0.56)	.924	-0.07 (0.71)	.477
Weight (kg)	n=57		n=53	
Mean baseline (SD)	40.77 (15.77)		39.87 (15.53)	
Mean change (SD)	-0.16 (1.04)	.263	0.18 (1.63)	.414

Abbreviations: bpm = beats per minute, n = number of subjects with non-missing data, SD = standard deviation.

Population: Enrolled subjects with at least one baseline and endpoint observation.

Changes analyzed using a paired t-test.

Baseline: Visits 1-2.

^a Endpoint: Visits 3-4.

^b Endpoint: Visits 5-6.

Due to Inv Site=2 error, removed visit if both readings were identical for all 3 vitals (diastolic, systolic, heart rate).

Table LYCI.12. Summary of Mean Change in Electrocardiogram and Heart Rate from Baseline to Endpoint Study Periods II and III Enrolled Subjects

ECG Assessment	Study Period II ^a	p-value	Study Period III ^b	p-value
Data corrected QT interval	n=60		n=57	
Mean baseline (SD)	404.63 (18.25)		405.20 (18.07)	
Mean change (SD)	2.89 (13.83)	.153	2.99 (16.34)	.331
Heart rate (bpm)	n=60		n=57	
Mean baseline (SD)	77.97 (12.14)		78.26 (10.62)	
Mean change (SD)	6.16 (10.36)	<.001	9.22 (11.58)	<.001
PR interval	n=60		n=57	
Mean baseline (SD)	135.89 (13.27)		135.44 (13.45)	
Mean change (SD)	-0.44 (10.06)	.698	-1.64 (9.88)	.237
QT interval	n=60		n=57	
Mean baseline (SD)	367.83 (26.05)		367.31 (25.09)	
Mean change (SD)	-8.11 (17.10)	<.001	-12.51 (23.21)	<.001
QTc interval (Bazett's Correction)	n=60		n=57	
Mean baseline (SD)	416.00 (21.20)		416.85 (19.87)	
Mean change (SD)	6.42 (17.86)	.012	8.11 (18.27)	.002
QTcF interval (msec)	n=60		n=57	
Mean baseline (SD)	398.95 (17.73)		399.38 (17.94)	
Mean change (SD)	1.13 (12.50)	.541	0.47 (16.20)	.922
RR interval	n=60		n=57	
Mean baseline (SD)	792.57 (136.89)		784.00 (109.01)	
Mean change (SD)	-58.33 (114.11)	<.001	-77.75 (98.17)	<.001

Abbreviations: bpm = beats per minute, ECG = electrocardiogram; n = number of subjects with nonmissing data, PR interval = the time elapsing between the beginning of the P wave and the beginning of the next QRS complex; QRS = deflections in an electrocardiographic tracing that represent ventricular activity of the heart; QTc = corrected QT interval; QTcF = corrected QT interval using Fridericia's correction; RR = The time elapsing between two consecutive R waves; SD = standard deviation.

Population: Enrolled subjects.

Wilcoxon's Signed-Rank test.

Baseline: Visits 1-2.

^a Endpoint: Visits 3-4.

^b Endpoint: Visits 5-6.

References

Funck-Brentano C, Jaillon P. 1993. Rate-corrected QT interval: techniques and limitations. Am J Cardiol 72(6):172B-22B

Summary ID# 7955

Clinical Study Summary: Study B4Z-MC-LYCK A Double-Blind, Crossover Comparison of Atomoxetine Hydrochloride and Placebo in Child Outpatients with Attention-Deficit/Hyperactivity Disorder, Reading Disorder, or Comorbid Attention-Deficit/Hyperactivity Disorder and Reading Disorder

Date summary approved by Lilly: 30 September 2008

Title of Study: A Double-Blind, Crossover Comparison of Atomoxetine Hydrochloride and Placebo in Child Outpatients with Attention-Deficit/Hyperactivity Disorder, Reading Disorder, or Comorbid Attention-Deficit/Hyperactivity Disorder and Reading Disorder	
Investigator(s): This multicenter study included 7 principal investigators all of whom enrolled subjects into the study.	
Study Center(s): This study was conducted at 7 study centers in 2 countries.	
Length of Study: Date of first patient enrolled: 25 April 2005 Date of last patient completed: 11 December 2007	Phase of Development: 3
Objectives: Primary Objective: Test the hypothesis that acute treatment with atomoxetine hydrochloride (atomoxetine) for approximately 4 weeks provides superior efficacy compared with placebo in patients with Attention-Deficit/Hyperactivity Disorder-Combined Type (ADHD-C), Reading Disorder (RD) without ADHD, and comorbid ADHD-C and RD (ADHD-C+RD) (3 study arms) as measured by improvement in speed of inhibition as shown by a statistically significantly shorter Stop Signal Reaction Time (SSRT) derived from the SSRT Paradigm. Secondary Objectives: • In a subset of patients aged 10 years and older, compare performance of patients in the 3 study arms with normal controls and untreated RD controls on SSRT and a phonological reading task; • Compare performance of all patients in the 3 study arms with normal controls and untreated RD controls on SSRT and a lexical decision; • Establish the specificity of atomoxetine effect upon SSRT and the phonological and lexical decision tasks by assessing the effect of atomoxetine on a) inhibitory function (SSRT) task only, b) influence on reading (phonological and lexical) tasks only and c) influences on both types of tasks (SSRT and phonological task; SSRT and lexical task). • Determine the effect of atomoxetine compared with placebo upon impulsivity (effect upon the trade-off between accuracy and speed of processing) in SSRT and a phonological and lexical decision task in patients in the 3 study arms; • Determine the effect of atomoxetine compared with placebo upon working memory as assessed by the Corsi Block Tapping Test (CBTT) in patients in the 3 study arms; • Test the hypothesis that atomoxetine is superior to placebo in reducing symptoms of ADHD, as measured by mean change in the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) in ADHD-C and ADHD-C+RD patients; • Compare the clinical effect of atomoxetine with placebo in reducing symptoms of ADHD, using the Clinical Global Impression-Attention-Deficit/Hyperactivity Disorder-Improvement Scale(CGI-ADHD-I) and Clinical Global Impression-Attention-Deficit/Hyperactivity Disorder-Severity Scale (CGI-ADHD-S) in patients with ADHD-C and ADHD-C+RD; • Compare the safety and tolerability of atomoxetine with placebo as assessed by adverse events (AEs) elicited during open-ended questioning.	
Study Design: Study B4Z-MC-LYCK was a multicenter, randomized, double-blind crossover study comparing atomoxetine with placebo in pediatric outpatients. Study Period I (Visits 1 and 2), consisted of an initial screening and washout period. In Study Period II (Visits 3 to 5), eligible patients were randomly assigned to receive atomoxetine or placebo in a 1:1 ratio for approximately 4 weeks. Patients then underwent a 2-week washout period after which they were crossed over to receive the alternate treatment (atomoxetine or placebo) at Visit 4 for an additional 4 weeks. Study Period III (Visits 6 to 12) was open label, long term treatment with atomoxetine of approximately 20 months for patients in 1 study country where atomoxetine was not commercially available at the end of Study Period II	

Number of Patients: Planned: 120, 40 per study arm Randomized: 74 Atomoxetine, 76 Placebo Completed Study Period II: 71 Atomoxetine, 74 Placebo Completed Study Period III: 16
Diagnosis and Main Criteria for Inclusion: Patients between the ages of 8 to 12 years of age at the time of enrollment and who met the <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition™</i> (DSM-IV™) for ADHD, RD, or both ADHD and RD.
Study Drug, Dose, and Mode of Administration: Atomoxetine was given orally as capsules containing 5 mg, 10 mg, 20 mg or 40 mg. The dose was weight based and was given once daily. Patients received an initial dose of 0.6 mg/kg daily for 7 days followed by 1.25 mg/kg daily for 21 days.
Comparator, Dose, and Mode of Administration: Placebo capsules identical to those containing atomoxetine were given orally once daily for 28 days.
Duration of Treatment: Atomoxetine or placebo once daily for 28 days followed by the alternative treatment for 28 days after a 2-week washout period. Total treatment time was 2 months.
Variables: Efficacy • Patient SSRT scores estimated using the SSRT Paradigm task assessed for all randomly assigned patients who received at least 1 dose of study medication • Phonological Task Response Time (RT), pseudo homophones, pseudo words in patients ≥ 10 years of age • Phonological accuracy defined as DEPRIMF, a composite score indicating the ability of the patient (≥ 10 years of age) to discriminate pseudo homophones and pseudo words • Lexical Decision Task RT, correct words, pseudo words • Lexical accuracy defined as DEPRIML, a composite score that indicates whether the patient can discriminate valid words from pseudo words • CBTT Visual Memory Span • ADHDRS-IV-Parent:Inv: Total Score, Inattention Subscale, Hyperactivity-Impulsivity (HI) subscale, Total T Score (data not collected for RD patients) • CGI-ADHD-S (data not collected for RD patients) • CGI-ADHD-I (data not collected for RD patients) <u>Safety:</u> • Deaths and other serious adverse events • Discontinuations due to adverse events • Treatment-emergent adverse events • Vital signs

Evaluation Methods:

Statistical: The primary efficacy parameter was a repeated measures analysis of SSRT scores conducted at posttreatment Visit 3 and Visit 5 during the acute crossover treatment phase (Study Period II), which compared atomoxetine to placebo. Baseline was defined as the SSRT value obtained at Visit 2. The repeated measures analysis was based on the restricted maximum likelihood method assuming an unstructured covariance matrix using a Satterthwaite approximation including model parameters of baseline score, study arm, treatment sequence, visit, treatment, and treatment-by-study-arm interaction. If in the original analysis the interaction between study arm and treatment was significant at the 0.10 level, additional analyses of SSRT were to have been performed separately for each study arm using a repeated measures analysis as described but including only baseline, treatment sequence, visit, and treatment as independent effects to evaluate potential causes of the interaction. No statistically significant interaction was observed and additional analyses are not included in this CTR.

Mean change from baseline analysis by treatment sequence and study arm were also conducted for SSRT scores. Treatment sequences were reported as atomoxetine followed by placebo (ATX-Placebo) and placebo followed by atomoxetine (Placebo-ATX). For patients in the ATX-Placebo sequence, endpoint for atomoxetine treatment was Visit 3 and endpoint for placebo treatment was Visit 5. For patients in the Placebo-ATX sequence, endpoint for atomoxetine treatments was Visit 5 and endpoint for placebo treatment was Visit 3. All statistical tests were performed using a 0.05 significance level. No adjustments for multiple comparisons were made.

The above analyses were computed for a Safety Sample which included all patients randomly assigned to double-blind treatment who received at least 1 dose of study drug and a Per-Protocol sample, which included all patients randomly assigned to double blind treatment who received at least 1 dose of study drug without major protocol violations.

Repeated measures and change from baseline analyses analogous to the analysis of the primary outcome variable were performed for most secondary outcomes. Results at each scheduled visit and change from baseline to each postbaseline visit were summarized. Differences between baseline and postbaseline results were assessed using the paired t-test. For CBTT, baseline contrast was assessed by an ANOVA with groups as the between-subject factor and visual memory span as the dependent variable. Descriptive statistics were used for comparisons of SSRT scores between atomoxetine-treated patients and untreated controls in subsets of patients ≥ 10 and < 10 years of age. Change from baseline analysis was computed using ANCOVA model for a subset of patients ≥ 10 years of age for SSRT and phonological scores in atomoxetine-treated patients and untreated controls.

For the parameters assessed, decreases in score indicate improvement and increases in score indicate worsening except for the CBTT and DEPRIME analyses for phonological and lexical tasks in which cases an increase in score indicates improvement.

The target sample size of at least 16 patients completed in each arm, ADHD-C, RD, and ADHD-C+RD, provided approximately 60% power to detect a significant difference between atomoxetine and placebo in mean SSRT, assuming the true difference was at least 50 msec between treatment and placebo with a standard deviation of 91 msec.

Safety: Safety analysis included all randomly assigned patients who took at least 1 dose of study medication during Study Period II and Study Period III. Unless otherwise specified, all safety analyses were pooled across study arms. Percentages of patients taking concomitant medications and who experienced treatment-emergent adverse events (TEAEs) were summarized. Treatment differences were assessed using McNemar's test for Study Period II. Data are presented as mean and standard deviations for Study Period III. Visit 2 was used as baseline for determining TEAEs for Study Period II and Study Period III. Changes in vital signs (including weight) during Study Period II were computed and treatment differences were assessed using a repeated measures analysis with independent effects for treatment, treatment sequence, and baseline values. Differences between

baseline and endpoint measurements were computed using the paired t-test. Descriptive statistics were used for assessment of vital signs during Study Period III.

Results

Patient Disposition

A total of 89 patients underwent screening and washout in Study Period I and 76 (85.0%) were enrolled into the study (Study Period II). A total of 74 patients received atomoxetine and 3 (4.1%) of these discontinued while receiving atomoxetine. A total of 76 patients received placebo and 2 (2.6%) of these discontinued while receiving placebo. There was no statistically significant difference in discontinuation rate between treatment groups.

A total of 25 patients entered the open-label Study Period III, and 16 (64.0%) completed this period. Discontinuations due to lack of efficacy were seen in Study Period III with 4 (22.2%) of 18 patients with RD and 2 (33.3%) of 6 patients with ADHD-C+RD discontinuing for this reason.

The number and percentage of patients in each study arm who completed Study Period I were 28 of 36 (77.8%) ADHD-C patients, 23 of 25 (92.0%) RD patients, and 25 of 28 (89.3%) ADHD-C+RD patients. The number and percentages of patients by study arm who completed Study Period II were 25 (89.3%) ADHD-C patients, 22 (95.7%) RD patients, and 24 (96.0%) ADHD-C+RD patients. There was no statistically significant difference between study arms in completion rate in Study Period I or II. One patient with ADHD-C entered Study Period III and completed the study. A total of 13 (72.2%) of the 18 patients with RD and 2 (33.3%) of the 6 patients with ADHD-C+RD who entered Study Period III completed this period.

Patient Demographics

The majority of patients [(53 (69.74%))] were male and there was a relatively even distribution among study arms as follows: ADHD-C [(n=28 (36.84%))]; ADHD-C+RD [(n=25 (32.89%))], RD [(n=23 (30.26%))]. The mean age was 10.0 years with a minimum age of 8 years and a maximum age of 13 years. There were no statistically significant differences between patients in the ATX-Placebo group compared to patients in the Placebo-ATX group in any of the baseline or other screening characteristics measured.

Efficacy

Primary Efficacy Measures:

Repeated measures analysis demonstrated that patients in the Safety Sample with ADHD-C and ADHD-C +RD had lower mean SSRT scores after atomoxetine treatment compared with placebo treatment as follows: ADHD-C (-8.92); ADHD-C+RD (-15.15). The overall score was also lower for atomoxetine-treated patients (-6.32) compared with placebo. Patients in the RD study arm demonstrated a higher mean SSRT score (5.10) after atomoxetine treatment compared with placebo treatment. No statistically significant atomoxetine treatment effect was observed. The same patterns were observed in the Per-Protocol sample of patients.

Within treatment sequence mean change from baseline analysis for patients in the ATX-Placebo sequence demonstrated a decrease of SSRT score of -16.2 at Visit 3 after atomoxetine treatment and a decrease of -2.3 at Visit 5 after subsequently receiving placebo. Mean change from baseline analysis for patients in the Placebo-ATX sequence demonstrated an increase of SSRT score of 3.4 at Visit 3 after receiving placebo and an increase of 0.298 at Visit 5 after a subsequent atomoxetine treatment. None of these observed mean SSRT score changes from baseline within each treatment sequence group were statistically significant.

Patients with ADHD-C in the ATX-Placebo sequence demonstrated no mean decreases from baseline in either sequence. Patients with ADHD-C+RD in the ATX-Placebo sequence demonstrated only nonstatistically significant decreases from baseline at Visit 3 (-23.8) after receiving atomoxetine and at Visit 5 (-9.1) after subsequently receiving placebo. Patients with ADHD-C+RD in the Placebo-ATX sequence demonstrated an increase in score at Visit 3 (16.1) after receiving placebo and a nonstatistically significant decrease at Visit 5 (-7.2) after subsequently receiving atomoxetine. A statistically significant decrease of -25.6 points ($p=0.031$) in mean SSRT score was seen only at Visit 3 after atomoxetine treatment in RD patients in the ATX-Placebo sequence. A nonstatistically significant further decrease was observed in these patients at Visit 5 (-18.0) after receiving placebo. The same pattern was observed in the Per-Protocol sample.

Secondary Efficacy Measures:

Mean Change from Baseline Comparisons of the Stop Signal Reaction Time in Atomoxetine-Treated Patients and Untreated Controls by Age

- *Patients ≥ 10 years of age:* Atomoxetine-treated patients with ADHD-C+RD or RD demonstrated a mean change from baseline in SSRT scores of -0.25 and -34.00, respectively, while the untreated RD controls had an increase of 0.05 in SSRT score. The atomoxetine-treated ADHD-C patients and normal controls demonstrated an increase in SSRT score of 7.95 and 11.22, respectively. There was no statistically significant difference between groups in these changes in SSRT scores from baseline.
- *Patients < 10 years of age:* Atomoxetine-treated patients with ADHD-C+RD or RD experienced a mean decrease from baseline in SSRT score of -52.22 and -7.36, respectively, while untreated RD controls demonstrated a mean decrease of -16.31. The atomoxetine-treated ADHD-C patients and normal controls demonstrated an increase in SSRT score of 13.41 and decrease of -0.04, respectively. There was no statistically significant difference between groups in these changes in SSRT scores from baseline.
- *SSRT, All Patients:* Mean change from baseline scores were -17.57 and -23.10 for atomoxetine-treated patients with ADHD-C+RD or RD, respectively, and -3.59 for the untreated RD controls. Mean change from baseline scores for patients

with ADHD-C was 12.32 compared with a mean change of 3.43 in normal controls. None of the observed changes from baseline were statistically significant.

Mean Change from Baseline Comparisons of Phonological Task Reaction Time in Atomoxetine-Treated and Untreated Controls in Patients ≥ 10 Years of Age

- *Pseudo homophones RT*: Atomoxetine-treated patients with ADHD-C+RD or RD demonstrated a mean decrease from baseline of -170.8 and -241.0, respectively. A greater decrease of -254.9 was observed in the untreated RD control group. Patients with ADHD-C demonstrated a decrease from baseline of -230.4 after atomoxetine treatment and the normal controls demonstrated a decrease of -339.2. There was no statistically significant difference between atomoxetine-treated patients and control groups in these comparisons.
- *Pseudo words RT*: A greater decrease from baseline (-368.1) was observed in the RD controls compared to decreases seen in atomoxetine-treated patients with ADHD-C+RD or RD (-113.1 and -213.0, respectively). Atomoxetine-treated patients with ADHD-C demonstrated a decrease of -523.2 and the normal controls demonstrated a higher decrease of -536.0. There was no statistically significant difference between atomoxetine-treated patients and control groups.

Mean Change from Baseline Comparisons of Lexical Task Reaction Time in Atomoxetine-Treated and Untreated Controls, All Patients

- *Correct words RT*: Atomoxetine-treated patients with ADHD-C+RD or RD demonstrated a mean decrease from baseline of -61.22 and -121.6, respectively. The RD control patients demonstrated a mean decrease from baseline of -90.50. A decrease in score was also seen in atomoxetine-treated patients with ADHD-C (-97.61) as well as in the normal controls (-81.46). None of these observed changes from baseline were statistically significant.
- *Pseudo words RT*: A pattern similar to that seen in correct words RT was seen in pseudo words RT. Atomoxetine-treated patients with ADHD-C+RD or RD demonstrated a mean decrease from baseline of -66.87 and -174.7, respectively. The RD control patients demonstrated a decrease of -210.4. A decrease in score was also seen in atomoxetine-treated patients with ADHD-C (-92.35) as well as in the normal controls (-117.2). None of these observed changes from baseline were statistically significant.

Phonological Task Reaction Time in Repeated Measures Analysis

- *Pseudo homophones RT*: Atomoxetine-treated patients with ADHD-C or RD demonstrated lower RT scores compared with placebo-treated patients, -42.64 and -32.57, respectively. Atomoxetine-treated patients with ADHD-C+RD demonstrated a higher RT score (16.46) compared with placebo-treated patients.

The overall RT score was lower (-19.58) in atomoxetine-treated patients compared to placebo-treated patients. No statistically significant treatment effect of atomoxetine compared with placebo was observed but there was a statistically significant visit effect ($p=.003$).

- *Pseudo words RT*: A similar pattern was observed in pseudo word RT that was observed in pseudo homophones RT. Atomoxetine-treated patients with ADHD-C or RD demonstrated lower RT scores compared to placebo-treated patients, -56.72 and -117.7, respectively. Atomoxetine-treated patients with ADHD-C+RD demonstrated a higher RT score (116.89) compared with placebo-treated patients. The overall RT score was lower (-19.19) in atomoxetine-treated patients compared with placebo-treated patients. There was no statistically significant treatment effect of atomoxetine versus placebo but there was a statistically significant visit effect ($p=.002$).

Phonological Task Reaction Time, Mean Change from Baseline, within Treatment Sequence

- *Pseudo homophones RT*: Patients in the ATX-Placebo sequence demonstrated a statistically significant decrease from baseline at Visit 3 after receiving atomoxetine (-175.4, $p=0.002$) and then a further decrease at Visit 5 after receiving placebo (-285.2, $p=0.000$). Patients in the Placebo-ATX sequence demonstrated a nonstatistically significant decrease from baseline at Visit 3 after receiving placebo (-89.1, $p=0.169$), and then a statistically significant decrease at Visit 5 after receiving atomoxetine (-236, $p=0.015$).

Patients with ADHD-C in the ATX-Placebo sequence demonstrated a nonstatistically significant decrease from baseline at Visit 3 (-147.8, $p=.050$) after receiving atomoxetine and a further significant decrease (-125.7, $p=.004$) at Visit 5 after receiving placebo. Patients with ADHD-C in the Placebo-ATX sequence demonstrated a statistically significant decrease (-147.8, $p=.050$) from baseline only at Visit 3 after receiving placebo. Patients with ADHD-C+RD demonstrated a statistically significant decrease in score at Visit 3 after receiving atomoxetine (-240.2, $p=.007$) and a further significant decrease at Visit 5 after receiving placebo (-373.5, $p=.006$). No statistically significant changes from baseline were observed in the Placebo-ATX sequence ADHD-C+RD patients. Patients with RD in the ATX-Placebo sequence demonstrated a statistically significant decrease in score only at Visit 5 (-234.6, $p=.035$) after receiving placebo. No statistically significant changes from baseline were observed in the Placebo-ATX sequence in RD patients.

- *Pseudo words RT*: Patients in the ATX-Placebo sequence demonstrated a nonstatistically significant decrease in score at Visit 3 after receiving atomoxetine (-71.1, $p=.395$), and then a further decrease at Visit 5 which was statistically significant (-266.3, $p=.011$) after receiving placebo. Patients in the Placebo-ATX

sequence demonstrated a decrease at Visit 3 (-192.7, $p=.047$) after receiving placebo and a further decrease at Visit 5 (-407.1, $p=.016$) after receiving atomoxetine.

There were no statistically significant changes from baseline in patients with ADHD-C in the ATX-Placebo sequence. Patients with ADHD-C in the Placebo-ATX sequence demonstrated a statistically significant decrease at Visit 3 (-514.5, $p=.029$) after receiving placebo and a further decrease at Visit 5 (-848.0, $p=.026$) after receiving atomoxetine. Patients with ADHD-C+RD in the ATX-Placebo sequence demonstrated a statistically significant decrease (-428.4, $p=.017$) only at Visit 5 after receiving placebo. No statistically significant changes from baseline were observed in RD patients in either sequence.

Lexical Decision Task Reaction Time, Repeated Measures Analysis

- *Correct words RT:* Lower RT scores were observed in atomoxetine-treated patients compared to placebo-treated patients in all study arms and overall as follows: ADHD-C (-109.0); RD (-26.26); ADHD-C+RD (-103.9); and overall (-79.74). Statistically significant visit and treatment effects were observed ($p=.006$ for visit, $p=.005$ for treatment).
- *Pseudo words RT:* A similar pattern was observed in pseudo words RT as seen in correct words RT. Lower RT scores were observed in atomoxetine-treated patients compared with placebo-treated patients in all study arms and overall as follows: ADHD-C (-72.37); RD (-47.24); ADHD-C+RD (-60.98); and overall (-60.20). No statistically significant treatment effect or treatment plus study arm effect was observed but there was a statistically significant visit effect ($p=0.014$).

Lexical Decision Task Reaction Time, Mean Change from Baseline, Comparison within Treatment Sequence

- *Correct words RT:* Patients in both the ATX-Placebo sequence and the Placebo-ATX sequence demonstrated a decrease at Visit 3 and a further decrease at Visit 5. Only patients in the Placebo-ATX sequence demonstrated a statistically significant decrease from baseline at Visit 5 (-172.2, $p=.008$) after receiving atomoxetine.

No statistically significant changes were observed with either sequence in patients with ADHD-C or ADHD-C+RD. Patients with RD in the ATX-Placebo sequence demonstrated a statistically significant decrease at Visit 3 after receiving atomoxetine (-60.1, $p=.020$) as well as in the Placebo-ATX sequence at Visit 5 (-183.1, $p=.001$) after receiving placebo. These patients also showed a statistically significant decrease in score while receiving placebo at Visit 5 in the ATX-Placebo sequence (-115.5, $p=.020$).

- *Pseudo words RT:* Patients in the ATX-Placebo sequence demonstrated nonstatistically significant decreases at Visit 3 (-25.2, $p=.542$) after receiving atomoxetine and at Visit 5 (56.2, $p=.275$) after receiving placebo. Patients in the Placebo-ATX sequence demonstrated a nonstatistically significant decrease (-56.6) at Visit 3 after receiving placebo and further statistically significant decrease (-218.2, $p=.005$) at Visit 5 after receiving atomoxetine.

No statistically significant changes were observed with either sequence in patients with ADHD-C or ADHD-C+RD.

Assessment of Specificity of Atomoxetine Effect on SSRT, Phonological Decision Task, and Lexical Task Compared with Placebo

Repeated measures analyses demonstrated no statistically significant treatments effect compared with placebo in SSRT scores. Only nonstatistically significant decreases in phonological task (both pseudo homophones RT and pseudo words RT) and lexical task (pseudo words RT only) were observed in atomoxetine treatment compared to placebo. A statistically significant decrease in lexical decision task (correct words RT only) was observed in atomoxetine-treated patients compared to placebo-treated patients.

Mean change from baseline analysis of the phonologic task reaction time (both pseudo homophones and pseudo words) showed a consistent decrease (improvement) from baseline at Visit 3 and further at Visit 5, regardless of treatment (atomoxetine or placebo), treatment sequences, and/or study arms while SSRT or lexical task RT (both correct words and pseudo words) demonstrated fluctuated changes (increase or decrease) from baseline at Visit 3 and further at Visit 5. Statistically significant changes from baseline were observed in some of the treatment sequences or study arms, but were not consistently associated with either atomoxetine or placebo, in SSRT, phonological task RT, or lexical task RT. Thus based on these data, specificity of atomoxetine effect on inhibitory function or influence on the reading tasks could not be established.

Assessment of Atomoxetine Effect on Impulsivity Compared with Placebo on Impulsivity, Trade-Off between Speed and Accuracy

- *Deprime Analysis for the Phonological Task:* Repeated measures analyses of treatment differences between atomoxetine-and placebo-treated patients demonstrated higher scores in atomoxetine-treated patients with ADHD-C+RD (0.33) and RD (0.08) compared with placebo while atomoxetine-treated patients with ADHD-C had a lower score (-0.07) compared with placebo. However, no statistically significant treatment effect was observed.

Mean change from baseline analysis showed that patients in the ATX-Placebo sequence demonstrated a statistically significant increase from baseline at Visit 3 after receiving atomoxetine (0.539, $p=0.000$) and maintained the change at Visit 5 after receiving placebo (0.317, $p=.008$). Patients in the Placebo-ATX sequence demonstrated a statistically significant increase from baseline at Visit 3 after

receiving placebo (0.224, $p=0.019$) and a further increase at Visit 5 after receiving atomoxetine (0.346, $p=0.032$).

Only patients with RD demonstrated a statistically significant increase in score after receiving atomoxetine in both the ATX-Placebo sequence (0.455, $p=.0009$ at Visit 3) and the Placebo-ATX sequence (0.552, $p=0.017$ at Visit 5). A sporadic response was observed in the other study arms.

Patients with ADHD-C+RD in the ATX-Placebo sequence demonstrated a statistically significant increase in score (0.640, $p=0.001$) at Visit 3 after receiving atomoxetine and maintained the increase at Visit 5 after receiving placebo (0.260, $p=.044$). These patients also exhibited a statistically significant change from baseline at Visit 5, after receiving atomoxetine in the Placebo-ATX sequence (0.498, $p=.024$).

Based on the repeated measure analyses of the phonological task described earlier and the DEPRIME measure described above, atomoxetine treatment did not demonstrate statistically significant differences compared with placebo, in either phonologic task reaction times (speed measure) or deprime (accuracy measure). Thus, the trade-off effect on speed and accuracy on phonological tasks due to atomoxetine treatment could not be assessed.

- *Deprime Analysis for the Lexical Task:* Repeated measure analyses of treatment differences between atomoxetine-and placebo-treated patients showed that atomoxetine-treated patients with ADHD-C had a lower score (-0.09) compared with placebo-treated patients. Atomoxetine-treated patients with RD, ADHD-C+RD and overall demonstrated higher scores compared with placebo (0.14, 0.22 and 0.09 respectively). However, no statistically significant treatment effect was observed.

Mean change analysis demonstrated that there were no statistically significant changes from baseline observed in patients receiving atomoxetine or placebo in either sequence. Only patients with ADHD-C+RD in the Placebo-ATX sequence demonstrated a statistically significant mean decrease from baseline (-0.3, $p=.003$) at Visit 3 after receiving placebo.

Based on the repeated measure analyses of the lexical task reaction time described previously, atomoxetine treatment demonstrated a statistically significant decrease in lexical task for correct words reaction time (speed measure) compared to placebo, but only a nonstatistically significant decrease in lexical task pseudo words reaction time (speed measure). Also atomoxetine-treated patients in general had an increase (not statistically significant) in deprime (accuracy measure) compared to placebo. Thus, the trade-off effect on speed and accuracy on lexical tasks due to atomoxetine treatment could not be assessed.

Assessment of Atomoxetine Effect Compared with Placebo on Working Memory by CBTT

- *Repeated measure analysis:* Atomoxetine-treated patients demonstrated higher mean scores (longer memory span) compared to placebo in all 3 study arms and overall as follows: 0.31 for ADHD-C patients; 0.36 for RD patients; 0.63 for ADHD-C+RD patients; and 0.43 overall. A statistically significant treatment effect was observed ($p=.003$)
- *Mean change from baseline:* A statistically significant increase in mean score was observed in patients after receiving atomoxetine in both the ATX-placebo sequence (0.514, $p=.004$ at Visit 3) and the placebo-ATX sequence (1.00, $p=.000$ at Visit 5).

Patients with ADHD-C+RD demonstrated a statistically significant increase in score after receiving atomoxetine in both treatment sequences; 0.643, $p=.022$ at Visit 3 for ATX-Placebo sequence and 1.2, $p=.030$ at Visit 5 for Placebo-ATX sequence.

Patients with ADHD-C or RD demonstrated a statistically significant increase in score after receiving atomoxetine but only in the Placebo-ATX sequence; 0.917, $p=.005$ at Visit 5 for ADHD-C patients and .909, $p=.016$ at Visit 5 for RD patients.

ADHDRS-IV-Parent: INV Total and Subscale Scores

- *Repeated measures analysis:* Atomoxetine-treated patients with ADHD-C or ADHD-C+RD demonstrated decreases in mean total score and overall and each subscale score (inattention, hyperactivity-impulsivity) as well as adjusted total T score. A statistically significant treatment effect ($p<.001$) was observed for total score and each subscale score.
- *Change from baseline analyses:* Statistically significant decreases were observed in atomoxetine-treated patients in both treatment sequences for total score and all subscale scores ($p=.001$ for total score, inattention subscale and total T score, and $p=.002$ at Visit 3 and .001 at Visit 5 for the hyperactivity/impulsivity subscale score). Atomoxetine-treated patients with ADHD-C+RD demonstrated statistically significant decreases in both treatment sequences [-11.2 ($p=.005$) at Visit 3 for the ATX-Placebo sequence and -1.7 ($p=.002$) at Visit 5 for the Placebo-ATX sequence]. A statistically significant decrease of -3.8 in mean IA subscale was observed in atomoxetine-treated ADHD-C patients in the ATX-Placebo group at Visit 3.

Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity

- *Repeated measure analysis:* Atomoxetine-treated patients with ADHD-C+RD demonstrated a lower (-0.69) score compared to placebo-treated patients. Atomoxetine-treated patients with ADHD-C had a higher (0.31) score compared with placebo-treated patients. The overall score for both ADHD-C and

ADHD-C+RD patients was -.019. A statistically significant treatment plus study arm effect ($p=.009$) was observed.

- *Change from Baseline Analyses:* A statistically significant mean change from baseline was observed in atomoxetine-treated patients in both sequences; -0.4 ($p=.008$) in the ATX-Placebo sequence and -0.7 ($p=0.033$) in the Placebo-ATX sequence. There was also a statistically significant change [-0.04 ($p=0.047$)] in placebo-treated patients in the Placebo-ATX sequence.

Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Improvement

- *Repeated measures analysis:* Atomoxetine-treated patients with ADHD-C and ADHD-C+RD demonstrated lower scores compared with placebo-treated patients as follows: (-0.01 for ADHD-C patients and -0.78 for ADHD-C+RD patients). The overall score was -.39. No statistically significant treatment effect was observed.

Safety

Extent of Exposure

The mean number of days on study medication in Study Period II was 29.7 for both atomoxetine and placebo. A total of 2 patients in the ATX-Placebo group discontinued before initiation of atomoxetine. Thus, there were 2 fewer patients exposed to atomoxetine than exposed to placebo. In addition, exposure data for 2 other patients were not available and their extent of exposure was imputed using the maximum exposure of 28 days which would have been received if they had taken all study medication. The mean total drug exposure for the 25 patients in Study Period III was 247.9 days.

Deaths and Others Serious Adverse Events

Terminology from the Medical Dictionary for Regulatory Activities®, Version 10.0 (MedDRA) was used to code and classify AEs. No deaths or other SAEs were reported during the study.

Adverse Events Leading to Patient Discontinuation

Two atomoxetine-treated patients with ADHD-C+RD discontinued due to an AE. One patient (1.3%) discontinued during Study Period II due to headache and 1 patient (4%) discontinued during Study Period III due to fatigue

Treatment-Emergent Adverse Events

An analysis of TEAEs by treatment and system organ class and treatment sequence during Study Period II demonstrated a higher frequency of TEAEs in patients receiving atomoxetine [$n=35(47.3\%)$] compared to patients receiving placebo [$n=27(35.5\%)$]. This difference was not statistically significant. There was a statistically significant increased frequency of abdominal pain ($p=.046$), fatigue ($p=.011$), and nausea ($p=.02$) observed in patients taking atomoxetine compared to patients taking placebo.

Frequently Reported ($\geq 5\%$) Adverse Events Study Period II

The most frequently reported TEAEs in atomoxetine-treated patients were headache (14.9%), fatigue (12.2%), nausea (10.8%), decreased appetite and abdominal pain (8.1%), abdominal pain upper and vomiting (6.8%), and diarrhea (5.4%). Only headache occurred at a frequency of $\geq 5\%$ (13.2%) in patients taking placebo.

A majority of the 25 patients who entered Period III experienced 1 or more TEAEs [n=24 (96.0%)].

Changes in Vital Signs

A comparison between treatment groups using a repeated measures analysis of Visit 3 and Visit 5 was computed for vital signs for Study Period II using independent effects for treatment, treatment sequence, and baseline. Changes in vital signs from baseline were computed based on the paired t-test model using independent effects for treatment and baseline.

A statistically significant difference in diastolic blood pressure ($p=0.026$), heart rate ($p=0.005$), and weight ($p=0.000$) was observed in atomoxetine-treated patients compared to placebo-treated patients by repeated measures analysis during Study Period II. The mean endpoint diastolic blood pressure, heart rate, and weight in the atomoxetine group was 63.6 mmHg, 82.3 bpm, and 35.0 kg, respectively. The mean endpoint diastolic blood pressure, heart rate, and weight in the placebo group was 62.5 mmHg, 80.2 bpm, and 38.0 kg, respectively. A statistically significant difference from baseline to endpoint was observed in diastolic blood pressure ($p=0.006$), heart rate ($p=0.001$), and weight ($p=0.001$) measurements during Study Period II. The mean change from baseline to endpoint in diastolic blood pressure, heart rate, and weight in the atomoxetine group was 3.0 mmHg, 5.0 bpm, and 0.1 kg, respectively while the mean change from baseline to endpoint in these same measures in the placebo group was 1.8 mmHg, 3.1 bpm, and 0.8 kg, respectively.

Summary

- A total of 76 patients entered Study Period II and 71(93.0%) completed this period. There was no statistically significant difference in completion rate between treatment groups. A total of 25 patients entered the open-label Study Period III and 16 (64%) completed this period. No statistically significant difference was observed between treatment sequences in any demographic and screening characteristics measured.
- No statistically significant difference was seen between treatment groups in any study arm by repeated measure analysis of SSRT. Change from baseline to endpoint analysis of SSRT demonstrated no statistical significance in different study arms whether the patient took atomoxetine or placebo first, except for a statistically significant decrease at Visit 3 in atomoxetine-treated patients with RD.

- There was no statistically significant difference in change from baseline in SSRT scores, phonological task RT or lexical task RT in any study arm in atomoxetine-treated patients compared with untreated controls.
- The specificity of atomoxetine effect on inhibitory function (SSRT) or influence on the reading tasks could not be established and there was no consistent statistically significant treatment difference on impulsivity or accuracy.
- A statistically significant atomoxetine treatment effect was seen compared to placebo by repeated measures of CBTT working memory span and in both treatment sequences by change from baseline analysis. A statistically significant change from baseline to endpoint was seen in ADHD-C+RD patients treated with atomoxetine in both treatment sequences and in ADHD-C patients and RD patients treated with atomoxetine in the Placebo-ATX sequence.
- A statistically significant atomoxetine treatment effect was seen in atomoxetine-treated patients compared to placebo by repeated measures analysis of ADHDRS-IV-Parent:Inv total score and all subscale scores. Statistically significant decreases from baseline were seen with atomoxetine treatment compared to placebo in both treatment sequences. Atomoxetine-treated patients with ADHD-C+RD also demonstrated statistically significant decreases in score in both treatment sequences.
- No statistically significant atomoxetine treatment effect in symptom reduction was seen in patients with ADHD by repeated measures analysis in CGI-ADHD-S and CGI-ADHD-I evaluations. A statistically significant mean change from baseline in symptom reduction was observed with atomoxetine compared to placebo in both treatment sequences for CGI-ADHD-S. Atomoxetine-treated patients with ADHD-C+RD also demonstrated statistically significant decreases in score in both treatment sequences.
- There were no deaths or other SAEs reported during the study. One (1.3%) of the 76 patients who entered Study Period II and 1 (4.0%) of the 25 patients who entered Study Period III discontinued due to headache and fatigue respectively.
- There was a statistically significant higher frequency of mild or moderate fatigue, abdominal pain and nausea during Study Period II in patients receiving atomoxetine compared to patients receiving placebo.
- Increases from baseline to endpoint were seen in both treatment groups in diastolic blood pressure, heart rate and weight

Summary ID# 7972

Clinical Study Summary: Study B4Z-US-LYCC

Evaluation of Continuous Symptom Treatment of ADHD: A Placebo-Controlled Double-Blind Assessment of Morning-Dosed or Evening-Dosed Strattera

Date summary approved by Lilly: 21 November 2006

Brief Summary of Results

Study B4Z-US-LYCC (LYCC) was a multicenter, randomized, placebo-controlled, double-blind study of once-daily Strattera® (or atomoxetine hydrochloride, hereafter referred to as atomoxetine) in the treatment of children with Attention-Deficit/Hyperactivity Disorder (ADHD). Patients were randomized (1:1:1) to receive atomoxetine or placebo in the morning or evening (before bedtime) in this double-blind trial for approximately 6 weeks.

The primary objective of Study LYCC was to test the hypothesis that atomoxetine at doses up to 1.4 mg/kg/day given once a day in the morning for approximately 6 weeks was superior to placebo in children with ADHD using the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) Total score and the Conners' Global Index Parent-Evening (CGIP-E) Total score.

The main results were as follows:

- The morning-dosed atomoxetine group showed statistical separation from the placebo-treated group at Visit 5 ($p < .001$) for the ADHDRS-IV-Parent:Inv Total score and the CGIP-E Total score.

- The overall improvement in the ADHDRS-IV-Parent:Inv Total score in patients dosed with atomoxetine in the evening (before bedtime) compared to the reduction in patients dosed with placebo was statistically significantly greater ($p=.009$).
- The reduction in the Daily Parent Ratings of Evening and Morning Behavior Revised (DPREMB-R) Evening subscore in patients dosed with atomoxetine in the morning compared to the reduction in patients dosed with placebo was statistically significantly different ($p=.001$).
- The reduction in the Conners' Global Index Parent-Morning (CGIP-M) Total score in patients dosed with atomoxetine in the morning compared to the reduction in patients dosed with placebo was statistically significantly different ($p=.023$).
- The reduction in the Brown Attention-Deficit Disorder (ADD) Scales Total score in patients dosed with atomoxetine in the morning compared to the reduction in patients dosed with placebo was statistically significantly different among patients aged 3- to 7-years-old ($p=.032$) and among patients aged 8- to 12-years-old ($p=.006$).
- The improvement in the Life Participation Scale Attention-Deficit Hyperactivity Disorder Revised (LPS-ADHD-R) Total score was statistically significantly improved for patients dosed with atomoxetine in the morning compared to patients dosed with placebo ($p<.001$).
- There were no statistically significant differences in the last observation carried forward (LOCF) for Expressions and Emotions Scale for Children (EESC) total score or in the comparison of the treatment groups.
- There were no deaths or serious adverse events (SAEs) in Study LYCC. A total of 5 patients discontinued the study due to an adverse event (AE): 2 patients in the placebo group (1 for aggression, 1 for mood swings), 1 patient in the morning-dose group (for tearfulness), and 2 patients in the evening-dose group (1 for nausea, 1 for suicidal ideation).
- A statistically significantly greater percentage of patients reported 1 or more treatment-emergent adverse events (TEAEs) in the morning-dosed atomoxetine group (73.96%) when compared with the placebo-treated group (43.48%, $p<.001$), or when compared with the evening-dosed atomoxetine group (48.89%, $p<.001$).
- A summary of laboratory analytes showed statistically significant within-group and between-group differences in mean change from baseline to several treatment visits and from baseline to endpoint. There were statistically significant differences in the morning-dosed atomoxetine group and placebo and the evening-

dosed group and placebo for electrocardiogram (ECG) results, and vitals including: weight, blood pressure (BP) and pulse rate.

Title of Study: Evaluation of Continuous Symptom Treatment of ADHD: A Placebo-Controlled Double-Blind Assessment of Morning-Dosed or Evening-Dosed Strattera	
Investigators: This multicenter study included 14 principal investigators.	
Study Centers: This study was conducted at 14 study centers in 1 country.	
Length of Study: Approximately 8 months Date of first patient enrolled: 13 October 2003 Date of last patient completed: 10 June 2004	Phase of Development: 3
Objectives: The primary objective of this study was to test the hypothesis that atomoxetine administered orally, once a day, at doses of up to 1.4 mg/kg/day for approximately 6 weeks given in the morning is superior to placebo in children with ADHD diagnosed using the <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision™</i> (DSM-IV-TR™) criteria. Efficacy was measured by comparing the differences in atomoxetine dosed in the morning with placebo at the end of 6 weeks using the ADHDRS-IV-Parent:Inv Total score and the CGIP-E Total score. If atomoxetine dosed in the morning was assessed to be statistically significantly superior to placebo based on the primary analyses of the ADHDRS-IV-Parent:Inv Total score and the CGIP-E Total score, then key secondary objectives were tested for possible label inclusion using the gatekeeper strategy. Atomoxetine and placebo (dosed as indicated for each analysis) were compared in the order indicated below. Testing would stop when a measure failed to show statistical significance favoring atomoxetine ($p \geq .05$). The secondary objectives to be considered for label inclusion were in order of preference, as follows: • To test the hypothesis that atomoxetine administered once daily in the evening (before bedtime) provides superior efficacy compared with placebo in children with ADHD based on the ADHDRS-IV-Parent:Inv Total score. • To test the hypothesis that atomoxetine administered once daily in the morning provides superior efficacy in the evenings compared with placebo in children with ADHD based on the DPREMB-R evening score. • To test the hypothesis that atomoxetine administered once daily in the morning provides superior efficacy in the mornings (before daily dosing; that is, nearly 24 hours since last dosing) compared with placebo in children with ADHD based on the CGIP-M Total score. • To assess the effect of dosing atomoxetine in the morning versus placebo on measures of executive functioning as measured by the Brown Attention-Deficit Disorder (ADD) Scales Total score. • To test the hypothesis that atomoxetine administered once daily in the morning provides superior efficacy compared with placebo for measures of adaptive functioning in children with ADHD based on the LPS-ADHD-R Total score. • To evaluate changes in expression and emotions in children diagnosed with ADHD treated with atomoxetine dosed in the morning or in the evening based on changes in the total score from baseline to endpoint on the EESC relative to placebo. Additional secondary objectives were: • To test the hypothesis that atomoxetine administered once daily in the evening provides superior efficacy in the evenings (before daily dosing; that is, nearly 24 hours since last dosing) compared with placebo in children with ADHD based on the CGIP-E Total score and the evening subscore of the DPREMB-R. • To test the hypothesis that atomoxetine administered once daily in the morning provides superior efficacy in the mornings (before daily dosing; that is, nearly 24 hours since last dosing) compared with placebo in children with ADHD, as measured by the morning subscore of DPREMB-R. • To examine the onset of action during the first week of treatment in the morning versus in the evening compared with placebo measured by the DPREMB-R Total score and the CGIP-M.	

The DPREMB-R and the CGIP-M were collected on a daily basis using real-time remote data entry beginning 5 days prior to Visit 2 and for 15 days following Visit 2. - To assess the effect of dosing atomoxetine in the evening versus placebo on measures of executive functioning as measured by the Brown ADD scales. - To compare morning versus evening dosing compared with placebo as assessed by the Clinical Global Impression-ADHD-Severity (CGI-ADHD-S) at each visit. - To assess the safety and tolerability of atomoxetine dosed in the morning versus in the evening compared with placebo.
Study Design: This study was a multicenter, randomized, placebo-controlled, double-blind, outpatient trial (see Figure 1). Patients were randomized (1:1:1) to receive atomoxetine in the morning and placebo in the evening, placebo in the morning and atomoxetine in the evening, or placebo in the morning and placebo in the evening in a double-blinded fashion for approximately 6 weeks.
Number of Patients: Planned: 184 atomoxetine, 92 placebo Randomized: 195 atomoxetine, 93 placebo Completed: 140 atomoxetine, 66 placebo
Diagnosis and Main Criteria for Inclusion: The study enrolled both male and female patients who were at least 6-years-old and no more than 12-years-old prior to Visit 2 that met the disease diagnostic criteria for ADHD (as defined by the DSM-IV-TR). The diagnosis was confirmed during the screening visit by administration of the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version: Behavioral Disorders Supplement (K-SADS-PL:Beh). Patients also had to score at least 1.5 standard deviations above the age/gender norm for their ADHD diagnostic subtype on the ADHDRS-IV-Parent:Inv at Visit 1 and Visit 2.
Study Drug, Dose, and Mode of Administration: Atomoxetine hydrochloride: target dose of 1.2 mg/kg/day, given orally daily, once in the morning or once in the evening, 2.5mg, 5mg, 10mg, 20mg, 25mg, and 40mg capsules.
Comparator, Dose, and Mode of Administration: Placebo: given orally twice daily or once in the morning or once in the evening.
Duration of Treatment: 6 weeks
Variables: Efficacy: ADHDRS-IV-Parent:Inv, CGIP-E, CGIP-M, DPREMB-R, CGI-ADHD-S, Brown ADD Scales, LPS-ADHD-R and EESC. Safety: AEs, laboratory data, vital signs, height and weight, and ECGs.
Evaluation Methods: Statistical: This study was designed to have adequate statistical power to detect a treatment effect using the ADHDRS-IV-Parent:Inv and the CGIP-E, and to detect differences in all secondary efficacy measures with the exception of the Brown ADD Scale and EESC. Two populations were considered for analysis in this study. One was based on the intent-to-treat (ITT) principle, and the other based on patients who had received at least 1 dose of study medication. For all efficacy analyses, an ITT population was analyzed. Both primary measures, the ADHDRS-IV-Parent:Inv Total score and the CGIP-E, were analyzed using a mixed models repeated measures (MMRM) technique. These analyses included the fixed categorical effects of treatment, investigator, visit, and treatment-by-visit interaction. The analyses also included the continuous, fixed covariate of baseline (last of scores at Visit 1 and Visit 2) score. The primary analyses compared atomoxetine dosed in the morning and placebo at the final postbaseline visit using a contrast from the MMRM analysis. The gatekeeper method was used to order secondary outcomes to be considered for label considerations. Each of the gatekeeper analyses specified the comparison of atomoxetine dosed in the morning or atomoxetine dosed in the evening with placebo from the overall treatment effect from an MMRM analysis except for the Life Participation Scale. It was

collected only at baseline and endpoint, and a last-observation-carried-forward (LOCF) analysis of covariance (ANCOVA) with terms for baseline, treatment and investigator was used. Continuous efficacy measures were analyzed using MMRM and LOCF ANCOVA as appropriate. Analyses of efficacy measures included all patients who had at least 1 baseline and 1 postbaseline score except for some secondary analyses of the DPREMB-R and CGIP-M that included only patients who were more compliant with their diaries. Analyses of safety included all patients who took at least 1 dose of study drug. Comparisons of categorical outcomes were made using the Fisher's Exact test. Analyses of change in safety measures were performed with LOCF ANCOVA. Within-group comparisons of change with zero were made using Wilcoxon's signed-rank test. All tests of significance in this study were 2-sided and assessed at a significance level of .05.

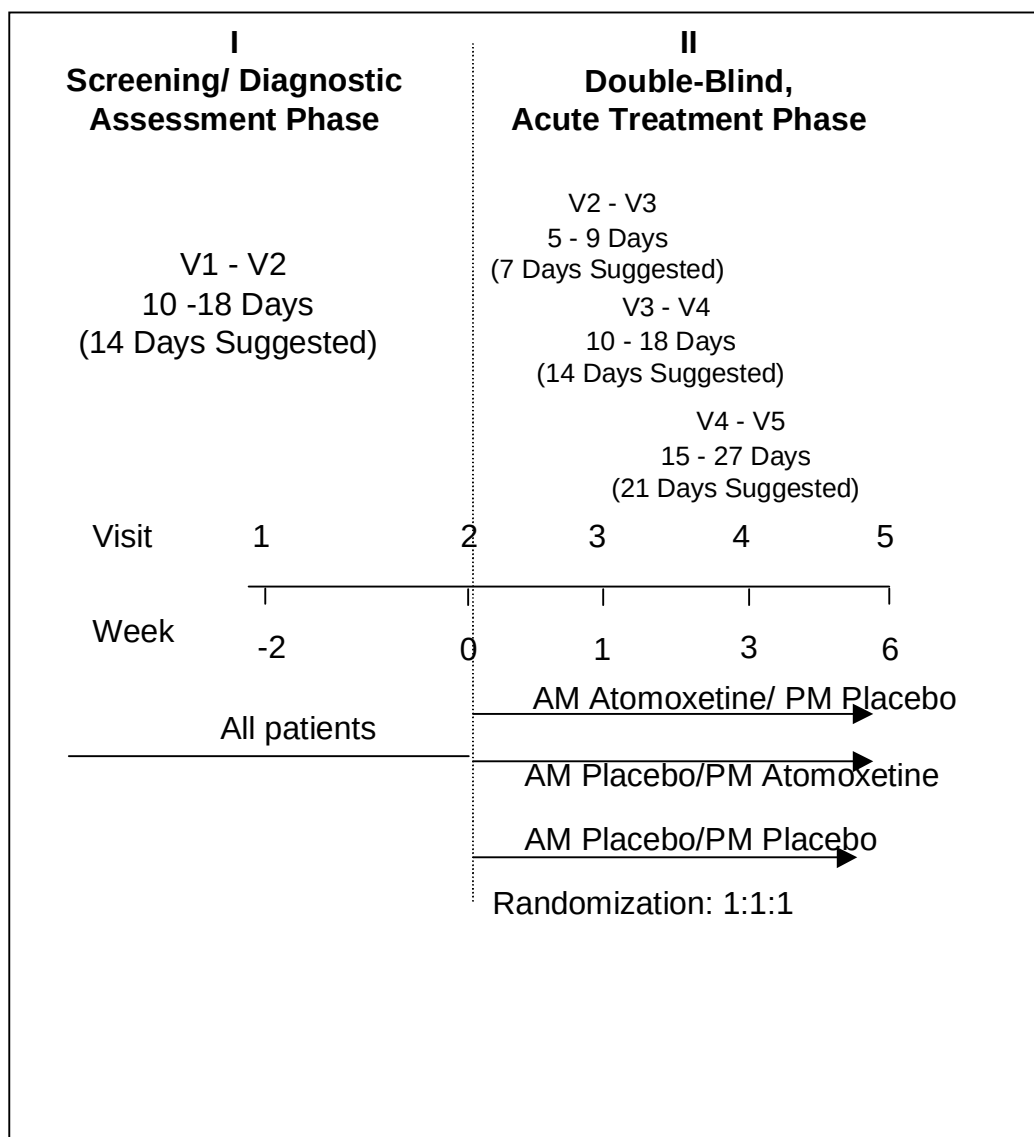


Figure 1. Illustration of study design for Protocol B4Z-US-LYCC.

Patient Demographics

Table 1 summarizes the demographic characteristics for all patients who were randomized to treatment. Of the 288 randomized patients, 72.6% were male, 68.8% were Caucasian, and 90.6% were extensive metabolizer (EM) patients of atomoxetine. Ages ranged from 6- to 12-years-old (per protocol, patients must have been 6-years-old by Visit 2). Statistically significantly more patients treated with atomoxetine met 1 of 2 response criteria (at least 25% reduction from baseline to endpoint on ADHDRS-IV-Parent:Inv Total score, or a decrease of ≥ 2 from baseline to endpoint, on the Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity [CGI-ADHD-S]) than patients treated with placebo ($p < .001$). Statistically significantly more patients treated with atomoxetine met 1 of 2 remission criteria (endpoint ADHDRS-IV-Parent:Inv Total T-score ≤ 65 or endpoint CGI-ADHD-S ≤ 2) than patients treated with placebo ($p = .004$ and $p = .014$, respectively).

**Table 1. Patient Demographic Characteristics at Baseline
All Randomized Patients
Study Period II**

DEMOGRAPHIC INFORMATION		TMX/PLA		PLA/TMX		PLA/PLA		*P-VALUE
		N	PERCENT	N	PERCENT	N	PERCENT	
CY2D6GEN	EXTN	93	93.00 %	81	90.00 %	87	93.55 %	.698
	SLOW	7	7.00 %	9	10.00 %	6	6.45 %	
GENDER	F	33	32.35 %	22	23.66 %	24	25.81 %	.366
	M	69	67.65 %	71	76.34 %	69	74.19 %	
ORIGIN	AF	15	14.71 %	14	15.05 %	11	11.83 %	.903
	CA	70	68.63 %	66	70.97 %	62	66.67 %	
	EA	1	0.98 %	0	0.00 %	0	0.00 %	
	HP	13	12.75 %	11	11.83 %	17	18.28 %	
	O	3	2.94 %	2	2.15 %	3	3.23 %	
REMIT1	N	47	50.00 %	53	60.23 %	67	73.63 %	.004
	Y	47	50.00 %	35	39.77 %	24	26.37 %	
REMIT2	N	72	76.60 %	78	88.64 %	83	91.21 %	.014
	Y	22	23.40 %	10	11.36 %	8	8.79 %	
RESPOND1	N	37	39.36 %	38	43.18 %	59	64.84 %	<.001
	Y	57	60.64 %	50	56.82 %	32	35.16 %	
RESPOND2	N	48	51.06 %	60	68.18 %	71	78.02 %	<.001
	Y	46	48.94 %	28	31.82 %	20	21.98 %	
SUBTYPE	HYP/IMP	3	2.94 %	1	1.08 %	3	3.23 %	.474
	INATTV	26	25.49 %	16	17.20 %	22	23.66 %	
	MIXED	73	71.57 %	76	81.72 %	68	73.12 %	

DEMOGRAPHIC INFORMATION		N	MEAN	MEDIAN	STD	MAX	MIN	P-VALUE**
AGE	TMX/PLA	102	8.76	8.72	1.65	11.92	5.98	0.374
	PLA/TMX	93	9.09	9.07	1.57	11.97	6.01	
	PLA/PLA	93	8.91	8.81	1.66	11.84	6.04	
BMIV1	TMX/PLA	102	18.49	17.60	3.26	28.54	14.12	0.574
	PLA/TMX	93	18.22	17.90	2.83	28.21	14.07	
	PLA/PLA	93	18.77	17.63	4.31	33.99	12.89	
HEIGHTV1	TMX/PLA	102	131.69	129.75	10.21	157.00	107.00	0.227
	PLA/TMX	93	134.13	133.00	10.25	161.00	115.00	
	PLA/PLA	93	132.21	131.50	10.45	163.00	117.00	
WEIGHTV1	TMX/PLA	102	32.57	30.45	9.17	60.00	20.00	0.832
	PLA/TMX	93	33.34	32.20	9.07	58.60	20.90	
	PLA/PLA	93	33.16	31.30	9.88	62.40	20.00	

*p-Value is from Fisher's Exact Test.

**p-Value is from an ANOVA model with term for treatment.

Patient Disposition

Of the 404 patients entered into the study, 288 were randomized to 1 of the 3 treatment groups: 102 patients received atomoxetine in the morning and placebo at night, 93 patients received placebo in the morning and atomoxetine at night, and 93 patients received placebo in both the morning and the night. In all, 206 patients completed the protocol (70 patients in the morning-dosed atomoxetine group, 70 patients in the evening-dosed atomoxetine group, and 66 in the placebo group [Figure 2]).

Table 2 shows the numbers and percentages of randomized patients who discontinued from Study Period II for specific reasons in each of the 3 treatment groups overall. A total of 10 (3.4%) patients discontinued the study due to lack of efficacy, and a total of 5 (1.7%) patients discontinued due to an AE. Overall, there were no statistically significant differences between treatment groups in any reasons for discontinuation.

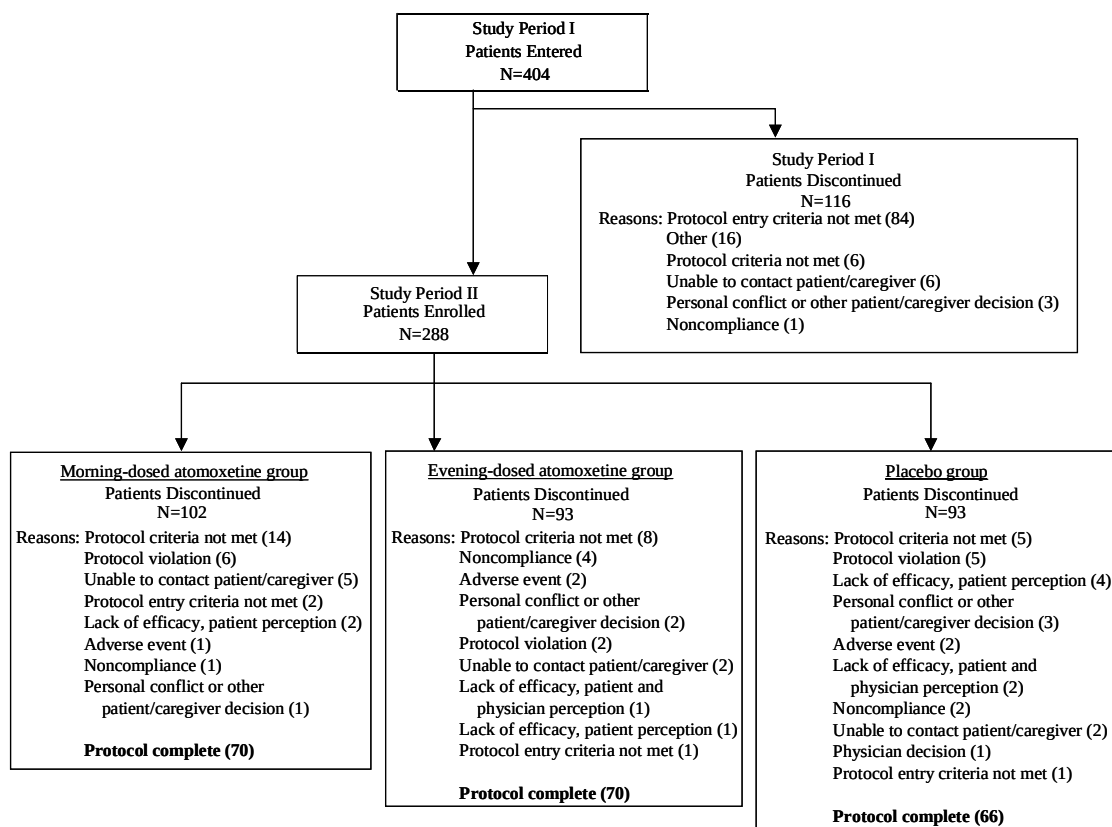


Figure 2. Patient disposition.

Atomoxetine

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**Table 2. Reasons for Discontinuation
Comparison of Treatment Groups
All Randomized Patients
Study Period II**

	TMX/PLA			PLA/TMX			PLA/PLA			Total			Fisher's Exact p- Value
	N	N	%	N	N	%	N	N	%	N	N	%	
Adverse Event	102	1	1.0	93	2	2.2	93	2	2.2	288	5	1.7	.743
Death	102	0	0.0	93	0	0.0	93	0	0.0	288	0	0	N/A
Lack of Efficacy, Patient and Physician perception	102	0	0.0	93	1	1.1	93	2	2.2	288	3	1.0	.311
Lack of Efficacy, Patient perception	102	2	2.0	93	1	1.1	93	4	4.3	288	7	2.4	.402
Lack of Efficacy, Physician perception	102	0	0.0	93	0	0.0	93	0	0.0	288	0	0.0	N/A
Noncompliance	102	1	1.0	93	4	4.3	93	2	2.2	288	7	2.4	.310
Other	102	0	0.0	93	0	0.0	93	0	0.0	288	0	0.0	N/A
Patient Moved	102	0	0.0	93	0	0.0	93	0	0.0	288	0	0.0	N/A
Personal Conflict or other Patient/Caregiver Decision	102	1	1.0	93	2	2.2	93	3	3.2	288	6	2.1	.528
Physician Decision	102	0	0.0	93	0	0.0	93	1	1.1	288	1	0.3	.646
Protocol Complete	102	70	68.6	93	70	75.3	93	66	71.0	288	206	71.5	.588
Protocol Criteria Not Met	102	14	13.7	93	8	8.6	93	5	5.4	288	27	9.4	.149
Protocol Entry Criteria Not Met	102	2	2.0	93	1	1.1	93	1	1.1	288	4	1.4	1.000
Protocol Violation	102	6	5.9	93	2	2.2	93	5	5.4	288	13	4.5	.430
Sponsor Decision	102	0	0.0	93	0	0.0	93	0	0.0	288	0	0.0	N/A
Unable to Contact Patient/Caregiver	102	5	4.9	93	2	2.2	93	2	2.2	288	9	3.1	.523

Abbreviations: TMX = Atomoxetine, PLA = Placebo

Analysis of Efficacy

The ITT population was analyzed for the primary and gatekeeper analyses. The ITT population was analyzed for the DPREMB-R and CGIP-M for the gatekeeper analyses; however, a subgroup of the ITT population was used for the other secondary analyses, based on patient compliance rate with their diaries. For the primary and gatekeeper analyses, baseline was defined to be the last of Visit 1 and Visit 2, and endpoint was defined to be the last of Visit 3 through Visit 5 during this 6-week trial. For the subgroup analyses, the DPREMB-R and the CGIP-M were collected on a daily basis using real-time remote data entry beginning 5 days prior to Visit 2 and for 15 days following Visit 2.

Of the 288 randomized patients, 273 were analyzed for the primary efficacy measures. The results were as follows:

- Tables 3 and 4 include pairwise treatment differences and statistical significance at each visit for the ADHDRS-IV-Parent:Inv Total score and the CGIP-E Total score, respectively. The treatment comparison of atomoxetine dosed in the morning versus placebo at Visit 5 is the primary analysis. Using the pairwise treatment differences, the morning-dosed atomoxetine group showed statistical separation from the placebo-treated group at Visit 5 for both primary efficacy measures ($p < .001$).
- At each visit during the treatment phase, a comparison of the mean change from baseline between the 3 groups from the repeated measures analysis of the ADHDRS-IV-Parent:Inv Total score showed a statistically significant decrease in atomoxetine versus placebo scores (morning-dosed versus placebo-dosed groups, $p < .001$; evening-dosed versus placebo-dosed groups, $p = .009$). In addition, the morning-dosed atomoxetine group showed a statistically significant decrease in ADHDRS-IV-Parent :Inv Total score compared to the evening-dosed atomoxetine group ($p = .014$).
- At each visit during the treatment phase, a comparison of the mean change from baseline between the 3 groups from the CGIP-E Total score repeated measures showed a statistically significant decrease in atomoxetine versus placebo scores (morning-dosed versus placebo-dosed groups, $p < .001$; evening-dosed versus placebo-dosed groups, $p = .002$) although the morning-dosed atomoxetine group did not show a statistically significant change in CGIP-E Total score compared to the evening-dosed atomoxetine group ($p = .838$).

Atomoxetine

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Table 3. **ADHDRS-IV-Parent:Inv Total Score**
Repeated Measures Least-Squares Means
All Randomized Patients
Study Period II

Visit	TMX/PLA	PLA/TMX	PLA/PLA	(TMX/PLA) VS (PLA/TMX)			(TMX/PLA) VS (PLA/PLA)			(PLA/TMX) VS (PLA/PLA)		
	LSMEAN	LSMEAN	LSMEAN	LSMEAN	SE	p-Value +	LSMEAN	SE	p-Value +	LSMEAN	SE	p-Value +
3	-12.35	-9.63	-6.16	-2.72	1.44	.060	-6.20	1.43	<.001	-3.47	1.45	.017
4	-15.15	-11.79	-8.04	-3.36	1.70	.049	-7.11	1.68	<.001	-3.75	1.72	.030
5	-17.76	-13.45	-9.51	-4.32	2.02	.034	-8.25	2.01	<.001	-3.93	2.03	.054
Summary of Model Parameters				f-Value			p-Value *					
Baseline				10.72			.001					
Treatment				13.49			<.001					
Visit				12.50			<.001					
Investigator				2.27			.009					
Treatment*Visit				0.28			.891					
				t-Value			p-Value #					
(TMX/PLA VS PLA/TMX)				-2.48			.014					
(TMX/PLA VS PLA/PLA)				-5.19			<.001					
(PLA/TMX VS PLA/PLA)				-2.64			.009					

RESULTS BASED ON A MIXED MODEL WITH BASELINE, TREATMENT, VISIT, INVESTIGATOR, AND TREATMENT BY VISIT.
INTERACTION TERMS USING UNSTRUCTURED COVARIANCE MATRIX TO MODEL CORRELATIONS WITHIN PATIENT ACROSS VISITS.
P-VALUES+ ARE FROM TESTS FOR A PAIRWISE TREATMENT DIFFERENCE IN LEAST SQUARES MEANS AT THE GIVEN VISIT.
P-VALUES* ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE BASED ON THE MODEL DESCRIBED ABOVE.
P-VALUES# ARE FROM TESTS FOR A PAIRWISE TREATMENT DIFFERENCE IN LEAST SQUARES MEANS.
POPULATION: ALL RANDOMIZED PATIENTS.

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**Table 4. Conners' Global Index Parent-Evening Total Score
Repeated Measures Least-Squares Means
All Randomized Patients
Study Period II**

Visit	TMX/PLA	PLA/TMX	PLA/PLA	(TMX/PLA) VS (PLA/TMX)			(TMX/PLA) VS (PLA/PLA)			(PLA/TMX) VS (PLA/PLA)		
	LSMEAN	LSMEAN	LSMEAN	LSMEAN	SE	p-Value ₊	LSMEAN	SE	p-Value ₊	LSMEAN	SE	p-Value ₊
3	-4.57	-4.51	-2.45	-0.06	0.83	.943	-2.12	0.83	.011	-2.06	0.84	.015
4	-4.28	-5.23	-2.44	-0.94	0.94	.315	-1.84	0.93	.048	-2.79	0.95	.004
5	-5.82	-4.46	-2.03	-1.35	1.08	.210	-3.78	1.07	<.001	-2.43	1.08	.026
Summary of Model Parameters				f-Value			p-Value *					
Baseline				58.92			<.001					
Treatment				7.21			<.001					
Visit				0.17			.841					
Investigator				1.97			.027					
Treatment*Visit				1.78			.134					
				t-Value			p-Value #					
(TMX/PLA VS PLA/TMX)				-0.20			.838					
(TMX/PLA VS PLA/PLA)				-3.41			<.001					
(PLA/TMX VS PLA/PLA)				-3.15			.002					

RESULTS BASED ON A MIXED MODEL WITH BASELINE, TREATMENT, VISIT, INVESTIGATOR, AND TREATMENT BY VISIT
INTERACTION TERMS USING UNSTRUCTURED COVARIANCE MATRIX TO MODEL CORRELATIONS WITHIN PATIENT ACROSS VISITS
P-VALUES+ ARE FROM TESTS FOR A PAIRWISE TREATMENT DIFFERENCE IN LEAST SQUARES MEANS AT THE GIVEN VISIT
P-VALUES* ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE BASED ON THE MODEL DESCRIBED ABOVE
P-VALUES# ARE FROM TESTS FOR A PAIRWISE TREATMENT DIFFERENCE IN LEAST SQUARES MEANS
POPULATION: ALL RANDOMIZED PATIENTS

Secondary Objectives Using the Gatekeeper Strategy

The results of the secondary objectives, in the prespecified gatekeeper order were:

- The first gatekeeper analysis tested the hypothesis that once-daily evening-dosed atomoxetine provided superior efficacy in children with ADHD compared to placebo based on the ADHDRS-IV-Parent:Inv Total score using the overall treatment contrast. As pairwise treatment differences in the summary Table 3 show, the improvement in the ADHDRS-IV-Parent:Inv Total score in patients dosed with atomoxetine in the evening (before bedtime) compared to the reduction in patients dosed with placebo was statistically significantly greater ($p=.009$).
- The evening subscores of the DPREMB-R scale for the morning-dosed atomoxetine group and placebo-treated group were compared to test the hypothesis that atomoxetine dosed once daily in the morning provided superior efficacy in the evenings compared to placebo in children with ADHD. The results from the repeated measures analysis of the DPREMB-R Evening subscore, with pairwise treatment differences and statistical significance at each day are contained in Table 5. Overall, the reduction in the DPREMB-R Evening subscores in patients dosed with atomoxetine in the morning compared to the reduction in patients dosed with placebo was statistically significantly greater ($p=.001$).
- The total scores of the CGIP-M scale for the morning-dosed atomoxetine group and placebo-treated group were compared to test the hypothesis that once daily morning-dosed atomoxetine provided superior efficacy in the mornings (before daily dosing; that is, nearly 24 hours since last dosing) compared to placebo in children with ADHD. The results from the repeated measures analysis of the CGIP-M Total score with pairwise treatment differences and statistical significance at each day are contained in Table 6. Overall, the reduction in the CGIP-M Total score in patients dosed with atomoxetine in the morning compared to the reduction in patients dosed with placebo was statistically significantly greater ($p=.023$).
- Table 7 contains the results from the repeated measures analysis of the Brown ADD Scales Total score in patients aged 8- through 12-years-old, with estimates of treatment differences and statistical significance at each visit. Overall, the reduction in the Brown ADD Scales Total score in patients dosed with atomoxetine in the morning compared to the reduction in patients dosed with placebo among patients aged 8- to 12-years-old was statistically significantly greater ($p=.006$).
- The mean change from baseline-to-LOCF endpoint was used to test the efficacy of once-daily morning-dosed atomoxetine compared to placebo on measures of

adaptive functioning in children with ADHD. Table 8 shows the improvement in the LPS-ADHD-R Total score was statistically significantly greater for patients dosed with atomoxetine in the morning compared to patients dosed with placebo ($p < .001$).

- Changes from baseline to LOCF endpoint in the EESC total score were analyzed using a fixed-effects ANCOVA model with terms for baseline score, treatment, and investigator. Both pairwise comparisons and treatment efficacy of morning-dosed atomoxetine compared to placebo and evening-dosed atomoxetine compared to placebo were tested. Table 9 shows there were no statistically significant differences in the LOCF for EESC total score or in the comparison of the treatment groups.

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**Table 5. DPREMB-R Evening Subscale
Repeated Measures Least-Squares Means
All Randomized Patients
Study Period II**

	TMX/PLA	PLA/TMX	PLA/PLA	(TMX/PLA) VS (PLA/TMX)			(TMX/PLA) VS (PLA/PLA)			(PLA/TMX) VS (PLA/PLA)		
DAY	LSMEAN	LSMEAN	LSMEAN	LSMEAN	SE	P-VALUE+	LSMEAN	SE	P-VALUE+	LSMEAN	SE	P-VALUE+
1	-2.75	-1.75	-1.65	-1.00	0.66	.134	-1.09	0.66	.096	-0.10	0.66	.884
2	-2.71	-1.83	-1.83	-0.88	0.74	.240	-0.88	0.74	.236	-0.00	0.74	.999
3	-2.97	-2.24	-2.14	-0.72	0.73	.325	-0.83	0.73	.258	-0.11	0.73	.885
4	-3.05	-2.35	-1.45	-0.70	0.73	.341	-1.60	0.72	.028	-0.90	0.73	.218
5	-3.21	-2.15	-0.60	-1.06	0.75	.156	-2.61	0.74	<.001	-1.55	0.74	.037
6	-3.46	-2.41	-1.40	-1.05	0.78	.180	-2.06	0.77	.008	-1.01	0.77	.193
7	-3.30	-2.98	-1.72	-0.32	0.78	.685	-1.58	0.78	.043	-1.26	0.78	.106
8	-3.61	-2.23	-1.90	-1.38	0.75	.068	-1.72	0.75	.023	-0.34	0.75	.656
9	-4.07	-3.52	-1.37	-0.54	0.75	.469	-2.70	0.75	<.001	-2.15	0.75	.005
10	-3.55	-4.03	-0.87	-0.48	0.77	.535	-2.69	0.76	<.001	-3.17	0.77	<.001
11	-3.52	-3.45	-1.75	-0.08	0.70	.914	-1.77	0.70	.011	-1.70	0.70	.017
12	-3.70	-2.68	-1.82	-1.02	0.76	.184	-1.87	0.75	.014	-0.86	0.77	.266
13	-3.35	-3.07	-1.44	-0.28	0.79	.722	-1.91	0.78	.015	-1.63	0.79	.040
14	-3.19	-3.18	-1.90	-0.01	0.78	.989	-1.29	0.77	.097	-1.28	0.79	.106
SUMMARY OF MODEL PARAMETERS				F-VALUE	P-VALUE*							
BASELINE				175.93	<.001							
TREATMENT				5.60	.004							
DAY				1.53	.107							
INVESTIGATOR				0.93	.515							
TREATMENT*DAY				1.51	.058							
				T-VALUE	P-VALUE#							
(TMX/PLA VS PLA/TMX)				-1.14	.257							
(TMX/PLA VS PLA/PLA)				-3.29	.001							
(PLA/TMX VS PLA/PLA)				-2.14	.034							
RESULTS BASED ON A MIXED MODEL WITH BASELINE, TREATMENT, DAY, INVESTIGATOR, AND TREATMENT BY DAY INTERACTION TERMS USING UNSTRUCTURED COVARIANCE MATRIX TO MODEL CORRELATIONS WITHIN PATIENTS ACROSS DAYS												
P-VALUES+ ARE FROM TESTS FOR A PAIRWISE TREATMENT DIFFERENCE IN LEAST SQUARES MEANS AT THE GIVEN DAY												
P-VALUES* ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE BASED ON THE MODEL DESCRIBED ABOVE												
P-VALUES# ARE FROM TESTS FOR A PAIRWISE TREATMENT DIFFERENCE IN LEAST SQUARES MEANS												
POPULATION: ALL RANDOMIZED PATIENTS												

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Table 6. **Conners' Global Index Parent-Morning Total Score**
Repeated Measures Least-Squares Means
All Randomized Patients
Study Period II

	TMX/PLA	PLA/TMX	PLA/PLA	(TMX/PLA) VS (PLA/TMX)			(TMX/PLA) VS (PLA/PLA)			(PLA/TMX) VS (PLA/PLA)		
DAY	LSMEAN	LSMEAN	LSMEAN	LSMEAN	SE	P-VALUE+	LSMEAN	SE	P-VALUE+	LSMEAN	SE	P-VALUE+
1	-4.15	-3.61	-3.38	-0.54	0.90	.546	-0.77	0.89	.385	-0.23	0.90	.799
2	-4.35	-3.60	-2.86	-0.75	0.91	.410	-1.49	0.91	.100	-0.74	0.91	.415
3	-4.56	-4.37	-2.67	-0.19	0.91	.833	-1.89	0.91	.038	-1.70	0.91	.063
4	-4.65	-4.28	-3.14	-0.37	0.90	.682	-1.50	0.89	.092	-1.13	0.90	.209
5	-4.32	-4.15	-3.03	-0.17	0.91	.853	-1.29	0.90	.153	-1.12	0.91	.219
6	-5.12	-5.18	-3.54	0.05	0.91	.954	-1.58	0.90	.080	-1.64	0.90	.071
7	-4.76	-5.30	-3.02	0.54	0.97	.579	-1.75	0.96	.071	-2.29	0.97	.019
8	-5.30	-4.24	-3.95	-1.06	0.98	.280	-1.36	0.97	.165	-0.29	0.98	.764
9	-5.62	-5.72	-2.66	0.09	1.01	.926	-2.96	1.01	.004	-3.06	1.02	.003
10	-5.97	-5.63	-3.36	-0.34	1.00	.731	-2.61	0.98	.008	-2.27	0.99	.023
11	-4.91	-5.85	-3.38	0.95	0.98	.336	-1.52	0.97	.118	-2.47	0.98	.013
12	-4.87	-5.79	-3.77	0.91	0.99	.358	-1.10	0.98	.261	-2.01	0.99	.044
13	-5.82	-6.32	-4.07	0.51	1.05	.629	-1.75	1.03	.090	-2.26	1.04	.031
14	-5.62	-6.02	-4.10	0.41	1.08	.706	-1.52	1.07	.155	-1.93	1.08	.076
SUMMARY OF MODEL PARAMETERS				F-VALUE		P-VALUE*						
BASELINE				74.42		<.001						
TREATMENT				3.47		.033						
DAY				2.54		.003						
INVESTIGATOR				1.80		.049						
TREATMENT*DAY				1.06		.389						
				T-VALUE		P-VALUE#						
(TMX/PLA VS PLA/TMX)				0.00		.998						
(TMX/PLA VS PLA/PLA)				-2.29		.023						
(PLA/TMX VS PLA/PLA)				-2.27		.024						

RESULTS BASED ON A MIXED MODEL WITH BASELINE, TREATMENT, DAY, INVESTIGATOR, AND TREATMENT BY DAY
INTERACTION TERMS USING UNSTRUCTURED COVARIANCE MATRIX TO MODEL CORRELATIONS WITHIN PATIENTS ACROSS DAYS
P-VALUES+ ARE FROM TESTS FOR A PAIRWISE TREATMENT DIFFERENCE IN LEAST SQUARES MEANS AT THE GIVEN DAY
P-VALUES* ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE BASED ON THE MODEL DESCRIBED ABOVE
P-VALUES# ARE FROM TESTS FOR A PAIRWISE TREATMENT DIFFERENCE IN LEAST SQUARES MEANS
POPULATION: ALL RANDOMIZED PATIENTS

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**Table 7. Brown ADD Scales Total Score
Repeated Measures Least-Squares Means
All Randomized Patients Aged 8 through 12 Years
Study Period II**

	TMX/PLA	PLA/TMX	PLA/PLA	(TMX/PLA) VS (PLA/TMX)			(TMX/PLA) VS (PLA/PLA)			(PLA/TMX) VS (PLA/PLA)		
VISIT	LSMEAN	LSMEAN	LSMEAN	LSMEAN	SE	P-VALUE+	LSMEAN	SE	P-VALUE+	LSMEAN	SE	P-VALUE+
3	-28.41	-23.08	-13.00	-5.33	4.52	.240	-15.41	4.56	<.001	-10.08	4.57	.029
4	-32.77	-32.51	-19.34	-0.27	5.21	.959	-13.43	5.30	.012	-13.16	5.35	.015
5	-35.83	-35.04	-27.22	-0.78	6.50	.904	-8.61	6.62	.195	-7.83	6.60	.238
SUMMARY OF MODEL PARAMETERS				F-VALUE		P-VALUE*						
BASELINE				2.47		.118						
TREATMENT				4.39		.014						
VISIT				8.38		<.001						
INVESTIGATOR				1.80		.053						
TREATMENT*VISIT				0.60		.663						
				T-VALUE		P-VALUE#						
(TMX/PLA VS PLA/TMX)				-0.48		.631						
(TMX/PLA VS PLA/PLA)				-2.79		.006						
(PLA/TMX VS PLA/PLA)				-2.30		.023						
RESULTS BASED ON A MIXED MODEL WITH VISIT, BASELINE, TREATMENT, INVESTIGATOR, AND TREATMENT BY VISIT INTERACTION USING UNSTRUCTURED COVARIANCE MATRIX TO MODEL CORRELATIONS WITHIN PATIENT ACROSS VISITS P-VALUES+ ARE FROM TESTS FOR A PAIRWISE TREATMENT DIFFERENCE IN LEAST SQUARES MEANS AT THE GIVEN DAY P-VALUES* ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE BASED ON THE MODEL DESCRIBED ABOVE P-VALUES# ARE FROM TESTS FOR A PAIRWISE TREATMENT DIFFERENCE IN LEAST SQUARES MEANS POPULATION: ALL RANDOMIZED PATIENTS												

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**Table 8. LPS-ADHD-R Mean Change from Baseline to LOCF Endpoint
All Randomized Patients
Study Period II**

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)	P-VALUE (C)
		MEAN	SD	MEAN	SD	MEAN	SD			
LIFE PARTICIPATION SCALE TOTAL SCORE										
TMX/PLA	91	32.08	9.80	44.21	13.65	12.13	14.12	<.001	.038	<.001
PLA/TMX	83	30.71	10.16	39.51	13.53	8.80	11.56	<.001	.090	
PLA/PLA	84	29.39	9.81	35.32	13.89	5.92	12.03	<.001	<.001	

A) P-VALUE IS FROM A WITHIN GROUP COMPARISON BASED ON WILCOXON SIGNED-RANK TEST.

B) PAIRWISE COMPARISON P-VALUES IN ORDER FROM TOP TO BOTTOM: TMX/PLA VS PLA/TMX, PLA/TMX VS PLA/PLA, TMX/PLA VS PLA/PLA

C) OVERALL TEST FOR TREATMENT EFFECT P-VALUE IS FROM BASELINE TO ENDPOINT (LOCF) SCORES

USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR BASELINE, TREATMENT AND INVESTIGATOR

POPULATION: ALL RANDOMIZED PATIENTS

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**Table 9. EESC Mean Change from Baseline to LOCF Endpoint
All Randomized Patients
Study Period II**

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)	P-VALUE (C)
		MEAN	SD	MEAN	SD	MEAN	SD			
EESC TOTAL SCORE										
TMX/PLA	63	62.21	16.02	58.51	18.38	-3.70	17.81	.011	.663	.887
PLA/TMX	59	64.27	19.56	61.00	17.47	-3.27	12.37	.028	.681	
PLA/PLA	57	66.91	19.59	61.68	18.32	-5.23	16.51	.022	.992	

A) P-VALUE IS FROM A WITHIN GROUP COMPARISON BASED ON WILCOXON SIGNED-RANK TEST.

B) PAIRWISE COMPARISON P-VALUES IN ORDER FROM TOP TO BOTTOM: TMX/PLA VS PLA/TMX, PLA/TMX VS PLA/PLA, TMX/PLA VS PLA/PLA

C) OVERALL TEST FOR TREATMENT EFFECT P-VALUE IS FROM BASELINE TO ENDPOINT (LOCF) SCORES

USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR BASELINE, TREATMENT AND INVESTIGATOR

POPULATION: ALL RANDOMIZED PATIENTS

Other Secondary Objectives

The results of both the CGIP-E Total score and the DPREMB-R Evening subscore, which were used to test the hypothesis that atomoxetine administered once daily in the evening provided superior efficacy in the evenings (before daily dosing; that is, nearly 24 hours since last dosing) compared with placebo in children with ADHD were as follows:

- Using an MMRM technique (versus LOCF), CGIP-E Total for evening dosed atomoxetine was statistically significant ($p=.002$ [Table 4]). Comparing the pairwise treatment differences in the LOCF change from baseline to endpoint of the CGIP-E Total score for the once-daily evening-dosed atomoxetine group compared to the placebo-treated group, Table 10 shows that symptom reduction in patients dosed once daily with atomoxetine in the evening was statistically significantly greater for the total score compared with symptom reduction in patients dosed with placebo ($p=.05$).
- Using a repeated measures analysis of treatment differences and statistical significance at each visit (by day, not week) for the DPREMB-R Evening subscore, Table 5 shows that the reduction in the DPREMB-R Evening subscore in patients dosed with atomoxetine in the evening was statistically significantly greater compared to patients dosed with placebo ($p=.034$).

A repeated measures analysis of the DPREMB-R Morning subscore with estimates of treatment differences at each visit was used to test the hypothesis that atomoxetine administered once daily in the morning provides superior efficacy in the mornings (before daily dosing; that is, nearly 24 hours since last dosing) compared to placebo in children with ADHD.

- Table 11 shows that the reduction in the DPREMB-R Morning subscore for the morning-dosed atomoxetine patients was not statistically significantly different from the reduction in patients dosed with placebo ($p=.343$).

The onset of action was examined during the first week of treatment in the morning versus evening versus placebo, and measured by the DPREMB-R Total score and the CGIP-M. The DPREMB-R and the CGIP-M were collected on a daily basis using real-time remote data entry beginning 5 days prior to Visit 2 and for 15 days following Visit 2. The results were as follows:

- Table 6 shows the results from the repeated measures analysis with pairwise and statistical significance at each day of the CGIP-M Total score. Overall, the reductions in the CGIP-M Total score in both the morning-dosed and evening-dosed atomoxetine patients were statistically significantly greater compared to the reduction in patients dosed with placebo ($p=.023$ and $p=.024$, respectively). Atomoxetine dosed in the morning separated from placebo sooner than atomoxetine dosed in the evening (Day 3 versus Day 7). There was substantial

day to day variability and statistical separation from placebo was not maintained at all subsequent days.

- Table 12 shows the results from the repeated measures analysis with pairwise treatment differences and statistical significance at each day of the DPREMB-R Total score. Overall, the reductions in the DPREMB-R Total score in both the morning-dosed and evening-dosed atomoxetine patients were statistically significantly greater compared to the reduction in patients dosed with placebo ($p=.028$ and $p=.023$, respectively). Atomoxetine dosed in the morning separated from placebo at the same time as atomoxetine dosed in the evening (Day 5). There was substantial day to day variability and statistical separation from placebo was not maintained at all subsequent days.

The Brown ADD Scales Total scores for the evening-dosed atomoxetine group and placebo-treated group were compared to test the hypothesis that atomoxetine dosed in the evening provides superior improvements in executive functioning compared to placebo.

- Table 13 contains the results from the repeated measures analysis of the Brown ADD Scales Total score in patients aged 3- through 7-years-old, with estimates of treatment differences and statistical significance at each visit. Overall, the reduction in the Brown ADD Scales Total score for patients aged 3 through 7 years in patients dosed with placebo was statistically significantly less from the reduction in patients dosed with atomoxetine in the morning ($p=.032$), but was not statistically significantly different from the reduction in patients dosed with atomoxetine in the evening. The activation subscale ($p=.019$), effort subscale ($p=.013$), memory ($p=.022$) subscale, and action subscale ($p=.036$) also showed statistically significant greater reductions in the morning dosed patients compared to placebo, but not in the evening dosed patients, while the focus ($p=.159$) and emotion ($p=.351$) subscales did not show statistically significant differences from placebo in the morning or evening dosed patients.

A repeated measures analysis of treatment differences and statistical significance at Visits 3, 4, and 5 were used to compare morning versus evening versus placebo dosing regimes at each visit, as assessed by the CGI-ADHD-S.

- Table 14 shows that overall the reductions in the CGI-ADHD-S score for both the morning-dosed and evening-dosed atomoxetine groups were statistically significantly greater than for placebo ($p<.001$ and $p=.009$, respectively). In addition, there was a statistically significant greater overall reduction CGI-ADHD-S scores for morning-dosed atomoxetine patients than for evening-dosed atomoxetine patients ($p=.009$). Morning-dosed atomoxetine patient had a statistically significant greater reduction in CGI-ADHD-S scores than placebo-dosed patients at each visit ($p<.001$ for Visits 3 through 5) while evening-dosed atomoxetine patients had a statistically significant greater

reduction in CGI-ADHD-S scores that placebo-dosed patients only at Visit 3 (p=.039) and Visit 4 (p=.010).

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**Table 10. Conners' Global Index Parent-Evening Total Score and Subscores
Change from Baseline to Endpoint
All Randomized Patients
Study Period II**

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)	P-VALUE (C)
		-----		-----		-----				
		MEAN	SD	MEAN	SD	MEAN	SD			
CGIP-E TOTAL SCORE										
TMX/PLA	94	18.80	5.91	13.27	7.74	-5.53	6.81	<.001	.164	.003
PLA/TMX	88	19.14	6.49	14.86	8.09	-4.28	7.41	<.001	.050	
PLA/PLA	90	19.26	5.97	16.74	7.50	-2.52	6.49	<.001	<.001	

A) P-VALUE IS FROM A WITHIN GROUP COMPARISON BASED ON WILCOXON SIGNED-RANK TEST.

B) PAIRWISE COMPARISON P-VALUES IN ORDER FROM TOP TO BOTTOM: TMX/PLA VS PLA/TMX, PLA/TMX VS PLA/PLA, TMX/PLA VS PLA/PLA

C) OVERALL TEST FOR TREATMENT EFFECT P-VALUE IS FROM BASELINE TO ENDPOINT (LOCF) SCORES

USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR BASELINE, TREATMENT AND INVESTIGATOR

POPULATION: ALL RANDOMIZED PATIENTS

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**Table 11. Daily Parent Rating of Evening and Morning Behavior-Revised Morning Subscore
Repeated Measures Analysis
All Randomized Patients Study Period II**

DAY	TMX/PLA	PLA/TMX	PLA/PLA	(TMX/PLA) VS (PLA/TXM)			(TMX/PLA) VS (PLA/PLA)			(PLA/TMX) VS (PLA/PLA)		
	LSMEAN	LSMEAN	LSMEAN	LSMEAN	SE	p-Value ⁺	LSMEAN	SE	p-Value ⁺	LSMEAN	SE	p-Value ⁺
1	-0.59	-0.51	-0.82	-0.08	0.36	.825	0.22	0.36	.535	0.30	0.36	.404
2	-0.85	-0.61	-0.49	-0.23	0.39	.552	-0.36	0.39	.354	-0.13	0.39	.742
3	-1.10	-1.18	-0.71	0.08	0.35	.826	-0.39	0.35	.272	-0.47	0.35	.190
4	-1.02	-1.04	-0.86	0.02	0.35	.954	-0.16	0.34	.638	-0.18	0.35	.601
5	-0.86	-0.87	-0.38	0.01	0.38	.982	-0.49	0.37	.194	-0.49	0.38	.191
6	-0.94	-1.06	-0.55	0.12	0.37	.734	-0.39	0.36	.284	-0.51	0.37	.162
7	-0.76	-0.88	-0.56	0.11	0.39	.768	-0.21	0.39	.595	-0.32	0.39	.412
8	-0.92	-0.78	-0.78	-0.14	0.39	.717	-0.14	0.39	.722	0.00	0.39	.992
9	-1.21	-1.24	-0.91	0.03	0.38	.929	-0.30	0.38	.433	-0.33	0.38	.385
10	-1.25	-1.09	-0.69	-0.16	0.35	.642	-0.57	0.35	.105	-0.40	0.35	.256
11	-1.28	-1.35	-0.94	0.08	0.35	.826	-0.34	0.35	.332	-0.41	0.35	.239
12	-0.99	-1.26	-0.74	0.27	0.39	.490	-0.26	0.39	.508	-0.53	0.39	.183
13	-0.92	-1.07	-0.56	0.16	0.38	.683	-0.36	0.38	.344	-0.51	0.38	.182
14	-0.69	-1.04	-0.92	0.35	0.38	.361	0.23	0.38	.541	-0.12	0.38	.762
Summary of Model Parameters				f-Value			p-Value *					
Baseline				189.37			<.001					
Treatment				0.72			.488					
DAY				2.06			.019					
Investigator				1.51			.125					
Treatment *DAY				0.66			.898					
				t-Value			p-Value #					
(TMX/PLA VS PLA/TMX)				0.17			.867					
(TMX/PLA VS PLA/PLA)				-0.95			.343					
(PLA/TMX VS PLA/PLA)				-1.11			.268					

Results based on a mixed model with baseline, treatment, day, investigator, and treatment by day.

Interaction terms using AN UNSTRUCTURED covariance matrix to model correlations within patients across days.

P-values⁺ are from tests for a pairwise treatment difference in least squares means at the given day.

P-values* are from F-tests for a nonzero coefficient estimate based on the model described above.

P-values# are from tests for a pairwise treatment difference in least squares means.

Population: All randomized patients who had at least 4 of 5 baseline scores and at least 6 of 7 scores in each of the two post-baseline weeks.

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**Table 12. Daily Parent Rating of Evening and Morning Behavior-Revised Total Score
Repeated Measures Analysis
All Randomized Patients
Study Period II**

DAY	TMX/PLA	PLA/TMX	PLA/PLA	(TMX/PLA) VS (PLA/TMX)			(TMX/PLA) VS (PLA/PLA)			(PLA/TMX) VS (PLA/PLA)		
	LSMEAN	LSMEAN	LSMEAN	LSMEAN	SE	p-Value ₊	LSMEAN	SE	p-Value ₊	LSMEAN	SE	p-Value ₊
1	-3.33	-2.28	-2.44	-1.05	1.07	.327	-0.89	1.06	.399	0.15	1.07	.885
2	-3.49	-2.66	-2.30	-.083	1.20	.487	-1.19	1.19	.319	-0.35	1.19	.767
3	-4.04	-3.94	-2.94	-0.10	1.17	.932	-1.10	1.17	.348	-1.00	1.18	.396
4	-4.43	-3.32	-2.25	-1.10	1.13	.331	-2.17	1.11	.053	-1.07	1.13	.343
5	-4.25	-3.84	-.077	-0.41	1.16	.722	-3.48	1.15	.003	-3.07	1.16	.009
6	-4.52	-4.02	-2.18	-0.50	1.21	.677	-2.34	1.19	.051	-1.84	1.20	.128
7	-3.71	-4.37	-2.40	0.65	1.28	.609	-1.31	1.26	.298	-1.97	1.28	.124
8	-4.34	-3.74	-2.67	-0.60	1.21	.620	-1.67	1.20	.164	-1.07	1.21	.377
9	-5.27	-5.88	-2.29	0.62	1.18	.603	-2.97	1.18	.013	-3.59	1.19	.003
10	-4.78	-6.29	-1.53	1.51	1.17	.200	-3.25	1.16	.006	-4.75	1.17	<.001
11	-4.95	-5.63	-2.71	0.69	1.10	.532	-2.23	1.09	.042	-2.92	1.10	.009
12	-4.64	-4.86	-2.70	0.22	1.23	.858	-1.94	1.22	.112	-2.16	1.24	.083
13	-3.95	-4.76	-1.65	0.82	1.21	.500	-2.29	1.19	.056	-3.11	1.21	.011
14	-3.61	-4.85	-2.66	1.24	1.19	.297	-0.95	1.18	.422	-2.19	1.19	.068
Summary of Model Parameters				f-Value			p-Value *					
Baseline				91.20			<.001					
Treatment				3.40			.036					
DAY				2.14			.014					
Investigator				0.86			.590					
Treatment *DAY				1.55			.051					
				t-Value			p-Value #					
(TMX/PLA VS PLA/TMX)				0.09			.928					
(TMX/PLA VS PLA/PLA)				-2.22			.028					
(PLA/TMX VS PLA/PLA)				-2.29			.023					

RESULTS BASED ON A MIXED MODEL WITH BASELINE, TREATMENT, DAY, INVESTIGATOR, AND TREATMENT BY DAY.

INTERACTION TERMS USING AN UNSTRUCTURED COVARIANCE MATRIX TO MODEL CORRELATIONS WITHIN PATIENTS ACROSS DAYS.

P-VALUES+ ARE FROM TESTS FOR A PAIRWISE TREATMENT DIFFERENCE IN LEAST SQUARES MEANS AT THE GIVEN DAY.

P-VALUES* ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE BASED ON THE MODEL DESCRIBED ABOVE.

P-VALUES# ARE FROM TESTS FOR A PAIRWISE TREATMENT DIFFERENCE IN LEAST SQUARES MEANS.

POPULATION: ALL RANDOMIZED PATIENTS WHO HAD AT LEAST 4 OF 5 BASELINE SCORES AND AT LEAST 6 OF 7 SCORES IN EACH OF THE TWO POST-BASELINE WEEKS.

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Table 13. **Brown ADD Scales Total Score**
Repeated Measures Least-Squares Means
All Randomized Patients Aged 3 through 7 years
Study Period II

	TMX/PLA	PLA/TMX	PLA/PLA	(TMX/PLA) VS (PLA/TMX)			(TMX/PLA) VS (PLA/PLA)			(PLA/TMX) VS (PLA/PLA)		
VISIT	LSMEAN	LSMEAN	LSMEAN	LSMEAN	SE	p-Value +	LSMEAN	SE	p-Value +	LSMEAN	SE	p-Value +
3	-14.04	-18.39	-15.19	4.35	7.14	.544	1.15	6.86	.868	-3.20	7.09	.653
4	-23.09	-24.27	-11.91	1.18	6.40	.855	-11.18	6.07	.070	-12.35	6.27	.053
5	-36.01	-23.78	-9.48	-12.22	8.11	.137	-26.53	7.71	.001	-14.31	7.88	.074
		SUMMARY OF MODEL PARAMETERS			f-Value		p-Value *					
		BASELINE			5.60		.021					
		TREATMENT			2.72		.073					
		VISIT			2.15		.122					
		INVESTIGATOR			1.31		.231					
		TREATMENT *VISIT			2.96		.023					
					t-Value		p-Value #					
		(TMX/PLA VS PLA/TMX)			-0.38		.704					
		(TMX/PLA VS PLA/PLA)			-2.18		.032					
		(PLA/TMX VS PLA/PLA)			-1.74		.086					

RESULTS BASED ON A MIXED MODEL WITH VISIT, BASELINE, TREATMENT, INVESTIGATOR, AND TREATMENT BY VISIT INTERACTION.

USING AN ARH(1) COVARIANCE MATRIX TO MODEL CORRELATIONS WITHIN PATIENT ACROSS VISITS.

P-VALUES+ ARE FROM TESTS FOR A TREATMENT DIFFERENCE IN LEAST SQUARES MEANS AT THE GIVEN VISIT.

P-VALUES* ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE BASED ON THE MODEL DESCRIBED ABOVE.

P-VALUES# ARE FROM TESTS FOR A PAIRWISE TREATMENT DIFFERENCE IN LEAST SQUARES MEANS.

POPULATION: ALL RANDOMIZED PATIENTS.

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Table 14. **CGI-ADHD-S Score**
Repeated Measures Least-Squares Means
All Randomized Patients
Study Period II

VISIT	TMX/PLA	PLA/TMX	PLA/PLA	(TMX/PLA) VS (PLA/TMX)			(TMX/PLA) VS (PLA/PLA)			(PLA/TMX) VS (PLA/PLA)		
	----- LSMEAN	----- LSMEAN	----- LSMEAN	----- LSMEAN	SE	P-VALUE+	----- LSMEAN	SE	P-VALUE+	----- LSMEAN	SE	P-VALUE+
3	-1.00	-0.72	-0.45	-0.28	0.13	.033	-0.55	0.13	<.001	-0.27	0.13	.039
4	-1.33	-1.02	-0.61	-0.31	0.16	.056	-0.72	0.16	<.001	-0.42	0.16	.010
5	-1.69	-1.24	-0.89	-0.45	0.19	.023	-0.80	0.19	<.001	-0.35	0.20	.074
SUMMARY OF MODEL PARAMETERS				F-VALUE		P-VALUE*						
BASELINE				17.94		<.001						
TREATMENT				14.09		<.001						
VISIT				25.13		<.001						
INVESTIGATOR				2.91		<.001						
TREATMENT*VISIT				0.60		.661						
				T-VALUE		P-VALUE#						
(TMX/PLA VS PLA/TMX)				-2.62		.009						
(TMX/PLA VS PLA/PLA)				-5.31		<.001						
(PLA/TMX VS PLA/PLA)				-2.63		.009						

RESULTS BASED ON A MIXED MODEL WITH BASELINE, TREATMENT, VISIT, INVESTIGATOR, AND TREATMENT BY VISIT
INTERACTION TERMS USING AN UNSTRUCTURED COVARIANCE MATRIX TO MODEL CORRELATIONS WITHIN PATIENT ACROSS VISITS
P-VALUES+ ARE FROM TESTS FOR A PAIRWISE TREATMENT DIFFERENCE IN LEAST SQUARES MEANS AT THE GIVEN DAY
P-VALUES* ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE BASED ON THE MODEL DESCRIBED ABOVE
P-VALUES# ARE FROM TESTS FOR A PAIRWISE TREATMENT DIFFERENCE IN LEAST SQUARES MEANS
POPULATION: ALL RANDOMIZED PATIENTS

Safety and Tolerability

Adverse Events (AEs)

All patients who took at least 1 dose of study medication were included in the analysis of AEs. There were no deaths or SAEs in Study LYCC. A total of 5 patients discontinued the study due to an AE: 2 patients in the placebo group (1 for aggression, 1 for mood swings), 1 patient in the morning-dose group (for tearfulness), and 2 patients in the evening-dose group (1 for nausea, 1 for suicidal ideation). Of the 278 randomly assigned patients that took at least 1 dose of study drug, 155 (55.76%) patients reported at least 1 treatment-emergent adverse event (TEAE). A statistically significantly greater percentage of patients reported one or more TEAEs in the morning-dosed atomoxetine group (73.96%) when compared with the placebo-treated group (43.48%, $p<.001$), or when compared with the evening-dosed atomoxetine group (48.89%, $p<.001$). Table 15 summarizes the TEAEs that occurred in $\geq 5\%$ of patients who took at least 1 dose of study drug in any of the 3 treatment groups. Overall, a statistically significantly greater percentage of patients in the morning-dosed group when compared with the placebo-treated group reported: vomiting ($p<.001$), upper abdominal pain ($p=.024$), decreased appetite ($p=.009$), somnolence ($p=.005$), nausea ($p=.014$), and stomach discomfort ($p=.029$). Vomiting was the only AE for which the incidence among patients in the evening-dosed atomoxetine group was statistically significantly greater compared to the placebo-treated group ($p=.034$).

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**Table 15. Treatment-Emergent Adverse Events (Preferred Term)
Occurring in ≥5% of Drug-Treated Patients
Ordered by Decreasing Frequency in the Morning Dose Arm Comparison of Treatment Groups
All Randomized Patients Who Took at Least One Dose of Study Drug
Study Period II**

EVENT CLASSIFICATION											(TMX/- PLA) VS (PLA/- TMX)	(TMX/- PLA) VS (PLA/- PLA)	(PLA/- TMX) VS (PLA/- PLA)
	TMX/PLA		PLA/TMX		PLA/PLA		TOTAL		FISHE- R'S EXACT P- VALUE				
	N= (96)		N= (90)		N= (92)		N= (278)						
	N	%	N	%	N	%	N	%					
PATIENTS WITH >=1 TESS	71	73.96 %	44	48.89 %	40	43.48 %	155	55.76 %	<.001	<.001	<.001	.552	
PATIENTS WITH NO TESS	25	26.04 %	46	51.11 %	52	56.52 %	123	44.24 %					
Vomiting	15	15.63 %	7	7.78 %	1	1.09 %	23	8.27 %	<.001	.115	<.001	.034	
Abdominal pain upper	14	14.58 %	10	11.11 %	4	4.35 %	28	10.07 %	.052	.518	.024	.101	
Decreased appetite	14	14.58 %	7	7.78 %	3	3.26 %	24	8.63 %	.021	.168	.009	.210	
Headache	12	12.50 %	5	5.56 %	4	4.35 %	21	7.55 %	.086	.128	.065	.746	
Somnolence	11	11.46 %	4	4.44 %	1	1.09 %	16	5.76 %	.007	.106	.005	.208	
Nausea	7	7.29 %	4	4.44 %	0	0.00 %	11	3.96 %	.016	.539	.014	.058	
Stomach discomfort	6	6.25 %	4	4.44 %	0	0.00 %	10	3.60 %	.039	.748	.029	.058	
Upper respiratory tract infection	5	5.21 %	0	0.00 %	4	4.35 %	9	3.24 %	.083	.060	1.000	.121	
Nasopharyngitis	4	4.17 %	4	4.44 %	6	6.52 %	14	5.04 %	.786	1.000	.530	.747	

P-VALUES ARE BASED ON FISHER'S EXACT TEST

POPULATION: ALL RANDOMIZED PATIENTS WHO TOOK AT LEAST ONE DOSE OF STUDY DRUG ARE INCLUDED

Laboratory Values

Table 16 is a summary of laboratory analytes that showed statistically significant overall differences in mean change from baseline to endpoint. As shown in this table, observations of the morning-dosed atomoxetine group found statistically significant differences in mean change from baseline for: albumin ($p=.012$), GGT ($p=.0194$) and MCV ($p=.046$). No patient discontinued from the study due to an abnormal laboratory value.

Treatment-emergent high, low, and abnormal laboratory values were determined for each patient who received at least 1 dose of study drug and had a baseline and at least 1 postbaseline measurement. The total number of patients who met the criteria for high creatinine values following baseline was the only treatment-emergent laboratory value which was statistically significant ($p=.041$).

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Table 16. Laboratory Analysis
Change from Baseline to LOCF Endpoint
Analytes with a Statistically Significant Within Group or Overall Change from Baseline
All Randomized Patients Who Took at Least One Dose of Study Drug

		BASELINE			CHANGE		WITHIN GROUP	OVERALL	OVERALL (RANKED)
		N	MEAN	STD	MEAN	STD	P-VALUE	P-VALUE	P-VALUE
ALBUMIN	TMX/PLA	86	44.26	3.01	0.38	2.58	.213	.012	.011
	PLA/TMX	84	44.45	2.73	-0.52	2.75	.129		
	PLA/PLA	78	44.59	2.61	-0.78	2.52	.003		
GGT (GGPT/SGGT- /YGGT)	TMX/PLA	85	13.71	5.08	-0.84	3.62	<.001	.194	.015
	PLA/TMX	84	12.92	3.68	-0.08	2.63	.845		
	PLA/PLA	78	12.44	3.07	-0.18	2.21	.300		
MEAN CELL VOLUME (MCV)	TMX/PLA	84	81.45	4.72	-0.57	3.30	.075	.046	.042
	PLA/TMX	80	81.46	3.35	-0.14	3.08	.845		
	PLA/PLA	78	82.06	3.55	0.63	3.47	.122		

OVERALL PVALUE IS BASED ON AN ANOVA MODEL WITH TERMS FOR TREATMENT AND INVESTIGATOR USING RAW DATA
 POPULATION: ALL RANDOMIZED PATIENTS WHO TOOK AT LEAST ONE DOSE OF STUDY DRUG

Vital Signs and Weight

There was a statistically significant difference ($p < .001$) between morning-dosed atomoxetine and placebo for weight change, as well as between evening-dosed atomoxetine and placebo for weight change. Additionally, there were statistically significant increases for morning-dosed atomoxetine compared with placebo and evening-dosed atomoxetine compared with placebo for: pulse rate ($p = .015$ and $p = .002$, respectively), systolic BP ($p = .005$ and $p < .001$, respectively), and diastolic BP ($p = .001$ and $p < .001$, respectively [see Table 17]).

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Table 17. Vital Signs
Mean Change from Baseline to LOCF Endpoint
All Randomized Patients Who Took at Least One Dose of Study Drug

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)	P-VALUE (C)
		-----		-----		-----				
		MEAN	SD	MEAN	SD	MEAN	SD			
WEIGHT (KG)										
TMX/PLA	94	32.84	9.34	32.16	9.15	-0.68	1.00	<.001	<.001	<.001
PLA/TMX	88	33.50	9.49	33.54	9.45	0.04	1.22	.518	<.001	
PLA/PLA	91	33.62	10.03	34.20	10.22	0.58	0.86	<.001	<.001	
HEIGHT (CM)										
TMX/PLA	94	131.36	9.80	132.24	9.81	0.89	1.43	<.001	.318	.433
PLA/TMX	88	134.28	10.45	135.01	10.48	0.73	1.34	<.001	.848	
PLA/PLA	91	132.58	10.56	133.26	10.76	0.69	1.20	<.001	.227	
SYSTOLIC BP										
TMX/PLA	94	104.50	10.07	106.39	9.07	1.89	9.07	.040	.274	<.001
PLA/TMX	88	103.52	8.77	107.41	9.23	3.89	10.38	<.001	<.001	
PLA/PLA	91	103.86	10.17	103.02	8.93	-0.84	10.03	.486	.005	
DIASTOLIC BP										
TMX/PLA	94	65.07	8.95	67.40	7.69	2.33	8.64	.005	.351	<.001
PLA/TMX	88	65.20	8.92	68.35	9.22	3.15	9.85	.007	<.001	
PLA/PLA	91	65.13	9.59	64.08	7.60	-1.05	8.69	.205	.001	
PULSE										
TMX/PLA	94	84.77	11.45	88.33	13.25	3.56	10.79	.001	.469	.005
PLA/TMX	88	84.66	10.93	89.59	13.43	4.93	14.77	.003	.002	
PLA/PLA	91	85.09	11.93	84.57	11.30	-0.52	12.81	.770	.015	

A) P-VALUE IS FROM A WITHIN GROUP COMPARISON BASED ON WILCOXON SIGNED-RANK TEST.

B) PAIRWISE COMPARISON P-VALUES IN ORDER FROM TOP TO BOTTOM: TMX/PLA VS PLA/TMX, PLA/TMX VS PLA/PLA, TMX/PLA VS PLA/PLA

C) OVERALL TEST FOR TREATMENT EFFECT P-VALUE IS FROM BASELINE TO ENDPOINT (LOCF) SCORES

USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR BASELINE, TREATMENT AND INVESTIGATOR,
 POPULATION: ALL RANDOMIZED PATIENTS WHO TOOK AT LEAST ONE DOSE OF STUDY DRUG

Electrocardiograms (ECGs)

ECG data analyses revealed statistically significant mean changes from baseline to endpoint among treatment groups for: heart rate ($p < .001$), PR interval ($p < .026$), risk ratio (RR) interval ($p < .001$), and QT interval ($p < .001$). The only statistically significant difference between the active treatment groups (morning-dosed and evening-dosed atomoxetine) was for the QT interval ($p < .049$). Relative to placebo, both active treatment groups were associated with a statistically significant mean decrease of the PR, RR, and QT intervals, and a statistically significant mean increase in heart rate. The only statistically significant difference in QTc changes between placebo-treated and active treatment groups was a statistically significantly greater decrease in the Fridericia-corrected QT interval for the evening-dosed group compared with the placebo-treated group ($p = .019$ [see Table 18]).

The categorical changes in corrected QTc interval and heart rate following baseline is summarized in Table 19. For each criterion (for example, maximum heart rate of at least 100 beats per minute), the percentage of patients meeting the criteria in a treatment-emergent manner (at any visit) was computed for each treatment group. Patients meeting the criteria at baseline were excluded from the analysis. The total number of patients who met the criteria for elevated heart rate following baseline was statistically significant ($p = .006$).

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Table 18. Electrocardiograms
Mean Change from Baseline to LOCF Endpoint
All Randomized Patients Who Took at Least One Dose of Study Drug

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)	P-VALUE (C)
		MEAN	SD	MEAN	SD	MEAN	SD			
ECG HEART RATE										
TMX/PLA	90	79.93	11.27	84.41	13.09	4.48	11.98	.001	.084	<.001
PLA/TMX	85	80.47	12.40	87.48	12.94	7.01	13.18	<.001	<.001	
PLA/PLA	84	80.52	12.55	80.04	11.92	-0.49	11.55	.634	.007	
ECG RR INTERVAL										
TMX/PLA	90	765.58	108.95	728.01	114.25	-37.57	111.35	.003	.078	<.001
PLA/TMX	85	761.59	107.07	701.08	106.15	-60.50	106.82	<.001	<.001	
PLA/PLA	84	763.87	124.23	766.13	114.03	2.26	117.87	.729	.011	
ECG PR INTERVAL										
TMX/PLA	90	133.09	18.24	131.62	17.84	-1.47	11.10	.160	.535	.026
PLA/TMX	85	131.18	17.93	129.11	17.31	-2.07	9.91	.032	.010	
PLA/PLA	84	133.36	18.04	134.83	18.49	1.48	8.56	.124	.044	
ECG QRS INTERVAL										
TMX/PLA	90	80.76	8.62	81.69	8.06	0.93	4.35	.045	.723	.403
PLA/TMX	85	81.44	8.73	82.59	10.09	1.15	7.80	.125	.193	
PLA/PLA	84	81.93	8.51	81.71	7.93	-0.21	4.77	.826	.334	
ECG QT INTERVAL										
TMX/PLA	90	358.29	23.67	351.31	23.81	-6.98	22.82	.006	.049	<.001
PLA/TMX	85	362.02	23.88	347.62	24.98	-14.40	22.73	<.001	<.001	
PLA/PLA	84	359.79	27.55	360.21	26.32	0.43	23.49	.902	.011	
FRIDERICIA QTC INTERVAL										
TMX/PLA	90	392.33	13.49	391.43	13.46	-0.89	11.38	.521	.141	.061
PLA/TMX	85	397.17	14.08	392.06	15.55	-5.11	13.49	<.001	.019	
PLA/PLA	84	394.36	13.18	394.29	13.69	-0.06	11.53	.972	.366	
DATABASE CORRECTED QTC INTERVAL										
TMX/PLA	90	398.51	13.14	398.80	13.53	0.29	11.08	.588	.318	.441
PLA/TMX	85	403.57	13.95	400.26	15.26	-3.31	13.60	.018	.231	
PLA/PLA	84	400.67	12.08	400.50	12.65	-0.17	11.30	.881	.833	

A) P-VALUE IS FROM A WITHIN GROUP COMPARISON BASED ON WILCOXON SIGNED-RANK TEST.
B) PAIRWISE COMPARISON P-VALUES IN ORDER FROM TOP TO BOTTOM: TMX/PLA VS PLA/TMX, PLA/TMX VS PLA/PLA, TMX/PLA VS PLA/PLA
C) OVERALL TEST FOR TREATMENT EFFECT P-VALUE IS FROM BASELINE TO ENDPOINT (LOCF) SCORES
USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR BASELINE, TREATMENT AND INVESTIGATOR,
POPULATION: ALL RANDOMIZED PATIENTS WHO TOOK AT LEAST ONE DOSE OF STUDY DRUG

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Table 19. Electrocardiograms
Analysis of Categorical Changes in QTc and ECG Heart Rate
All Randomized Patients Who Took at Least One Dose of Study Drug

		TMX/PLA			PLA/TMX			PLA/PLA			FISHER'S EXACT P- VALUE
		N	N	%	N	N	%	N	N	%	
HEART RATE	HIGH	85	3	3.5%	76	10	13.2%	78	1	1.3%	.006
	LOW	88	0	0.0%	83	0	0.0%	82	0	0.0%	
QTCD (DATA CORRECTED)	HIGH	89	0	0.0%	85	1	1.2%	84	0	0.0%	.655
QTCF (FRIDERI- CIA)	HIGH	90	0	0.0%	85	1	1.2%	83	0	0.0%	.651

HEART RATE - HIGH: INCREASE OF AT LEAST 20 TO A VALUE OF AT LEAST 100

- LOW : DECREASE OF AT LEAST 15 TO A VALUE OF AT MOST 60

QTCF (FRIDERICIA) - HIGH: INCREASE OF AT LEAST 30 TO A VALUE OF AT LEAST 435

QTCD (DATA CORRECTED) - HIGH: INCREASE OF AT LEAST 30 TO A VALUE OF AT LEAST 440

PATIENTS COUNTED AS MEETING CRITERIA IF CRITERIA WAS MET AT ANY POSTBASELINE VISIT

POPULATION: ALL RANDOMIZED PATIENTS WHO TOOK AT LEAST ONE DOSE OF STUDY DRUG

N: PATIENTS WHO DO NOT MEET CRITERIA AT BASELINE

Summary ID# 7974

Clinical Study Summary: Study B4Z-US-LYCD

Maintenance of Benefit after 8-Week and 52-Week Treatment with Atomoxetine Hydrochloride in Adolescents with Attention-Deficit/Hyperactivity Disorder

Date summary approved by Lilly: 01 November 2007

Brief Summary of Results

The primary objective of this study was to assess the difference in maintenance of response at 48 weeks (due to an adjustment in the study schedule, the actual duration of the study should be 48 weeks versus 52 weeks) between atomoxetine therapy at a dose of 0.8 mg/kg/day versus therapy at a dose of 1.4 mg/kg/day as measured by the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) in adolescent patients, 13 to 16 years of age, with Attention-Deficit/Hyperactivity Disorder (ADHD). In this study, there were 3 study periods: the screening and diagnostic assessment phase, the double-blind acute phase, and the maintenance phase. In the double-blind acute phase (Study Period II), 2 titration regimens of atomoxetine were compared: 0.5 mg/kg/day to 1.2 mg/kg/day (label dose titration) and 0.5 mg/kg/day to 1.0 mg/kg/day to 1.2 mg/kg/day (slow dose titration). In the maintenance phase (Study Period III), treatment response at the end of 48 weeks was assessed for atomoxetine at a dose of 0.8 mg/kg/day versus atomoxetine at a dose of 1.4 mg/kg/day in patients who responded in the initial 8-week period. Results of the study are as follows:

Efficacy

Primary Efficacy

ADHDRS-IV-Parent:Inv

- Within-group changes in ADHDRS-IV-Parent:Inv total score from post-acute phase baseline to endpoint were statistically significant in the 0.8 mg/kg/day group ($p < .001$) indicating a loss of benefit, but not in the 1.4 mg/kg/day group ($p = .068$). No statistically significant difference was demonstrated between the 2 groups for ADHDRS-IV-Parent:Inv total score. Within-group changes in ADHDRS-IV-Parent: hyperactive/impulsive subscore were statistically significant in the 0.8 mg/kg/day; $p = .025$ indicating a loss of benefit, but not in the 1.4 mg/kg/day group; $p = .314$. No statistically significant difference was demonstrated between the 2 groups for ADHDRS-IV-Parent: hyperactive/impulsive subscore. Within-group changes in ADHDRS-IV-Parent:Inv inattentive subscore were statistically significant in the 0.8 mg/kg/day group ($p < .001$) indicating a loss of benefit and in the 1.4 mg/kg/day group ($p = .034$). No statistically significant difference was demonstrated between the 2 groups for ADHDRS-IV-Parent: inattentive subscore.

Safety

- No deaths occurred in the acute phase of the study. There was 1 death (respiratory fume inhalation disorder), which was not related to study medication, which occurred in the maintenance phase (0.8 mg/kg/day group). No serious adverse events (SAEs) were demonstrated during acute phase. There were 6 SAEs, which were not related to the study medication, demonstrated for the maintenance phase. Four of these events were reported in the 0.8 mg/kg/day group: personality disorder, self-injurious ideation, intentional drug misuse, and respiratory fume inhalation disorder, and 2 were reported in the 1.4 mg/kg/day group: mental status changes and ligament injury.

Discontinuations

- Out of 267 patients in the acute phase, 21 patients discontinued due to adverse events (13 in label dose titration and 8 in slow dose titration) though there was not a statistically significant difference between the 2 groups ($p = .26$). For those patients continuing into the maintenance phase ($n = 178$), 27 patients discontinued due to adverse events (12 in the 0.8 mg/kg/day group and 15 in the 1.4 mg/kg/day group) with no statistically significant difference between the 2 groups ($p = .68$).

Treatment-Emergent Adverse Events

Acute Phase

- A total of 81.4% (n=214) of patients during the acute phase reported at least 1 treatment-emergent adverse event (TEAE) (78.3% in label dose titration and 84.33% in slow dose titration group; p=.267). The most commonly demonstrated adverse events were nausea (19.8%), fatigue (18.6%), decreased appetite (17.9 %), somnolence (17.9%), headache (12.9%), and vomiting (10.3%).

Maintenance Phase

- A total of 54.8% (n=97) of patients experienced at least 1 TEAE (56.7% in the 1.4 mg/kg/day group and 52.9% in the 0.8 mg/kg/day group; p=.652). The most commonly demonstrated adverse event was nausea (9.0%). Dizziness was statistically significant between the 0.8 mg/kg/day and 1.4 mg/kg/day groups (p=.027), with 5 patients experiencing this in the 0.8 mg/kg/day group and 0 patients experiencing this in the 1.4 mg/kg/day group.

Electrocardiogram (ECG)

Acute Phase

- In the acute phase, statistically significant within-group changes ($p \leq .05$) were demonstrated in Heart Rate, RR interval, QT Interval, and QTcD in both the groups. No statistically significant differences were demonstrated in ECG changes between groups from baseline to endpoint.

Maintenance Phase

- Statistically significant changes ($p < .05$) were demonstrated in Heart Rate and RR interval within both the groups. Statistically significant changes ($p < .05$) were demonstrated in QTcF, QTcD, and the PR interval in the 1.4 mg/kg/day group. Statistical significance of the difference in the changes in PR Interval ($p = .04$) between the 0.8 mg/kg/day and 1.4 mg/kg/day groups from baseline to endpoint was noted.

Vital Signs

Acute Phase

- Statistically significant changes ($p \leq .05$) were demonstrated within both the groups in pulse and blood pressure from baseline to endpoint. There was a statistically significant decrease ($p < .05$) in weight from baseline to endpoint in both the label dose titration and slow dose titration. No statistically significant difference was observed in any of the vital signs between label dose titration and slow dose titration.

Maintenance Phase

- Statistically significant increases ($p < .001$) were demonstrated in height and weight within both the groups. No statistically significant difference was observed in pulse and blood pressure within the 0.8 mg/kg/day group and 1.4 mg/kg/day group. No statistically significant change was observed between the 0.8 mg/kg/day and 1.4 mg/kg/day groups.

Lab Values

Acute Phase

- Statistically significant mean changes ($p < .05$) were demonstrated within both the groups in alkaline phosphatase, alanine transaminase/serum glutamate pyruvate transaminase (ALT/SGPT), uric acid, erythrocyte count, monocytes, bicarbonate, chloride, and sodium from baseline to end point. Statistically significant mean changes ($p < .05$) were noted for bilirubin total, urea nitrogen, lymphocytes, and potassium in the label dose titration group. Statistically significant mean change ($p < .001$) was demonstrated for cholesterol in the slow dose titration group. There was a statistically significant difference ($p = .04$) in cholesterol between the 2 groups.

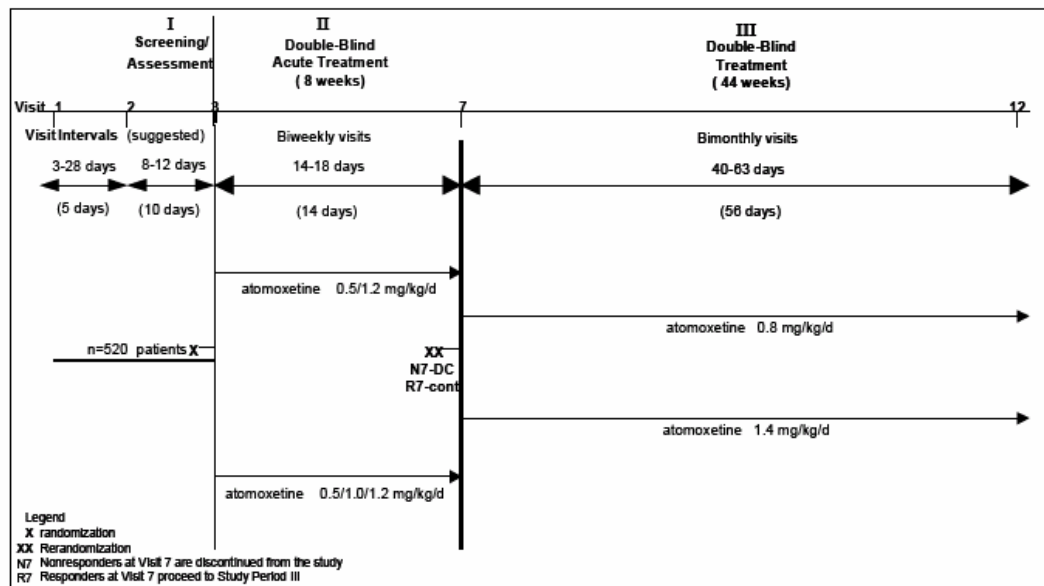
Maintenance Phase

- A statistically significant ($p < .001$) decrease from baseline to endpoint was demonstrated in alkaline phosphatase for both groups. Statistically significant increases ($p \leq .05$) were demonstrated in creatinine and potassium in the 0.8 mg/kg/day group and in uric acid and gamma glutamyl transferase (GGT [GGPT/SGGT/YGGT]) in the 1.4 mg/kg/day group. There was a statistically significant difference demonstrated between groups in albumin ($p = .04$) and bilirubin total ($p = .03$).

Title of Study: Maintenance of Benefit after 8-Week and 52-Week Treatment with Atomoxetine Hydrochloride in Adolescents with Attention-Deficit/Hyperactivity Disorder	
Investigators: This multicenter study included 26 principal investigators.	
Study Centers: This study was conducted at 26 study center(s) in one country.	
Length of Study: 32 months [from FPV to LPV] Date of first patient visit: 8 March 2004 Date last patient completed entire study: 20 November 2006	Phase of Development: 4
Objectives: Primary Objective The primary objective of this study was to assess the difference in maintenance of response at 52 weeks between atomoxetine therapy at a dose of 0.8 mg/kg/day vs. therapy at a dose of 1.4 mg/kg/day as measured by the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv). Secondary Objectives The secondary objectives of the study were as follows: - To assess the relationship between initial atomoxetine dosing titration strategies and tolerability at 4 weeks. - To assess the relationships between initial atomoxetine dosing titration strategies and efficacy at 8 weeks. - To assess the effect of atomoxetine in adolescents with ADHD on the following: - In maintaining measures of social, emotional, cognitive, educational, and affiliative (family, friends) functioning as assessed by the Life Participation Scale for ADHD-Revised (LPS-ADHD-R). - On family functioning as assessed by parental reports on the General Scale of the Family Assessment Measure Version III (FAMIII) and as assessed by the adolescent on the Self-Rating Scale of the FAMIII during long-term treatment with atomoxetine. - On academic performance as measured by the Woodcock Johnson-III Tests of Achievement (WJ-III) and the Kaufman Brief Intelligence Test (K-BIT). - On Grade Point Average (GPA) as measured by the patient's report card, in the core subjects of English, Math, Science, and Social Studies. - On the health status during long-term treatment as measured by the Child Health and Illness Profile – Adolescent Edition (CHIP-AE). - On health risk behaviors during long-term treatment as measured by the Youth Risk Behavior Survey (YRBS). Note: Due to an adjustment in study schedule, the actual duration of the study was 48 weeks (not 52 weeks).	
Study Design: This was a randomized, double-blind trial with 3 phases: the screening and diagnostic assessment phase, the double-blind acute phase, and the maintenance phase. See Figure 1 for the study design diagram.	
Number of Patients: Planned: 520 total patients (260 per arm) Randomized/Entered: 267 active drug Completed: acute phase: 178; maintenance phase: 66	

Diagnosis and Main Criteria for Inclusion: Male and female patients ages 13 to 16 years with ADHD defined by 1) DSM-IV-TR diagnostic criteria confirmed by the Kiddie Schedule of Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS) behavioral module and 2) scoring at least 1.5 standard deviations above the age/gender norm for their ADHD diagnostic subtype on the ADHDRS-IV-Parent:Inv at both Visit 2 and Visit 3. Patients were to be of normal intelligence confirmed by a score of ≥ 70 on the Kaufman Brief Intelligence Test (K-BIT).
Study Drug, Dose, and Mode of Administration: Atomoxetine hydrochloride was given orally once a day in capsule form. During the acute and maintenance phase, atomoxetine was supplied to patients in blisters or bottles in the following dose strengths: 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, and 40 mg. Acute phase = 0.5/1.2/mg/kg/day and 0.5/1.0/1.2/mg/kg/day. Maintenance phase = 0.8 mg/kg/day and 1.4 mg/kg/day. Dosing in Study Period II and III was based on weight and a dosing table for atomoxetine dosage based on mg/kg was provided in the protocol. The maximum dose was 1.4 mg/kg/day, but did not exceed 100 mg (whichever was less) for any patient regardless of weight.
Duration of Treatment: 48 weeks Study Drug name: Atomoxetine titrated from 0.5 to 1.2 mg/kg/day or 0.5 to 1.0 to 1.2 mg/kg/day: 8 weeks. Atomoxetine 0.8 mg/kg/day or 1.4 mg/kg/day: 40 weeks.
Variables <u>Efficacy:</u> Primary: mean change in total score for ADHDRS-IV-Parent:Inv Secondary: mean change in ADHDRS-IV-Parent:Inv subscale score; CGI-ADHD-S; LPS-ADHD-R (investigator and parent rated); FAMIII; WJ-III; K-BIT; GPA; YRBS <u>Safety:</u> Deaths, Treatment-Emergent Adverse Events (TEAEs), Serious Adverse Events (SAE), Discontinuations due to adverse events, Lab values, Electrocardiogram (ECG), Vital Signs <u>Health Outcomes:</u> CHIP-AE
Evaluation Methods: <u>Statistical:</u> For the primary efficacy analysis, Visit 7 served as the baseline. The last observation during Visits 1-3 was considered baseline for Study Period II while the last observation during Visits 4-7 was considered baseline for Study Period III for all other analyses except for the incidence of TEAEs and treatment-emergent abnormal laboratory analytes. For the analysis of TEAEs or abnormal laboratory analytes during Study Period II, Visits 1-3 served as baseline, and for the analysis of these safety measures during Study Period III, Visits 1-7 served as baseline. The primary efficacy analysis for this study was a dose group comparison of change from baseline (Visit 7) to last observation carried forward (LOCF) endpoint ADHD-RS Total score during Study Period III using a fixed-effects analysis of covariance (ANCOVA) model with terms for baseline score, treatment, and investigative site. Secondary efficacy measures as well as health outcomes were also analyzed using ANCOVA models with terms for baseline score, treatment, and investigative site. The incidence rates of adverse events were analyzed using Fisher's Exact test while laboratory measures, ECGs, and vital signs used an ANCOVA model with terms for group, investigative site, and baseline value.

Study Design:



Abbreviation: n = number of patients.

Figure 1. Illustration of the study design for B4Z-US-LYCD.

Results:

Patient Demographics

Tables 1 and 2 summarize baseline characteristics for patients entering the acute phase and continuing into the maintenance phase. A total of 333 patients entered the study; 267 patients were randomized to either label dose titration (n=132) or slow dose titration (n=135) (Table 1). The mean age of patients entering the trial was 14.6 years old, and the majority of patients were Caucasian (74.2%) and male (64%). The ADHD subtype for patients entering the trial was primarily inattentive (49.8%) or mixed (47.9%) subtype. There were no statistically significant differences between the randomized groups.

Only patients who met response criteria at the end of 8 weeks, defined as a decrease of ≥ 1 point on the CGI-ADHD-S scale, were allowed to continue to the maintenance phase of the study. A total of 178 patients continued into the maintenance phase and were rerandomized to atomoxetine at either 0.8 mg/kg/day (n=88) or 1.4 mg/kg/day (n=90) (Table 2). There were no statistically significant differences in characteristics between the 2 groups.

Atomoxetine

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Table 1. Baseline Demographic Characteristics - All Entered Patients - Acute Phase

Variable	Response	Not Enrolled (N=66)		ATX0.5/1.2 (N=132)		ATX0.5/1.0/1.2 (N=135)		Total (N=333)		P-value
		n	%	n	%	n	%	n	%	
Age in Years	Number of Patients	66		132		135		333		0.086
	Mean		14.72		14.45		14.67		14.59	
	standard deviation		1.13		0.99		1.10		1.07	
Gender	Number of patients	66		132		135		333		0.527
	Female	24	36.36	50	37.88	46	34.07	120	36.04	
	Male	42	63.64	82	62.12	89	65.93	213	63.96	
Origin	Number of patients	66		132		135		333		0.547
	African Descent	9	13.64	14	10.61	18	13.33	41	12.31	
	Western Asian	1	1.52	0	0.00	0	0.00	1	0.30	
	Caucasian	48	72.73	98	74.24	101	74.81	247	74.17	
	East/Southeast Asian	0	0.00	0	0.00	1	0.74	1	0.30	
	Hispanic	5	7.58	10	7.58	10	7.41	25	7.51	
	Other	3	4.55	10	7.58	5	3.70	18	5.41	
Previous Stimulant Use	Number of patients	0		132		135		267		0.623
	No	0		60	45.45	57	42.22	117	43.82	
	Yes	0		72	54.55	78	57.78	150	56.18	
DSM-IV ADHD Subtype	Number of patients	0		132		135		267		0.434
	HYP/IMP	0		2	1.52	4	2.96	6	2.25	
DSM-IV ADHD Subtype	INATTV	0		62	46.97	71	52.59	133	49.81	
	MIXED	0		68	51.52	60	44.44	128	47.94	
CY2D6 Phenotype Extn Slow	Number of patients	5		129		133		267		0.282
	EXTN	4	80.00	120	93.02	128	96.24	252	94.38	
	SLOW	1	20.00	9	6.98	5	3.76	15	5.62	

Abbreviations: ADHD = Attention Deficit/Hyperactivity Disorder; ATX = atomoxetine; ATX 0.5/1.2 = label dose titration; ATX 0.5/1.0/1.2 = slow dose titration; DSM-IV ADHD subtype = Diagnostic and Statistical Manual of Mental Disorders Attention Deficit/Hyperactivity Disorder subtype; EXTN = extension; HYP/IMP = hyperactive impulsive; INATTV = inattentive; N = sample size; n = number of patients.

Dosages are in mg/kg per day.

Population: All Entered Patients.

For Continuous data, p-value is given using model 'dependent variable' = treatment.

For Categorical data, p-value is given using a Fisher's Exact Test.

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Table 2. Baseline Demographic Characteristics – All Randomized Patients - Maintenance Phase

Variable	Response	ATX0.8 (N=88)		ATX1.4 (N=90)		Total (N=178)		P-value
		n	%	n	%	n	%	
Age in Years	Number of Patients	88		90		178		0.228
	Mean	14.67		14.48		14.57		
	Standard deviation	1.08		1.00		1.04		
Gender	Number of patients	88		90		178		0.279
	Female	37	42.05	30	33.33	67	37.64	
	Male	51	57.95	60	66.67	111	62.36	
Origin	Number of patients	88		90		178		0.349
	African Descent	9	10.23	15	16.67	24	13.48	
	Caucasian	70	79.55	61	67.78	131	73.60	
	East/Southeast Asian	0	0.00	1	1.11	1	0.56	
	Hispanic	5	5.68	9	10.00	14	7.87	
	Other	4	4.55	4	4.44	8	4.49	
Previous Stimulant Use	Number of patients	88		90		178		0.173
	No	43	48.86	34	37.78	77	43.26	
	Yes	45	51.14	56	62.22	101	56.74	
DSM-IV ADHD Subtype	Number of patients	88		90		178		0.240
	HYP/IMP	4	4.55	1	1.11	5	2.81	
	INATTV	42	47.73	51	56.67	93	52.25	
	MIXED	42	47.73	38	42.22	80	44.94	
CY2D6 Phenotype Extn Slow	Number of patients	88		87		175		0.248
	EXTN	84	95.45	79	90.80	163	93.14	
	SLOW	4	4.55	8	9.20	12	6.86	

Abbreviations: ADHD = Attention Deficit/Hyperactivity Disorder; ATX = atomoxetine; ATX 0.5/1.2 = label dose titration; ATX 0.5/1.0/1.2 = slow dose titration; DSM-IV ADHD subtype = Diagnostic and Statistical Manual of Mental Disorders Attention Deficit/Hyperactivity Disorder subtype; EXTN = extension; HYP/IMP = hyperactive impulsive; INATTV = inattentive; N = sample size; n = number of patients.

Dosages are in mg/kg per day.

Population: All Entered Patients.

For Continuous data, p-value is given using model 'dependent variable' = treatment.

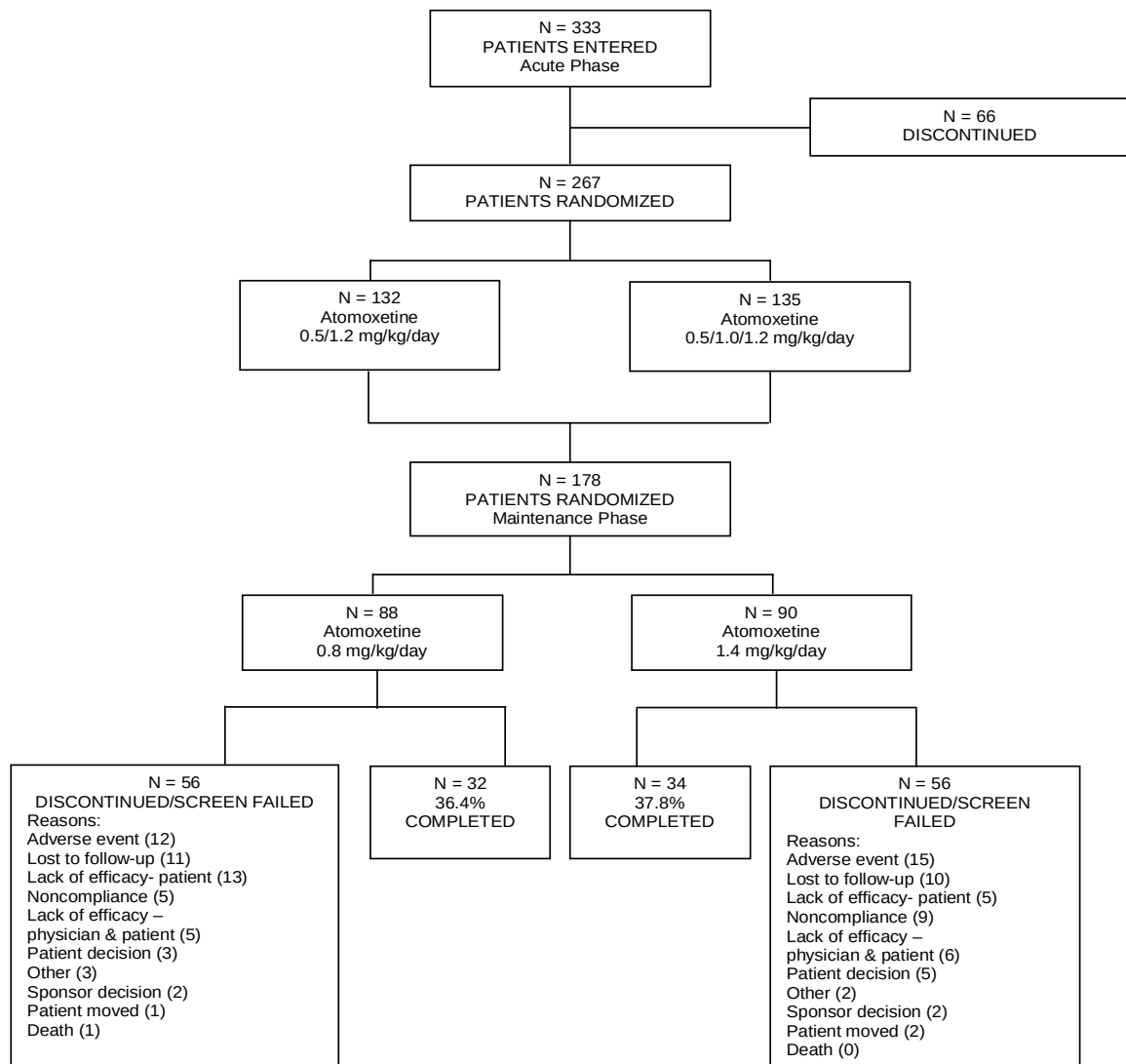
For Categorical data, p-value is given using a Fisher's Exact Test.

Patient Disposition

Figure 2 summarizes patient disposition.

The reasons for discontinuation in acute phase are summarized in Table 3. A total of 333 patients entered the study; 267 patients were randomized to either label dose titration (n=132) or slow dose titration (n=135). The primary reason for discontinuation in the acute phase for both groups was failure to meet response criteria (10.6% for label dose titration group and 8.2% for the slow dose titration group). The reasons for discontinuation in the acute phase were not statistically different between groups with the exception of the reason of “personal conflict or other patient decision” which was statistically significantly greater in the label dose titration group (p=.02).

A summary of reasons for discontinuation in the maintenance phase are summarized in Table 4. A total of 66 patients completed the protocol. Of the patients in the acute phase, 178 patients continued into the maintenance phase and were re-randomized to atomoxetine at either 0.8 mg/kg/day (n=88) or 1.4 mg/kg/day (n=90). Adverse events were the primary reason for discontinuations in the maintenance phase in both the groups (13.6% in 0.8 mg/kg/day group and 16.7% in 1.4 mg/kg/day group). The reasons for discontinuation in the maintenance phase were not statistically different between groups with the exception of “perception of lack of efficacy by patient or caregiver” which was statistically significantly greater in the 0.8 mg/kg/day group (14.8%) than in the 1.4 mg/kg/day group (5.6%, p=.049).



Abbreviation: N = number of patients.

Figure 2. B4Z-US-LYCD Patient Disposition.

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Table 3. Reasons for Discontinuation - Acute Phase

Reason for Discontinuation	ATX0.5/1.2 (N=132)	ATX0.5/ 1.0/1.2 (N=135)	Total (N=267)	Fisher's exact p-value
Continuing to Maintenance Phase	80 (60.61%)	98 (72.59%)	178 (66.67%)	0.051
Protocol response criteria not met	14 (10.61%)	11 (8.15%)	25 (9.36%)	0.534
Adv. evt.	13 (9.85%)	8 (5.93%)	21 (7.87%)	0.262
Unable to contact patient/caregiver	5 (3.79%)	6 (4.44%)	11 (4.12%)	>0.999
Personal conflict or other pat decision	8 (6.06%)	1 (0.74%)	9 (3.37%)	0.018
Noncompl	3 (2.27%)	5 (3.70%)	8 (3.00%)	0.723
Lack of efficacy, pat/caregivr & phys per	5 (3.79%)	1 (0.74%)	6 (2.25%)	0.117
Lack of efficacy, patient/caregiver perc	1 (0.76%)	2 (1.48%)	3 (1.12%)	>0.999
Other	1 (0.76%)	1 (0.74%)	2 (0.75%)	>0.999
Patient moved	0 (0.00%)	1 (0.74%)	1 (0.37%)	>0.999
Physician decision	1 (0.76%)	0 (0.00%)	1 (0.37%)	0.494
Protocol Violation	1 (0.76%)	0 (0.00%)	1 (0.37%)	0.494
Sponsor's decision	0 (0.00%)	1 (0.74%)	1 (0.37%)	>0.999

Abbreviations: Adv evt = adverse event; ATX = atomoxetine; ATX 0.5/1.2 = label dose titration; ATX 0.5/1.0/1.2 = slow dose titration; DSM-IV ADHD subtype = Diagnostic and Statistical Manual of Mental Disorders Attention Deficit/Hyperactivity Disorder subtype; N = sample size; noncompl = noncompliance; pat/caregivr = patient caregiver; phys perc = physician perception.

Dosages are in mg/kg per day.

Population: All randomized patients.

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Table 4. Summary of Reasons for Discontinuations in Maintenance Phase

Reason for Discontinuation	ATX0.8 (N=88)	ATX1.4 (N=90)	Total (N=178)	Fisher's exact p-value
Protocol completed	32 (36.36%)	34 (37.78%)	66 (37.08%)	0.878
Adv. evt.	12 (13.64%)	15 (16.67%)	27 (15.17%)	0.677
Unable to contact patient/caregiver	11 (12.50%)	10 (11.11%)	21 (11.80%)	0.820
Lack of efficacy, patient/caregiver perc	13 (14.77%)	5 (5.56%)	18 (10.11%)	0.049
Noncompliance	5 (5.68%)	9 (10.00%)	14 (7.87%)	0.405
Lack of efficacy, pat/cargivr & phys per	5 (5.68%)	6 (6.67%)	11 (6.18%)	>0.999
Personal conflict or other pat decision	3 (3.41%)	5 (5.56%)	8 (4.49%)	0.720
Other	3 (3.41%)	2 (2.22%)	5 (2.81%)	0.680
Sponsor's decision	2 (2.27%)	2 (2.22%)	4 (2.25%)	>0.999
Patient moved	1 (1.14%)	2 (2.22%)	3 (1.69%)	>0.999
Death	1 (1.14%)	0 (0.00%)	1 (0.56%)	0.494

Abbreviations: Adv evt = adverse event; ATX = atomoxetine; DSM-IV ADHD subtype = Diagnostic and Statistical Manual of Mental Disorders Attention; Deficit/Hyperactivity Disorder subtype; N = sample size; pat/cargivr = patient caregiver; phys per = physician perception.

Dosages are in mg/kg per day.

Population: All randomized patients.

Primary Efficacy Measure

ADHDRS-IV-Parent:Inv

Reduction in the ADHDRS-IV-Parent:Inv and CGI-ADHD-S score indicates improvement.

Table 5 presents mean change for the ADHDRS-IV-Parent:Inv total score, inattentive and hyperactive/impulsive subscores from end of acute phase to the endpoint in the maintenance phase of the study. Within-group changes in ADHDRS-IV-Parent:Inv total score from post-acute phase baseline to endpoint were statistically significant in the 0.8 mg/kg/day group ($p < .001$) indicating a loss of benefit, but not in the 1.4 mg/kg/day group ($p = .068$). No statistically significant change was demonstrated between the 2 groups for ADHDRS-IV-Parent:Inv total score. Within-group changes in ADHDRS-IV-Parent: hyperactive/impulsive subscore were statistically significant in the 0.8 mg/kg/day; $p = .025$ indicating a loss of benefit, but not in the 1.4 mg/kg/day group; $p = .314$. No statistically significant change was demonstrated between the 2 groups for ADHDRS-IV-Parent: hyperactive/impulsive subscore. Within-group changes in ADHDRS-IV-Parent:Inv inattentive subscore were statistically significant in the 0.8 mg/kg/day group ($p < .001$) indicating a loss of benefit, and in the 1.4 mg/kg/day group ($p = .034$). No statistically significant difference was demonstrated between the 2 groups for ADHDRS-IV-Parent: inattentive subscore.

Atomoxetine

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Table 5. Mean Change from Baseline to LOCF Endpoint in Maintenance Phase for Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator-Administered and Scored Total and Subscores and Clinical Global Impressions-ADHD-Severity

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
ADHDRS-INV Total Score Imputed	ATX0.8	83	13.99	7.40	16.98	10.04	3.80	1.05	<0.001	0.194
	ATX1.4	83	12.98	7.13	14.52	10.00	1.93	1.05	0.068	
ADHDRS-INV HYP/IMP Score Imputed	ATX0.8	83	4.84	4.28	5.65	5.36	1.16	0.51	0.025	0.357
	ATX1.4	83	4.42	3.94	4.71	5.32	0.51	0.51	0.314	
ADHDRS-INV Inatten Score Imputed	ATX0.8	83	9.16	4.70	11.33	6.08	2.63	0.65	<0.001	0.167
	ATX1.4	83	8.55	4.43	9.81	5.65	1.39	0.65	0.034	
CGI ADHD Severity	ATX0.8	83	2.65	0.79	3.01	1.03	0.46	0.11	<0.001	0.008
	ATX1.4	83	2.57	0.84	2.60	1.07	0.04	0.11	0.699	

Abbreviations: ADHDRS-INV = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator-Administered and Scored; ATX = atomoxetine mg/kg/day; CGI-ADHD-Severity = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity; HYP/IMP = hyperactive impulsive; INATTV = inattentive; LOCF = Last Observation Carried Forward; LSMean = Least Squares Mean; N = sample size; SD = standard deviation; SE = standard error.

Dosages are in mg/kg per day.

* P-value is from LSMean change from baseline to endpoint using Student's t-test.

** P-value is from a LSMean Type III Sum of Squares using model: change = baseline treatment investigator.

Baseline: last of Visits 4-7. Endpoint: last of Visits 8-12.

Population: All randomized patients.

Secondary Efficacy Measures

Titration Strategies/Tolerability 4 week

No statistically significant within-group changes were demonstrated in ECG values, except for PR interval, from baseline to endpoint ($p > .050$). Mean change in QTcD was statistically significant between groups ($p = .023$). No statistically significant changes were demonstrated for Heart Rate, $1000 \times 60/\text{HR}$, PR interval, QRS Interval, QT Interval, and QTcF between groups from baseline to endpoint.

No statistically significant between group changes were demonstrated for albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, calcium, cholesterol, creatinine phosphokinase, creatinine, GGT (GGPT/SGGT/YGGT), non-fasting or random glucose, inorganic phosphorus, total protein, urea nitrogen, uric acid, basophils, eosinophils, erythrocyte count, hematocrit, hemoglobin, leukocyte count, lymphocytes, mean cell volume (MCV), segmented neutrophils, platelet count, bicarbonate, chloride, potassium, sodium, or UA-specific gravity ($p > .050$). Mean change in monocytes from baseline to endpoint was statistically significant in label dose titration ($p = .009$) and was not statistically significant in slow dose titration ($p = .600$). Mean change in monocytes from baseline to endpoint was statistically significant between treatment groups ($p = .016$).

At the end of 4 weeks, statistically significant changes ($p < .01$) were demonstrated within both the groups in pulse, diastolic and systolic blood pressure. There was a statistically significant decrease ($p < .001$) in weight from baseline to endpoint. No statistically significant difference was observed in any of the vital signs or weight between label dose titration and slow dose titration.

The frequency of TEAEs occurring in 10% or more of patients is summarized in Table 6. A total of 73.4% ($n = 193$) of patients experienced at least 1 TEAE (74.4% in the label dose titration and 72.4% in the slow dose titration group; $p = .781$). The most commonly demonstrated adverse events were nausea (15.2%), decreased appetite (14.8%), fatigue (14.8%), and somnolence (17.1%).

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Table 6. Frequency of Treatment-Emergent Adverse Events (≥10%) During Titration

Preferred Term	ATX0.5/1.2 (N=129)		ATX0.5/ 1.0/1.2 (N=134)		Total (N=263)		p-value
	n	%	n	%	n	%	
Patients with ≥1 TEAE	96	74.42	97	72.39	193	73.38	0.781
Nausea	25	19.38	15	11.19	40	15.21	0.085
Decreased appetite	23	17.83	16	11.94	39	14.83	0.225
Fatigue	20	15.50	19	14.18	39	14.83	0.863
Somnolence	20	15.50	25	18.66	45	17.11	0.517

Abbreviations: ATX = atomoxetine; ATX0.5/1.2 = label dose titration; ATX 0.5/1.0/1.2 = Slow dose titration; N = sample size; n = number of patients in the category; TEAE = treatment-emergent adverse event.

Dosages are in mg/kg per day.

Baseline: last of Visits 1-3. Follow-up: Visits 4-5.

Population: All randomized patients who took at least 1 dose of study medication.

ADHDRS-IV-Parent:Inv

Acute Phase

Reduction in ADHDRS-IV-Parent:Inv Score indicates improvement.

Table 7 presents mean change for ADHDRS-IV-Parent:Inv total and inattentive and hyperactive/impulsive subscores from baseline to endpoint in the acute phase of the study. The mean change for the ADHDRS-IV-Parent:Inv total and subscores were statistically significant ($p < .001$) from baseline to endpoint within both the groups in the acute phase. There were no statistically significant differences in mean change between the label dose titration and slow dose titration groups for ADHDRS-IV-Parent:Inv total and subscores.

CGI-ADHD-S

Acute Phase

Reduction in CGI-ADHD-S Score indicates improvement.

The mean CGI-ADHD-S change was statistically significant ($p < .001$) from baseline to endpoint within both the groups in the acute phase (Table 7). There was no statistically significant difference in the mean change between the label dose titration and slow dose titration groups for the CGI-ADHD-S score.

Maintenance Phase

Within-group changes in CGI-ADHD-S score from the post-acute phase baseline to endpoint was statistically significant ($p < .001$) in the 0.8 mg/kg/day group (Table 5), indicating loss of benefit, but not in the 1.4 mg/kg/day group ($p = .699$). There was a statistically significantly greater increase (indicating loss of benefit) in mean CGI-ADHD-S score in the 0.8 mg/kg/day group compared with the 1.4 mg/kg/day group ($p = .008$).

Life Participation Scale for ADHD-Revised (LPS-ADHD-R; based on patient interviews and parent rated)

Acute Phase

Increase in the LPS-ADHD-R indicates improvement.

Table 8 presents mean change for LPS-ADHD-R total and the Happy/Social and Self-Control subscale scores from baseline to endpoint in acute phase of the study. Mean change in LPS-ADHD-R total score, parent-rated and self-rated, were statistically significantly improved for both the label dose titration and slow dose titration ($p < .001$). LPS-ADHD-R parent-rated and self-rated subscale scores of Happy/Social and Self-Control from baseline to endpoint were statistically significantly improved for both the groups ($p < .001$). There were no statistically significant differences between the 2 groups for total scores and subscores.

Maintenance Phase

Increase in the LPS-ADHD-R and LPS-ADHD-R indicates improvement.

Table 9 presents mean change for LPS-ADHD-R total and subscores from baseline to endpoint in the maintenance phase of the study. The mean change from the post-acute phase baseline to endpoint in LPS-ADHD-R Self-rated total score ($p=.009$) and self-control subscale score ($p=.001$) and LPS-ADHD-R parent-rated self-control score ($p=.007$) for the 0.8 mg/kg/day group were statistically significantly decreased, indicating loss of benefit. LPS-ADHD-R self-rated Happy/Social subscale score for the 0.8 mg/kg/day group was not statistically significant. LPS-ADHD-R parent-rated and self-rated total and subscale scores for the 1.4 mg/kg/day group were not statistically significant. There were no statistically significant differences between the 2 groups.

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Table 7. Mean Change from Baseline to LOCF Endpoint in Acute Phase for Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored Total and Subscores and Clinical Global Impressions-ADHD-Severity

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
ADHDRS-INV Total Score Imputed	ATX0.5/1.2	122	35.15	8.05	18.25	10.34	-16.48	0.81	<0.001	0.483
	ATX0.5/1.0/1.2	129	33.28	8.68	16.31	9.70	-17.26	0.79	<0.001	
ADHDRS-INV HYP/IMP Score Imputed	ATX0.5/1.2	122	13.90	6.18	6.68	5.43	-6.76	0.39	<0.001	0.992
	ATX0.5/1.0/1.2	129	12.53	6.68	5.96	5.24	-6.75	0.39	<0.001	
ADHDRS-INV Inatten Score Imputed	ATX0.5/1.2	122	21.25	3.57	11.57	6.24	-9.73	0.51	<0.001	0.276
	ATX0.5/1.0/1.2	129	20.75	4.15	10.34	5.82	-10.49	0.50	<0.001	
CGI ADHD Severity	ATX0.5/1.2	122	4.58	0.61	3.11	1.06	-1.45	0.09	<0.001	0.504
	ATX0.5/1.0/1.2	130	4.43	0.58	2.93	1.01	-1.53	0.09	<0.001	

Abbreviations: ADHDRS-INV = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored; ATX = atomoxetine; ATX0.5/1.2 = label dose titration; ATX 0.5/1.0/1.2 = slow dose titration; HYP/IMP = Hyperactive/impulsive; CGI-ADHD-Severity = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity; LOCF = Last Observation Carried Forward; LSMean = Least Squares Mean; N = number of patients; SD = standard deviation; SE = standard error.

Dosages are in mg/kg per day.

* P-value is from LSMean change from baseline to endpoint using Student's t-test.

** P-value is from a LSMean Type III Sum of Squares using model: change = baseline treatment investigator.

Baseline: last of Visits 1-3. Endpoint: last of Visits 4-7.

Population: All randomized patients.

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Table 8. Mean Change from Baseline to LOCF Endpoint in Acute Phase for Life Participation Scale for ADHD-Revised Total and Subscores

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
LPS Total Imputed (LPSHAPI + LPSSELF)	ATX0.5/1.2	102	34.44	11.05	43.18	11.84	9.66	1.06	<0.001	0.356
	ATX0.5/1.0/1.2	114	32.18	11.63	43.73	12.10	10.99	1.02	<0.001	
LPS-INV vers Happy/Soc subscale imputed	ATX0.5/1.2	109	17.29	5.92	19.49	5.50	2.45	0.48	<0.001	0.862
	ATX0.5/1.0/1.2	119	16.52	6.02	19.35	6.14	2.56	0.46	<0.001	
LPS-INV vers Self-cntl subscale imputed	ATX0.5/1.2	102	17.16	6.65	23.71	7.55	7.19	0.67	<0.001	0.287
	ATX0.5/1.0/1.2	114	15.73	7.03	24.24	7.20	8.16	0.64	<0.001	
LPSP Total Imputed (LPSPHAPI + LPSPSLFI)	ATX0.5/1.2	101	31.03	10.63	39.91	11.35	9.19	1.01	<0.001	0.613
	ATX0.5/1.0/1.2	107	30.18	11.02	38.87	12.09	8.49	1.00	<0.001	
LPSP-INV vers Happy/Soc subscale imputed	ATX0.5/1.2	108	15.92	5.59	18.25	5.78	2.36	0.47	<0.001	0.620
	ATX0.5/1.0/1.2	117	15.75	6.06	17.78	6.30	2.04	0.46	<0.001	
LPSP-INV vers Self-cntl subscale imputed	ATX0.5/1.2	102	15.25	6.33	21.56	6.76	6.47	0.62	<0.001	0.935
	ATX0.5/1.0/1.2	107	14.92	6.60	21.45	7.10	6.40	0.62	<0.001	

Abbreviations: ATX = atomoxetine; ATX0.5/1.2 = label dose titration; ATX 0.5/1.0/1.2 = slow dose titration; LOCF = Last Observation Carried Forward; LPS ADHD-R = Life Participation Scale for ADHD-Revised; LSMean = Least Squares Mean; LPS-INV = Life Participation Scale Investigator-rated; LPSHAPI = Life participation scale happy/social imputed; LPSSELF = Life participation scale self-control imputed; LPSP = Life Participation Scale Parent-rated; LPSPHAPI = Life participation scale parent-rated happy/social imputed; LPSPSLFI = Life participation scale parent-rated self-control imputed; SD = standard deviation; SE = standard error; self-cntl = self control; vers = versus.

Dosages are in mg/kg per day.

* P-value is from LSMean change from baseline to endpoint using Student's t-test.

** P-value is from a LSMean Type III Sum of Squares using model: change = baseline treatment investigator.

Baseline: last of Visits 1-3. Endpoint: last of Visits 4-7.

Population: All randomized patients.

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Table 9. Mean Change from Baseline to LOCF Endpoint in Maintenance Phase for LPS-ADHD-R Total and Subscores

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
LPS Total Imputed (LPSHAPI + LPSSELF I)	ATX0.8	58	45.31	9.99	43.07	11.33	-4.09	1.54	0.009	0.289
	ATX1.4	64	47.90	9.09	45.65	11.41	-2.07	1.38	0.138	
LPS-INV vers Happy/Soc subscale imputed	ATX0.8	60	20.00	5.21	19.78	5.07	-0.68	0.69	0.332	0.727
	ATX1.4	66	21.02	4.61	20.37	5.45	-0.38	0.63	0.549	
LPS-INV vers Self-cntl subscale imputed	ATX0.8	58	25.26	6.10	23.21	7.35	-3.49	0.98	0.001	0.130
	ATX1.4	64	26.95	5.88	25.34	6.93	-1.64	0.88	0.067	
LPSP Total Imputed (LPSPHAPI + LPSPSLFI)	ATX0.8	53	42.73	11.25	41.24	12.19	-3.16	1.69	0.066	0.482
	ATX1.4	62	42.39	9.65	41.76	11.80	-1.76	1.46	0.232	
LPSP-INV vers Happy/Soc subscale imputed	ATX0.8	55	18.57	5.65	19.00	5.10	-0.39	0.74	0.597	0.793
	ATX1.4	65	18.75	5.22	19.15	6.28	-0.17	0.65	0.800	
LPSP-INV vers Self-cntl subscale imputed	ATX0.8	54	23.92	6.92	21.94	8.34	-2.89	1.04	0.007	0.261
	ATX1.4	62	23.64	5.64	22.78	6.54	-1.46	0.93	0.121	

Abbreviations: ATX = atomoxetine; ATX0.5/1.2 = label dose titration; ATX 0.5/1.0/1.2 = slow dose titration; LOCF = Last Observation Carried Forward; LPS ADHD-R = Life Participation Scale for ADHD-Revised; LSMean = Least Squares Mean; LPS-INV = Life Participation Scale Investigator-rated; LPSHAPI = Life participation scale happy/social imputed; LPSSELF I = Life participation scale self-control imputed; LPSP = Life Participation Scale Parent-rated; LPSPHAPI = Life participation scale parent-rated happy/social imputed; LPSPSLFI = Life participation scale parent-rated self-control imputed; SD = standard deviation; SE = standard error; self-cntl = self control; vers = versus.

Dosages are in mg/kg per day.

* P-value is from LSMean change from baseline to endpoint using Student's t-test.

** P-value is from a LSMean Type III Sum of Squares using model: change = baseline treatment investigator.

Baseline: last of Visits 4-7. Endpoint: last of Visits 8-12.

Population: All randomized patients.

Family Functioning

Acute Phase

Table 10 presents mean change in Family Assessment Measure Version III (FAMIII): General scale and FAMIII: Self-Rated scale total and subscores from baseline to endpoint in acute phase of the study. A statistically significant mean change ($p < .05$) was demonstrated for FAMIII-General scale items: overall rating total t-score, control total raw score, affective expression total raw score, task accomplishment total raw score, and FAMIII: Self-rated scale for the values and norms total raw score for both treatment groups. The slow dose titration group demonstrated statistically significant mean change ($p < .05$) from baseline to endpoint for additional General scale items: defensiveness total raw score, involvement total raw score, and the role performance total raw score. For the FAMIII: Self-rated scale items, mean change ($p < .05$) from baseline to endpoint was statistically significant for the slow dose titration group on the affective expression total raw score and task accomplishment total raw score. There were no statistically significant differences between the 2 groups for any of the FAMIII General or Self-Rated scale items.

Maintenance Phase

Table 11 presents mean change for FAMIII: General scale and FAMIII: Self-Rated scale total and subscores from baseline to endpoint in the maintenance phase of the study. Mean change from baseline to endpoint was statistically significant ($p = .05$) for the FAMIII: General scale social desirability total raw score in 0.8 mg/kg/day group and for the FAMIII: Self-Rated scale communication total raw score ($p < .02$) in the 1.4 mg/kg/day group. There was a statistically significant difference between the 0.8 mg/kg/day and 1.4 mg/kg/day groups in the FAMIII: Self-Rated task accomplishment total raw score ($p = .04$).

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Table 10. Mean Change from Baseline to LOCF Endpoint in Acute Phase for Family Assessment Measure III: General and Self-Rated Total and Subscores

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
FAM-3G Overall Rating total t-score	ATX0.5/1.2	85	59.18	3.18	58.09	2.89	-0.84	0.32	0.009	0.323
	ATX0.5/1.0/1.2	97	58.92	3.27	57.53	3.04	-1.25	0.31	<0.001	
FAM-3G control total raw	ATX0.5/1.2	103	7.11	1.72	6.54	1.74	-0.41	0.14	0.005	0.640
	ATX0.5/1.0/1.2	113	6.71	1.58	6.42	1.41	-0.32	0.14	0.022	
FAM-3G Communication total raw	ATX0.5/1.2	103	7.80	1.26	8.01	1.28	0.25	0.13	0.060	0.678
	ATX0.5/1.0/1.2	116	7.88	1.33	7.98	1.40	0.17	0.12	0.164	
FAM-3G Defensiveness total raw	ATX0.5/1.2	101	11.03	1.66	10.98	1.69	-0.08	0.15	0.579	0.058
	ATX0.5/1.0/1.2	108	11.11	1.79	11.43	1.45	0.31	0.15	0.040	
FAM-3G Involvement total raw	ATX0.5/1.2	102	7.38	1.54	7.22	1.15	-0.14	0.13	0.284	0.357
	ATX0.5/1.0/1.2	110	7.35	1.54	7.01	1.55	-0.31	0.13	0.019	
FAM-3G Affective Expression tot raw	ATX0.5/1.2	103	7.33	1.62	6.94	1.16	-0.28	0.14	0.043	0.609
	ATX0.5/1.0/1.2	114	7.09	1.50	6.84	1.58	-0.37	0.13	0.005	
FAM-3G Role Performance total raw	ATX0.5/1.2	106	7.49	1.48	7.45	1.81	-0.05	0.15	0.752	0.143
	ATX0.5/1.0/1.2	112	7.54	1.72	7.10	1.36	-0.35	0.15	0.021	
FAM-3G Social Desirability tot raw	ATX0.5/1.2	104	11.19	1.50	11.23	1.52	-0.02	0.15	0.889	0.874
	ATX0.5/1.0/1.2	110	11.38	1.65	11.35	1.66	0.01	0.15	0.937	
FAM-3G Task Accomplishment total raw	ATX0.5/1.2	100	8.32	1.35	7.69	1.38	-0.64	0.14	<0.001	0.444

continued

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Table 10. Mean Change from Baseline to LOCF Endpoint in Acute Phase for Family Assessment Measure III: General and Self-Rated Total and Subscores (Concluded)

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
FAM-3G Task Accomplishment total raw	ATX0.5/1.0/1.2	113	8.28	1.40	7.84	1.48	-0.49	0.14	<0.001	
FAM-3G Values & Norms total raw	ATX0.5/1.2	101	7.25	1.44	7.02	1.32	-0.20	0.13	0.124	0.685
	ATX0.5/1.0/1.2	113	7.15	1.50	7.04	1.62	-0.13	0.13	0.295	
FAM-3S Affective Expression total raw	ATX0.5/1.2	98	8.42	1.67	8.43	1.70	0.14	0.16	0.381	0.214
	ATX0.5/1.0/1.2	108	8.29	2.00	8.65	1.45	0.40	0.15	0.008	
FAM-3S Control total raw	ATX0.5/1.2	102	9.02	1.88	8.82	1.66	-0.06	0.15	0.712	0.453
	ATX0.5/1.0/1.2	112	8.75	1.97	8.86	1.54	0.10	0.15	0.502	
FAM-3S Communication total raw	ATX0.5/1.2	102	9.22	2.00	9.34	1.74	0.07	0.19	0.717	0.542
	ATX0.5/1.0/1.2	113	9.40	1.82	9.22	1.89	-0.09	0.18	0.634	
FAM-3S Involvement total raw	ATX0.5/1.2	99	8.93	1.76	8.81	1.65	-0.03	0.17	0.871	0.541
	ATX0.5/1.0/1.2	103	8.71	2.08	8.61	1.52	-0.16	0.16	0.309	
FAM-3S Role Performance total raw	ATX0.5/1.2	94	9.14	1.96	9.10	2.11	0.02	0.18	0.928	0.317
	ATX0.5/1.0/1.2	108	9.05	1.89	8.80	1.55	-0.23	0.17	0.190	
FAM-3S Task Accomplishment total raw	ATX0.5/1.2	99	8.09	1.92	8.30	1.88	0.11	0.17	0.502	0.131
	ATX0.5/1.0/1.2	105	8.31	1.95	8.63	1.45	0.46	0.16	0.006	
FAM-3S Values & Norms total raw	ATX0.5/1.2	97	7.46	2.25	7.93	2.40	0.53	0.20	0.009	0.803
	ATX0.5/1.0/1.2	117	7.56	2.11	7.91	1.60	0.47	0.18	0.011	

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Abbreviations: ATX = atomoxetine; ATX0.5/1.2 = label dose titration; ATX 0.5/1.0/1.2 = slow dose titration; FAM-3G = Family Assessment Measure Version III – General Scale; FAM-3S = Family Assessment Measure Version III – Self-Rated Scale; LOCF = Last Observation Carried Forward; LSMean = Least Squares Mean; N = sample size; SD = standard deviation; SE = standard error; tot = total.

Dosages are in mg/kg per day.

* P-value is from LSMean change from baseline to endpoint using Student's t-test.

** P-value is from a LSMean Type III Sum of Squares using model: change = baseline treatment investigator.

Baseline: last of Visits 1-3. Endpoint: last of Visits 4-7.

Population: All randomized patients.

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Table 11. Mean Change from Baseline to LOCF Endpoint in Maintenance Phase for Family Assessment Measure III: General and Self-Rated Total and Subscores

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
FAM-3G Overall Rating total t-score	ATX0.8	47	58.41	5.79	58.29	2.57	-0.13	0.41	0.747	0.748
	ATX1.4	55	57.95	2.96	58.20	3.13	-0.30	0.37	0.424	
FAM-3G control total raw	ATX0.8	52	6.63	2.00	6.67	1.58	0.18	0.25	0.476	0.649
	ATX1.4	65	6.20	1.42	6.40	1.76	0.04	0.22	0.849	
FAM-3G Communication total raw	ATX0.8	53	8.06	1.49	7.83	1.27	-0.31	0.21	0.141	0.668
	ATX1.4	63	8.10	1.24	7.94	1.28	-0.20	0.18	0.268	
FAM-3G Defensiveness total raw	ATX0.8	53	11.26	2.28	11.30	1.32	0.07	0.22	0.746	0.139
	ATX1.4	62	11.18	1.77	10.85	1.71	-0.33	0.20	0.096	
FAM-3G Involvement total raw	ATX0.8	53	7.30	1.65	7.40	1.36	0.14	0.20	0.499	0.413
	ATX1.4	63	6.98	1.20	7.14	1.37	-0.06	0.17	0.717	
FAM-3G Affective Expression tot raw	ATX0.8	54	6.74	1.81	6.81	1.36	-0.17	0.23	0.473	0.485
	ATX1.4	63	6.95	1.11	7.08	1.47	0.03	0.21	0.883	
FAM-3G Role Performance total raw	ATX0.8	55	7.33	1.93	7.31	1.56	0.04	0.20	0.849	0.159
	ATX1.4	64	7.30	1.47	7.00	1.38	-0.31	0.18	0.088	
FAM-3G Social Desirability tot raw	ATX0.8	53	11.75	1.92	11.11	1.50	-0.51	0.25	0.045	0.335
	ATX1.4	62	11.10	1.65	11.06	1.88	-0.21	0.23	0.354	
FAM-3G Task Accomp total raw	ATX0.8	54	7.93	1.80	7.65	1.42	-0.24	0.19	0.229	0.055

continued

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Table 11. Mean Change from Baseline to LOCF Endpoint in Maintenance Phase for Family Assessment Measure III: General and Self-Rated Total and Subscores (Concluded)

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
FAM-3G Task Accomplishment total raw	ATX1.4	62	7.73	1.32	8.03	1.31	0.23	0.17	0.197	
FAM-3G Values & Norms total raw	ATX0.8	54	6.94	1.72	7.13	1.36	0.09	0.20	0.636	0.240
	ATX1.4	65	7.06	1.34	6.92	1.47	-0.19	0.17	0.278	
FAM-3S Affective Expression total raw	ATX0.8	53	8.17	1.50	8.17	1.79	-0.19	0.29	0.511	0.687
	ATX1.4	61	8.74	1.35	8.31	1.77	-0.33	0.25	0.183	
FAM-3S Control total raw	ATX0.8	52	8.42	1.56	8.63	1.56	-0.02	0.22	0.929	0.768
	ATX1.4	61	8.87	1.53	8.89	1.34	0.06	0.19	0.756	
FAM-3S Communication total raw	ATX0.8	55	9.05	1.46	9.27	1.87	-0.22	0.26	0.408	0.247
	ATX1.4	60	9.62	1.98	8.95	1.58	-0.61	0.25	0.018	
FAM-3S Involvement total raw	ATX0.8	51	8.61	1.51	8.82	1.32	0.29	0.20	0.156	0.277
	ATX1.4	60	8.73	1.45	8.65	1.27	0.02	0.18	0.927	
FAM-3S Role Performance total raw	ATX0.8	51	9.00	1.97	9.10	1.51	0.11	0.20	0.573	0.075
	ATX1.4	56	8.64	1.72	8.54	1.31	-0.33	0.18	0.067	
FAM-3S Task Accomplishment total raw	ATX0.8	54	8.33	1.76	8.46	1.99	-0.23	0.25	0.356	0.044
	ATX1.4	62	8.56	1.52	8.92	1.35	0.40	0.22	0.079	
FAM-3S Values & Norms total raw	ATX0.8	50	7.88	1.55	7.78	2.23	0.18	0.35	0.602	0.386
	ATX1.4	61	7.89	2.04	7.67	2.01	-0.18	0.30	0.545	

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Abbreviations: ATX = atomoxetine; FAM-3G = Family Assessment Measure Version III – General Scale; FAM-3S = Family Assessment Measure Version III – Self-Rated Scale; LOCF = Last Observation Carried Forward; LSMean = Least Squares Mean; N = sample size; SD = standard deviation; SE = standard error; tot = total.

Dosages are in mg/kg per day.

* P-value is from LSMean change from baseline to endpoint using Student's t-test.

** P-value is from a LSMean Type III Sum of Squares using model: change = baseline treatment investigator.

Baseline: last of Visits 4-7. Endpoint: last of Visits 8-12.

Population: All randomized patients.

Academic Performance

Acute Phase

Table 12 presents mean change for Woodcock-Johnson III (WJ III) from baseline to endpoint in the acute phase of the study.

Mean change from baseline to endpoint for both the label dose titration and slow dose titration groups was statistically significant ($p < .01$) for oral language, oral expression, listening comprehension, broad reading, broad written language, basic reading skills, reading comprehension, basic writing skills, written expression, academic skills, academic fluency, and academic knowledge standard score measures of the WJ-III. The label dose titration group had statistically significant mean change from baseline to endpoint for the academic application and phonological/graph standard scores ($p < .03$). For the W scores (raw scores converted based on Rasch ability scale), mean change from baseline to endpoint for both the label dose titration and slow dose titration groups were statistically significant ($p \leq .002$) for oral language, oral expression, listening comprehension, broad reading, broad written language, basic reading skills, reading comprehension, basic writing skills, written expression, academic skills, academic fluency, and academic knowledge W scores of the WJ-III. Additionally, the label dose titration group had statistically significant change for the broad math and academic application items W scores ($p < .03$). There were no statistically significant differences for WJ-III standard total and subscores or W scores from baseline to endpoint between the 2 groups.

Maintenance Phase

Table 13 presents mean change for WJ-III from baseline to endpoint in the maintenance phase of the study. Mean change from post-acute baseline to endpoint was statistically significant ($p < .05$) for both the 0.8 mg/kg/day and 1.4 mg/kg/day groups on the standard scores for Math Reasoning and on the W score for Academic Skills and Academic Knowledge. For the 0.8 mg/kg/day group, statistically significant mean change was demonstrated for the standard scores for reading comprehension ($p = .01$) and academic applications ($p = .050$) and for the 1.4 mg/kg/day group on the standard scores for broad math ($p = .04$). For the W scores, mean change from baseline to endpoint was statistically significant for the 1.4 mg/kg/day group for broad and basic reading skills ($p \leq .01$), reading comprehension ($p = .02$), and academic fluency ($p = .025$). Statistically significant differences between the 0.8 mg/kg/day and 1.4 mg/kg/day group were evident only for reading comprehension standard score ($p = .05$).

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Table 12. Mean Change from Baseline to LOCF Endpoint in Acute Phase for Woodcock-Johnson III

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Woodcock/Johnson Total Score	ATX0.5/1.2	98	295.95	37.52	303.21	39.92	7.48	1.58	<0.001	0.834
	ATX0.5/1.0/1.2	112	291.34	41.47	299.36	44.88	7.93	1.51	<0.001	
Oral Language STD score	ATX0.5/1.2	101	99.22	12.06	103.72	12.48	4.55	0.68	<0.001	0.713
	ATX0.5/1.0/1.2	112	99.18	12.12	103.29	14.88	4.21	0.66	<0.001	
Oral Expression STD score	ATX0.5/1.2	101	99.29	11.10	102.24	12.25	2.86	0.62	<0.001	0.332
	ATX0.5/1.0/1.2	112	99.88	11.03	101.94	13.11	2.04	0.60	0.001	
Listening Comp STD score	ATX0.5/1.2	101	99.42	12.38	104.38	12.22	5.32	0.93	<0.001	0.847
	ATX0.5/1.0/1.2	113	98.24	12.85	103.71	14.85	5.56	0.90	<0.001	
Broad Reading STD score	ATX0.5/1.2	101	99.50	14.83	102.55	15.79	2.93	0.76	<0.001	0.348
	ATX0.5/1.0/1.2	113	97.00	15.14	101.47	16.67	3.90	0.74	<0.001	
Broad Math STD score	ATX0.5/1.2	100	95.57	12.66	96.25	14.06	1.05	0.77	0.177	0.569
	ATX0.5/1.0/1.2	112	94.59	12.84	94.60	16.14	0.45	0.74	0.543	
Broad Written Language STD score	ATX0.5/1.2	99	100.34	16.37	103.99	15.39	3.67	0.75	<0.001	0.725
	ATX0.5/1.0/1.2	112	99.79	17.03	103.28	16.93	3.31	0.72	<0.001	
Basic Reading Skills STD score	ATX0.5/1.2	101	100.56	13.52	102.99	14.79	2.53	0.55	<0.001	0.519
	ATX0.5/1.0/1.2	113	99.42	14.50	101.55	14.84	2.05	0.53	<0.001	
Reading COMP STD score	ATX0.5/1.2	101	102.14	12.70	104.63	13.57	2.43	0.76	0.002	0.619

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Table 12. Mean Change from Baseline to LOCF Endpoint in Acute Phase for Woodcock-Johnson III

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Reading COMP STD score	ATX0.5/1.0/1.2	113	102.57	15.69	104.58	16.43	1.92	0.73	0.009	
Math Calc Skills STD score	ATX0.5/1.2	100	94.90	14.79	95.59	14.22	1.26	0.79	0.113	0.849
	ATX0.5/1.0/1.2	113	92.93	14.77	94.37	16.30	1.46	0.76	0.055	
Math Reasoning STD score	ATX0.5/1.2	101	97.17	12.85	98.07	14.85	1.35	0.96	0.164	0.785
	ATX0.5/1.0/1.2	111	95.82	15.28	96.98	16.44	1.70	0.94	0.071	
Basic Writing Skills STD score	ATX0.5/1.2	101	98.39	14.55	101.11	13.48	3.05	0.69	<0.001	0.301
	ATX0.5/1.0/1.2	113	96.96	14.50	99.19	14.23	2.09	0.67	0.002	
Written Express STD score	ATX0.5/1.2	98	99.31	17.00	103.20	16.73	3.91	0.95	<0.001	0.870
	ATX0.5/1.0/1.2	112	98.85	17.45	103.24	18.11	4.12	0.91	<0.001	
Academic Skills STD score	ATX0.5/1.2	101	100.57	17.04	102.44	16.74	2.05	0.60	0.001	0.783
	ATX0.5/1.0/1.2	113	98.39	17.89	100.67	18.58	2.27	0.58	<0.001	
Academic Fluency STD score	ATX0.5/1.2	99	96.28	14.86	99.95	15.97	3.49	0.92	<0.001	0.692
	ATX0.5/1.0/1.2	113	94.24	14.55	99.09	15.59	3.99	0.88	<0.001	
Academic Apps STD score	ATX0.5/1.2	99	97.80	12.57	99.61	13.55	2.31	0.85	0.007	0.482
	ATX0.5/1.0/1.2	112	97.69	15.44	98.58	18.05	1.51	0.82	0.067	
Academic Knowledge STD score	ATX0.5/1.2	101	98.00	15.24	100.72	15.53	2.51	0.86	0.004	0.586
	ATX0.5/1.0/1.2	111	97.15	16.40	100.72	17.94	3.14	0.84	<0.001	

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Table 12. Mean Change from Baseline to LOCF Endpoint in Acute Phase for Woodcock-Johnson III

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Phon/Graph Know STD score	ATX0.5/1.2	101	96.73	13.90	98.96	14.36	2.08	0.93	0.027	0.505
	ATX0.5/1.0/1.2	111	96.15	13.57	97.87	15.78	1.24	0.91	0.174	
Oral Language W score†	ATX0.5/1.2	101	511.40	8.72	515.00	9.08	3.57	0.45	<0.001	0.415
	ATX0.5/1.0/1.2	112	511.66	8.69	514.69	10.22	3.08	0.44	<0.001	
Oral Expression W score	ATX0.5/1.2	101	510.64	8.39	513.23	9.30	2.51	0.46	<0.001	0.176
	ATX0.5/1.0/1.2	112	511.47	8.05	513.13	9.41	1.66	0.45	<0.001	
Listening Comp W score	ATX0.5/1.2	101	512.11	10.80	516.74	10.49	4.83	0.74	<0.001	0.944
	ATX0.5/1.0/1.2	113	511.55	11.58	516.31	12.40	4.90	0.72	<0.001	
Broad Reading W score	ATX0.5/1.2	101	530.36	25.24	536.40	26.96	5.85	1.22	<0.001	0.325
	ATX0.5/1.0/1.2	113	527.54	25.77	535.59	28.03	7.48	1.18	<0.001	
Broad Math W score	ATX0.5/1.2	100	519.65	13.57	521.15	14.93	1.72	0.71	0.017	0.288
	ATX0.5/1.0/1.2	112	519.42	13.64	519.78	16.28	0.70	0.68	0.311	
Broad Written Language W score	ATX0.5/1.2	99	517.05	14.58	520.52	13.29	3.39	0.64	<0.001	0.926
	ATX0.5/1.0/1.2	112	516.97	15.01	520.42	14.75	3.31	0.62	<0.001	
Basic Reading Skills W score	ATX0.5/1.2	101	523.18	20.59	526.60	21.17	3.51	0.69	<0.001	0.752
	ATX0.5/1.0/1.2	113	522.11	21.99	525.34	22.02	3.22	0.67	<0.001	
Reading COMP W score	ATX0.5/1.2	101	518.98	12.75	521.40	12.90	2.19	0.60	<0.001	0.978

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Table 12. Mean Change from Baseline to LOCF Endpoint in Acute Phase for Woodcock-Johnson III

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Reading COMP W score	ATX0.5/1.0/1.2	113	519.29	15.23	521.68	15.37	2.17	0.58	<0.001	
Math Calc Skills W score	ATX0.5/1.2	100	516.59	12.29	518.33	11.74	1.80	1.01	0.077	0.982
	ATX0.5/1.0/1.2	113	516.99	13.23	518.82	15.92	1.76	0.97	0.070	
Math Reasoning W score	ATX0.5/1.2	101	524.08	18.79	526.05	21.35	2.12	1.11	0.057	0.724
	ATX0.5/1.0/1.2	111	524.04	18.44	525.19	22.50	1.59	1.08	0.142	
Basic Writing Skills W score	ATX0.5/1.2	101	519.93	19.58	524.23	17.23	4.29	0.87	<0.001	0.225
	ATX0.5/1.0/1.2	113	519.60	18.22	522.70	18.44	2.86	0.84	0.001	
Written Express W score	ATX0.5/1.2	98	515.15	12.81	518.97	13.01	3.77	0.80	<0.001	0.631
	ATX0.5/1.0/1.2	112	515.16	13.03	518.53	13.10	3.25	0.76	<0.001	
Academic Skills W score	ATX0.5/1.2	101	526.42	19.88	529.32	18.61	2.99	0.56	<0.001	0.729
	ATX0.5/1.0/1.2	113	525.04	20.05	527.79	20.46	2.72	0.55	<0.001	
Academic Fluency W score	ATX0.5/1.2	99	525.19	22.63	531.64	24.88	5.93	1.34	<0.001	0.958
	ATX0.5/1.0/1.2	113	523.42	21.29	530.65	22.87	6.02	1.28	<0.001	
Academic Apps W score	ATX0.5/1.2	99	515.76	11.98	517.97	14.92	2.23	1.01	0.028	0.290
	ATX0.5/1.0/1.2	112	516.54	15.29	517.04	16.44	0.79	0.96	0.412	
Academic Knowledge W score	ATX0.5/1.2	101	519.67	18.40	524.04	19.12	3.89	1.08	<0.001	0.695
	ATX0.5/1.0/1.2	111	519.90	19.76	523.71	20.39	3.32	1.06	0.002	

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Table 12. Mean Change from Baseline to LOCF Endpoint in Acute Phase for Woodcock-Johnson III (concluded)

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Phon/Graph Know W score	ATX0.5/1.2	101	508.81	13.95	511.03	13.68	1.80	0.92	0.052	0.903
	ATX0.5/1.0/1.2	111	508.82	13.61	511.07	16.58	1.64	0.90	0.068	

Abbreviations: Apps = Applications; ATX = atomoxetine; ATX0.5/1.2 = label dose titration; ATX 0.5/1.0/1.2 = slow dose titration; Calc = Calculation; COMP = Comprehension; LOCF = Last Observation Carried Forward; LSMean = Least Squares Mean; N = sample size; Phon/Graph Know = Phoneme/Grapheme Knowledge; SD = standard deviation; SE = standard error; STD = Standard.

Dosages are in mg/kg per day.

* P-value is from LSMean change from baseline to endpoint using Student's t-test.

** P-value is from a Lumen Type III Sum of Squares using model: change = baseline treatment investigator.

† W scores, which are the converted raw scores, are a special transformation of the Rasch ability scale.

Baseline: last of Visits 1-3. Endpoint: last of Visits 4-7.

Population: All randomized patients.

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Table 13. Mean Change from Baseline to LOCF Endpoint in Maintenance Phase for Woodcock-Johnson III

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Woodcock/Johnson Total Score	ATX0.8	41	308.02	37.57	306.59	35.31	-4.39	3.63	0.231	0.865
	ATX1.4	46	317.93	37.68	314.13	40.28	-3.66	3.18	0.254	
Oral Language STD score	ATX0.8	41	103.63	11.21	103.71	9.42	-2.03	1.29	0.122	0.643
	ATX1.4	46	110.54	12.66	109.20	11.96	-1.31	1.12	0.247	
Oral Expression STD score	ATX0.8	41	102.63	10.30	102.20	9.56	-1.82	1.36	0.186	0.576
	ATX1.4	46	108.54	10.70	107.43	10.52	-0.92	1.16	0.433	
Listening Comp STD score	ATX0.8	41	103.71	11.63	104.27	9.96	-1.73	1.55	0.269	0.940
	ATX1.4	46	110.07	12.92	108.59	13.46	-1.59	1.36	0.247	
Broad Reading STD score	ATX0.8	41	105.46	14.81	104.27	13.09	-2.17	1.42	0.132	0.072
	ATX1.4	46	107.24	15.59	108.37	15.82	0.91	1.25	0.471	
Broad Math STD score	ATX0.8	41	96.98	12.53	96.02	11.73	-2.33	1.42	0.105	0.862
	ATX1.4	46	101.93	12.57	99.22	13.19	-2.63	1.26	0.040	
Broad Written Language STD score	ATX0.8	41	105.59	15.62	106.29	15.90	-0.24	1.61	0.880	0.406
	ATX1.4	46	108.76	15.58	106.54	16.38	-1.82	1.40	0.197	
Basic Reading Skills STD score	ATX0.8	41	101.63	11.16	101.80	11.97	-0.95	1.30	0.465	0.756
	ATX1.4	46	106.67	12.91	106.52	13.31	-0.47	1.12	0.676	
Reading COMP STD score	ATX0.8	41	107.71	13.05	106.07	10.41	-3.80	1.41	0.009	0.046

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Table 13. Mean Change from Baseline to LOCF Endpoint in Maintenance Phase for Woodcock-Johnson III

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Reading COMP STD score	ATX1.4	46	110.37	13.57	110.57	13.60	-0.41	1.24	0.740	
Math Calc Skills STD score	ATX0.8	41	96.00	15.37	95.44	13.85	-1.16	1.59	0.470	0.660
	ATX1.4	46	100.76	13.96	98.30	14.16	-1.99	1.40	0.160	
Math Reasoning STD score	ATX0.8	41	98.22	11.51	98.41	10.40	3.83	1.38	0.007	0.525
	ATX1.4	46	104.67	12.49	104.15	18.25	2.77	1.20	0.024	
Basic Writing Skills STD score	ATX0.8	41	100.44	12.59	100.05	13.20	-2.10	1.33	0.118	0.976
	ATX1.4	46	104.74	13.07	102.98	14.12	-2.05	1.15	0.079	
Written Express STD score	ATX0.8	41	107.12	17.94	108.80	17.73	0.96	2.10	0.650	0.344
	ATX1.4	46	108.15	18.09	106.50	18.45	-1.40	1.85	0.451	
Academic Skills STD score	ATX0.8	41	101.22	14.89	101.10	15.53	-1.40	1.32	0.293	0.735
	ATX1.4	46	108.46	13.97	106.59	14.92	-1.94	1.15	0.097	
Academic Fluency STD score	ATX0.8	41	103.24	15.16	102.56	13.58	-0.98	1.53	0.525	0.786
	ATX1.4	46	103.65	16.14	103.30	16.32	-0.49	1.35	0.720	
Academic Apps STD score	ATX0.8	41	102.41	12.39	101.34	10.13	-3.34	1.67	0.050	0.205
	ATX1.4	46	105.52	12.78	104.91	14.71	-0.81	1.47	0.585	
Academic Knowledge STD score	ATX0.8	41	101.15	12.74	103.39	14.30	0.40	1.50	0.792	0.612
	ATX1.4	46	107.91	14.73	107.87	13.33	-0.49	1.26	0.698	

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Table 13. Mean Change from Baseline to LOCF Endpoint in Maintenance Phase for Woodcock-Johnson III

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Phon/Graph Know STD score	ATX0.8	41	98.32	12.71	99.20	12.26	-0.33	1.67	0.844	0.906
	ATX1.4	46	102.04	15.04	101.96	14.37	-0.57	1.45	0.699	
Oral Language W score†	ATX0.8	41	515.37	8.00	516.90	6.89	0.66	0.90	0.470	0.910
	ATX1.4	46	519.17	8.21	520.09	8.83	0.78	0.78	0.325	
Oral Expression W score	ATX0.8	41	514.05	7.75	516.66	12.31	2.27	1.54	0.145	0.405
	ATX1.4	46	517.28	7.44	518.30	7.91	0.76	1.32	0.569	
Listening Comp W score	ATX0.8	41	516.66	10.08	518.76	8.48	-0.05	1.77	0.976	0.434
	ATX1.4	46	521.04	10.07	523.15	14.46	1.61	1.56	0.306	
Broad Reading W score	ATX0.8	41	542.54	24.73	545.07	21.54	1.61	1.90	0.401	0.133
	ATX1.4	46	543.13	24.41	548.80	24.02	5.02	1.68	0.004	
Broad Math W score	ATX0.8	41	522.56	12.70	525.73	14.01	2.29	1.38	0.103	0.182
	ATX1.4	46	525.63	11.29	526.24	13.05	0.07	1.22	0.954	
Broad Written Language W score	ATX0.8	41	522.34	13.14	525.07	12.77	2.16	1.14	0.063	0.354
	ATX1.4	46	523.65	12.33	524.35	12.79	0.91	1.00	0.368	
Basic Reading Skills W score	ATX0.8	41	526.68	15.66	529.73	15.77	2.15	1.19	0.076	0.664
	ATX1.4	46	531.04	16.42	534.33	16.11	2.77	1.04	0.010	
Reading COMP W score	ATX0.8	41	525.05	11.39	527.22	13.68	2.44	1.71	0.157	0.511

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Table 13. Mean Change from Baseline to LOCF Endpoint in Maintenance Phase for Woodcock-Johnson III

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Reading COMP W score	ATX1.4	46	525.52	10.95	529.80	13.56	3.77	1.51	0.015	
Math Calc Skills W score	ATX0.8	41	520.54	16.15	522.02	15.75	1.67	1.12	0.139	0.457
	ATX1.4	46	521.50	10.43	522.28	11.15	0.68	0.99	0.490	
Math Reasoning W score	ATX0.8	41	527.32	16.21	530.46	14.06	1.61	1.73	0.356	0.429
	ATX1.4	46	533.83	15.68	533.93	18.73	-0.02	1.51	0.987	
Basic Writing Skills W score	ATX0.8	41	524.37	15.77	526.44	16.00	0.25	1.38	0.854	0.886
	ATX1.4	46	527.76	15.48	528.72	16.69	0.49	1.21	0.687	
Written Express W score	ATX0.8	41	521.59	13.01	524.17	12.44	2.47	1.31	0.065	0.325
	ATX1.4	46	521.07	12.06	521.91	12.40	0.93	1.16	0.428	
Academic Skills W score	ATX0.8	41	529.27	15.80	532.22	15.82	2.17	1.00	0.033	0.735
	ATX1.4	46	534.22	13.58	536.04	14.56	1.76	0.87	0.047	
Academic Fluency W score	ATX0.8	41	537.56	23.89	540.29	21.26	3.04	1.97	0.128	0.672
	ATX1.4	46	535.04	23.01	539.59	23.81	4.04	1.76	0.025	
Academic Apps W score	ATX0.8	41	520.73	10.84	521.83	8.74	-0.36	1.29	0.780	0.262
	ATX1.4	46	522.09	10.25	523.78	12.33	1.37	1.14	0.235	
Academic Knowledge W score	ATX0.8	41	525.59	14.34	529.63	16.45	3.41	1.49	0.026	0.800
	ATX1.4	46	529.85	16.71	533.46	15.30	2.97	1.27	0.023	

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Table 13. Mean Change from Baseline to LOCF Endpoint in Maintenance Phase for Woodcock-Johnson III (concluded)

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Phon/Graph Know W score	ATX0.8	41	512.76	15.31	513.66	11.11	-0.14	1.54	0.929	0.437
	ATX1.4	46	513.39	13.78	515.35	12.87	1.29	1.36	0.347	

Abbreviations: Apps = Applications; ATX = atomoxetine; ATX0.5/1.2 = label dose titration; ATX 0.5/1.0/1.2 = slow dose titration; Calc = Calculation; COMP = Comprehension; LOCF = Last Observation Carried Forward; LSMean = Least Squares Mean; N = sample size; Phon/Graph Know = Phoneme/Grapheme Knowledge; SD = standard deviation; SE = standard error; STD = Standard.

Dosages are in mg/kg per day.

* P-value is from LSMean change from baseline to endpoint using Student's t-test.

** P-value is from a LSMean Type III Sum of Squares using model: change = baseline treatment investigator.

† W scores, which are the converted raw scores, are a special transformation of the Rasch ability scale.

Baseline: last of Visits 4-7. Endpoint: last of Visits 8-12.

Population: All randomized patients.

Academic Performance and Verbal and Nonverbal Intelligence

Table 14 presents mean change for Grade Point Average (GPA) and Kaufman Brief Intelligence Test (K-BIT) from baseline to endpoint.

Mean change from pre-acute phase baseline to endpoint was statistically significant for the 0.8 mg/kg/day group in the GPA math measure ($p=.03$). There was no statistically significant difference between the 2 groups in GPA scores from baseline to endpoint. No statistically significant changes from baseline to endpoint were noted for the K-BIT in either dosing group.

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Table 14. Mean Change from Baseline to LOCF Endpoint in Maintenance Phase for GPA and K-BIT

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
GPA ENGLISH	ATX0.8	43	1.88	1.16	2.26	1.29	0.15	0.25	0.561	0.562
	ATX1.4	52	2.13	1.24	2.48	1.24	0.34	0.22	0.136	
GPA MATH	ATX0.8	43	1.87	1.28	2.37	1.23	0.70	0.31	0.032	0.289
	ATX1.4	51	1.90	1.27	2.49	1.16	0.25	0.28	0.394	
GPA SCIENCE	ATX0.8	39	1.86	1.08	2.23	1.27	-0.08	0.32	0.810	0.870
	ATX1.4	48	2.37	1.40	2.32	1.22	0.00	0.31	0.989	
GPA SOCIAL STUDIES	ATX0.8	41	1.90	1.29	2.37	1.28	0.58	0.32	0.086	0.421
	ATX1.4	48	2.19	1.18	2.51	1.29	0.23	0.28	0.427	
K-BIT - IQ Composite	ATX0.8	44	102.00	12.31	105.32	12.99	3.77	2.27	0.101	0.809
	ATX1.4	45	106.18	11.30	109.93	18.87	3.09	2.12	0.150	

Abbreviations: ATX = atomoxetine; GPA = Grade Point Average; K-BIT = Kaufman Brief Intelligence Test; LOCF = Last Observation Carried Forward; LSMean = Least Squares Mean; N = sample size; SD = standard deviation; SE = standard error.

Dosages are in mg/kg per day.

* P-value is from LSMean change from baseline to endpoint using Student's t-test.

** P-value is from a LSMean Type III Sum of Squares using model: change = baseline treatment investigator IQ-Score.

P-value for K-BIT-IQ Composite is from a LSMean Type III Sum of Squares using model: change = baseline treatment investigator.

Baseline: last of Visits 1-3. Endpoint: last of Visits 8-12.

Population: All randomized patients.

Health Outcome

Acute Phase

Table 15 presents mean Change from Baseline to Endpoint in the acute phase for the Child Health and Illness Profile-Adolescent Edition (CHIP-AE) scores. No statistically significant differences were demonstrated in any of the domains (satisfaction, discomfort, resilience, risks, achievement, and disorders) of the CHIP-AE between label dose titration and slow dose titration from baseline to endpoint.

Statistically significant changes ($p < .05$) were demonstrated within both treatment groups in risks domain and achievement domain. Statistically significant changes ($p < .05$) were demonstrated in discomfort domain in label titration and in disorder domain in slow dose titration from baseline to endpoint.

No statistically significant differences were demonstrated in any of the subdomains of the CHIP-AE between label dose titration and slow dose titration from baseline to endpoint.

Statistically significant changes ($p < .05$) were demonstrated within both treatment groups in Emotional Discomfort subdomain imputed, Family involvement subdomain imputed, Threats to Achievement subdomain imputed, Long-Term medical disorders subdomain imputed, and Academic performance subdomain imputed.

Statistically significant changes ($p < .05$) were demonstrated in Limitations of Activity subdomain imputed and Work Performance subdomain imputed in label titration Acute Major Disorder subdomain imputed and Recurrent disorder subdomain imputed in slow dose titration from baseline to endpoint.

Maintenance Phase

Table 16 presents mean Change from Baseline to LOCF Endpoint in maintenance phase for CHIP-AE scores. No statistically significant changes were demonstrated in any of the domains of the CHIP-AE between the 0.8 mg/kg/day and 1.4 mg/kg/day groups.

Statistically significant changes ($p < .05$) were demonstrated within groups in risks domain.

No statistically significant changes were demonstrated in any of the subdomains of the CHIP-AE between 0.8 mg/kg/day and 1.4 mg/kg/day group.

A statistically significant change was demonstrated in Threats to Achievement subdomain ($p < .01$) in the 0.8 mg/kg/day group from baseline to endpoint.

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Table 15. Mean Change from Baseline to LOCF Endpoint in Acute Phase for Child Health and Illness Profile-Adolescent Edition Total and Subscores

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Satisfaction with health sub imputed	ATX0.5/1.2	107	49.76	8.84	49.02	9.35	-0.46	0.65	0.481	0.636
	ATX0.5/1.0/1.2	116	48.76	8.97	47.85	9.24	-0.87	0.63	0.166	
Self-esteem subdomain imputed	ATX0.5/1.2	107	45.16	10.04	46.14	8.85	0.99	0.71	0.165	0.131
	ATX0.5/1.0/1.2	115	45.41	10.55	44.95	10.55	-0.47	0.69	0.496	
Physical Discomfort subdomain imputed	ATX0.5/1.2	107	49.15	8.44	48.50	10.04	-0.65	0.82	0.433	0.656
	ATX0.5/1.0/1.2	118	49.62	9.24	48.44	9.28	-1.14	0.79	0.152	
Emotional Discomfort subdomain imputed	ATX0.5/1.2	107	47.15	9.44	50.41	9.28	3.39	0.75	<0.001	0.180
	ATX0.5/1.0/1.2	118	47.83	9.74	49.55	9.05	2.03	0.72	0.005	
Limitations of Activity sub imputed	ATX0.5/1.2	106	54.67	4.22	55.49	4.37	1.29	0.50	0.010	0.171
	ATX0.5/1.0/1.2	117	54.32	6.95	54.59	5.60	0.37	0.48	0.448	
Physical Activity subdomain imputed	ATX0.5/1.2	106	51.25	9.83	51.15	10.34	-0.13	0.85	0.878	0.997
	ATX0.5/1.0/1.2	117	51.07	9.84	50.99	10.87	-0.14	0.81	0.868	

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Table 15. Mean Change from Baseline to LOCF Endpoint in Acute Phase for Child Health and Illness Profile-Adolescent Edition Total and Subscores

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Social Problem Solving sub imputed	ATX0.5/1.2	106	49.78	8.82	50.62	7.29	0.70	0.71	0.326	0.943
	ATX0.5/1.0/1.2	117	50.81	8.50	51.10	8.29	0.63	0.69	0.358	
Home Safety and Health sub imputed	ATX0.5/1.2	107	59.32	8.87	59.50	9.01	0.65	0.67	0.337	0.532
	ATX0.5/1.0/1.2	117	57.59	9.91	59.14	8.73	1.22	0.65	0.063	
Family Involvement subdomain imputed	ATX0.5/1.2	107	48.24	9.45	49.72	8.13	2.08	0.72	0.005	0.992
	ATX0.5/1.0/1.2	117	46.93	10.48	49.22	9.76	2.09	0.70	0.003	
Individual Risks subdomain imputed	ATX0.5/1.2	107	60.52	9.99	60.78	10.42	0.27	0.54	0.623	0.768
	ATX0.5/1.0/1.2	118	61.11	8.33	61.01	8.69	0.05	0.52	0.924	
Threats to Achievement sub imputed	ATX0.5/1.2	107	46.89	9.54	50.70	8.73	3.95	0.64	<0.001	0.133
	ATX0.5/1.0/1.2	117	46.36	9.46	51.76	7.61	5.26	0.62	<0.001	
Peer Influences subdomain imputed	ATX0.5/1.2	106	53.14	12.74	54.53	10.71	1.25	0.85	0.146	0.113
	ATX0.5/1.0/1.2	117	53.80	10.44	53.08	11.60	-0.59	0.82	0.476	

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Table 15. Mean Change from Baseline to LOCF Endpoint in Acute Phase for Child Health and Illness Profile-Adolescent Edition Total and Subscores

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Acute Minor Disorder subdomain imputed	ATX0.5/1.2	107	47.09	10.83	48.36	11.38	1.16	0.98	0.238	0.682
	ATX0.5/1.0/1.2	118	48.31	10.42	48.43	10.81	0.61	0.94	0.515	
Acute Major Disorder subdomain imputed	ATX0.5/1.2	107	35.62	9.46	34.54	8.34	-0.51	0.75	0.501	0.250
	ATX0.5/1.0/1.2	118	33.88	12.72	32.66	9.24	-1.68	0.73	0.021	
Recurrent disorders subdomain imputed	ATX0.5/1.2	105	50.15	9.25	51.27	9.09	1.34	0.79	0.091	0.496
	ATX0.5/1.0/1.2	118	49.46	9.77	51.65	8.80	2.07	0.76	0.007	
Long-term medical disorders sub imputed	ATX0.5/1.2	105	51.68	5.47	52.16	4.22	0.83	0.38	0.031	0.443
	ATX0.5/1.0/1.2	118	50.84	9.56	52.38	4.29	1.23	0.37	0.001	
Long-term surgical disorders sub imputed	ATX0.5/1.2	104	45.20	14.28	47.30	13.47	1.86	1.13	0.102	0.735
	ATX0.5/1.0/1.2	116	46.49	14.96	47.36	13.26	1.34	1.08	0.218	
Psychosocial disorders sub imputed	ATX0.5/1.2	105	34.55	18.45	36.15	18.46	0.97	1.50	0.518	0.427
	ATX0.5/1.0/1.2	116	35.72	19.25	38.51	15.64	2.58	1.44	0.074	
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Table 15. Mean Change from Baseline to LOCF Endpoint in Acute Phase for Child Health and Illness Profile-Adolescent Edition Total and Subscores

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Academic Performance sub imputed	ATX0.5/1.2	103	46.80	7.80	49.22	7.61	2.35	0.56	<0.001	0.578
	ATX0.5/1.0/1.2	114	47.84	8.49	49.63	8.30	1.93	0.54	<0.001	
Work Performance subdomain imputed	ATX0.5/1.2	25	47.78	11.98	52.06	12.39	4.49	1.85	0.021	0.659
	ATX0.5/1.0/1.2	26	48.19	11.22	53.88	7.06	3.29	2.11	0.129	
Satisfaction Domain	ATX0.5/1.2	107	47.20	9.03	47.32	9.16	0.30	0.66	0.652	0.225
	ATX0.5/1.0/1.2	115	46.72	9.83	45.94	9.88	-0.79	0.64	0.220	
Discomfort Domain	ATX0.5/1.2	106	51.25	6.82	52.79	7.68	1.78	0.69	0.011	0.275
	ATX0.5/1.0/1.2	117	51.46	8.23	51.99	8.03	0.76	0.67	0.256	
Resilience Domain	ATX0.5/1.2	105	52.35	9.53	53.34	9.38	1.40	0.84	0.097	0.979
	ATX0.5/1.0/1.2	114	51.47	10.97	53.01	10.31	1.43	0.81	0.080	
Risks Domain	ATX0.5/1.2	106	53.30	10.83	55.80	9.98	2.50	0.55	<0.001	0.983
	ATX0.5/1.0/1.2	116	53.48	9.07	55.89	8.93	2.49	0.53	<0.001	
Disorder Domain	ATX0.5/1.2	102	39.57	11.48	41.48	11.76	1.68	0.98	0.089	0.719
	ATX0.5/1.0/1.2	115	40.17	13.72	42.27	10.33	2.16	0.93	0.022	
Achievement Domain	ATX0.5/1.2	24	60.15	7.36	63.52	7.04	3.61	1.15	0.004	0.611
	ATX0.5/1.0/1.2	25	62.32	7.11	65.83	4.83	2.73	1.31	0.047	

Abbreviations: ATX = atomoxetine mg/kg/day; ATX0.5/1.2 = label dose titration; ATX 0.5/1.0/1.2 = slow dose titration; LOCF = Last Observation Carried Forward; LSMean = Least Squares Mean; N = sample size; SD = standard deviation; SE = standard error; sub = subdomain.

Dosages are in mg/kg per day.

* P-value is from LSMean change from baseline to endpoint using Student's t-test.

** P-value is from a LSMean Type III Sum of Squares using model: change = baseline treatment investigator.

Baseline: last of Visits 1-3. Endpoint: last of Visits 4-7.

Population: All randomized patients.

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Table 16. Mean Change from Baseline to LOCF Endpoint in Maintenance phase for Child Health and Illness Profile-Adolescent Edition Total and Subscores

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Satisfaction with health sub imputed	ATX0.8	53	48.43	10.18	47.23	10.23	-0.55	1.10	0.620	0.248
	ATX1.4	63	47.69	9.70	48.40	8.08	0.99	0.95	0.300	
Self-esteem subdomain imputed	ATX0.8	53	44.53	10.27	44.11	8.81	0.30	1.30	0.821	0.821
	ATX1.4	63	45.94	10.16	45.91	10.67	0.65	1.13	0.565	
Physical Discomfort subdomain imputed	ATX0.8	53	48.88	8.18	47.47	9.80	-0.67	1.22	0.585	0.070
	ATX1.4	64	47.89	10.03	49.44	9.46	2.02	1.05	0.057	
Emotional Discomfort subdomain imputed	ATX0.8	53	49.16	9.50	49.43	7.64	0.39	1.01	0.701	0.792
	ATX1.4	64	50.44	8.70	50.19	8.87	0.71	0.87	0.417	
Limitations of Activity sub imputed	ATX0.8	53	55.64	4.10	55.33	3.49	0.01	0.65	0.992	0.669
	ATX1.4	63	54.48	5.94	54.80	5.99	0.34	0.56	0.541	
Physical Activity subdomain imputed	ATX0.8	53	49.33	9.71	52.57	10.65	1.37	1.49	0.359	0.137
	ATX1.4	63	54.04	10.02	52.00	11.24	-1.35	1.27	0.292	

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Table 16. Mean Change from Baseline to LOCF Endpoint in Maintenance phase for Child Health and Illness Profile-Adolescent Edition Total and Subscores

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Social Problem Solving sub imputed	ATX0.8	53	50.97	6.44	51.12	7.86	-0.45	1.22	0.711	0.650
	ATX1.4	64	51.47	7.19	51.57	8.67	0.21	1.05	0.839	
Home Safety and Health sub imputed	ATX0.8	53	60.57	7.77	61.13	7.75	0.39	1.03	0.706	0.123
	ATX1.4	64	62.07	7.60	60.10	7.36	-1.55	0.89	0.084	
Family Involvement subdomain imputed	ATX0.8	53	48.38	8.95	48.41	9.08	0.25	1.29	0.848	0.643
	ATX1.4	64	50.51	8.44	49.16	10.94	-0.49	1.12	0.665	
Individual Risks subdomain imputed	ATX0.8	53	60.66	8.02	59.47	8.24	-1.09	0.74	0.143	0.918
	ATX1.4	64	62.73	8.35	61.67	9.94	-1.00	0.64	0.123	
Threats to Achievement sub imputed	ATX0.8	53	52.61	6.40	49.37	9.08	-3.30	1.13	0.004	0.152
	ATX1.4	64	53.31	6.27	51.98	8.33	-1.34	0.97	0.174	
Peer Influences subdomain imputed	ATX0.8	53	52.51	12.35	50.48	10.32	-0.91	1.54	0.556	0.907
	ATX1.4	63	55.53	9.14	52.45	12.81	-1.13	1.33	0.396	

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Table 16. Mean Change from Baseline to LOCF Endpoint in Maintenance phase for Child Health and Illness Profile-Adolescent Edition Total and Subscores

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Acute Minor Disorder subdomain imputed	ATX0.8	53	48.95	8.24	48.07	10.69	1.49	1.49	0.320	0.978
	ATX1.4	64	48.50	11.35	49.21	11.63	1.44	1.28	0.265	
Acute Major Disorder subdomain imputed	ATX0.8	53	33.89	7.88	34.34	8.19	-0.66	1.30	0.615	0.458
	ATX1.4	64	34.31	9.90	34.59	11.34	0.51	1.12	0.650	
Recurrent disorders subdomain imputed	ATX0.8	53	51.02	9.31	50.07	9.93	-1.58	1.25	0.208	0.143
	ATX1.4	64	50.87	9.41	51.50	9.84	0.64	1.07	0.553	
Long-term medical disorders sub imputed	ATX0.8	53	52.94	0.00	51.07	7.00	-2.00	1.63	0.225	0.647
	ATX1.4	64	51.13	7.29	49.48	13.17	-1.09	1.39	0.438	
Long-term surgical disorders sub imputed	ATX0.8	53	46.31	13.48	45.57	13.38	-1.42	1.91	0.461	0.125
	ATX1.4	64	45.57	13.75	48.02	12.66	2.15	1.64	0.193	
Psychosocial disorders sub imputed	ATX0.8	53	35.68	14.87	34.25	17.40	-3.01	2.62	0.254	0.177
	ATX1.4	64	36.92	17.18	37.60	18.43	1.29	2.25	0.568	

Continued

Atomoxetine

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Table 16. Mean Change from Baseline to LOCF Endpoint in Maintenance phase for Child Health and Illness Profile-Adolescent Edition Total and Subscores

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Academic Performance sub imputed	ATX0.8	52	49.84	7.51	49.73	6.92	0.15	0.94	0.877	0.307
	ATX1.4	62	50.93	7.54	51.64	7.56	1.31	0.82	0.110	
Work Performance subdomain imputed	ATX0.8	10	53.37	6.93	43.51	11.49	-5.18	4.36	0.273	0.712
	ATX1.4	13	53.88	6.38	51.98	9.58	-2.81	3.52	0.450	
Satisfaction Domain	ATX0.8	53	46.11	10.36	45.19	9.50	-0.20	1.15	0.861	0.441
	ATX1.4	63	46.46	9.98	46.84	9.45	0.87	1.00	0.385	
Discomfort Domain	ATX0.8	53	52.51	7.12	52.04	6.58	-0.14	0.83	0.866	0.266
	ATX1.4	63	51.99	8.22	52.53	8.42	0.98	0.72	0.176	
Resilience Domain	ATX0.8	53	52.27	8.75	54.13	9.53	0.98	1.31	0.453	0.103
	ATX1.4	63	56.28	8.19	54.02	11.27	-1.68	1.14	0.144	
Risks Domain	ATX0.8	53	55.99	7.99	53.20	8.76	-2.07	0.95	0.032	0.782
	ATX1.4	63	58.19	7.81	55.95	10.00	-1.75	0.83	0.038	
Disorder Domain	ATX0.8	53	41.20	9.23	39.66	11.34	-2.06	1.64	0.212	0.066
	ATX1.4	64	40.99	12.36	42.17	14.45	1.61	1.41	0.257	
Achievement Domain	ATX0.8	9	66.12	3.66	63.78	6.51	-0.07	2.12	0.974	0.999
	ATX1.4	12	65.91	4.86	65.03	5.81	-0.07	1.67	0.969	

Abbreviations: ATX = atomoxetine mg/kg/day; LOCF = Last Observation Carried Forward; LSMean = Least Squares Mean; N = sample size; SD = standard deviation; SE = standard error.

Dosages are in mg/kg per day.

* P-value is from LSMean change from baseline to endpoint using Student's t-test.

** P-value is from a LSMean Type III Sum of Squares using model: change = baseline treatment investigator.

Baseline: last of Visits 4-7. Endpoint: last of Visits 8-12.

Population: All randomized patients.

Health Risk Behaviors

Acute Phase

Table 17 presents the mean change from baseline to endpoint for the Youth Risk Behavior Survey (YRBS) in the acute phase. Mean change from baseline to endpoint for the behaviors control - unintentional injuries item was statistically significant for both the label dose titration and slow dose titration groups ($p < .001$). No statistically significant differences were demonstrated in any of the scores of the YRBS between the 2 groups from baseline to endpoint.

Maintenance Phase

Table 18 presents the mean change from baseline to endpoint for YRBS in the maintenance phase. Mean change from baseline to endpoint for the behaviors control - unintentional injuries item was statistically significant for the 1.4 mg group ($p < .04$). Additionally, this measure was statistically significantly different between the 0.8 mg/kg/day and 1.4 mg/kg/day groups ($p = .03$).

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Table 17. Mean Change from Baseline to LOCF Endpoint in Acute Phase for Youth Risk Behavior Survey

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Total of YRBS subscores	ATX0.5/1.2	97	157.02	18.31	157.42	20.72	-0.04	1.32	0.976	0.660
	ATX0.5/1.0/1.2	105	156.87	17.28	156.92	17.82	-0.82	1.27	0.519	
Tobacco use	ATX0.5/1.2	107	13.24	4.82	13.51	5.15	0.21	0.27	0.439	0.279
	ATX0.5/1.0/1.2	115	13.44	5.15	13.39	4.65	-0.19	0.26	0.472	
Unhealthy dietary behaviors	ATX0.5/1.2	106	50.84	5.55	50.67	5.24	-0.25	0.51	0.620	0.793
	ATX0.5/1.0/1.2	115	49.90	6.60	49.99	6.47	-0.43	0.49	0.382	
Inadequate physical activity	ATX0.5/1.2	103	31.81	8.16	32.50	8.44	0.63	0.77	0.416	0.922
	ATX0.5/1.0/1.2	114	31.54	8.13	32.28	9.01	0.53	0.74	0.476	
Alcohol and other drug use	ATX0.5/1.2	105	23.36	6.75	23.51	7.34	0.15	0.31	0.623	0.869
	ATX0.5/1.0/1.2	116	22.90	6.28	23.28	6.04	0.22	0.30	0.460	
Sexual behaviors (unintend preg/STD)	ATX0.5/1.2	106	9.77	4.57	10.36	5.24	0.59	0.33	0.078	0.330
	ATX0.5/1.0/1.2	116	10.78	5.73	10.89	5.92	0.15	0.32	0.641	
Behaviors cont unintentional injuries	ATX0.5/1.2	104	27.85	3.69	26.68	3.33	-1.40	0.25	<0.001	0.197
	ATX0.5/1.0/1.2	115	28.47	4.34	27.33	2.96	-0.95	0.24	<0.001	

Abbreviations: ATX = atomoxetine; cont = contributing to; LOCF = Last Observation Carried Forward; LSMean = Least Squares Mean; N = sample size; SD = standard deviation; SE = standard error; YRBS = Youth Risk Behavior Survey.

Dosages are in mg/kg per day.

* P-value is from LSMean change from baseline to endpoint using Student's t-test.

** P-value is from a LSMean Type III Sum of Squares using model: change = baseline treatment investigator.

Baseline: last of Visits 1-3. Endpoint: last of Visits 4-7.

Population: All randomized patients.

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Table 18. Mean Change from Baseline to LOCF Endpoint in Maintenance Phase for Youth Risk Behavior Survey

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	LSMean	SE		
Total of YRBS subscores	ATX0.8	45	156.19	19.08	159.17	20.47	3.38	2.21	0.131	0.218
	ATX1.4	58	153.91	16.90	154.00	19.02	0.00	1.87	0.999	
Tobacco use	ATX0.8	51	13.05	3.97	13.37	4.11	-0.08	0.49	0.875	0.977
	ATX1.4	62	12.81	3.78	12.87	3.94	-0.06	0.42	0.886	
Unhealthy dietary behaviors	ATX0.8	50	50.44	5.77	50.07	5.48	-0.25	0.92	0.789	0.953
	ATX1.4	63	49.23	6.45	49.39	6.20	-0.31	0.79	0.693	
Inadequate physical activity	ATX0.8	50	31.34	8.49	31.71	7.79	0.52	1.16	0.657	0.647
	ATX1.4	61	31.66	8.66	31.27	8.34	-0.13	0.99	0.897	
Alcohol and other drug use	ATX0.8	52	23.54	5.64	25.04	7.07	0.89	0.66	0.179	0.496
	ATX1.4	62	23.03	6.38	23.68	7.55	0.34	0.57	0.547	
Sexual behaviors (unintend preg/STD)	ATX0.8	51	10.43	5.24	11.50	6.53	1.00	0.51	0.054	0.753
	ATX1.4	63	10.03	5.09	10.70	5.94	0.80	0.44	0.073	
Behaviors cont unintentional injuries	ATX0.8	49	27.41	3.66	27.33	3.33	0.35	0.41	0.404	0.032
	ATX1.4	64	27.44	2.16	26.41	2.57	-0.73	0.34	0.036	

Abbreviations: ATX = atomoxetine; cont = contributing to; LOCF = Last Observation Carried Forward; LSMean = Least Squares Mean; N = sample size; SD = standard deviation; SE = standard; unintend preg/STD = unintended pregnancy/sexually transmitted disease; YRBS = Youth Risk Behavior Survey.

Dosages are in mg/kg per day.

* P-value is from LSMean change from baseline to endpoint using Student's t-test.

** P-value is from a LSMean Type III Sum of Squares using model: change = baseline treatment investigator.

Baseline: last of Visits 4-7. Endpoint: last of Visits 8-12.

Population: All randomized patients.

Safety

No deaths occurred in the acute phase of the study. There was 1 death (respiratory fume inhalation disorder), which was not related to study medication, occurred in the maintenance phase (0.8 mg/kg/day group).

No SAEs were reported during the acute phase. There were 6 SAEs, which were not related to study medication, reported during the maintenance phase. Four of these events were reported in the 0.8 mg/kg/day group: personality disorder, self-injurious ideation, intentional drug misuse, and respiratory fume inhalation disorder, and 2 were in the 1.4 mg/kg/day group: mental status changes and ligament injury.

Out of 267 patients in acute phase, 21 patients discontinued due to adverse events (13 in label dose titration and 8 in slow dose titration) though there were no statistically significant difference between the 2 groups ($p=.26$). For those patients continuing into the maintenance phase ($n=178$), 27 patients discontinued due to adverse events (12 in 0.8 mg/kg/day group and 15 in 1.4 mg/kg/day group) with no statistically significant difference between the 2 groups ($p=.68$).

Treatment–Emergent Adverse Events

Acute Phase

The frequency of TEAEs occurring in 10% or more of patients is summarized in Table 19. In the acute phase, a total of 81.4% ($n=214$) of patients reported at least 1 TEAE (78.3% in label dose titration and 84.3% in slow dose titration group, $p=.267$). The most commonly reported adverse events were nausea (19.8%), fatigue (18.6%), decreased appetite (17.9%), somnolence (17.9%), headache (12.9%), and vomiting (10.3%).

Maintenance Phase

In the maintenance phase, a total of 54.8% ($n=97$) of patients experienced at least 1 TEAE (56.7% in the 1.4 mg/kg/day group and 52.9% in the 0.8 mg/kg/day group; $p=.652$). The most commonly reported adverse event was nausea (9.0%). Dizziness was statistically significant between the 0.8 mg/kg/day and 1.4 mg/kg/day group ($p=.027$), with 5 patients experiencing this in the 0.8 mg/kg/day group and 0 patients experiencing this in the 1.4 mg/kg/day group.

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Table 19. Frequency of Treatment Emergent Adverse Events (≥10%) During the Acute Phase

Preferred Term	ATX0.5/1.2 (N=129)		ATX0.5/ 1.0/1.2 (N=134)		TOTAL (N=263)		p-value
	n	%	n	%	n	%	
Patients with ≥1 TEAE	101	78.29	113	84.33	214	81.37	0.267
Nausea	29	22.48	23	17.16	52	19.77	0.353
Decreased appetite	27	20.93	20	14.93	47	17.87	0.260
Fatigue	24	18.60	25	18.66	49	18.63	>0.999
Somnolence	21	16.28	26	19.40	47	17.87	0.524
Headache	20	15.50	14	10.45	34	12.93	0.271
Vomiting	10	7.75	17	12.69	27	10.27	0.225

Abbreviations: ATX = atomoxetine; ATX0.5/1.2 = label dose titration; ATX 0.5/1.0/1.2 = slow dose titration; N = sample size; TEAE = treatment-emergent adverse event.

Dosages are in mg/kg per day.

Baseline: last of Visits 1-3. Follow-up: Visits 4-7.

Population: All randomized patients who took at least 1 dose of study medication.

Clinical Laboratory Evaluations

Electrocardiogram

Acute Phase

Table 20 presents the mean change from baseline to endpoint for ECG values in the acute phase of the study. Within group, statistically significant changes ($p \leq .03$) were demonstrated in Heart Rate, RR interval, QT Interval, and QTcD in both groups.

No statistically significant differences were demonstrated in ECG changes between groups from baseline to endpoint.

Maintenance Phase

Table 21 presents the mean change from baseline to endpoint for ECG values in the maintenance phase of the study. Statistically significant changes ($p \leq .02$) were demonstrated in Heart Rate and RR interval within both the groups.

Statistically significant changes ($p \leq .02$) were demonstrated in QTcF, QTcD, and the PR interval in the 1.4 mg/kg/day group.

Statistical significance of the difference in the changes in PR interval ($p = .04$) between the 0.8 mg/kg/day and 1.4 mg/kg/day groups from baseline to endpoint was noted.

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Table 20. Mean change from Baseline to LOCF Endpoints in Acute Phase for ECG values

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	Mean	SD		
Heart Rate (BPM)	ATX0.5/1.2	112	70.69	11.06	76.81	12.21	6.13	12.58	<0.001	0.591
	ATX0.5/1.0/1.2	113	69.88	10.98	77.47	11.31	7.59	13.23	<0.001	
1000*60/HR	ATX0.5/1.2	112	869.24	134.46	801.77	133.89	-67.47	141.68	<0.001	0.427
	ATX0.5/1.0/1.2	113	881.19	148.90	791.33	118.57	-89.87	162.97	<0.001	
PR Interval (MSEC)	ATX0.5/1.2	112	144.98	18.62	145.04	17.28	0.05	17.91	0.975	0.445
	ATX0.5/1.0/1.2	113	142.10	17.18	142.03	19.04	-0.07	15.52	0.961	
QRS Interval (MSEC)	ATX0.5/1.2	112	83.59	7.44	83.91	7.93	0.32	7.44	0.649	0.917
	ATX0.5/1.0/1.2	113	84.04	7.96	84.23	8.42	0.19	7.91	0.794	
QT Interval (MSEC)	ATX0.5/1.2	112	377.70	29.62	369.32	27.66	-8.38	27.51	0.002	0.272
	ATX0.5/1.0/1.2	113	378.09	24.97	366.16	22.21	-11.93	27.65	<0.001	
QT/Cubic Root RR	ATX0.5/1.2	112	396.53	17.96	398.56	16.95	2.03	18.50	0.247	0.430
	ATX0.5/1.0/1.2	113	395.66	17.73	396.94	16.93	1.28	16.06	0.400	
QT/(RR/1000)**0.40	ATX0.5/1.2	112	399.93	17.40	403.88	16.94	3.95	19.00	0.030	0.547
	ATX0.5/1.0/1.2	113	398.84	18.67	402.52	17.92	3.68	16.68	0.021	

Abbreviations: ATX = atomoxetine; ATX 0.5/1.2 = label dose titration, ATX 0.5/1.0/1.2 = slow dose titration; BPM = beats per minute; MSEC = Millisecond; N = sample size, SD = standard deviation.

Dosages are in mg/kg per day.

* P-value is from change from baseline to endpoint using Student's t-test.

** P-value is from a Type III Sum of Squares using model: change = baseline treatment pooled-investigator.

Baseline: last of Visits 1-3. Endpoint: last of Visits 4-7.

Population: All randomized patients who took at least 1 dose of study medication.

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Table 21. Mean change from Baseline to LOCF Endpoints in maintenance Phase for ECG values

Variables	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	Mean	SD		
Heart Rate (BPM)	ATX0.8	60	77.57	10.83	72.88	12.81	-4.68	10.79	0.001	0.278
	ATX1.4	68	79.56	11.09	76.41	11.49	-3.15	11.17	0.023	
1000*60/HR	ATX0.8	60	789.27	116.67	849.39	156.00	60.12	123.82	<0.001	0.137
	ATX1.4	68	769.47	114.75	802.91	120.81	33.44	114.45	0.019	
PR Interval (MSEC)	ATX0.8	60	141.17	16.88	142.92	19.47	1.75	14.98	0.369	0.039
	ATX1.4	68	148.09	20.53	142.68	19.40	-5.41	12.13	<0.001	
QRS Interval (MSEC)	ATX0.8	60	82.50	7.95	84.13	9.58	1.63	8.09	0.123	0.768
	ATX1.4	68	83.97	8.13	85.56	9.14	1.59	8.38	0.123	
QT Interval (MSEC)	ATX0.8	60	366.17	24.43	374.63	35.98	8.47	34.09	0.059	0.190
	ATX1.4	68	368.38	24.77	368.82	23.91	0.44	25.00	0.885	
QT/Cubic Root RR	ATX0.8	60	397.03	15.74	396.54	22.10	-0.49	24.31	0.877	0.797
	ATX1.4	68	402.92	18.70	397.68	12.92	-5.24	18.47	0.022	
QT/(RR/1000)**0.40	ATX0.8	60	402.61	15.79	400.53	21.30	-2.08	23.63	0.497	0.941
	ATX1.4	68	409.20	19.26	402.90	12.90	-6.29	18.90	0.008	

Abbreviations: ATX = atomoxetine; BPM = beats per minute; MSEC = Millisecond; N = Sample size, SD = Standard Deviation.

Dosages are in mg/kg per day.

* P-value is from change from baseline to endpoint using Student's t-test.

** P-value is from a Type III Sum of Squares using model: change = baseline treatment pooled-investigator.

Baseline: last of Visits 1-7. Endpoint: last of Visits 8-12.

Population: All randomized patients who took at least 1 dose of study medication.

Vital Signs

Acute Phase

Table 22 presents baseline to endpoint change scores for vital sign measures. In the acute phase, statistically significant changes ($p \leq .05$) were demonstrated within both the groups in pulse and blood pressure from baseline to endpoint. There was a statistically significant decrease ($p < .05$) in weight from baseline to endpoint in both the label dose titration and slow dose titration.

No statistically significant difference was observed in any of the vital signs between label dose titration and slow dose titration.

Maintenance Phase

Table 23 presents baseline to endpoint change scores for vital sign measures in the maintenance phase. Statistically significant increases ($p < .001$) were demonstrated in height and weight within both the groups. No statistically significant difference was observed in pulse and blood pressure between the 0.8 mg/kg/day and 1.4 mg/kg/day groups.

Lab Values

Acute Phase

Table 24 presents mean change from baseline to endpoint for lab values in the acute phase. Statistically significant changes ($p < .05$) were demonstrated within both the groups in alkaline phosphatase ALT/SGPT, uric acid, erythrocyte count, monocytes, bicarbonate, chloride, and sodium from baseline to end point. Statistically significant mean changes ($p < .05$) were also noted for bilirubin total, urea nitrogen, lymphocytes, and potassium in the label dose titration group. Statistically significant mean change ($p < .001$) was demonstrated for cholesterol in the slow dose titration group. There was a statistically significant difference in cholesterol between slow dose titration and label dose titration ($p = .04$).

Maintenance Phase

Table 25 presents mean change from baseline to endpoint for lab values in the maintenance phase. Mean change from baseline to endpoint in alkaline phosphatase was statistically significant ($p < .001$) for both groups. Statistically significant changes ($p \leq .05$) were also demonstrated in creatinine and potassium in the 0.8 mg/kg/day group and in uric acid and GGT (GGT/SGGT/YGGT) in the 1.4 mg/kg/day group. There was a statistically significant difference demonstrated between groups in albumin ($p = .04$) and bilirubin total ($p = .03$).

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Table 22. Mean Change from Baseline to LOCF Endpoint in Acute Phase for Vital Signs

Vitals	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	Mean	SD		
Weight (Kg)	ATX0.5/1.2	126	57.06	8.13	56.56	7.96	-0.50	1.96	0.005	0.531
	ATX0.5/1.0/1.2	134	56.43	8.89	56.04	9.12	-0.39	1.96	0.023	
Pulse	ATX0.5/1.2	126	74.81	9.46	78.53	10.93	3.72	11.83	<0.001	0.148
	ATX0.5/1.0/1.2	134	73.49	9.45	80.14	10.67	6.65	11.63	<0.001	
Diastolic Blood Pressure	ATX0.5/1.2	126	64.89	7.95	67.31	8.11	2.42	7.61	<0.001	0.862
	ATX0.5/1.0/1.2	134	64.37	8.20	67.21	7.35	2.84	8.58	<0.001	
Systolic Blood Pressure	ATX0.5/1.2	126	107.92	10.40	110.20	9.37	2.28	10.22	0.014	0.146
	ATX0.5/1.0/1.2	134	106.67	10.24	108.39	9.12	1.72	9.85	0.046	

Abbreviations: ATX = atomoxetine; ATX 0.5/1.2 = label dose titration; ATX 0.5/1.0/1.2 = slow dose titration; Kg = Kilogram; N = sample size; SD = standard Deviation.

Dosages are in mg/kg per day.

* P-value is from change from baseline to endpoint using Student's t-test.

** P-value is from a Type III Sum of Squares using model: change = baseline treatment investigator.

Baseline: last of Visits 1-3. Endpoint: last of Visits 4-7.

Population: All randomized patients who took at least 1 dose of study medication.

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Table 23. Mean Change from Baseline to LOCF Endpoint in Maintenance Phase for Vital Signs

Vitals	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
			Mean	SD	Mean	SD	Mean	SD		
Height (CM)	ATX0.8	62	163.12	6.63	166.29	7.07	3.16	4.82	<0.001	0.443
	ATX1.4	70	164.99	8.98	167.48	8.94	2.49	2.87	<0.001	
Weight (Kg)	ATX0.8	82	55.35	7.80	57.65	7.82	2.30	2.81	<0.001	0.564
	ATX1.4	83	56.46	9.60	58.35	9.44	1.89	3.21	<0.001	
Body Mass Index	ATX0.8	62	20.61	2.68	20.72	2.63	0.11	1.50	0.550	0.909
	ATX1.4	70	20.89	3.01	20.95	3.10	0.06	1.54	0.733	
Pulse	ATX0.8	82	80.09	9.80	79.40	11.61	-0.68	11.55	0.594	0.892
	ATX1.4	83	79.84	11.02	78.90	11.73	-0.94	10.91	0.435	
Diastolic Blood Pressure	ATX0.8	82	67.07	7.16	68.24	8.03	1.17	8.06	0.192	0.154
	ATX1.4	83	68.00	8.20	66.65	8.33	-1.35	10.27	0.235	
Systolic Blood Pressure	ATX0.8	82	108.52	9.17	109.94	14.26	1.41	14.86	0.391	0.514
	ATX1.4	83	109.54	9.33	109.46	9.23	-0.08	10.36	0.941	

Abbreviations: atomoxetine; CM = centimeter; Kg = kilogram; N = sample size; SD = standard deviation.

Dosages are in mg/kg per day.

* P-value is from change from baseline to endpoint using Student's t-test.

** P-value is from a Type III Sum of Squares using model: change = baseline treatment investigator.

Baseline: last of Visits 1-7. Endpoint: last of Visits 8-12.

Population: All randomized patients who took at least 1 dose of study medication.

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Table 24. Mean Change from Baseline to LOCF Endpoint in Acute Phase for Lab Values

Lab Group	Analyte	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
				Mean	SD	Mean	SD	Mean	SD		
Chem	Alkaline Phosphatase	ATX0.5/1.2	117	231.47	127.37	218.25	121.87	-13.22	39.63	<0.001	0.326
		ATX0.5/1.0/1.2	124	246.44	123.82	235.94	123.07	-10.51	38.59	0.003	
	ALT/SGPT	ATX0.5/1.2	116	16.46	7.02	14.86	5.45	-1.59	7.15	0.018	0.838
		ATX0.5/1.0/1.2	122	17.35	7.81	15.08	5.82	-2.27	7.52	0.001	
	Bilirubin, Total	ATX0.5/1.2	108	7.42	4.09	8.35	4.70	0.94	3.50	0.007	0.249
		ATX0.5/1.0/1.2	117	8.31	4.88	8.66	5.42	0.35	3.94	0.338	
	Cholesterol	ATX0.5/1.2	117	4.05	0.62	4.01	0.68	-0.04	0.48	0.336	0.042
		ATX0.5/1.0/1.2	124	4.09	0.72	3.92	0.63	-0.17	0.52	<0.001	
	Urea Nitrogen	ATX0.5/1.2	117	4.80	1.29	4.56	1.14	-0.24	1.13	0.022	0.194
		ATX0.5/1.0/1.2	124	4.33	1.15	4.17	0.99	-0.16	1.15	0.128	
	Uric Acid	ATX0.5/1.2	117	309.99	72.83	295.38	69.29	-14.62	48.04	0.001	0.719
		ATX0.5/1.0/1.2	124	307.32	77.01	295.05	69.03	-12.27	54.60	0.014	
Heme	Erythrocyte Count	ATX0.5/1.2	114	4.97	0.49	5.02	0.51	0.06	0.27	0.030	0.979
		ATX0.5/1.0/1.2	120	4.94	0.42	5.01	0.43	0.06	0.28	0.015	
	Lymphocytes	ATX0.5/1.2	114	2.18	0.54	2.06	0.50	-0.12	0.52	0.011	0.356
		ATX0.5/1.0/1.2	120	2.20	0.63	2.12	0.58	-0.08	0.56	0.100	
	Monocytes	ATX0.5/1.2	114	0.37	0.14	0.34	0.12	-0.03	0.14	0.017	0.854
		ATX0.5/1.0/1.2	120	0.38	0.15	0.34	0.12	-0.04	0.15	0.007	

continued

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Table 24. Mean Change from Baseline to LOCF Endpoint in Acute Phase for Lab Values (concluded)

Lab Group	Analyte	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
				Mean	SD	Mean	SD	Mean	SD		
Lytes	Bicarbonate, HCO ₃	ATX0.5/1.2	116	24.89	2.48	26.22	1.98	1.33	2.97	<0.001	0.170
		ATX0.5/1.0/1.2	121	25.44	2.60	26.67	2.33	1.23	2.91	<0.001	
	Chloride	ATX0.5/1.2	117	103.72	2.05	102.93	1.96	-0.79	2.44	<0.001	0.365
		ATX0.5/1.0/1.2	123	103.29	1.93	102.59	1.81	-0.71	2.11	<0.001	
	Potassium	ATX0.5/1.2	117	4.25	0.43	4.15	0.34	-0.10	0.44	0.017	0.171
		ATX0.5/1.0/1.2	123	4.23	0.35	4.21	0.37	-0.02	0.44	0.622	
	Sodium	ATX0.5/1.2	117	140.85	1.98	140.25	2.09	-0.61	2.66	0.015	0.242
		ATX0.5/1.0/1.2	123	140.46	1.81	139.89	1.60	-0.57	2.10	0.003	

Abbreviations: ALT/SGPT = alanine transaminase/serum glutamate pyruvate transaminase; ATX = atomoxetine; ATX 0.5/1.2 = label dose titration, ATX 0.5/1.0/1.2 = slow dose titration, SD = standard deviation.

* P-value is from change from baseline to endpoint using Student's t-test.

** P-value is from a Type III Sum of Squares using model: change = baseline treatment investigator.

Baseline: last of Visits 1-3. Endpoint: last of Visits 4-7.

Population: All randomized patients who took at least 1 dose of study medication.

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Table 25. Mean Change from Baseline to LOCF Endpoint in Maintenance Phase for Lab Values

Lab Group	Analyte	Group	N	Baseline		Endpoint		Change		Within Group p-value*	Between Group p-value**
				Mean	SD	Mean	SD	Mean	SD		
Chem	Albumin	ATX0.8	57	43.81	3.12	43.58	2.69	-0.23	2.59	0.509	0.041
		ATX1.4	64	43.34	2.82	42.81	2.42	-0.53	2.81	0.136	
	Alkaline Phosphatase	ATX0.8	57	219.65	126.97	195.63	107.80	-24.02	46.10	<0.001	0.123
		ATX1.4	64	244.89	124.14	205.16	115.05	-39.73	39.07	<0.001	
	ALT/SGPT	ATX0.8	57	13.63	4.04	14.91	6.09	1.28	4.86	0.052	0.994
		ATX1.4	64	15.81	6.13	16.80	9.02	0.98	8.67	0.367	
	Bilirubin, Total	ATX0.8	56	8.68	4.08	9.05	4.47	0.38	3.24	0.391	0.034
		ATX1.4	61	7.69	4.99	7.13	3.56	-0.56	3.56	0.226	
	Creatinine	ATX0.8	57	62.75	11.49	65.12	10.03	2.37	8.71	0.045	0.342
		ATX1.4	64	61.41	10.90	62.42	10.32	1.02	7.50	0.283	
	GGT (GGPT/SGGT/YGGT)	ATX0.8	57	12.75	4.05	13.60	5.68	0.84	3.60	0.083	0.561
		ATX1.4	64	13.28	4.38	13.95	5.17	0.67	2.65	0.047	
	Total Protein	ATX0.8	57	73.56	4.33	73.16	4.32	-0.40	3.92	0.440	0.092
		ATX1.4	64	72.83	4.36	71.88	3.35	-0.95	3.90	0.055	
	Uric Acid	ATX0.8	57	301.81	64.97	310.81	57.96	9.00	47.56	0.159	0.925
		ATX1.4	64	287.16	58.80	299.95	66.50	12.80	49.03	0.041	
Lytes	Potassium	ATX0.8	57	4.19	0.42	4.35	0.49	0.16	0.49	0.015	0.100
		ATX1.4	63	4.17	0.35	4.23	0.41	0.06	0.40	0.266	

Abbreviations: ALT/SGPT = alanine transaminase/serum glutamate pyruvate transaminase; ATX = atomoxetine; ATX 0.5/1.2 = label dose titration; ATX 0.5/1.0/1.2 = slow dose titration ; GGT (GGPT/SGGT/YGGT) = gamma glutamyl transferase; SD = standard deviation.

* P-value is from change from baseline to endpoint using Student's t-test.

** P-value is from a Type III Sum of Squares using model: change = baseline treatment investigator.

Baseline: last of visits 1-7. Endpoint: last of visits 8-12.

Population: All randomized patients who took at least 1 dose of study medication.

Summary ID# 7975

Clinical Study Summary: Study B4Z-US-LYCE

Open-Label Treatment with Atomoxetine Hydrochloride in Children and Adolescents with Attention- Deficit/Hyperactivity Disorder and Comorbid Dyslexia

Date summary approved by Lilly: 13 March 2007

Brief Summary of Results:

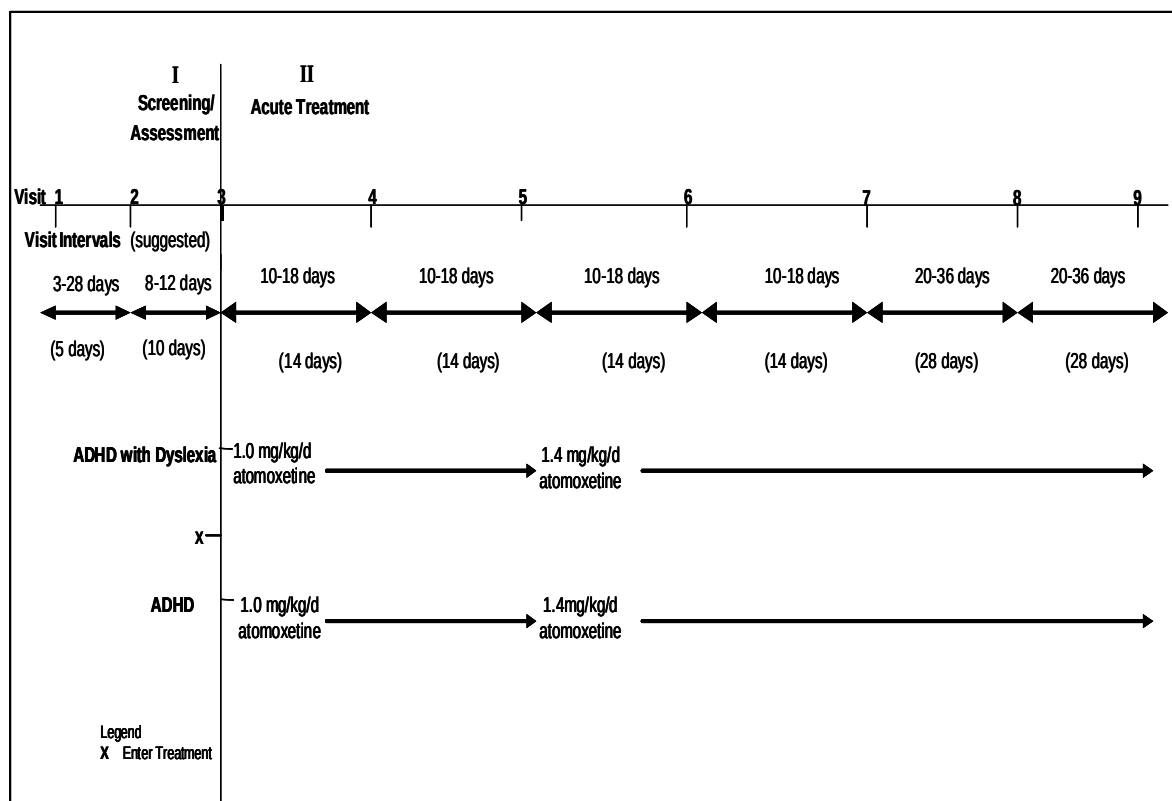
The primary objective of this open-label, multicenter, outpatient, parallel design, fixed dose study was to investigate the efficacy of atomoxetine hydrochloride in reducing symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD) in individuals aged between 10 to 16 years diagnosed with ADHD and ADHD with Dyslexia (ADHD+D). The primary efficacy measure was the Attention Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator- Administered and Scored (ADHDRS). The results of the study are as follows:

- There was a statistically significant mean change from baseline to endpoint for the ADHDRS total score, hyperactive/impulsive subscore, and inattentive subscore in both the ADHD and ADHD+D groups ($p < .001$). However, there were no statistically significant differences in ADHDRS measures between the groups.
- Mean change from baseline to endpoint for all standard scores on the Kaufman Test of Educational Achievement Comprehensive Form (K-TEA) subtests measured for this study were statistically significant for both the ADHD and ADHD+D groups ($p < .05$) with the exception of the spelling standard and reading decoding standard scores. The mean change from baseline to endpoint score for the ADHD group only was statistically significant on the standard score in spelling ($p = .005$) while the reading decoding score was statistically significant for the ADHD+D group ($p = .003$). Mean change in age equivalence scores (measured in months) was statistically significant from baseline to endpoint for both groups on reading decoding, spelling, reading comprehension, and reading composite ($p < .01$). There were no differences between the groups for any of the K-TEA parameters.
- From the Working Memory Test Battery for Children (WMTB-C), mean change for the phonological loop total standard score in the ADHD+D group was statistically significant from baseline to endpoint ($p = .028$). Conversely, mean changes on the central executive total standard score and component score were statistically significant for ADHD group ($p = .017$ and $p = .032$). The remaining standard or component total scores for the phonological loop, central executive, or visuospatial sketchpad measures were not statistically significant. Of the subtests for the WMTB-C, mean change was statistically significant on the listening recall standard score for the ADHD group only ($p = .016$) and the non-word list recall standard score was statistically significant for both the ADHD ($p = .024$) and ADHD+D groups ($p = .004$). Evaluation of the effect of atomoxetine treatment on only patients previously treated with stimulants showed that the ADHD+D group had a statistically significant mean change on the phonological loop component score ($p = .008$). Furthermore, mean change on the phonological loop subtests of the digit recall trial ($p = .049$), word list match trial ($p = .033$), word list recall trial ($p = .022$), and non-word list recall trial ($p = .005$) were also statistically significant for the ADHD+D group. There were no statistically significant mean changes on any other total standard or component scores or standard subtest scores in the two groups.

- Both groups had statistically significant mean change from baseline to endpoint on both investigator- and parent-rated versions of the Life Participation Scale-Revised (LPS-R) total scores. Mean change was statistically significant for all LPS-R subscales in both the groups ($p < .05$) with the exception of the “happy/social” subscale which was not statistically significant for the ADHD group ($p = .550$) on the investigator-rated version of the scale. There was no statistically significant difference between groups for LPS-R total score or any subscales on either investigator- or parent-rated versions.
- There were no deaths reported during the study. There were no serious adverse events reported during the study.
- Approximately 84% ($n=47$) of patients enrolled in the trial reported treatment-emergent adverse events (TEAEs; 90% in ADHD and 81% in ADHD+D group, $p = .466$). The most common adverse events were somnolence (34%) and nausea (30%). Further, adverse events occurring in 10% or more of patients included: decreased appetite, headache, nasopharyngitis, upper abdominal pain, vomiting, cough, pharyngitis, and upper respiratory tract infection.
- Four patients discontinued due to adverse events (1 in ADHD and 3 in ADHD+D, $p = 1.0$) which were reported to be study drug-related.
- There were statistically significant baseline to endpoint changes for many laboratory tests including clinical chemistry, hematology, and urinalysis in both the groups ($p < .001$). There were statistically significant differences between the two groups for cholesterol ($p = .037$), uric acid ($p = .007$), hematocrit ($p = .014$), hemoglobin ($p = .028$), and urine specific gravity ($p = .015$).
- There was no statistically significant change in blood pressure in either of the groups. Pulse rate change was statistically significant for the ADHD group ($p = .05$). Both the groups reported statistically significant change in body mass index ($p \leq .012$).
- Both groups showed a statistically significant increase in PR interval ($p = .030$ for ADHD and $.028$ for ADHD+D). A statistically significant decrease in QT interval and $RR-1000 \times 60 / HR$ ($p < .001$) was shown by the ADHD+D group. There was a statistically significant difference between the two groups for the following ECG parameters: PR interval ($p = .003$) and $RR-1000 \times 60 / HR$ ($p = .018$).

Title of Study: Open-Label Treatment with Atomoxetine Hydrochloride in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder and Comorbid Dyslexia	
Investigators: This multicenter study included 11 principal investigators.	
Study Centers: This study was conducted at 11 study centers in one country.	
Length of Study: 2 years 5 months Date of first patient enrolled: 20 October 2003 Date of last patient completed: 15 March 2006	Phase of Development: 4
Objectives: Primary Objective: To assess the effect of atomoxetine given orally for approximately 16 weeks in children and adolescents aged 10-16 years, in the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) with Dyslexia (ADHD+D) as measured by the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator- Administered and Scored (ADHDRS-IV-Parent:Inv). Secondary Objectives: • To assess the effect of atomoxetine given orally for 16 weeks in the treatment of children and adolescents with ADHD only and ADHD with Dyslexia (ADHD+D) as measured by the Kaufman Test of Educational Achievement Comprehensive Form (K-TEA): Reading Decoding, Reading Comprehension and Spelling Subtests and Reading Composite Scale. • To assess the effect of atomoxetine on working memory in children and adolescents with ADHD only and ADHD with Dyslexia as assessed by the Working Memory Test Battery for Children (WMTB-C). • To assess the effect of atomoxetine in improving measures of social, emotional, cognitive, educational and affiliative (family, friends) functioning in children and adolescents with ADHD only and ADHD with Dyslexia as assessed by the Life Participation Scale for ADHD-Revised (LPS-ADHD-R). • To assess the benefit of atomoxetine treatment in children and adolescents with ADHD only and ADHD with Dyslexia who had been previously treated with stimulants in improving working memory as assessed by the WMTB-C. • To assess the safety and tolerability of atomoxetine at doses up to 1.4mg/kg/day as assessed by adverse events elicited during open-ended questioning.	
Study Design: This study was an open-label, multicenter, outpatient, parallel design, fixed dose study investigating the efficacy of atomoxetine in reducing symptoms of ADHD in individuals aged 10 to 16 years meeting Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnostic criteria for ADHD and ADHD with comorbid dyslexia. Target dose was 1.4 mg/kg/day with patients permitted to down titrate to a minimum of 1.0 mg/kg/day for safety reasons. See Figure 1 for the study design.	
Number of Patients: Planned: 105 (80 ADHD+D and 25 ADHD group) Randomized: 56 (36 ADHD+D and 20 ADHD group) Completed: 47 (31 ADHD+D and 16 ADHD group)	
Diagnosis and Main Criteria for Inclusion: Male and female children and adolescents aged between 10-16 years with ADHD or ADHD with comorbid dyslexia. ADHD was defined by DSM-IV diagnostic criteria and scoring at least 1.5 standard deviations above the age and gender norm at both Visits 1 and 2 for their diagnostic subtype using published norms for the ADHDRS-IV-Parent:Inv. ADHD with comorbid dyslexia criteria was defined by meeting ADHD criteria along with dyslexia criteria by having a score of at least a 22-point discrepancy between ability (using the highest intelligence quotient score of the Vocabulary [verbal] subtest standard score; the Matrices [non-verbal/performance] subtest standard score; or the IQ Composite Score on the K-BIT) and achievement (Reading Composite Standard Score on the KTEA).	
Test Product, Dose, and Mode of Administration: Atomoxetine hydrochloride target dose of 1.4 mg/kg/day (not to exceed 100 mg/day), was given orally once a day in capsule form in the following dose strengths: 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, and 40 mg.	

Reference Therapy, Dose, and Mode of Administration: No comparator
Duration of Treatment: 16 weeks
Variables: Efficacy: • Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv). • Kaufman Test of Educational Achievement Comprehensive (K-TEA) • Working Memory Test Battery for Children (WMTB-C). • Life Participation Scale for ADHD-Revised (Parent-rated and Investigator-rated versions) (LPSADHD-R) Safety: 1) Treatment-emergent adverse events; 2) serious adverse events; 3) discontinuations due to adverse events; 4) labs; 5) ECG; 6) vital signs
Evaluation Methods: <u>Statistical:</u> The primary hypothesis was whether there was a significant change from baseline on the ADHD-RS Total score for patients with comorbid ADHD and Dyslexia and was analyzed using a Student's t-test applied to the least squares mean change from baseline score. Change scores were computed for each patient as the difference between the last observation carried forward (LOCF) score and baseline score. The least square mean change and associated standard error used in the Student's t-test were derived from an ANCOVA model with terms for diagnostic group, investigator, gender, age, baseline score, and baseline score by diagnostic group interaction. All intent-to-treat (ITT) patients with comorbid ADHD and Dyslexia and at least 1 baseline and 1 post-baseline score were included in the primary analysis. Between-group changes from baseline to endpoint in efficacy measure variables were analyzed using a fixed-effects ANCOVA model with terms for diagnostic group, investigator, gender, baseline score, age, and baseline score by diagnostic group interaction. Type III sums of squares were used for between-group tests. Changes within diagnostic group were assessed using Student's t-test applied to the least squares mean for the diagnostic group from the ANCOVA model. Between-group changes in efficacy measure variables over time were analyzed using the relevant contrast from a restricted maximum likelihood repeated measures model with terms for diagnostic group, investigator, visit, baseline score, diagnostic group by visit interaction, and baseline score by diagnostic group interaction. This model used the covariance structure that maximizes the Schwartz Bayes Criterion and the Kenward-Roger method for estimating denominator degrees of freedom. Student's t test were applied to the least squares mean and standard error to estimate within group change to endpoint based on the relevant contrast from the diagnostic group by visit interaction from this model. Incidence of categorical response variables were compared across diagnostic groups using Fisher's Exact test. Correlations between change and baseline (Visit 1) scores for LPS-R Investigator and Parent rated scales were computed to assess the consistency of responses using alternate sources for rating the patient's behavior. To assess the incremental benefit of atomoxetine treatment for patients who had already received stimulant therapy, WMTB-C scores were analyzed using a fixed-effects ANCOVA model with terms for diagnostic group and investigator. Changes within diagnostic group were assessed using Student's t-test applied to the least squares mean for diagnostic group from the ANCOVA model. These analyses only included patients with prior stimulant experience and a diagnosis of either ADHD or ADHD with Dyslexia; for these analyses, Visit 1 served as baseline as the patients were on stimulant therapy only for that visit. Sample size calculation was done based on previous studies.



Abbreviation: ADHD = Attention-Deficit/Hyperactivity Disorder.

Figure 1. Illustration of the study design for B4Z-US-LYCE

Results:

Patient Demographics

In this study 20 patients were randomized to the Attention Deficit/Hyperactivity Disorder (ADHD) group and 36 to the Attention Deficit/Hyperactivity Disorder with comorbid dyslexia (ADHD+D) group. Median age for the ADHD group was 12.6 years and for the ADHD+D group it was 11.4 years. Males comprised approximately 70% of both groups. A total 47 out of 56 randomized patients completed the study. With the exception of height, in which there was a statistically significant difference, demographic characteristics including weight, origin, and age were comparable between both groups. Additionally, prior stimulant use was at or over 50% for both groups. ADHD subtype was comparable between groups with most patients diagnosed as predominantly inattentive (>40%) or as mixed subtype (>50%). At study entry, there was no statistically significant difference between the two groups in mean scores of Kaufman Brief Intelligence Test Intelligence Quotient (K-BIT IQ) Composite score. However, the ADHD group had a statistically significantly lower K-BIT matrices subtest standard score compared to the

ADHD+D group. Baseline demographics and other diagnostic characteristics are summarized in Table 1.

Table 1. Baseline Demographics and Diagnostic Characteristics

Characteristic	ADHD (n=20)	ADHD + Dyslexia (n=36)
Gender		
Male, n (%)	15 (75.0)	24 (66.7)
Age, y		
Mean (SD)	12.7 (1.5)	12.2 (2.0)
Age range		
Min – Max	10.4 – 15.7	10.0 – 16.8
Weight		
Mean (SD)	47.6 (8.8)	47.5 (13.7)
Height		
Mean (SD)	154.9 (9.3)	148.4 (12.2)*
Ethnic origin, n (%)		
Caucasian	14 (70.0)	24 (66.7)
African American	1 (5.0)	5 (13.9)
Hispanic	4 (20.0)	4 (11.1)
Other	1 (5.0)	3 (8.3)
DSM-IV ADHD subtype, n (%)		
Hyperactive/Impulsive	0 (0)	2 (5.6)
Inattentive	9 (45.0)	15 (41.7)
Mixed	11 (55.0)	19 (52.8)
Positive prior prescribed stimulant use, n (%)	10 (50)	22 (61.1)
K-BIT, Mean (SD)		
IQ composite	97.2 (11.9)	102.1 (11.0)
Vocabulary subtest standard score	95.3 (10.0)	94.2 (11.9)
Matrices subset standard score	99.9 (13.6)	109.5 (10.3)*

Abbreviations: ADHD=Attention Deficit/Hyperactivity Disorder, ADHD+D= Attention Deficit/Hyperactivity Disorder with Comorbid Dyslexia, DSM-IV = Diagnostic and Statistics Manual of Mental Disorders, Fourth Edition; KBIT=Kaufman Brief Intelligence Test, K-BIT-IQ= Kaufman Brief Intelligence Test Intelligence Quotient, n=Sample size, SD=Standard Deviation

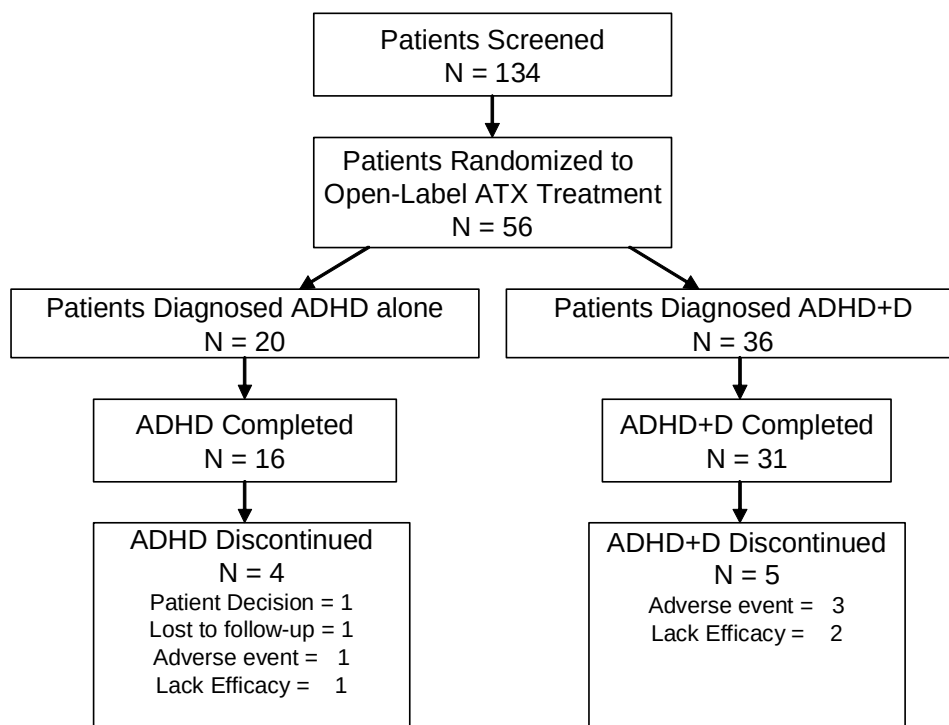
* = p<.05 between groups

Patient Disposition

Figure 2 presents patient disposition. In this study, 134 patients were screened. Fifty-six patients were enrolled and randomized to open-label atomoxetine treatment (36 in ADHD+D arm and 20 in ADHD arm). Out of the 56 total patients enrolled in the study 47 patients completed the study; 31 patients in the ADHD+D group and 16 in the ADHD group (p=.707). Only patients with at least one post-baseline (Visit 3) measure were included in the primary and secondary analyses.

A total of 9 patients discontinued from the study in both the arms (4 in ADHD and 5 in ADHD+D group). The most common reason for discontinuation from the study overall

was adverse events (n=4). Reasons for discontinuation from the study are summarized in Table 2.



Abbreviations: ATX = Atomoxetine

Figure 2. Patient Disposition for Study B4Z-US-LYCE

Table 2. Summary of Reasons for Discontinuation – All Randomized Patients

Reason for Discontinuation	ADHD	ADHD + D	TOTAL	p-Value
Adverse event	1	3	4	1.00
Lack of efficacy, parent/guardian perception	1	2	3	1.00
Patient decision	1	0	1	0.357
Unable to contact patient/caregiver	1	0	1	0.357

Abbreviations: ADHD=Attention Deficit/Hyperactivity Disorder; ADHD+D = ADHD with comorbid dyslexia.

Primary Efficacy Measures

Reduction in the ADHDRS Score indicates improvement.

Table 3 presents mean change from baseline to endpoint for the ADHDRS, the primary efficacy measure for this study. There was a statistically significant reduction in the mean total score from baseline to endpoint for both groups on the ADHDRS ($p < .001$).

Within-group change (mean $\pm$ SE) from baseline to endpoint total score was -20.15 ± 2.81 for the ADHD group and -17.73 ± 2.46 for the ADHD+D group. The hyperactive/impulsive and inattentive mean subscores of the ADHDRS were also statistically significantly reduced from baseline to endpoint for both the ADHD and ADHD+D groups ($p < .001$).

For both the total score and subscores, there was no statistically significant difference between the two groups (Table 3).

Table 3. ADHDRS Baseline to Endpoint (LOCF) Change Scores

ADHDRS Score (Imputed)	Group [†]	Baseline Mean $\pm$ SD	Endpoint Mean $\pm$ SD	Change LS Mean $\pm$ SE	p-Value	
					(A)	(B)
Total Score	ADHD	38.8 ± 8.5	18.5 ± 14.1	-20.2 ± 2.8	$<.001$	.503
	ADHD+D	36.0 ± 8.2	17.8 ± 12.3	-17.7 ± 2.5	$<.001$	
Hyperactivity/Impulsivity Score	ADHD	16.7 ± 6.9	8.2 ± 7.4	-8.5 ± 1.4	$<.001$	.660
	ADHD+D	15.1 ± 7.0	7.3 ± 6.9	-7.7 ± 1.2	$<.001$	
Inattention Score	ADHD	22.1 ± 3.1	10.4 ± 7.3	-11.0 ± 1.6	$<.001$	.769
	ADHD+D	20.9 ± 3.2	10.5 ± 6.1	-10.4 ± 1.4	$<.001$	

Abbreviations: (A) = within group change from baseline to endpoint is from Student's T-Test; (B) = between diagnostic group p-Value is from the Type III Sums of Squares; ADHD= Attention-Deficit/Hyperactivity Disorder, ADHD+D= Attention-Deficit/Hyperactivity Disorder with Comorbid Dyslexia, ADHDRS= Attention-Deficit/Hyperactivity Disorder Rating Scale-Investigator, LOCF=Last Observation Carried Forward; LS Mean – Least square means.

[†] N=20 for ADHD and N=35 for ADHD+D

Secondary Efficacy Measures

Kaufman Test of Educational Achievement Comprehensive Form (K-TEA):

An increase in the K-TEA standard or age equivalency score indicates improvement.

Table 4 presents mean change from baseline to endpoint for the K-TEA. There was statistically significant mean change increase ($p < .05$) for reading comprehension standard

and age equivalent score, reading composite standard and age equivalent scores, spelling age equivalent scores, and reading decoding age equivalent scores in both the ADHD and ADHD+D groups.

The ADHD group had statistically significant mean change increases in spelling standard score ($p=.005$) while the ADHD+D group showed a statistically significant increase in reading decoding standard score ($p=.003$). There were no statistically significant differences between groups in the mean change scores for any of the K-TEA measures (Table 4).

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Table 4. Kaufman Test of Educational Achievement Comprehensive Form (K-TEA) Baseline to Endpoint (LOCF) Change Scores

KTEA SCORE	GROUP	N	BASELINE		ENDPOINT		CHANGE		95% CL		P-VALUE	
			MEAN	SD	MEAN	SD	LSMEAN	SE	LOWER	UPPER	(A)	(B)
READING DECODING STANDARD	ADHD	20	94.25	9.08	100.20	13.45	3.88	2.13	-0.41	8.18	.075	.517
	ADHD+DYSLEXIA	35	80.17	7.63	84.77	10.59	5.64	1.77	2.07	9.21	.003	
READING DECODING AGE EQV	ADHD	20	137.70	30.62	158.10	40.89	17.76	5.26	7.16	28.36	.002	.911
	ADHD+DYSLEXIA	35	103.97	12.22	115.46	22.19	16.92	5.68	5.47	28.38	.005	
SPELLING STANDARD	ADHD	20	90.20	15.63	93.00	16.93	3.23	1.10	1.01	5.45	.005	.219
	ADHD+DYSLEXIA	35	80.11	8.62	82.06	9.97	1.48	0.99	-0.52	3.47	.143	
SPELLING AGE EQV	ADHD	20	132.60	40.43	140.55	41.61	9.66	2.41	4.79	14.52	<.001	.752
	ADHD+DYSLEXIA	35	106.29	18.91	112.11	25.73	8.67	2.22	4.20	13.14	<.001	
READING COMPREHENSION STANDARD	ADHD	20	98.90	13.98	104.00	15.20	5.58	2.01	1.52	9.63	.008	.118
	ADHD+DYSLEXIA	35	81.60	10.79	89.29	13.81	9.83	1.71	6.38	13.28	<.001	
READING COMPREHENSION AGE EQV	ADHD	20	148.35	40.99	163.50	43.75	17.01	5.73	5.46	28.57	.005	.252
	ADHD+DYSLEXIA	35	106.49	23.61	124.80	35.57	25.95	5.19	15.50	36.40	<.001	
READING COMPOSITE STANDARD	ADHD	20	96.55	11.57	102.55	14.86	4.45	1.83	0.76	8.15	.019	.136
	ADHD+DYSLEXIA	35	80.26	8.55	86.40	11.44	8.11	1.57	4.94	11.28	<.001	
READING COMPOSITE AGE EQV	ADHD	20	144.30	35.76	161.85	40.16	17.19	4.37	8.39	26.00	<.001	.308
	ADHD+DYSLEXIA	35	105.26	16.61	120.94	26.49	23.49	4.32	14.77	32.20	<.001	

(A) WITHIN GROUP CHANGE FROM BASELINE TO ENDPOINT (LOCF) SCORE P-VALUE IS FROM STUDENT'S T-TEST

(B) BETWEEN DIAGNOSTIC GROUPS P-VALUE IS FROM TYPE III SUMS OF SQUARES

P-VALUES (A), (B), LSMEAN, AND STDERR ARE FROM AN ANCOVA MODEL: CHANGE = BASELINE QUESDIAG INVP GENDER AGE BASELINE*QUESDIAG

BASELINE : LAST OF (VISITS 1-3), ENDPOINT : LAST OF (VISITS 4-9)

Abbreviations: K-TEA= Kaufman Test of Educational Achievement, ADHD=Attention Deficit/Hyperactivity Disorder, LOCF=Last Observation Carried Forward

Working Memory Test Battery For Children (WMTB-C)

An increase in the WMTB-C standard or component score indicates improvement.

For components of the WMTB-C, the ADHD group showed a statistically significant mean increase from baseline to endpoint on the central executive total standard ($p=.017$) and component scores ($p=.032$), while the ADHD+D group showed a statistically significant mean increase on the phonological loop total standard score ($p=.028$). Mean change for all other total and component scores was not statistically significant. Further, there were no differences between the two groups for any of the standard or component scores (Table 5). However when analyzing by visit (repeated measures) as shown in Table 6 and Table 7, between group differences were revealed on both component and standard scores. Specifically, by the end of treatment, the LS Mean change for the central executive component and total standard scores were statistically significantly greater for the ADHD group over the ADHD+D group ($p=.012$ and $p=.003$). The repeated measures analyses also revealed a statistically significant increase in LS mean score for the ADHD+D group in the visuo-spatial sketchpad component score ($p=.009$) and total standard score ($p=.025$) and the phonological loop component and total standard score which was statistically significant at every visit ($p<.05$).

The subtests of the WMTB-C which include items such as word and non-word list recall and word list match, digit recall, block recall, listening recall, counting recall, and backward digit recall, and maze memory tests were also analyzed. A statistically significant mean increase was achieved for the listening recall standard score for the ADHD group ($p=.016$) while the non-word list recall standard score was statistically significant for both the ADHD ($p=.024$) and ADHD+D groups ($p=.004$). Change for all other subscale scores was not statistically significant (Table 5).

Working Memory Test Battery for Children (WMTB-C) Previously Treated With Stimulants

Table 8 presents mean change in WMTB-C scores from baseline (Visit 1, treatment with stimulants) to endpoint (after atomoxetine treatment); to assess the effect of atomoxetine treatment on patients previously treated with stimulants. The ADHD+D group showed statistically significant mean change on the phonological loop component score ($p=.008$). Further, mean change on the phonological loop subtests of the digit recall trial ($p=.049$), word list match trial ($p=.033$), word list recall trial ($p=.022$), and non-word list recall trial ($p=.005$) were statistically significant. There were no statistically significant mean changes on any other standard or component scores in the two groups.

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Table 5. WMTB-C Baseline to Endpoint (LOCF) Change Score

WMTB SCORE	GROUP	N	BASELINE		ENDPOINT		LSMEAN	SE	CHANGE		P-VALUE	
			MEAN	SD	MEAN	SD			95% CL		(A)	(B)
									LOWER	UPPER		
DIGIT RECALL STD SCR	ADHD	20	95.75	18.86	98.70	17.65	3.89	2.21	-0.57	8.35	.086	.751
	ADHD+DYSLEXIA	35	87.63	11.15	90.49	11.60	2.96	2.08	-1.23	7.15	.162	
WORD LIST MATCH STD SCR	ADHD	20	92.90	15.40	93.30	15.29	-1.36	3.80	-9.03	6.30	.722	.854
	ADHD+DYSLEXIA	34	91.50	15.76	94.44	15.59	-0.47	3.48	-7.48	6.54	.893	
WORD LIST RECALL STD SCR	ADHD	19	95.26	15.64	98.16	17.48	-1.66	2.75	-7.20	3.88	.549	.347
	ADHD+DYSLEXIA	35	93.89	16.17	98.43	14.52	1.72	2.54	-3.40	6.83	.503	
NON-WORD LIST RECALL STD SCR	ADHD	20	96.85	15.91	107.30	16.74	7.38	3.15	1.04	13.72	.024	.747
	ADHD+DYSLEXIA	35	99.37	15.44	107.54	15.59	8.68	2.87	2.91	14.46	.004	
BLOCK RECALL STD SCR	ADHD	20	88.30	20.44	92.70	16.29	3.26	4.08	-4.97	11.48	.429	.448
	ADHD+DYSLEXIA	34	88.76	15.87	94.00	17.30	7.27	3.79	-0.36	14.91	.061	
MAZES MEMORY STD SCR	ADHD	20	86.10	14.02	90.20	18.65	5.40	4.53	-3.75	14.56	.240	.800
	ADHD+DYSLEXIA	30	87.40	18.24	93.23	19.86	6.86	4.30	-1.83	15.55	.118	
LISTENING RECALL STD SCR	ADHD	19	93.05	18.54	109.58	19.09	11.69	4.67	2.25	21.13	.016	.290
	ADHD+DYSLEXIA	33	99.82	15.58	107.12	19.81	5.69	3.73	-1.85	13.24	.135	
COUNTING RECALL STD SCR	ADHD	20	88.85	14.64	92.45	23.67	3.12	4.38	-5.71	11.96	.480	.401
	ADHD+DYSLEXIA	35	86.60	16.16	89.40	19.27	-1.83	4.16	-10.22	6.56	.662	
BACKWARD DIGIT RECALL STD SCR	ADHD	20	90.80	14.00	96.30	17.61	3.45	2.25	-1.08	7.99	.132	.641
	ADHD+DYSLEXIA	35	84.06	10.82	85.74	11.33	2.10	2.01	-1.95	6.15	.301	
PHONOLOGICAL LOOP TOTAL STD SCR	ADHD	20	376.00	39.25	386.40	49.84	5.23	9.65	-14.22	24.68	.591	.233
PHONOLOGICAL LOOP TOTAL STD SCR	ADHD+DYSLEXIA	35	365.46	55.59	385.54	54.20	20.21	8.92	2.24	38.18	.028	
PHONOLOGICAL LOOP COMPONENT SCR	ADHD	20	92.40	12.78	95.50	16.16	1.47	3.18	-4.94	7.88	.645	.435
	ADHD+DYSLEXIA	34	90.82	13.52	96.74	14.38	4.75	3.01	-1.33	10.82	.122	

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Table 5. WMTB-C Baseline to Endpoint (LOCF) Change Score (Concluded)

WMTB SCORE	GROUP	N	BASELINE		ENDPOINT		CHANGE		95% CL		P-VALUE	
			MEAN	SD	MEAN	SD	LSMEAN	SE	LOWER	UPPER	(A)	(B)
VISUO-SPATIAL TOTAL STD SCR	ADHD	20	170.25	33.86	178.65	35.12	6.19	9.13	-12.21	24.60	.501	.417
	ADHD+DYSLEXIA	35	162.83	47.02	173.77	50.67	15.99	8.47	-1.08	33.06	.066	
VISUO-SPATIAL COMPONENT SCR	ADHD	20	83.85	16.92	85.55	13.12	0.64	4.27	-8.01	9.29	.882	.253
	ADHD+DYSLEXIA	29	87.93	17.54	93.21	20.05	6.87	4.07	-1.36	15.10	.099	
CENTRAL EXECUTIVE TOTAL STD SCR	ADHD	20	268.05	40.12	292.80	51.39	24.31	9.83	4.49	44.13	.017	.152
	ADHD+DYSLEXIA	35	262.40	45.74	270.83	44.81	5.90	9.07	-12.38	24.17	.519	
CENTRAL EXECUTIVE COMPONENT SCR	ADHD	19	87.79	15.69	97.47	23.37	8.42	3.79	0.75	16.08	.032	.449
	ADHD+DYSLEXIA	32	88.31	13.30	94.22	14.52	4.89	3.31	-1.79	11.58	.147	

(A) WITHIN GROUP CHANGE FROM BASELINE TO ENDPOINT (LOCF) SCORE P-VALUE IS FROM STUDENT'S T-TEST

(B) BETWEEN DIAGNOSTIC GROUPS P-VALUE IS FROM TYPE III SUMS OF SQUARES

P-VALUES (A), (B), LSMEAN, AND STDERR ARE FROM AN ANCOVA MODEL: CHANGE = BASELINE QUESDIAG INVP GENDER AGE BASELINE*QUESDIAG
 BASELINE : LAST OF (VISITS 1-3), ENDPOINT : LAST OF (VISITS 4-9)

Abbreviations: ADHD=Attention Deficit/Hyperactivity Disorder, LOCF=Last Observation Carried Forward, WMTB-C= Working Memory Test Battery for Children.

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Table 6. Repeated Measures Analysis of Change for WMTBC Component Scores

WMTB Score	Group	N	LSMean	LSMean Change	Within Group p-Value	Between Group p-Value
Central Executive Component Score						
Visit 5	ADHD	17	94.32	6.05	.057	.132
	ADHD+D	29	88.12	-0.15	.954	
Visit 7	ADHD	17	92.59	4.32	.176	.589
	ADHD+D	31	90.37	2.10	.407	
Visit 9	ADHD	14	102.66	14.39	<.001	.012*
	ADHD+D	27	91.41	3.15	.233	
Visuo-Spatial Component Score						
Visit 5	ADHD	19	84.99	-1.69	.638	.120
	ADHD+D	26	92.69	6.01	.069	
Visit 7	ADHD	18	90.55	3.87	.295	.959
	ADHD+D	24	90.80	4.12	.215	
Visit 9	ADHD	14	89.52	2.84	.472	.255
	ADHD+D	24	95.49	8.81	.009*	
Phonological Loop Component Score						
Visit 5	ADHD	20	93.46	2.70	.321	.556
	ADHD+D	31	95.63	4.87	.044*	
Visit 7	ADHD	18	93.95	3.18	.258	.315
	ADHD+D	32	97.71	6.95	.004*	
Visit 9	ADHD	16	92.53	1.77	.548	.128
	ADHD+D	30	98.52	7.76	.002*	

Abbreviations: ADHD=Attention Deficit/Hyperactivity Disorder; ADHD+D = ADHD and dyslexia; WMTB-C= Working Memory Test Battery for Children

* = statistically significant.

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Table 7. Repeated Measures Analysis of Change for WMTBC Standard Scores

WMTB Score	Group	N	LSMean	LSMean Change	Within Group p-Value	Between Group p-Value
Central Executive Standard Score						
Visit 5	ADHD	20	273.73	7.62	.349	.184
	ADHD+D	34	259.42	-6.69	.321	
Visit 7	ADHD	19	279.05	12.94	.123	.539
	ADHD+D	33	272.32	6.21	.361	
Visit 9	ADHD	16	303.14	37.04	<.001*	.003*
	ADHD+D	31	267.41	1.30	.851	
Visuo-Spatial Standard Score						
Visit 5	ADHD	20	166.04	-0.19	.981	.274
	ADHD+D	33	177.80	11.57	.089	
Visit 7	ADHD	19	175.07	8.84	.281	.773
	ADHD+D	32	171.95	5.72	.399	
Visit 9	ADHD	16	178.08	11.85	.179	.746
	ADHD+D	31	181.79	15.56	.025*	
Phonological Loop Standard Score						
Visit 5	ADHD	20	378.19	9.86	.239	.664
	ADHD+D	33	383.05	14.72	.042*	
Visit 7	ADHD	19	376.77	8.43	.323	.230
	ADHD+D	33	390.43	22.10	.003*	
Visit 9	ADHD	16	375.08	6.74	.455	.107
	ADHD+D	31	394.23	25.89	<.001*	

Abbreviations: ADHD=Attention Deficit/Hyperactivity Disorder; ADHD+D = ADHD and dyslexia; WMTB-C= Working Memory Test Battery for Children

* = statistically significant.

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Table 8. Comparison of WMTB-C for Patients While On Stimulants versus After Atomoxetine Treatment

WMTB SCORE	GROUP	N	BASELINE		ENDPOINT		CHANGE FROM BASELINE				P-VALUE	
			MEAN	SD	MEAN	SD	LSMEAN	SE	95% CL		(A)	(B)
									LOWER	UPPER		
DIGIT RECALL TRIAL STD SCORE	ADHD	10	91.70	11.70	95.00	16.08	3.34	2.57	-1.95	8.64	0.224	0.697
	ADHD+DYSLEXIA	21	84.43	10.55	87.76	13.08	1.99	2.03	-2.20	6.17	0.049	
WORD LIST MATCH TRIAL STD SCORE	ADHD	10	88.00	15.57	98.20	17.84	11.27	6.52	-2.22	24.75	0.142	0.986
	ADHD+DYSLEXIA	20	86.70	11.89	95.90	18.61	11.42	5.17	0.72	22.12	0.033	
WORD LIST RECALL TRIAL STD SCORE	ADHD	9	88.44	13.47	97.67	18.79	3.83	4.97	-6.46	14.12	0.115	0.351
	ADHD+DYSLEXIA	21	90.52	15.22	98.48	15.96	10.03	3.68	2.41	17.64	0.022	
NON-WORD LIST RECALL TRIAL STD SCORE	ADHD	10	104.30	24.06	105.90	18.30	0.12	5.12	-10.43	10.68	0.768	0.109
	ADHD+DYSLEXIA	21	97.33	15.42	107.33	17.73	11.56	4.04	3.21	19.90	0.005	
BLOCK RECALL TRIAL STD SCORE	ADHD	10	93.00	9.99	96.40	20.09	5.83	5.02	-4.56	16.22	0.491	0.394
	ADHD+DYSLEXIA	20	89.85	14.30	88.75	13.95	-0.10	4.04	-8.45	8.25	0.714	
MAZES MEMORY TRIAL STD SCORE	ADHD	10	92.50	14.43	96.00	21.11	6.14	6.21	-6.90	19.18	0.628	0.334
	ADHD+DYSLEXIA	14	81.50	14.76	81.64	14.55	-3.60	6.74	-17.75	10.55	0.978	
LISTENING RECALL TRIAL STD SCORE	ADHD	9	96.33	17.81	107.11	21.87	12.25	6.32	-0.97	25.47	0.082	0.417
	ADHD+DYSLEXIA	17	98.18	15.96	102.71	16.81	5.60	4.94	-4.75	15.95	0.317	
COUNTING RECALL TRIAL STD SCORE	ADHD	9	87.56	20.38	99.00	26.77	8.31	6.15	-4.41	21.02	0.183	0.058
	ADHD+DYSLEXIA	21	86.52	15.46	88.33	18.67	-7.90	4.91	-18.05	2.25	0.661	
BACKWARD DIGIT RECALL STD SCORE	ADHD	10	88.50	10.39	91.70	16.51	2.73	4.79	-7.16	12.62	0.290	0.830
	ADHD+DYSLEXIA	21	85.33	17.71	83.76	11.18	1.32	3.79	-6.49	9.14	0.617	
PHONOLOGICAL LOOP COMPONENT SCORE	ADHD	10	92.70	17.35	95.70	16.85	2.38	4.94	-7.84	12.60	0.601	0.331
	ADHD+DYSLEXIA	20	87.75	12.46	96.05	17.06	8.98	3.92	0.87	17.08	0.008	
VISUO-SPATIAL SKETCHPAD COMPONENT SCORE	ADHD	10	90.50	12.63	87.40	12.21	-2.25	5.50	-13.81	9.31	0.489	0.925
	ADHD+DYSLEXIA	14	81.79	13.75	81.57	12.54	-1.42	5.97	-13.97	11.13	0.963	
CENTRAL EXECUTIVE COMPONENT SCORE	ADHD	7	89.71	19.79	97.14	26.58	7.58	5.80	-4.66	19.81	0.232	0.425
	ADHD+DYSLEXIA	17	88.35	18.02	91.53	13.12	1.63	4.31	-7.46	10.72	0.400	

(A) WITHIN GROUP CHANGE FROM BASELINE TO ENDPOINT SCORE P-VALUE IS FROM STUDENT'S T-TEST

(B) BETWEEN DIAGNOSTIC GROUPS P-VALUE IS FROM TYPE III SUMS OF SQUARES

P-VALUES (A), (B), LSMEAN, AND STDERR ARE FROM AN ANOVA MODEL: CHANGE = QUESDIAG INVP

BASELINE : VISIT 1, ENDPOINT : LAST OF VISIT 4 - VISIT 9

Abbreviations: ADHD=Attention Deficit/Hyperactivity Disorder; WMTB-C = Working Memory Test Battery for Children

Life Participation Scale for ADHD-Revised (LPS-ADHD-R)

An increase in the LPS-ADHD-R score indicates improvement.

Both the ADHD and ADHD+D groups showed a statistically significant mean increase on the total score for both the investigator- and parent-rated versions of the Life Participation Scale for ADHD-Revised (LPS-ADHD-R). Further, both groups showed a statistically significant within-group change in all the other scales ($p \leq .05$) with the exception of the “happy/social subscale,” which was not statistically significant for the ADHD group for the investigator-rated version of the scale. There were no statistically significant differences between the diagnostic groups for total score or any of the subscales scores (Table 9).

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Table 9. Baseline to Endpoint (LOCF) Mean Change for Life Participation Total Score-Investigator- and Parent-Rated

LPS OR LPSP SCORE (IMPUTED)	GROUP	N	MEAN	SD	MEAN	SD	LSMEAN	SE	LOWER	UPPER	(A)	(B)
LPS-INV VS HAPPY/SOC SUBSCALE	ADHD	20	15.35	4.90	15.40	3.79	0.60	1.00	-1.41	2.61	.550	.306
	ADHD+DYSLEXIA	35	13.86	3.52	15.31	4.88	1.92	0.90	0.10	3.73	.039	
LPS-INV VS SELF-CNTL SUBSCALE	ADHD	20	19.70	7.02	28.10	10.83	7.21	2.28	2.61	11.80	.003	.197
	ADHD+DYSLEXIA	35	20.20	8.53	29.96	9.74	11.05	2.06	6.89	15.21	<.001	
LPS TOTAL	ADHD	20	35.05	9.86	43.50	13.36	7.46	3.12	1.17	13.74	.021	.174
	ADHD+DYSLEXIA	35	34.06	10.61	45.27	13.65	12.99	2.83	7.28	18.70	<.001	
LPSP-INV VS HAPPY/SOC SUBSCALE	ADHD	20	11.90	5.41	14.90	4.12	3.01	0.94	1.11	4.90	.003	.519
	ADHD+DYSLEXIA	35	13.26	3.06	14.80	4.70	2.21	0.84	0.51	3.91	.012	
LPSP-INV VS SELF-CNTL SUBSCALE	ADHD	20	16.43	8.31	26.35	10.80	8.53	2.53	3.43	13.63	.002	.645
	ADHD+DYSLEXIA	35	20.54	6.88	28.30	10.02	10.07	2.19	5.66	14.49	<.001	
LPSP TOTAL	ADHD	20	28.33	12.42	41.25	13.64	11.27	3.32	4.57	17.96	.001	.787
	ADHD+DYSLEXIA	35	33.80	8.41	43.10	14.04	12.45	2.87	6.67	18.22	<.001	

(A) WITHIN GROUP CHANGE FROM BASELINE TO ENDPOINT (LOCF) SCORE P-VALUE IS FROM STUDENT'S T-TEST

(B) BETWEEN DIAGNOSTIC GROUPS P-VALUE IS FROM TYPE III SUMS OF SQUARES

P-VALUES (A), (B), LSMEAN, AND STDERR ARE FROM AN ANCOVA MODEL: CHANGE = BASELINE QUESDIAG INVP GENDER AGE BASELINE*QUESDIAG
 BASELINE: LAST OF (VISITS 1-3), ENDPOINT: LAST OF (VISITS 4-9)

Abbreviations: ADHD=Attention Deficit/Hyperactivity Disorder, LPS-INV=Life Participation Score-Investigator, LPSP-INV=Life Participation Scale-Parent

LOCF=Last Observation Carried Forward, WMTB-C= Working Memory Test Battery for Children.

Safety

Deaths

There were no deaths reported in the study.

Serious adverse events

No serious adverse events were reported during the study.

Discontinuation due to Adverse Events

Out of 56 patients, 4 patients discontinued due to adverse events (1 in ADHD and 3 in ADHD+D group), reasons being nausea, mood swings, and abdominal pain. All 4 observed adverse events were related to study medication as reported by the investigator.

Treatment-emergent adverse events (TEAE)

Approximately 84% (n=47) of patients enrolled in the trial reported at least one treatment emergent adverse event (90% in ADHD and 81% in ADHD+D group, p=.466). The most common adverse events were somnolence (34%) and nausea (30%). In addition, adverse events occurring in 10% or more of patients included: decreased appetite, headache, nasopharyngitis, upper abdominal pain, vomiting, cough, pharyngitis, and upper respiratory tract infection. The frequency of TEAEs occurring in 10% or more of patients is summarized in Table 10.

Table 10. Frequency of Treatment Emergent Adverse Events (>10%)

Event Classification	ADHD (N=20)	ADHD+D (N=36)	Total (N=56)	p-Value
	% (n)	% (n)	% (n)	
Patients with ≥ 1 TEAE	90.00 (18)	80.56 (29)	83.93 (47)	0.466
Somnolence	40.00 (8)	30.56 (11)	33.93 (19)	0.561
Nausea	30.00 (6)	30.56 (11)	30.36 (17)	1.000
Decreased appetite	25.00 (5)	19.44 (7)	21.43 (12)	0.737
Headache	25.00 (5)	16.67 (6)	19.64 (11)	0.497
Nasopharyngitis	25.00 (5)	5.56 (2)	12.50 (7)	0.084
Abdominal pain upper	20.00 (4)	19.44 (7)	19.64 (11)	1.000
Vomiting	15.00 (3)	16.67 (6)	16.07 (9)	1.000
Cough	10.00 (2)	5.56 (2)	7.14 (4)	0.611
Pharyngitis	10.00 (2)	0.00 (0)	3.57 (2)	0.123
Upper respiratory tract infection	10.00 (2)	2.78 (1)	5.36 (3)	0.288

Abbreviations: n=No. of patients, N=Sample size, TEAE=Treatment Emergent Adverse Event.

Clinical Laboratory Evaluation

Table 11 presents the complete mean change from baseline to endpoint for all lab values. Statistically significant changes from baseline to endpoint were observed in both the ADHD and ADHD+D groups for many of the laboratory tests including clinical chemistry, hematology, and urinalysis parameters ($p \leq .001$).

For the ADHD group, statistically significant mean changes ($p < .05$) were:

Chemistry: ALT/SGPT, total bilirubin, creatine phosphokinase, creatinine, and hematocrit.

Hematology: Leukocyte count, lymphocytes, mean cell volume, and segmented neutrophils.

For the ADHD+D group, statistically mean changes ($p < .05$) were:

Chemistry: Alkaline phosphatase, ALT/SGPT, AST/SGOT, calcium, creatine phosphokinase, GGT (GGPT/SGGT/YGGT), total protein, urea nitrogen, and uric acid.

Hematology: Hemoglobin, leukocyte count, and platelet count.

Urinalysis: specific gravity.

Comparisons between groups were done using the ranks of the raw data. There were statistically significant differences between the two groups for cholesterol ($p = .037$), uric acid ($p = .007$), hematocrit ($p = .014$), hemoglobin ($p = .028$), and urine specific gravity ($p = .015$).

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Table 11. Change from Baseline to Endpoint for Laboratory Analytes

Lab Group	Analyte	Group	N	Baseline		Endpoint		Change		Within Group P-Value*	Between Group P-Value**
				Mean	SD	Mean	SD	Mean	SD		
CHEM	ALBUMIN	ADHD	18	44.28	2.63	44.72	2.67	0.44	3.18	0.562	0.078
		ADHD+DYSLEXIA	35	43.66	2.86	42.91	2.43	-0.74	2.57	0.096	
	ALKALINE PHOSPHATASE	ADHD	18	275.06	94.89	260.83	108.72	-14.22	62.60	0.349	0.631
		ADHD+DYSLEXIA	35	247.91	107.03	232.09	100.84	-15.83	37.70	0.018	
	ALT/SGPT	ADHD	18	16.50	6.05	14.56	5.35	-1.94	2.69	0.007	0.443
		ADHD+DYSLEXIA	35	23.71	16.52	19.00	13.00	-4.71	10.71	0.014	
	AST/SGOT	ADHD	18	23.28	6.38	22.33	5.09	-0.94	4.05	0.336	0.179
		ADHD+DYSLEXIA	35	28.14	14.65	23.57	8.67	-4.57	9.54	0.008	
	BILIRUBIN, TOTAL	ADHD	16	5.88	1.78	7.19	2.17	1.31	2.18	0.029	0.104
		ADHD+DYSLEXIA	28	8.29	4.78	7.89	4.49	-0.39	2.62	0.434	
	CALCIUM	ADHD	18	2.48	0.10	2.50	0.08	0.02	0.13	0.584	0.094
		ADHD+DYSLEXIA	35	2.51	0.11	2.47	0.10	-0.04	0.09	0.015	
	CHOLESTEROL	ADHD	18	3.82	0.69	3.90	0.55	0.08	0.71	0.638	0.037
		ADHD+DYSLEXIA	35	4.23	0.90	4.11	0.85	-0.13	0.40	0.068	
	CREATINE PHOSPHOKINASE	ADHD	18	137.39	107.73	103.06	56.04	-34.33	65.81	0.041	0.892
		ADHD+DYSLEXIA	35	133.60	89.76	109.69	46.23	-23.91	65.72	0.039	
	CREATININE	ADHD	18	49.50	9.33	55.50	10.15	6.00	10.24	0.024	0.261
		ADHD+DYSLEXIA	35	53.97	17.54	51.20	9.71	-2.77	17.00	0.342	
	GGT (GGPT/SGGT/YGGT)	ADHD	18	12.28	3.12	11.22	3.54	-1.06	2.15	0.053	0.496
		ADHD+DYSLEXIA	35	19.29	13.62	15.89	9.92	-3.40	8.00	0.017	
	GLUCOSE, NON-FASTING	ADHD	18	5.00	0.49	4.89	1.21	-0.11	1.19	0.696	0.133
		ADHD+DYSLEXIA	35	4.81	0.93	4.94	0.84	0.13	1.00	0.442	
	INORGANIC PHOSPHORUS	ADHD	18	1.55	0.19	1.50	0.23	-0.05	0.14	0.183	0.181
		ADHD+DYSLEXIA	35	1.57	0.17	1.51	0.19	-0.05	0.16	0.056	

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Table 11. Change from Baseline to Endpoint for Laboratory Analytes (Continued)

Lab Group	Analyte	Group	N	Baseline		Endpoint		Change		Within Group P-Value*	Between Group P-Value**
				Mean	SD	Mean	SD	Mean	SD		
	TOTAL PROTEIN	ADHD	18	73.00	4.54	73.22	2.96	0.22	4.93	0.851	0.375
		ADHD+DYSLEXIA	35	73.26	5.29	71.37	4.74	-1.89	4.44	0.017	
	UREA NITROGEN	ADHD	18	4.68	1.29	4.56	1.29	-0.12	1.28	0.703	0.670
		ADHD+DYSLEXIA	35	5.26	1.31	4.79	1.13	-0.47	1.36	0.049	
	URIC ACID	ADHD	18	262.17	57.67	269.06	44.46	6.89	46.71	0.540	0.007
		ADHD+DYSLEXIA	35	272.69	75.53	246.09	64.83	-26.60	44.97	0.001	
HEME	BANDS	ADHD	17	0.00	0.00	0.00	0.00	0.00	0.00	†	0.683
		ADHD+DYSLEXIA	35	0.00	0.00	0.00	0.01	0.00	0.01	0.324	
	BASOPHILS	ADHD	17	0.04	0.02	0.05	0.02	0.00	0.02	0.922	0.369
		ADHD+DYSLEXIA	35	0.04	0.02	0.04	0.02	0.00	0.03	0.845	
	EOSINOPHILS	ADHD	17	0.27	0.27	0.19	0.19	-0.08	0.21	0.124	0.449
		ADHD+DYSLEXIA	35	0.21	0.13	0.19	0.15	-0.02	0.15	0.462	
	ERYTHROCYTE COUNT	ADHD	17	4.83	0.32	4.88	0.34	0.05	0.25	0.440	0.077
		ADHD+DYSLEXIA	35	4.91	0.35	4.83	0.37	-0.08	0.27	0.090	
	HEMATOCRIT	ADHD	17	0.41	0.02	0.42	0.03	0.01	0.02	0.022	0.014
		ADHD+DYSLEXIA	35	0.41	0.03	0.40	0.03	-0.01	0.02	0.135	
	HEMOGLOBIN	ADHD	17	8.72	0.43	8.80	0.57	0.08	0.40	0.424	0.028
		ADHD+DYSLEXIA	35	8.35	0.76	8.20	0.65	-0.15	0.44	0.049	
	LEUKOCYTE COUNT	ADHD	17	7.63	2.32	6.38	1.76	-1.25	1.47	0.003	0.312
		ADHD+DYSLEXIA	35	6.73	1.82	6.25	1.78	-0.48	1.36	0.044	
	LYMPHOCYTES	ADHD	17	2.65	0.54	2.28	0.52	-0.37	0.35	<0.001	0.190
		ADHD+DYSLEXIA	35	2.45	0.79	2.32	0.71	-0.13	0.59	0.204	
	MEAN CELL VOLUME (MCV)	ADHD	17	84.41	4.12	86.41	3.41	2.00	3.81	0.046	0.110
		ADHD+DYSLEXIA	35	82.77	5.33	82.77	5.54	0.00	2.98	>0.999	

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Table 11. Change from Baseline to Endpoint for Laboratory Analytes (Concluded)

Lab Group	Analyte	Group	N	Baseline		Endpoint		Change		Within Group P-Value*	Between Group P-Value**
				Mean	SD	Mean	SD	Mean	SD		
	MONOCYTES	ADHD	17	0.43	0.13	0.37	0.14	-0.06	0.13	0.065	0.962
		ADHD+DYSLEXIA	35	0.37	0.11	0.34	0.11	-0.03	0.12	0.141	
	NEUTROPHILS, SEGMENTED	ADHD	17	4.24	1.98	3.50	1.43	-0.74	1.32	0.035	0.645
		ADHD+DYSLEXIA	35	3.65	1.36	3.35	1.32	-0.29	1.21	0.159	
	PLATELET COUNT	ADHD	17	326.24	64.90	312.06	56.66	-14.18	46.20	0.224	0.401
		ADHD+DYSLEXIA	35	310.94	67.35	296.46	57.51	-14.49	41.76	0.048	
LYTES BICARBONATE, HCO ₃		ADHD	18	24.54	2.34	25.43	2.87	0.88	2.86	0.208	0.892
		ADHD+DYSLEXIA	35	24.28	2.40	25.00	2.78	0.71	2.99	0.166	
	CHLORIDE	ADHD	18	105.61	2.09	104.56	2.33	-1.06	2.51	0.092	0.241
		ADHD+DYSLEXIA	35	104.00	2.38	103.23	1.94	-0.77	2.57	0.084	
	POTASSIUM	ADHD	18	4.29	0.42	4.30	0.40	0.01	0.52	0.964	0.271
		ADHD+DYSLEXIA	35	4.31	0.36	4.16	0.31	-0.15	0.47	0.068	
LYTES SODIUM		ADHD	18	141.44	1.82	140.94	1.95	-0.50	2.38	0.386	0.906
		ADHD+DYSLEXIA	35	140.14	1.90	139.57	1.77	-0.57	2.38	0.165	
UA	UA-SPECIFIC GRAVITY	ADHD	18	1.03	0.01	1.03	0.00	0.00	0.01	0.768	0.015
		ADHD+DYSLEXIA	35	1.02	0.01	1.03	0.01	0.01	0.01	0.002	

* P-VALUE IS FROM CHANGE FROM BASELINE TO ENDPOINT USING STUDENT'S T-TEST

** P-VALUE IS FROM A TYPE III SUM OF SQUARES USING MODEL: RANKED CHANGE = QUESDIAG INVESTIGATOR

† Baseline and endpoint values were less than 0.01 and rounded to 0.0. Standard deviation was 0 and p-value cannot be derived.

BASELINE: LAST OF VISITS 1-3 ENDPOINT: LAST OF VISITS 4-9

POPULATION: ALL RANDOMIZED PATIENTS WHO TOOK AT LEAST ONE DOSE OF STUDY MEDICATION

Abbreviations: ADHD=Attention Deficit/Hyperactivity Disorder

Vital Signs

Table 12 presents baseline to endpoint change scores for vital sign measures. For vital sign measures of diastolic and systolic blood pressure and weight, there were no statistically significant changes from baseline to endpoint.

Mean pulse rate change was statistically significant for the ADHD group (6.31 ± 3.14 , $p=.05$).

There was a statistically significant mean change for body mass index in the ADHD (-0.76 ± 0.29 , $p=.012$) and ADHD+D (-0.63 ± 0.22 , $p=.006$) groups.

Mean change for height from baseline to endpoint was statistically significant for both the groups ($p<0.001$).

There was no statistically significant difference between the two groups in change from baseline to endpoint for any vital sign measures.

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Table 12. LOCF Mean Change from Baseline to Endpoint for Vital Signs

VITAL SIGNS	GROUP	N	BASELINE		ENDPOINT		CHANGE		95% CL		P-VALUE	
			MEAN	SD	MEAN	SD	LSMEAN	STDERR	LOWER	UPPER	(A)	(B)
HEIGHT (CM)	ADHD	17	155.59	9.13	157.56	8.83	1.74	0.49	0.75	2.73	<.001	.484
	ADHD+DYSLEXIA	35	148.64	12.24	150.47	12.15	2.19	0.37	1.44	2.95	<.001	
WEIGHT (KG)	ADHD	20	48.10	8.91	46.98	8.56	-0.82	0.53	-1.89	0.25	.129	.794
	ADHD+DYSLEXIA	36	47.86	13.52	47.49	13.69	-0.63	0.44	-1.52	0.26	.159	
BODY MASS INDEX	ADHD	17	20.03	2.66	19.14	2.20	-0.76	0.29	-1.34	-0.18	.012	.733
	ADHD+DYSLEXIA	35	21.04	4.39	20.62	4.50	-0.63	0.22	-1.07	-0.19	.006	
PULSE	ADHD	20	74.40	7.38	81.90	13.05	6.31	3.14	0.01	12.62	.050	.701
	ADHD+DYSLEXIA	36	78.69	11.77	81.03	11.26	4.69	2.61	-0.56	9.94	.079	
DIASTOLIC BLOOD PRESSURE	ADHD	20	69.65	9.43	69.75	6.32	1.24	2.55	-3.88	6.35	.630	.935
	ADHD+DYSLEXIA	36	65.72	6.63	67.22	8.25	0.96	2.12	-3.31	5.22	.654	
SYSTOLIC BLOOD PRESSURE	ADHD	20	108.55	9.94	104.95	8.25	-2.62	2.24	-7.12	1.89	.249	.303
	ADHD+DYSLEXIA	36	102.33	9.98	104.03	9.13	0.50	1.87	-3.25	4.25	.788	

 (A) WITHIN GROUP CHANGE FROM BASELINE TO ENDPOINT (LOCF) SCORE P-VALUE IS FROM STUDENT'S T-TEST

(B) BETWEEN DIAGNOSTIC GROUPS CHANGE P-VALUE IS FROM TYPE III SUMS OF SQUARES

P-VALUES (A), (B), LSMEAN, AND STDERR ARE FROM AN ANCOVA MODEL: CHANGE = QUESDIAG INVP

BASELINE : LAST OF (VISITS 1-3), ENDPOINT : LAST OF (VISITS 4-9)

Abbreviations: ADHD=Attention Deficit/Hyperactivity Disorder

Electrocardiogram

Table 13 presents mean change from baseline to endpoint for ECG parameters.

A statistically significant decrease in PR interval occurred in the ADHD (8.73 ± 3.91 ; $p=.03$) and the ADHD+D (-7.39 ± 0.28 ; $p=.028$) groups. The ADHD+D group also showed statistically significant decrease in QT interval and RR-1000*60/HR ($p<0.001$).

There was a statistically significant difference between the two groups in PR interval ($p=.003$) and RR-1000*60/HR ($p=.018$).

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Table 13. LOCF Mean Change from Baseline for ECG Parameters

ECG	GROUP	N	BASELINE		ENDPOINT		CHANGE		95% CL		P-VALUE	
			MEAN	SD	MEAN	SD	LSMEAN	STDERR	LOWER	UPPER	(A)	(B)
PR INTERVAL (MSEC)	ADHD	20	136.50	14.96	143.00	20.55	8.73	3.91	0.87	16.58	.030	.003
	ADHD+DYSLEXIA	36	138.89	17.85	131.75	15.34	-7.39	3.26	-13.93	-0.84	.028	
QRS INTERVAL (MSEC)	ADHD	20	82.50	6.39	83.50	7.45	1.25	1.84	-2.45	4.95	.501	.988
	ADHD+DYSLEXIA	36	83.47	8.44	84.72	9.41	1.21	1.53	-1.87	4.30	.433	
QT INTERVAL (MSEC)	ADHD	20	370.00	25.55	362.50	28.26	-5.56	4.93	-15.47	4.34	.265	.068
	ADHD+DYSLEXIA	36	375.44	28.40	363.06	26.06	-17.90	4.11	-26.16	-9.65	<.001	
QT/(RR/1000)**0.39	ADHD	20	404.17	20.33	402.15	13.94	-1.63	3.93	-9.53	6.27	.680	.610
	ADHD+DYSLEXIA	36	400.67	17.23	402.80	16.20	1.08	3.28	-5.51	7.66	.744	
QT/CUBIC ROOT RR	ADHD	20	398.91	19.37	396.03	14.56	-2.26	3.74	-9.76	5.25	.549	.937
	ADHD+DYSLEXIA	36	396.79	17.16	396.67	16.04	-1.86	3.11	-8.11	4.40	.553	
QT/(RR/1000)**0.37	ADHD	20	402.30	19.91	399.98	14.05	-1.85	3.85	-9.58	5.88	.632	.716
	ADHD+DYSLEXIA	36	399.29	17.11	400.62	16.05	0.03	3.20	-6.41	6.47	.992	
RR - 1000*60/HR	ADHD	20	805.78	136.91	772.30	134.04	-24.46	26.30	-77.32	28.40	.357	.018
	ADHD+DYSLEXIA	36	854.66	151.92	772.41	122.52	-110.47	21.91	-154.51	-66.43	<.001	

(A) WITHIN GROUP CHANGE FROM BASELINE TO ENDPOINT (LOCF) SCORE P-VALUE IS FROM STUDENT'S T-TEST

(B) BETWEEN DIAGNOSTIC GROUPS CHANGE P-VALUE IS FROM TYPE III SUMS OF SQUARES

P-VALUES (A), (B), LSMEAN, AND STDERR ARE FROM AN ANCOVA MODEL: CHANGE = QUESDIAG INVP

BASELINE : LAST OF (VISITS 1-3), ENDPOINT : LAST OF (VISITS 4-9)

Abbreviations: ADHD=Attention Deficit/Hyperactivity Disorder

Summary ID# 8160

Clinical Study Summary: Study B4Z-TW-S010

Efficacy, Tolerability, and Safety of Once-Daily Atomoxetine Hydrochloride versus Placebo in Taiwanese Children and Adolescents with Attention-Deficit/Hyperactivity Disorder

Date summary approved by Lilly: 20 October 2005

Brief Summary of Results

- The Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) total score decreased by 16.9 ± 10.8 (mean $\pm$ SD change from baseline to Visit 6, $p < .001$) with atomoxetine treatment. A decrease of 7.5 ± 13.1 (mean $\pm$ SD change from baseline to Visit 6, $p = .002$) in the ADHDRS-IV-Parent:Inv total score was observed with placebo treatment. At each visit during the treatment phase, comparison of the mean change from baseline between the two groups showed that atomoxetine was more effective than placebo at decreasing the ADHDRS-IV-Parent:Inv total score ($p < .001$).
- At each visit during the treatment phase, comparison of the mean change from baseline between the two groups showed that atomoxetine was more effective than placebo at decreasing the ADHDRS-IV-Parent:Inv Inattention subscale score and Hyperactivity/Impulsive subscale scores ($p < .01$).
- At the end of the treatment phase (Visit 6), 74% of subjects from the atomoxetine group were categorized as responders compared with 38% of subjects from the placebo group ($p < .001$). A responder was defined as having a $>25\%$ reduction from baseline in the ADHDRS-IV-Parent:Inv total score.

- Comparison of the mean change from baseline to the end of Study Period II (SPII) between the two groups showed that atomoxetine was more effective than placebo at decreasing the mean Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) total score as well as all mean CPRS-R:S subscale scores ($p < .05$).
- Comparison of the mean change from baseline to Visit 6 between the two groups showed that atomoxetine was more effective than placebo at decreasing the mean Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R:S) total score as well as mean CTRS-R:S Cognitive Problems, Hyperactivity, and ADHD Index subscale scores ($p < .05$). The CTRS-R:S Oppositional subscale score was not statistically significantly altered compared to baseline in either treatment group.
- From the safety population ($n=105$), 70 (66.7 %) subjects reported one or more TEAE(s) ($n=54$ from the atomoxetine group, $n=16$ from the placebo group; $p=.004$). Of these 70 subjects, 45 ($n=40$ from the atomoxetine group, $n=5$ from the placebo group; $p<.001$) experienced drug-related treatment-emergent adverse events (TEAEs) in the opinion of the investigator. Two serious adverse events (SAEs) were reported during the study, with one being categorized as a serious TEAE. Both were assessed to be related to either study drug or study procedures.
- The most common TEAE reported by subjects from the atomoxetine group was anorexia, which was reported by 26 (36.6 %) subjects from this group compared with five (14.7 %) subjects from the placebo group ($p=.02$). Nausea was reported by 12 (16.9 %) subjects from the atomoxetine group, while no subjects receiving placebo reported this TEAE ($p<.01$). Anorexia was the most common drug-related TEAE reported by subjects from the atomoxetine group, with 23 cases categorized as drug-related.
- At all visits, there was a statistically significant weight decrease in the atomoxetine group ($p<.001$) and a statistically significant weight increase in the placebo group ($p<.05$). The difference between the two groups was statistically significant at all visits ($p<.001$). No between-group differences were observed for systolic blood pressure, diastolic blood pressure, heart rate, temperature, or weight.
- Statistically significant differences between treatment groups were observed for mean changes in some laboratory parameters compared to baseline, however these changes were, in the opinion of the treating investigator and the lead clinical research physician, clinically insignificant.

Title of Study: Efficacy, Tolerability, and Safety of Once-Daily Atomoxetine Hydrochloride versus Placebo in Taiwanese Children and Adolescents with Attention-Deficit/Hyperactivity Disorder.	
Investigator(s): This multi-center study included three principal investigators.	
Study Center(s): This study was conducted at three study centers in one country.	
Length of Study: 9 months Date of first subject visit: 26 February 2004 Date of last subject visit: 19 November 2004	Phase of Development: IIIb.
Objectives: Primary Objective: - To test the hypothesis that atomoxetine administered as a single-daily dose provides superior efficacy compared with placebo in Taiwanese children and adolescents with attention-deficit/hyperactivity disorder (ADHD). Assessment was measured by reduction from baseline to endpoint by the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) total score in the once-daily atomoxetine- and placebo-treated groups. Secondary Objectives: - To compare the improvement in symptoms associated with ADHD in children and adolescents achieved by once-daily dosing of atomoxetine or placebo as defined by a >25% reduction in the ADHDRS-IV-Parent:Inv score and by mean reductions in the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) and ADHDRS-IV-Parent:Inv subscale scores. - To compare the reduction in school-related symptoms between atomoxetine and placebo as assessed by the Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R:S). - To assess the safety and tolerability of once-daily dosing of atomoxetine.	
Study Design: This was a multi-center, randomized, double-blind, placebo-controlled study in children and adolescents aged 6 through 16 years who met the <i>Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition</i> TM (DSM-IV TM) criteria for ADHD, as well as criteria for enrollment. The protocol comprised three study periods and included an initial randomization of all subjects to acute treatment after an initial screening and washout period. Randomization was performed with 2:1 proportions of subjects being assigned to atomoxetine (target dose: 1.2 mg/kg/day) and placebo. During the acute treatment phase (Study Period II), study drug dosage were adjusted by the physician based on assessment of symptom response and tolerability. Following Study Period II, subjects entered a discontinuation phase comprised of one follow up visit.	
Number of Subjects: Planned: 70 atomoxetine, 35 placebo. Randomized/Entered: 72 atomoxetine (65 male, 7 female), 34 placebo (29 male, 5 female). Completed: 69 atomoxetine (63 male, 6 female), 29 placebo (24 male, 5 female).	
Diagnosis and Main Criteria for Inclusion: Subjects were aged 6 through 16 years with ADHD that met the DSM-IV TM disease diagnostic criteria as well as severity criteria. Diagnosis was assessed by clinical evaluation as well as administration of several modules of K-SADS:E-C structured interview. Subjects must also have had a total ADHDRS-IV-Parent:Inv score of at least 25 for boys or 22 for girls, or >12 for their diagnostic subtype at both Visit 1 and Visit 2. In addition, a Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity (CGI-ADHD-S) score $\geq$ 4 at both Visit 1 and Visit 2 was necessary. If subjects had taken any medication used to treat ADHD previously, they had to have completed the appropriate washout procedures.	
Test Product, Dose, and Mode of Administration: Atomoxetine Hydrochloride, given orally once daily. The target dose was 1.2 mg/kg/day up to a maximal daily dose of 100mg, provided as capsules (2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, and 40 mg).	

Reference Therapy, Dose, and Mode of Administration: Placebo, given orally once daily as capsules identical in appearance to test product.

Duration of Treatment: 6 weeks.
Atomoxetine Hydrochloride Frequency: 6 weeks.
Placebo Frequency: 6 weeks.

Variables:

Efficacy:

Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) scale.

Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) scale.

Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) scale.

Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R:S) scale.

Safety:

Vital signs.

Adverse events.

Clinical laboratory tests.

Evaluation Methods:

Statistical:

Descriptive statistics such as the number of observations, mean, median, standard deviations, minimum, maximum, and 95% confidence interval were used to summarize the continuous variables. Frequency and proportion were used to summarize the categorical variables. All statistical tests for efficacy endpoints and other clinical endpoints were two-sided and evaluated at $p=.05$ level of significance. The primary analysis for efficacy endpoints were performed based on the intent-to-treat (ITT) population.

The last-observation-carried-forward (LOCF) procedure was used to account for missing data among the efficacy parameters. No imputation was done for estimating the missing value for safety variables.

For demographic data and baseline characteristics, the comparability between treatment groups was examined by using two-way analysis of variance (ANOVA) with fixed factor treatment and investigator as terms in the model for continuous variables. Fisher's exact test was used to compare between treatment groups for categorical variables.

The primary efficacy endpoint, changes in the ADHDRS-IV-Parent:Inv total score, was compared between treatment groups using an analysis of covariance (ANCOVA) with terms of baseline score, treatment, and investigator in the model. The point estimators and 95% confidence intervals of treatment difference were also provided. The paired t test was used to analyze the change from baseline within each treatment group.

The secondary analyses of changes in the ADHDRS-IV-Parent:Inv total score also included an ANOVA (excluding the baseline term from the primary analysis ANCOVA). Secondary efficacy variables, including the ADHDRS-IV-Parent:Inv subscale scores, CGI-ADHD-S, CPRS-R:S total and subscale scores, and CTRS-R:S total and subscale scores were analyzed in a similar fashion as ADHDRS-IV-Parent:Inv total score. The Cochran-Mantel-Haenszel test stratified by site was used to assess the ADHD responder rate. For time to onset of sustained response, treatment differences were assessed using a Cox proportional hazards cure model.

Compliance condition was summarized by visits and by treatment groups. All adverse events were coded by the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) code system. The frequency and percentage of treatment-emergent adverse events (TEAEs) during Study Period II were presented for each treatment group. The treatment groups, body systems, COSTART preferred term, and severity were summarized for TEAEs. Fisher's exact test was used to compare the number of subjects with TEAEs between treatment groups.

For the laboratory parameters, the treatment differences in changes from baseline to endpoint (last assessment during Study Period II) scores were computed using ANOVA and within group changes were assessed with paired *t* tests. Transition tables from baseline to endpoint for laboratory parameters were provided by treatment groups.

For vital signs and body weight, the comparison between treatment groups was analyzed based on the change from baseline by using ANOVA and paired *t* test for within each treatment group. The categorical analyses for vital signs were based on the normal (< 90th percentile), high-normal (90th – 95th percentile), and hypertension (≥95th percentile) ranges (by age group) for blood pressure and the low, normal, and high ranges for heart rates. Transition tables from baseline to each visit for blood pressure and heart rate were summarized.

Results:

Subject Demographics

Of all randomized subjects, there were more males than females in both atomoxetine (90.28 % versus 9.72 %) and placebo (85.29 % versus 14.71 %) groups (Table 1). The average age was 8.5 years in the atomoxetine group, and 9.0 years in the placebo group with comparable height and weight. A statistically significant difference was observed in the education level ($p=.014$), due to different distributions of school grade levels between the two treatment groups.

Forty-one (56.94 %) and 20 (58.82 %) subjects from the atomoxetine group and the placebo group respectively, had received treatment of psychostimulants before entering the study. Forty-three (59.72 %) and 20 (58.82 %) subjects from the atomoxetine group and the placebo group respectively, had previous ADHD therapy. Eighteen (25 %) subjects from the atomoxetine group and 12 (35.29 %) subjects from the placebo group were categorized as “inattention” for their ADHD subtype in accordance with DSM-IV criteria, while 54 (75 %) subjects from the atomoxetine group and 22 (64.71 %) subjects from the placebo group, had “combined” ADHD subtypes. The mean age of onset among subjects from both atomoxetine and placebo groups was 5.4 years. No statistically significant differences were observed.

The Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version: Behavioral Disorders Supplement (KSADS-PL:Behavioral) includes ADHD, oppositional disorder, and conduct disorder, and subjects may have more than one of the disorders. From the atomoxetine group, 71 (98.61 %) subjects had ADHD, 14 (19.44 %) subjects had oppositional disorder, and seven (9.72 %) subjects had conduct disorder. From the placebo group, all subjects had ADHD, three (8.82 %) subjects had oppositional disorder, and two (5.88 %) subjects had conduct disorder. There were no cases of KSADS-PL Affective Disorder or KSADS-PL Anxiety Disorder in either treatment group.

Table 1. Baseline Demographics

Characteristic	Statistics	Atomoxetine (N=72)	Placebo (N=34)	Difference
Sex	Female	7 (9.72%)	5 (14.71%)	0.516 ^a
	Male	65 (90.28%)	29 (85.29%)	
Age (year)	N	72	34	-0.5
	Mean ± SD	8.5 ±2.0	9.0 ±2.5	
	Median	8.0	8.5	
	Min - Max	6.0 - 13.0	6.0 - 15.0	
	95% CI	8.1 - 9.0	8.1 - 9.9	-1.3 - 0.4 0.284 ^b
	P-value			
Origin	East/Southern Asian	72 (100.0%)	34 (100.0%)	
Education	Kindergarten	3 (4.17%)	0 (0.00%)	0.014 ^a
	Elementary School Grade 1	11 (15.28%)	7 (20.59%)	
	Elementary School Grade 2	17 (23.61%)	7 (20.59%)	
	Elementary School Grade 3	12 (16.67%)	5 (14.71%)	
	Elementary School Grade 4	10 (13.89%)	6 (17.65%)	
	Elementary School Grade 5	12 (16.67%)	0 (0.00%)	
	Elementary School Grade 6	0 (0.00%)	3 (8.82%)	
	Junior High School Grade 1	3 (4.17%)	3 (8.82%)	
	Junior High School Grade 2	4 (5.56%)	1 (2.94%)	
	Junior High School Grade 3	0 (0.00%)	2 (5.88%)	
Family History ^c	Mother	0 (0.00%)	0 (0.00%)	
	Father	5 (6.94%)	1 (2.94%)	
	Grandparents	1 (1.39%)	0 (0.00%)	
	Siblings	7 (9.72%)	4 (11.76%)	
Height (cm)	N	72	34	-0.4
	Mean ±SD	133.5 ±11.8	133.9 ±13.2	
	Median	132.0	128.9	
	Min - Max	114.3 - 168.0	115.5 - 168.0	
	95% CI	130.8 - 136.3	129.3 - 138.5	-5.4 - 4.7 0.843 ^b
	P-value			
Weight (kg) ^d	N	72	34	-1
	Mean ±SD	31.3 ±8.9	32.3 ±9.1	
	Median	29.5	28.5	
	Min - Max	20.0 - 57.6	20.0 - 54.0	
	95% CI	29.2 - 33.4	29.1 - 35.5	-4.7 - 2.8 0.530 ^b
	P-value			

(continued)

Table 1. Baseline Demographics (continued)

Characteristic	Statistics	Atomoxetine (N=72)	Placebo (N=34)	Difference
Previous Psychostimulants	Yes	41 (56.94%)	20 (58.82%)	1.000 ^a
	No	31 (43.06%)	14 (41.18%)	
Previous ADHD Therapy	Yes	43 (59.72%)	20 (58.82%)	1.000 ^a
	No	29 (40.28%)	14 (41.18%)	
DSM-IV ADHD Subtype	Inattention	18 (25.00%)	12 (35.29%)	0.356 ^a
	Hyperactivity	0 (0.00%)	0 (0.00%)	
	Combined	54 (75.00%)	22 (64.71%)	
Age at Onset of ADHD (year)	N	72	34	0.0 -0.5 - 0.5 0.942 ^b
	Mean ±SD	5.4 ±1.3	5.4 ±1.3	
	Median	5.5	5.3	
	Min - Max	1.0 - 7.0	2.0 - 7.0	
	95% CI	5.1 – 5.7	5.0 – 5.9	
	P-value			
KSADS-PL Behavior Disorders ^c	ADHD	71 (98.61%)	34 (100.0%)	
	Oppositional Defiant	14 (19.44%)	3 (8.82%)	
	Conduct Disorder	7 (9.72%)	2 (5.88%)	
KSADS-PL Affective Disorders ^c	Major Depressive Disorder	0 (0.00%)	0 (0.00%)	
	Seasonal Pattern	0 (0.00%)	0 (0.00%)	
	Dysthymia	0 (0.00%)	0 (0.00%)	
	Adjustment Disorder	0 (0.00%)	0 (0.00%)	
	Any Other Depressive Disorder	0 (0.00%)	0 (0.00%)	

(continued)

Table 1. Baseline Demographics (concluded)

Characteristic	Statistics	Atomoxetine (N=72)	Placebo (N=34)	Difference
KSADA-PL Anxiety Disorders ^c	Panic Disorder	0 (0.00%)	0 (0.00%)	
	Separation Anxiety Disorder	0 (0.00%)	0 (0.00%)	
	Avoidant Disorder/Social Phobia	0 (0.00%)	0 (0.00%)	
	Agoraphobia and Specific Phobias	0 (0.00%)	0 (0.00%)	
	Overanxious/Generalized Anxiety Disorder	0 (0.00%)	0 (0.00%)	
	Obsessive Compulsive Disorder	0 (0.00%)	0 (0.00%)	

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CI = confidence interval; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; KSADS-PL Affective Disorders = Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version: Affective Disorders Supplement; KSADA-PL Anxiety Disorders = ;KSADS-PL Behavior Disorders = Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version: Behavioral Disorders Supplement; SD = standard deviation.

a p-value from Fisher's exact test.

b p-value between treatment groups was using ANOVA with terms of treatment and investigator.

c Subjects may choose more than one answer.

d Weight was assessed at Visit 2.

Subject Disposition

A total of 114 subjects were entered into the screening phase. Of these, eight subjects were screen failures, and the remaining 106 subjects were randomized to receive treatment of atomoxetine hydrochloride (n=72) or placebo (n=34). Table 2 shows the number of subjects at each visit during the study. From the atomoxetine group, 69 (95.83 %) subjects completed Study Period II, compared with 29 (85.29 %) subjects from the placebo group (p=.107). All of these subjects proceeded into Study Period III, with the exception of one subject from the atomoxetine group.

Table 3 summarizes the reasons given for early discontinuation from Study Period II. Of those subjects who discontinued early from the atomoxetine group, one (1.39 %) subject discontinued due to an adverse event (dizziness), one (1.39 %) subject discontinued due to a lack of efficacy based on subject/caregiver's perception, and one (1.39 %) subject discontinued due to personal conflict or other subject/caregiver decision. From the placebo group, four (11.76 %) subjects withdrew due to a lack of efficacy based on subject/caregiver's perception and one (2.94 %) subject withdrew due to a lack of efficacy based on subject/caregiver and physician's perception.

Table 2. Subject Disposition by Visit

Number of Subjects at Each Visit	Atomoxetine (N=72)	Placebo (N=34)	Total (N=106)
Visit 1 (Screening)	72	34	106
Visit 2 (Baseline)	72	34	106
Visit 3 (Week 1)	72	34	106
Visit 4 (Week 2)	71	34	105
Visit 5 (Week 4)	69	32	101
Visit 6 (Week 6)	69	29	98
Visit 7 (Study Period III)	68	29	97

Table 3. Reasons for Discontinuation

	Atomoxetine (N=72)	Placebo (N=34)	p-value*
Completed Study Period II	69 (95.83%)	29 (85.29%)	0.107
Early Discontinued Study Period II	3 (4.17%)	5 (14.71%)	
Reason for Early Discontinuation			
Adverse event	1 (1.39%)	0 (0.00%)	
Lack of efficacy, subject/caregiver perception	1 (1.39%)	4 (11.76%)	
Lack of efficacy, subject/caregiver and physician perception	0 (0.00%)	1 (2.94%)	
Personal conflict or other subject/caregiver decision	1 (1.39%)	0 (0.00%)	

* p-value is from Fisher's exact test.

Primary Efficacy Measure

The primary efficacy measure was the mean change in Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) total score from baseline to Visits 3, 4, 5, and 6 (Table 4). At baseline, the mean total score for ADHDRS-IV-Parent:Inv was 36.7±6.7 for the atomoxetine group and 37.1±6.4 for the placebo group (p=.741). At Visit 3, the mean total score for ADHDRS-IV-Parent:Inv had decreased by 12.2±9.7 (p<.001) and 5.5±7.2 (p<.001) compared to baseline for the atomoxetine and placebo groups respectively. At Visit 4, these decreases were 14.3±10.4 (p<.001) and 7.5±11.0 (p<.001) for the atomoxetine and placebo groups respectively. At Visit 5 and Visit 6, the mean decreases from baseline in ADHDRS-IV-Parent:Inv total score were 15.5±10.2 (p<.001) and 16.9±10.8 (p<.001) respectively in the atomoxetine group. For the placebo group, the mean decreases from baseline in ADHDRS-IV-Parent:Inv total score were 5.8±12.1 (p<.001) and 7.5±13.1 (p=.002) at Visit 5 and Visit 6 respectively. At each visit, the differences observed between the two groups were statistically significant (p<.001).

**Table 4. ADHDRS-IV-Parent:Inv Total Score
Change from Baseline to Visits 3, 4, 5, and 6**

Visit	Statistics	Atomoxetine (N=72)	Placebo (N=34)	Difference	P-value ^a	P-value ^b
Baseline	N	72	34			
	Mean ±SD	36.7 ±6.7	37.1 ±6.4	-0.4		
	Median	36.5	37.5			
	Min - Max	23.0 - 50.0	25.0 - 52.0			
	95% CI	35.2 - 38.3	34.8 - 39.3	-3.1 - 2.4		
	P-value					0.741
Visit 3	N	72	34			
	Mean ±SD	24.5 ±9.3	31.6 ±7.4	-7.1		
	Median	25.5	32.5			
	Min - Max	4.0 - 45.0	13.0 - 46.0			
	95% CI	22.3 - 26.7	29.0 - 34.2	-10.7 - -3.5		

(continued)

**Table 4. ADHDRS-IV-Parent:Inv Total Score
Change from Baseline to Visits 3, 4, 5, and 6 (continued)**

Visit	Statistics	Atomoxetine (N=72)	Placebo (N=34)	Difference	P-value ^a	P-value ^b
Change from Baseline to Visit 3	N	72	34			
	Mean ±SD	-12.2 ±9.7	-5.5 ±7.2	-6.7		
	Median	-10.5	-3.0			
	Min - Max	-40.0 - 4.0	-27.0 - 4.0			
	95% CI	-14.5 - -9.9	-8.0 - -3.0	-10.1 - -3.4		
	P-value ^c	< 0.001	< 0.001		< 0.001	< 0.001
Visit 4	N	72	34			
	Mean ±SD	22.4 ±10.1	29.6 ±10.8	-7.2		
	Median	21.0	31.0			
	Min - Max	1.0 - 44.0	10.0 - 45.0			
	95% CI	20.0 - 24.7	25.8 - 33.4	-11.5 - -3.0		
Change from Baseline to Visit 4	N	72	34			
	Mean ±SD	-14.3 ±10.4	-7.5 ±11.0	-6.9		
	Median	-16.0	-5.0			
	Min - Max	-44.0 - 7.0	-32.0 - 9.0			
	95% CI	-16.8 - -11.9	-11.3 - -3.6	-11.3 - -2.5		
	P-value ^c	< 0.001	< 0.001		< 0.001	0.002
Visit 5	N	72	34			
	Mean ±SD	21.2 ±10.1	31.3 ±11.9	-10.0		
	Median	21.0	35.0			
	Min - Max	1.0 - 42.0	6.0 - 46.0			
	95% CI	18.9 - 23.6	27.1 - 35.4	-14.4 - -5.6		

(continued)

**Table 4. ADHDRS-IV-Parent:Inv Total Score
Change from Baseline to Visits 3, 4, 5, and 6 (concluded)**

Visit	Statistics	Atomoxetine	Placebo	Difference	P-value ^a	P-value ^b
		(N=72)	(N=34)			
Change from Baseline to Visit 5	N	72	34			
	Mean ±SD	-15.5 ±10.2	-5.8 ±12.1	-9.7		
	Median	-15.5	-3.0			
	Min - Max	-40.0 - 7.0	-37.0 - 10.0			
	95% CI	-17.9 - -13.1	-10.0 - -1.6	-14.1 - -5.2		
	P-value ^c	< 0.001	0.008		< 0.001	< 0.001
Visit 6	N	72	34			
	Mean ±SD	19.8 ±10.7	29.6 ±12.6	-9.8		
	Median	18.5	34.5			
	Min - Max	0.0 - 54.0	6.0 - 52.0			
	95% CI	17.3 - 22.3	25.2 - 34.0	-14.5 - -5.2		
Change from Baseline to Visit 6	N	72	34			
	Mean ±SD	-16.9 ±10.8	-7.5 ±13.1	-9.5		
	Median	-18.5	-5.5			
	Min - Max	-40.0 - 7.0	-39.0 - 11.0			
	95% CI	-19.5 - -14.4	-12.0 - -2.9	-14.2 - -4.7		
	P-value ^c	< 0.001	0.002		< 0.001	< 0.001

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CI = confidence interval; SD = standard deviation.

^a p-value between treatment groups using ANCOVA with terms of baseline score, treatment, and investigator.

^b p-value between treatment groups using ANOVA with terms of treatment and investigator.

^c p-value within each treatment group was derived from paired *t* test.

Secondary Efficacy Measures

Table 5 shows the ADHDRS-IV-Parent:Inv Inattention subscale scores at each visit for both treatment groups. Baseline scores were not statistically significantly different between the two groups ($p=.455$). Mean scores from the atomoxetine group statistically significantly decreased from baseline by 6.6 ± 5.7 ($p<.001$), 7.5 ± 6.3 ($p<.001$), 8.0 ± 6.1 ($p<.001$), and 8.5 ± 6.2 ($p<.001$) at Visit 3, Visit 4, Visit 5, and Visit 6 respectively. For the placebo group, the mean scores at Visit 3, Visit 4, Visit 5, and Visit 6 had decreased by 3.1 ± 4.5 ($p<.001$), 4.1 ± 5.8 ($p<.001$), 3.2 ± 6.3 ($p=.005$), and 4.1 ± 7.2 ($p=.002$) respectively, compared to baseline. Statistically significant differences were observed between the two groups in the changes from baseline at each visit ($p<.01$).

Table 5. ADHDRS-IV-Parent:Inv Inattention Subscale Score

Visit	Statistics	Atomoxetine	Placebo	Difference	P-value ^a	P-value ^b
		(N=72)	(N=34)			
Baseline	N	72	34			
	Mean $\pm$ SD	19.7 $\pm$ 3.8	20.2 $\pm$ 3.4	-0.5		
	Median	19.0	19.5			
	Min - Max	8.0 - 27.0	14.0 - 27.0			
	95% CI	18.8 - 20.6	19.0 - 21.4	-2.0 - 1.0		
	P-value					0.455
Visit 3	N	72	34			
	Mean $\pm$ SD	13.0 $\pm$ 4.6	17.1 $\pm$ 4.2	-4.1		
	Median	13.5	17.5			
	Min - Max	3.0 - 23.0	7.0 - 25.0			
	95% CI	11.9 - 14.1	15.6 - 18.5	-5.9 - -2.2		

(continued)

Table 5. ADHDRS-IV-Parent:Inv Inattention Subscale Score (continued)

Visit	Statistics	Atomoxetine	Placebo	Difference	P-value ^a	P-value ^b
		(N=72)	(N=34)			
Change from Baseline to Visit 3	N	72	34			
	Mean ±SD	-6.6 ±5.7	-3.1 ±4.5	-3.6		
	Median	-6.0	-2.0			
	Min - Max	-24.0 - 4.0	-17.0 - 2.0			
	95% CI	-8.0 - -5.3	-4.7 - -1.5	-5.7 - -1.4		
	P-value ^c	< 0.001	< 0.001		< 0.001	0.002
Visit 4	N	72	34			
	Mean ±SD	12.2 ±5.6	16.0 ±5.7	-3.9		
	Median	12.0	17.5			
	Min - Max	0.0 - 24.0	3.0 - 25.0			
	95% CI	10.8 - 13.5	14.0 - 18.0	-6.2 - -1.6		
Change from Baseline to Visit 4	N	72	34			
	Mean ±SD	-7.5 ±6.3	-4.1 ±5.8	-3.4		
	Median	-7.0	-2.5			
	Min - Max	-27.0 - 6.0	-21.0 - 4.0			
	95% CI	-9.0 - -6.0	-6.2 - -2.1	-5.9 - -0.8		
	P-value ^c	< 0.001	< 0.001		0.002	0.010
Visit 5	N	72	34			
	Mean ±SD	11.6 ±5.4	16.9 ±6.5	-5.3		
	Median	10.5	20.0			
	Min - Max	1.0 - 25.0	4.0 - 25.0			
	95% CI	10.4 - 12.9	14.7 - 19.2	-7.7 - -2.9		

(continued)

Table 5. ADHDRS-IV-Parent:Inv Inattention Subscale Score (concluded)

Visit	Statistics	Atomoxetine	Placebo	Difference	P-value ^a	P-value ^b
		(N=72)	(N=34)			
Change from Baseline to Visit 5	N	72	34			
	Mean ±SD	-8.0 ±6.1	-3.2 ±6.3	-4.8		
	Median	-8.0	-2.0			
	Min - Max	-21.0 - 5.0	-19.0 - 7.0			
	95% CI	-9.5 - -6.6	-5.4 - -1.0	-7.3 - -2.2		
	P-value ^c	< 0.001	0.005		< 0.001	< 0.001
Visit 6	N	72	34			
	Mean ±SD	11.2 ±5.8	16.0 ±6.5	-4.8		
	Median	10.0	18.5			
	Min - Max	0.0 - 27.0	4.0 - 27.0			
	95% CI	9.8 - 12.6	13.8 - 18.3	-7.3 - -2.3		
Change from Baseline to Visit 6	N	72	34			
	Mean ±SD	-8.5 ±6.2	-4.1 ±7.2	-4.3		
	Median	-9.5	-2.0			
	Min - Max	-20.0 - 5.0	-22.0 - 7.0			
	95% CI	-9.9 - -7.0	-6.7 - -1.6	-7.0 - -1.6		
	P-value ^c	< 0.001	0.002		< 0.001	0.002

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CI = confidence interval; SD = standard deviation.

^a p-value between treatment groups using ANCOVA with terms of baseline score, treatment, and investigator.

^b p-value between treatment groups using ANOVA with terms of treatment and investigator.

^c p-value within each treatment group was derived from paired *t* test.

Table 6 shows the ADHDRS-IV-Parent:Inv Hyperactivity/Impulsive subscale scores at each visit for both treatment groups. Baseline scores were not statistically significantly different between the two groups ($p=.885$). Mean scores for the Hyperactivity/Impulsive subscale from the atomoxetine group statistically significantly decreased compared to baseline by 5.6 ± 5.0 ($p<.001$), 6.8 ± 5.1 ($p<.001$), 7.5 ± 4.9 ($p<.001$), and 8.5 ± 5.5 ($p<.001$) at Visit 3, Visit 4, Visit 5, and Visit 6 respectively. For the placebo group, the mean scores at Visit 3, Visit 4, Visit 5, and Visit 6 had decreased by 2.4 ± 4.1 ($p=.002$), 3.3 ± 5.9 ($p=.002$), 2.6 ± 6.3 ($p=.022$), and 3.3 ± 6.7 ($p=.007$) respectively compared to baseline. Statistically significant differences were observed between the two groups in the changes from baseline to the scores at each visit ($p<0.01$).

Table 6. ADHDRS-IV-Parent:Inv Hyperactivity/Impulsive Subscale Score

Visit	Statistics	Atomoxetine (N=72)	Placebo (N=34)	Difference	P-value ^a	P-value ^b
Baseline	N	72	34			
	Mean $\pm$ SD	17.1 $\pm$ 4.8	16.9 $\pm$ 4.6	0.1		
	Median	16.0	18.0			
	Min - Max	5.0 - 26.0	9.0 - 26.0			
	95% CI	15.9 - 18.2	15.3 - 18.5	-1.8 - 2.1		
	P-value ^c					0.885
Visit 3	N	72	34			
	Mean $\pm$ SD	11.5 $\pm$ 5.5	14.5 $\pm$ 4.4	-3.0		
	Median	11.5	15.0			
	Min - Max	1.0 - 25.0	6.0 - 22.0			
	95% CI	10.2 - 12.8	13.0 - 16.0	-5.2 - -0.9		
Change from Baseline to Visit 3	N	72	34			
	Mean $\pm$ SD	-5.6 $\pm$ 5.0	-2.4 $\pm$ 4.1	-3.2		
	Median	-5.0	-2.0			
	Min - Max	-16.0 - 4.0	-13.0 - 4.0			
	95% CI	-6.8 - -4.4	-3.8 - -1.0	-5.1 - -1.2		
	P-value ^c	< 0.001	0.002		0.001	0.002

(continued)

Table 6. ADHDRS-IV-Parent:Inv Hyperactivity/Impulsive Subscale Score (continued)

Visit	Statistics	Atomoxetine	Placebo	Difference	P-value ^a	P-value ^b
		(N=72)	(N=34)			
Visit 4	N	72	34			
	Mean ±SD	10.2 ±5.5	13.6 ±6.1	-3.4		
	Median	10.0	12.0			
	Min - Max	0.0 - 22.0	3.0 - 24.0			
	95% CI	8.9 - 11.5	11.5 - 15.7	-5.7 - -1.0		
Change from Baseline to Visit 4	N	72	34			
	Mean ±SD	-6.8 ±5.1	-3.3 ±5.9	-3.5		
	Median	-7.0	-3.5			
	Min - Max	-17.0 - 5.0	-17.0 - 5.0			
	95% CI	-8.0 - -5.6	-5.4 - -1.3	-5.7 - -1.3		
	P-value ^c	< 0.001	0.002		0.001	0.002
Visit 5	N	72	34			
	Mean ±SD	9.6 ±5.6	14.3 ±6.2	-4.7		
	Median	9.0	14.5			
	Min - Max	0.0 - 21.0	2.0 - 24.0			
	95% CI	8.3 - 10.9	12.2 - 16.5	-7.1 - -2.3		
Change from Baseline to Visit 5	N	72	34			
	Mean ±SD	-7.5 ±4.9	-2.6 ±6.3	-4.9		
	Median	-7.0	-1.0			
	Min - Max	-19.0 - 2.0	-18.0 - 7.0			
	95% CI	-8.6 - -6.3	-4.8 - -0.4	-7.1 - -2.7		
	P-value ^c	< 0.001	0.022		< 0.001	< 0.001

(continued)

Table 6. ADHDRS-IV-Parent:Inv Hyperactivity/Impulsive Subscale Score (concluded)

Visit	Statistics	Atomoxetine	Placebo	Difference	P-value ^a	P-value ^b
		(N=72)	(N=34)			
Visit 6	N	72	34			
	Mean ±SD	8.6 ±5.5	13.6 ±6.8	-5.0		
	Median	8.5	14.5			
	Min - Max	0.0 - 27.0	0.0 - 25.0			
	95% CI	7.3 - 9.9	11.2 - 16.0	-7.5 - -2.6		
Change from Baseline to Visit 6	N	72	34			
	Mean ±SD	-8.5 ±5.5	-3.3 ±6.7	-5.2		
	Median	-9.0	-4.0			
	Min - Max	-21.0 - 3.0	-21.0 - 8.0			
	95% CI	-9.8 - -7.2	-5.7 - -1.0	-7.6 - -2.7		
	P-value ^c	< 0.001	0.007		< 0.001	< 0.001

Abbreviations: ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CI = confidence interval; SD = standard deviation.

^a p-value between treatment groups using ANCOVA with terms of baseline score, treatment, and investigator.

^b p-value between treatment groups using ANOVA with terms of treatment and investigator.

^c p-value within each treatment group was derived from paired *t* test.

Table 7 shows the Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity (CGI-ADHD-S) scores at each visit for both treatment groups. Baseline scores were not statistically significantly different between the two groups ($p=.703$). Mean CGI-ADHD-S scores from the atomoxetine group had decreased compared to baseline by 1.3 ± 1.0 ($p<.001$), 1.6 ± 1.1 ($p<.001$), 1.7 ± 1.2 ($p<.001$), and 2.0 ± 1.3 ($p<.001$) at Visit 3, Visit 4, Visit 5, and Visit 6 respectively. For the placebo group, the mean scores at Visit 3, Visit 4, Visit 5, and Visit 6 had decreased compared to baseline by 0.5 ± 1.0 ($p=.006$), 0.5 ± 1.2 ($p=.016$), 0.5 ± 1.4 ($p=.029$), and 0.8 ± 1.5 ($p=.003$) respectively. Statistically significant differences were observed between the two groups in the changes from baseline to the scores at each visit ($p<.05$).

Table 7. CGI-ADHD-S Score

Visit	Statistics	Atomoxetine	Placebo	Difference	P-value ^a	P-value ^b
		(N=72)	(N=34)			
Baseline	N	72	34			
	Mean ±SD	5.3 ±0.8	5.2 ±0.8	0.1		
	Median	5.0	5.0			
	Min - Max	4.0 - 7.0	4.0 - 7.0			
	95% CI	5.1 - 5.5	4.9 - 5.5	-0.3 - 0.4		
	P-value ^c					0.703
Visit 3	N	72	34			
	Mean ±SD	4.0 ±1.0	4.7 ±1.0	-0.7		
	Median	4.0	5.0			
	Min - Max	2.0 - 6.0	3.0 - 6.0			
	95% CI	3.7 - 4.2	4.4 - 5.1	-1.2 - -0.3		
Change from Baseline to Visit 3	N	72	34			
	Mean ±SD	-1.3 ±1.0	-0.5 ±1.0	-0.8		
	Median	-1.0	0.0			
	Min - Max	-3.0 - 1.0	-4.0 - 1.0			
	95% CI	-1.5 - -1.1	-0.8 - -0.2	-1.2 - -0.4		
	P-value ^c	< 0.001	0.006		< 0.001	< 0.001
Visit 4	N	72	34			
	Mean ±SD	3.7 ±1.1	4.7 ±1.2	-1.0		
	Median	4.0	5.0			
	Min - Max	1.0 - 6.0	2.0 - 7.0			
	95% CI	3.4 - 3.9	4.3 - 5.1	-1.5 - -0.6		

(continued)

Table 7. CGI-ADHD-S Score (continued)

Visit	Statistics	Atomoxetine	Placebo	Difference	P-value ^a	P-value ^b
		(N=72)	(N=34)			
Change from Baseline to Visit 4	N	72	34			
	Mean ±SD	-1.6 ±1.1	-0.5 ±1.2	-1.1		
	Median	-2.0	0.0			
	Min - Max	-4.0 - 1.0	-4.0 - 1.0			
	95% CI	-1.9 - -1.4	-1.0 - -0.1	-1.6 - -0.6		
	P-value	< 0.001	0.016		< 0.001	< 0.001
Visit 5	N	72	34			
	Mean ±SD	3.6 ±1.1	4.7 ±1.3	-1.1		
	Median	3.0	5.0			
	Min - Max	1.0 - 6.0	2.0 - 7.0			
	95% CI	3.3 - 3.8	4.2 - 5.1	-1.6 - -0.6		
Change from Baseline to Visit 5	N	72	34			
	Mean ±SD	-1.7 ±1.2	-0.5 ±1.4	-1.2		
	Median	-2.0	0.0			
	Min - Max	-4.0 - 1.0	-4.0 - 2.0			
	95% CI	-2.0 - -1.5	-1.0 - -0.1	-1.7 - -0.7		
	P-value	< 0.001	0.029		< 0.001	< 0.001
Visit 6	N	72	34			
	Mean ±SD	3.3 ±1.3	4.4 ±1.4	-1.1		
	Median	3.0	4.5			
	Min - Max	1.0 - 6.0	2.0 - 7.0			
	95% CI	3.0 - 3.6	3.9 - 4.9	-1.6 - -0.6		

(continued)

Table 7. CGI-ADHD-S Score (concluded)

Visit	Statistics	Atomoxetine	Placebo	Difference	P-value ^a	P-value ^b
		(N=72)	(N=34)			
Change from Baseline to Visit 6	N	72	34			
	Mean ±SD	-2.0 ±1.3	-0.8 ±1.5	-1.2		
	Median	-2.0	-0.5			
	Min - Max	-5.0 - 1.0	-5.0 - 2.0			
	95% CI	-2.3 - -1.7	-1.3 - -0.3	-1.7 - -0.6		
	P-value	< 0.001	0.003		< 0.001	< 0.001

Abbreviations: CGI-ADHD-S = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity; CI = confidence interval; SD = standard deviation.

^a p-value between treatment groups using ANCOVA with terms of baseline score, treatment, and investigator.

^b p-value between treatment groups using ANOVA with terms of treatment and investigator.

^c p-value within each treatment group was derived from paired *t* test.

The change in Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) total score from baseline to the end of Study Period II for each treatment group is presented in Table 8. Baseline scores were not statistically significantly different between the two groups ($p=.614$). At the end of Study Period II, the mean CPRS-R:S total scores had decreased by 12.2 ± 11.3 ($p<.001$) in the atomoxetine group, while the decrease of 3.5 ± 15.3 in the placebo group was not statistically significant ($p=.193$). The difference between the score changes in the two treatment groups was statistically significant ($p=.002$).

Table 8. CPRS-R:S Total Score

Visit	Statistics	Atomoxetine	Placebo	Difference	P-value ^a	P-value ^b
		(N=72)	(N=34)			
Baseline	N	69	33			
	Mean ±SD	44.6 ±13.0	43.2 ±15.2	1.4		
	Median	45.0	42.0			
	Min - Max	15.6 - 68.0	7.0 - 65.4			
	95% CI	41.5 - 47.7	37.8 - 48.6	-4.4 - 7.2		
	P-value					0.614
SPII	N	69	33			
	Mean ±SD	32.4 ±14.8	39.7 ±18.0	-7.2		
	Median	33.0	38.0			
	Min - Max	0.0 - 73.0	7.0 - 73.0			
	95% CI	28.9 - 36.0	33.3 - 46.1	-13.9 - -0.6		
	P-value					
Change from Baseline to SPII	N	69	33			
	Mean ±SD	-12.2 ±11.3	-3.5 ±15.3	-8.6		
	Median	-10.0	0.0			
	Min - Max	-46.0 - 11.7	-50.0 - 23.0			
	95% CI	-14.9 - -9.4	-9.0 - 1.9	-14.6 - -2.6		
	P-value	< 0.001	0.193		0.002	0.002

Abbreviations: CPRS-R:S = Conners' Parent Rating Scale-Revised: Short Form; CI = confidence interval; SD = standard deviation; SPII = Study Period II.

^a p-value between treatment groups using ANCOVA with terms of baseline score, treatment, and investigator.

^b p-value between treatment groups using ANOVA with terms of treatment and investigator.

^c p-value within each treatment group was derived from paired *t* test.

The change in CPRS-R:S Oppositional subscale score from baseline to the end of Study Period II for each treatment group is presented in Table 9. Baseline scores were not statistically different between the two groups ($p=.069$). At the end of Study Period II, the mean CPRS-R:S Oppositional subscale score had decreased by 1.1 ± 3.4 ($p<.01$) in the atomoxetine group, while the decrease of 0.6 ± 3.8 in the placebo group was not statistically significant ($p=.403$). The difference between the score changes in the two treatment groups was not statistically significant when analyzed using ANCOVA with terms of baseline score, treatment, and investigator in the model ($p=.098$), however this

difference was statistically significant when analyzed using ANOVA with terms of treatment and investigator in the model ($p=.027$).

Table 9. CPRS-R:S Oppositional Subscale Score

Visit	Statistics	Atomoxetine	Placebo	Difference	P-value ^a	P-value ^b
		(N=72)	(N=34)			
Baseline	N	71	34			
	Mean $\pm$ SD	8.2 $\pm$ 3.8	6.8 $\pm$ 3.9	1.5		
	Median	8.0	7.0			
	Min - Max	0.0 - 17.0	0.0 - 16.0			
	95% CI	7.3 - 9.1	5.4 - 8.1	-0.1 - 3.0		
	P-value ^c					0.069
SPII	N	71	34			
	Mean $\pm$ SD	7.1 $\pm$ 3.9	7.3 $\pm$ 4.8	-0.2		
	Median	7.0	6.0			
	Min - Max	0.0 - 18.0	0.0 - 18.0			
	95% CI	6.2 - 8.0	5.6 - 9.0	-2.0 - 1.5		
	P-value ^c					
Change from Baseline to SPII	N	71	34			
	Mean $\pm$ SD	-1.1 $\pm$ 3.4	0.6 $\pm$ 3.8	-1.7		
	Median	-1.0	1.0			
	Min - Max	-10.0 - 6.0	-9.0 - 8.0			
	95% CI	-1.9 - -0.3	-0.8 - 1.9	-3.2 - -0.2		
	P-value ^c	0.006	0.403		0.098	0.027

Abbreviations: CPRS-R:S = Conners' Parent Rating Scale-Revised: Short Form; CI = confidence interval; SD = standard deviation; SPII = Study Period II.

^a p-value between treatment groups using ANCOVA with terms of baseline score, treatment, and investigator.

^b p-value between treatment groups using ANOVA with terms of treatment and investigator.

^c p-value within each treatment group was derived from paired *t* test.

The change in CPRS-R:S Cognitive Problems subscale score from baseline to the end of Study Period II for each treatment group is presented in Table 10. Baseline scores were not statistically different between the two groups ($p=.961$). At the end of Study Period II, the mean CPRS-R:S Cognitive Problems subscale score had decreased by 3.5 ± 3.6 ($p<.001$) in the atomoxetine group, while the decrease of 0.8 ± 4.6 in the placebo group was not statistically significant ($p=.316$). The difference between the score changes in the two treatment groups was statistically significant ($p<.001$).

Table 10. CPRS-R:S Cognitive Problems Subscale Score

Visit	Statistics	Atomoxetine	Placebo	Difference	P-value ^a	P-value ^b
		(N=72)	(N=34)			
Baseline	N	71	34			
	Mean $\pm$ SD	10.4 $\pm$ 3.8	10.5 $\pm$ 4.4	-0.1		
	Median	11.0	11.0			
	Min - Max	1.2 - 18.0	1.0 - 18.0			
	95% CI	9.5 - 11.4	9.0 - 12.0	-1.7 - 1.6		
	P-value					0.961
SPII	N	71	34			
	Mean $\pm$ SD	7.0 $\pm$ 4.2	9.7 $\pm$ 4.8	-2.7		
	Median	7.0	9.5			
	Min - Max	0.0 - 18.0	1.0 - 18.0			
	95% CI	6.0 - 8.0	8.0 - 11.4	-4.5 - -0.9		
	P-value					
Change from Baseline to SPII	N	71	34			
	Mean $\pm$ SD	-3.5 $\pm$ 3.6	-0.8 $\pm$ 4.6	-2.7		
	Median	-3.0	-0.6			
	Min - Max	-13.2 - 5.0	-13.0 - 7.0			
	95% CI	-4.3 - -2.6	-2.4 - 0.8	-4.3 - -1.1		
	P-value	< 0.001	0.316		< 0.001	0.001

Abbreviations: CPRS-R:S = Conners' Parent Rating Scale-Revised: Short Form; CI = confidence interval; SD = standard deviation; SPII = Study Period II.

^a p-value between treatment groups using ANCOVA with terms of baseline score, treatment, and investigator.

^b p-value between treatment groups using ANOVA with terms of treatment and investigator.

^c p-value within each treatment group was derived from paired *t* test.

The change in CPRS-R:S Hyperactivity subscale score from baseline to the end of Study Period II for each treatment group is presented in Table 11. Baseline scores were not statistically different between the two groups ($p=.688$). At the end of Study Period II, the mean CPRS-R:S Hyperactivity subscale scores had decreased by 3.1 ± 3.3 ($p<.001$) in the atomoxetine group and 1.5 ± 3.2 ($p=.011$) in the placebo group. The difference between the score changes in the two treatment groups was statistically significant ($p<.05$).

Table 11. CPRS-R:S Hyperactivity Subscale Score

Visit	Statistics	Atomoxetine	Placebo	Difference	P-value ^a	P-value ^b
		(N=72)	(N=34)			
Baseline	N	71	34			
	Mean $\pm$ SD	9.1 $\pm$ 3.8	8.8 $\pm$ 4.3	0.3		
	Median	9.0	9.0			
	Min - Max	0.0 - 17.0	0.0 - 17.0			
	95% CI	8.2 - 10.0	7.3 - 10.3	-1.4 - 1.9		
	P-value ^c					0.688
SPII	N	71	34			
	Mean $\pm$ SD	5.9 $\pm$ 3.8	7.3 $\pm$ 4.4	-1.4		
	Median	6.0	6.0			
	Min - Max	0.0 - 17.0	0.0 - 16.0			
	95% CI	5.0 - 6.8	5.8 - 8.9	-3.1 - 0.2		
	P-value ^c					
Change from Baseline to SPII	N	71	34			
	Mean $\pm$ SD	-3.1 $\pm$ 3.3	-1.5 $\pm$ 3.2	-1.7		
	Median	-3.0	-1.0			
	Min - Max	-12.0 - 6.0	-11.0 - 5.0			
	95% CI	-3.9 - -2.4	-2.6 - -0.4	-3.0 - -0.3		
	P-value ^c	< 0.001	0.011		0.014	0.016

Abbreviations: CPRS-R:S = Conners' Parent Rating Scale-Revised: Short Form; CI = confidence interval; SD = standard deviation; SPII = Study Period II.

^a p-value between treatment groups using ANCOVA with terms of baseline score, treatment, and investigator.

^b p-value between treatment groups using ANOVA with terms of treatment and investigator.

^c p-value within each treatment group was derived from paired *t* test.

The change in CPRS-R:S ADHD Index subscale score from baseline to the end of Study Period II for each treatment group is presented in Table 12. Baseline scores were not statistically different between the two groups ($p=.938$). At the end of Study Period II, the mean CPRS-R:S ADHD Index subscale score had decreased by 6.6 ± 5.8 ($p<.001$) in the atomoxetine group, while the decrease of 2.3 ± 7.6 in the placebo group was not statistically significant ($p=.100$). The difference between the score changes in the two treatment groups was statistically significant ($p<.01$).

Table 12. CPRS-R:S ADHD Index Subscale Score

Visit	Statistics	Atomoxetine (N=72)	Placebo (N=34)	Difference	P-value ^a	P-value ^b
Baseline	N	70	33			
	Mean $\pm$ SD	22.1 $\pm$ 6.1	22.2 $\pm$ 6.8	-0.1		
	Median	22.0	23.0			
	Min - Max	7.6 - 32.0	6.0 - 33.0			
	95% CI	20.6 - 23.6	19.8 - 24.6	-2.8 - 2.5		
	P-value ^c					0.938
SPII	N	70	33			
	Mean $\pm$ SD	15.5 $\pm$ 7.1	20.0 $\pm$ 8.6	-4.5		
	Median	15.0	21.0			
	Min - Max	0.0 - 36.0	5.0 - 34.0			
	95% CI	13.8 - 17.1	16.9 - 23.0	-7.7 - -1.3		
Change from Baseline to SPII	N	70	33			
	Mean $\pm$ SD	-6.6 $\pm$ 5.8	-2.3 $\pm$ 7.6	-4.4		
	Median	-5.1	0.0			
	Min - Max	-25.0 - 4.4	-24.0 - 9.0			
	95% CI	-8.0 - -5.3	-5.0 - 0.5	-7.1 - -1.7		
	P-value ^c	< 0.001	0.100		0.001	0.002

Abbreviations: CPRS-R:S = Conners' Parent Rating Scale-Revised: Short Form; CI = confidence interval; SD = standard deviation; SPII = Study Period II.

^a p-value between treatment groups using ANCOVA with terms of baseline score, treatment, and investigator.

^b p-value between treatment groups using ANOVA with terms of treatment and investigator.

^c p-value within each treatment group was derived from paired *t* test.

The change in Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R:S) total score from baseline to Visit 6 for each treatment group is presented in Table 13. Baseline scores were not statistically different between the two groups ($p=.161$). At Visit 6, the mean CTRS-R:S total score had decreased by 6.8 ± 16.9 ($p=.004$) in the atomoxetine group, while the decrease of 0.8 ± 10.3 in the placebo group was not statistically significant ($p=.699$). The difference between the score changes in the two treatment groups was statistically significant ($p<.05$).

Table 13. CTRS-R:S Total Score

Visit	Statistics	Atomoxetine (N=72)	Placebo (N=34)	Difference	P-value ^a	P-value ^b
Baseline	N	57	28			
	Mean $\pm$ SD	33.8 $\pm$ 16.1	39.6 $\pm$ 15.6	-5.8		
	Median	34.0	38.2			
	Min - Max	0.0 - 74.0	10.0 - 69.0			
	95% CI	29.5 - 38.1	33.5 - 45.6	-13.1 - 1.5		
	P-value ^c					0.161
Visit 6	N	57	28			
	Mean $\pm$ SD	27.0 $\pm$ 14.9	40.4 $\pm$ 15.9	-13.4		
	Median	29.0	42.0			
	Min - Max	0.0 - 65.0	10.0 - 68.0			
	95% CI	23.1 - 31.0	34.3 - 46.6	-20.4 - -6.4		
Change from Baseline to Visit 6	N	57	28			
	Mean $\pm$ SD	-6.8 $\pm$ 16.9	0.8 $\pm$ 10.3	-7.6		
	Median	-6.0	1.5			
	Min - Max	-47.0 - 47.0	-23.4 - 19.0			
	95% CI	-11.3 - -2.3	-3.1 - 4.8	-13.5 - -1.7		
	P-value ^c	0.004	0.669		< 0.001	0.028

Abbreviations: CTRS-R:S = Conners' Teacher Rating Scale-Revised: Short Form; CI = confidence interval; SD = standard deviation.

^a p-value between treatment groups using ANCOVA with terms of baseline score, treatment, and investigator.

^b p-value between treatment groups using ANOVA with terms of treatment and investigator.

^c p-value within each treatment group was derived from paired *t* test.

The change in CTRS-R:S Oppositional subscale score from baseline to Visit 6 for each treatment group is presented in Table 14. Baseline scores were not statistically different between the two groups ($p=.365$). At Visit 6, there were no statistically significant changes in the mean CTRS-R:S Oppositional subscale score compared to baseline in either treatment group ($p=.765$ for atomoxetine and $p=.814$ for placebo). The between-group difference was also statistically insignificant.

Table 14. CTRS-R:S Oppositional Subscale Score

Visit	Statistics	Atomoxetine	Placebo	Difference	<i>P</i> -value ^a	<i>P</i> -value ^b
		(N=72)	(N=34)			
Baseline	N	61	29			
	Mean $\pm$ SD	2.9 $\pm$ 3.2	3.6 $\pm$ 3.9	-0.8		
	Median	1.0	2.0			
	Min - Max	0.0 - 11.0	0.0 - 13.0			
	95% CI	2.0 - 3.7	2.1 - 5.1	-2.3 - 0.8		
	<i>P</i> -value					0.365
Visit 6	N	61	29			
	Mean $\pm$ SD	2.7 $\pm$ 3.1	3.8 $\pm$ 3.4	-1.0		
	Median	1.0	4.0			
	Min - Max	0.0 - 11.0	0.0 - 15.0			
	95% CI	1.9 - 3.5	2.5 - 5.1	-2.5 - 0.4		
	<i>P</i> -value					
Change from Baseline to Visit 6	N	61	29			
	Mean $\pm$ SD	-0.1 $\pm$ 3.0	0.1 $\pm$ 3.1	-0.3		
	Median	0.0	0.0			
	Min - Max	-10.0 - 7.0	-6.0 - 7.0			
	95% CI	-0.9 - 0.6	-1.1 - 1.3	-1.6 - 1.1		
	<i>P</i> -value	0.765	0.814		0.339	0.719

Abbreviations: CTRS-R:S = Conners' Teacher Rating Scale-Revised: Short Form; CI = confidence interval; SD = standard deviation.

^a *p*-value between treatment groups using ANCOVA with terms of baseline score, treatment, and investigator.

^b *p*-value between treatment groups using ANOVA with terms of treatment and investigator.

^c *p*-value within each treatment group was derived from paired *t* test.

The change in CTRS-R:S Cognitive Problems subscale score from baseline to Visit 6 for each treatment group is presented in Table 15. Baseline scores were not statistically different between the two groups ($p=.437$). At Visit 6, the mean CTRS-R:S Cognitive Problems subscale score had decreased by 0.8 ± 3.0 ($p=.047$) in the atomoxetine group, while the mean increase of 0.6 ± 2.2 in the placebo group was not statistically significant ($p=.189$). The difference between the score changes in the two treatment groups was statistically significant ($p<.05$).

Table 15. CTRS-R:S Cognitive Problems Subscale Score

Visit	Statistics	Atomoxetine (N=72)	Placebo (N=34)	Difference	P-value ^a	P-value ^b
Baseline	N	61	28			
	Mean $\pm$ SD	5.6 $\pm$ 4.2	6.4 $\pm$ 3.4	-0.8		
	Median	5.0	6.3			
	Min - Max	0.0 - 15.0	1.0 - 15.0			
	95% CI	4.5 - 6.7	5.1 - 7.8	-2.6 - 1.0		
	P-value ^c					0.437
Visit 6	N	61	28			
	Mean $\pm$ SD	4.8 $\pm$ 3.9	7.0 $\pm$ 3.7	-2.2		
	Median	4.0	7.0			
	Min - Max	0.0 - 15.0	0.0 - 15.0			
	95% CI	3.8 - 5.8	5.6 - 8.4	-3.9 - -0.4		
Change from Baseline to Visit 6	N	61	28			
	Mean $\pm$ SD	-0.8 $\pm$ 3.0	0.6 $\pm$ 2.2	-1.3		
	Median	0.0	1.0			
	Min - Max	-8.0 - 10.0	-6.3 - 4.0			
	95% CI	-1.6 - -0.0	-0.3 - 1.4	-2.5 - -0.2		
	P-value ^c	0.047	0.189		0.010	0.034

Abbreviations: CTRS-R:S = Conners' Teacher Rating Scale-Revised: Short Form; CI = confidence interval; SD = standard deviation.

^a p-value between treatment groups using ANCOVA with terms of baseline score, treatment, and investigator.

^b p-value between treatment groups using ANOVA with terms of treatment and investigator.

^c p-value within each treatment group was derived from paired *t* test.

The change in CTRS-R:S Hyperactivity subscale score from baseline to Visit 6 for each treatment group is presented in Table 16. Baseline scores were not statistically different between the two groups ($p=.328$). At Visit 6, the mean CTRS-R:S Hyperactivity subscale score had decreased by 2.3 ± 4.8 ($p<.001$) in the atomoxetine group, while the mean increase of 0.2 ± 3.5 in the placebo group was not statistically significant ($p=.726$). The difference between the score changes in the two treatment groups was statistically significant ($p<.05$).

Table 16. CTRS-R:S Hyperactivity Subscale Score

Visit	Statistics	Atomoxetine (N=72)	Placebo (N=34)	Difference	P-value ^a	P-value ^b
Baseline	N	58	29			
	Mean $\pm$ SD	8.6 $\pm$ 4.9	9.9 $\pm$ 4.8	-1.3		
	Median	9.0	10.0			
	Min - Max	0.0 - 21.0	0.0 - 20.0			
	95% CI	7.3 - 9.9	8.0 - 11.7	-3.5 - 0.9		
	P-value ^c					0.328
Visit 6	N	58	29			
	Mean $\pm$ SD	6.3 $\pm$ 4.6	10.1 $\pm$ 4.6	-3.8		
	Median	6.5	10.0			
	Min - Max	0.0 - 17.0	0.0 - 18.0			
	95% CI	5.1 - 7.5	8.4 - 11.8	-5.9 - -1.7		
Change from Baseline to Visit 6	N	58	29			
	Mean $\pm$ SD	-2.3 $\pm$ 4.8	0.2 $\pm$ 3.5	-2.5		
	Median	-1.5	0.0			
	Min - Max	-15.0 - 13.0	-8.0 - 6.0			
	95% CI	-3.5 - -1.0	-1.1 - 1.6	-4.3 - -0.7		
	P-value ^c	< 0.001	0.726		< 0.001	0.013

Abbreviations: CTRS-R:S = Conners' Teacher Rating Scale-Revised: Short Form; CI = confidence interval; SD = standard deviation.

^a p-value between treatment groups using ANCOVA with terms of baseline score, treatment, and investigator.

^b p-value between treatment groups using ANOVA with terms of treatment and investigator.

^c p-value within each treatment group was derived from paired *t* test.

The change in CTRS-R:S ADHD Index subscale score from baseline to Visit 6 for each treatment group is presented in Table 17. Baseline scores were not statistically different between the two groups ($p=.281$). At Visit 6, the mean CTRS-R:S ADHD Index subscale score had decreased by 3.6 ± 8.5 ($p=.002$) in the atomoxetine group, while the mean increase of 0.7 ± 5.6 in the placebo group was not statistically significant ($p=.485$). The difference between the score changes in the two treatment groups was statistically significant ($p<.05$).

Table 17. CTRS-R:S ADHD Index Subscale Score

Visit	Statistics	Atomoxetine (N=72)	Placebo (N=34)	Difference	P-value ^a	P-value ^b
Baseline	N	58	29			
	Mean $\pm$ SD	18.5 $\pm$ 7.9	20.6 $\pm$ 7.2	-2.1		
	Median	19.0	21.0			
	Min - Max	0.0 - 36.0	5.0 - 33.0			
	95% CI	16.4 - 20.6	17.8 - 23.3	-5.6 - 1.4		
	P-value					0.281
Visit 6	N	58	29			
	Mean $\pm$ SD	14.9 $\pm$ 7.3	21.3 $\pm$ 7.9	-6.4		
	Median	14.0	22.0			
	Min - Max	0.0 - 33.0	6.0 - 34.0			
	95% CI	13.0 - 16.8	18.3 - 24.3	-9.8 - -3.0		
Change from Baseline to Visit 6	N	58	29			
	Mean $\pm$ SD	-3.6 $\pm$ 8.5	0.7 $\pm$ 5.6	-4.3		
	Median	-4.0	0.0			
	Min - Max	-24.0 - 25.0	-12.0 - 13.2			
	95% CI	-5.8 - -1.3	-1.4 - 2.8	-7.3 - -1.3		
	P-value	0.002	0.485		< 0.001	0.016

Abbreviations: CTRS-R:S = Conners' Teacher Rating Scale-Revised: Short Form; CI = confidence interval; SD = standard deviation.

^a p-value between treatment groups using ANCOVA with terms of baseline score, treatment, and investigator.

^b p-value between treatment groups using ANOVA with terms of treatment and investigator.

^c p-value within each treatment group was derived from paired *t* test.

A summary of the distribution of responders and non-responders at each visit is presented in Table 18. A responder was defined as having a >25% reduction from baseline in the ADHDRS-IV-Parent:Inv total score. At Visit 3, 41 (56.9%) out of 72 subjects from the atomoxetine group were classified as responders compared with six (17.6%) out of 34 subjects from the placebo group ($p<.001$). At Visit 4, Visit 5, and Visit 6, there were 50 (69.4%), 52 (72.2%), and 53 (73.6%) subjects respectively, from the atomoxetine group who were classified as responders. These proportions were statistically significantly different from the placebo group, from which there were 14 (41.2%), 11 (32.4%), and 13 (38.2%) subjects classified as responders at Visit 4, Visit 5, and Visit 6 respectively ($p<.01$ for all visits).

Table 18. By-visit Summary of Responders and Non-responders

Visit	Responder	Atomoxetine (N=72)	Placebo (N=34)	P-value*
Visit 3	YES	41 (56.9%)	6 (17.6%)	< 0.001
	NO	31 (43.1%)	28 (82.4%)	
Visit 4	YES	50 (69.4%)	14 (41.2%)	0.006
	NO	22 (30.6%)	20 (58.8%)	
Visit 5	YES	52 (72.2%)	11 (32.4%)	< 0.001
	NO	20 (27.8%)	23 (67.6%)	
Visit 6	YES	53 (73.6%)	13 (38.2%)	< 0.001
	NO	19 (26.4%)	21 (61.8%)	

* p-value from Cochran-Mantel-Haenszel test, stratified by site.

Safety

During the period from subject enrolled to the end of Study Period II, a total of 262 adverse events (AEs) were reported (204 AEs in the atomoxetine group and 58 AEs in the placebo group). Of these, 208 were treatment-emergent adverse events (TEAE): 164 events in the atomoxetine group and 44 events in the placebo group. There were 103 events that were classified as drug-related TEAEs with 96 of these events occurring in the atomoxetine group and the remaining seven events occurring in placebo group. One serious adverse event (SAE) was reported during this period and it was determined to be not related to study treatment.

Table 19 shows that 80 (76.2 %) of the 105 subjects who comprised the safety population reported one or more AE(s) (59 subjects receiving atomoxetine and 21 subjects receiving placebo; $p=.026$). Of these, 70 (66.7%) subjects reported their AE(s) after treatment administration (54 subjects receiving atomoxetine and 16 subjects receiving placebo; $p=.004$). Of these 70 subjects, 45 (42.9%) experienced drug-related TEAE(s) (40 subjects receiving atomoxetine and five subjects receiving placebo; $p<.001$). One subject from the atomoxetine group discontinued due to dizziness.

Two SAEs were reported during the study by subjects receiving atomoxetine. One was an acute asthma attack requiring hospitalization and was considered to be a serious TEAE because it was reported during Study Period II. The other SAE was reported during Study Period III when a subject suffered from an upper respiratory infection and fever and was then admitted to a local clinic with bronchiolitis. In the opinion of the investigator in both cases, these events were not related to either the study medication or to protocol procedures.

Table 19. Distribution of Subjects Reporting Adverse Events by Category

Category	Atomoxetine (N=71) n (%)	Placebo (N=34) n (%)	Total (N=105) n (%)	P-value*
Number of Subjects with Adverse Events	59 (83.1%)	21 (61.8%)	80 (76.2%)	0.026
Number of Subjects with Treatment-Emergent Adverse Events	54 (76.1%)	16 (47.1%)	70 (66.7%)	0.004
Number of Subjects with Serious Adverse Events	1 (1.4%)	0 (0.0%)	1 (1.0%)	1.000
Number of Subjects with Serious Treatment-Emergent Adverse Events	1 (1.4%)	0 (0.0%)	1 (1.0%)	1.000
Number of Subjects with Drug-Related Adverse Events	40 (56.3%)	6 (17.6%)	46 (43.8%)	< 0.001
Number of Subjects with Drug-Related Treatment-Emergent Adverse Events	40 (56.3%)	5 (14.7%)	45 (42.9%)	< 0.001
Number of Subjects with Drug-Related Serious Adverse Events	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Number of Subjects with Drug-Related Serious Treatment-Emergent Adverse Events	0 (0.0%)	0 (0.0%)	0 (0.0%)	

* p-value: Comparisons between treatment groups by Fisher's exact test.

TEAEs that were reported by >10% of subjects receiving atomoxetine were anorexia, somnolence, nausea, and increased cough. The most common TEAE reported by subjects from the atomoxetine group was anorexia, which was reported by 26 (36.6%) subjects from this group, compared with five (14.7%) subjects from the placebo group (p=.02; Table 20). Nausea was reported by 12 (16.9 %) subjects from the atomoxetine group, while no subjects receiving placebo reported this TEAE (p<.01). The frequencies of other TEAEs were not statistically significantly different between the two treatment groups (Table 20).

Table 21 presents those TEAEs that were categorized as drug-related in the opinion of the investigator. Anorexia was the most common drug-related TEAE reported by subjects from the atomoxetine group. Of the 26 cases of anorexia reported by subjects from the atomoxetine group, 23 were categorized as drug-related. Nineteen of the 22 cases of somnolence and nine of the 12 cases of nausea, reported by subjects from the atomoxetine group, were categorized as drug-related.

Table 20. Treatment Emergent Adverse Events in Decreasing Frequency for the Atomoxetine Group

TEAE	Atomoxetine (N=71)	Placebo (N=34)	P-value*
Anorexia	26 (36.6%)	5 (17.4%)	0.02
Somnolence	22 (31.0%)	4 (11.8%)	0.05
Nausea	12 (16.9%)	0 (0.0%)	<0.01
Cough increased	9 (12.7%)	7 (20.6%)	0.38
Headache	7 (9.9%)	2 (5.9%)	0.71
Dizziness	7 (9.9%)	1 (2.9%)	0.43
Asthenia	7 (9.9%)	0 (0.0%)	0.09
Rhinitis	6 (8.5%)	5 (14.7%)	0.33
Abdominal pain	6 (8.5%)	0 (0.0%)	0.17
Pharyngitis	5 (7.0%)	4 (11.8%)	0.47
Vomiting	5 (7.0%)	2 (5.9%)	1.00
Diarrhea	4 (5.6%)	0 (0.0%)	0.30
Weight Loss	4 (5.6%)	0 (0.0%)	0.30
Fever	3 (4.2%)	5 (14.7%)	0.11
Twitching	1 (1.4%)	2 (5.9%)	0.24

* p-value: Comparisons between treatment groups by Fisher's exact test.

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Table 21 **Number of Subjects with One or More Drug-Related Treatment-Emergent Adverse Events by Body System, COSTART Term, and Severity**

Body System COSTART Preferred Term	Atomoxetine (N=71)				Placebo (N=34)			
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
Body as a Whole								
Abdominal Pain	3 (4.2%)	1 (1.4%)	0 (0.0%)	4 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asthenia	5 (7.0%)	1 (1.4%)	0 (0.0%)	6 (8.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Headache	3 (4.2%)	0 (0.0%)	0 (0.0%)	3 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total				11 (15.5%)				0 (0.0%)
Cardiovascular System								
Palpitation	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tachycardia	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total				2 (2.8%)				0 (0.0%)
Digestive System								
Anorexia	17 (23.9%)	6 (8.5%)	0 (0.0%)	23 (32.4%)	3 (8.8%)	0 (0.0%)	0 (0.0%)	3 (8.8%)
Diarrhea	3 (4.2%)	0 (0.0%)	0 (0.0%)	3 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nausea	6 (8.5%)	3 (4.2%)	0 (0.0%)	9 (12.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vomiting	4 (5.6%)	0 (0.0%)	0 (0.0%)	4 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total				29 (40.8%)				3 (8.8%)
Metabolic and Nutritional Disorders								
Weight Loss	4 (5.6%)	0 (0.0%)	0 (0.0%)	4 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total				4 (5.6%)				0 (0.0%)
Nervous System								
Dizziness	5 (7.0%)	1 (1.4%)	0 (0.0%)	6 (8.5%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
Insomnia	2 (2.8%)	0 (0.0%)	0 (0.0%)	2 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Somnolence	18 (25.4%)	1 (1.4%)	0 (0.0%)	19 (26.8%)	3 (8.8%)	0 (0.0%)	0 (0.0%)	3 (8.8%)
Total				24 (33.8%)				4 (11.8%)

Systolic blood pressure (Table 22), diastolic blood pressure (Table 23), heart rate (Table 24), temperature (Table 25), and weight (Table 26) were measured at baseline, Visit 3, Visit 4, Visit 5, and Visit 6. At all visits, there was a statistically significant weight decrease in the atomoxetine group ($p<.001$) and a statistically significant weight increase in the placebo group ($p<.05$). Furthermore, at all visits, the difference between the two groups was statistically significant ($p<.001$). No between-group differences were observed for systolic blood pressure, diastolic blood pressure, heart rate, temperature, or weight.

Serum levels of aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), creatine kinase (CK), total bilirubin, blood urea nitrogen (BUN), creatinine, glucose, uric acid, calcium, phosphorus, total protein, albumin, sodium, potassium, chloride, bicarbonate, cholesterol, and HbA_{1C} were also measured. The following statistically significant changes from baseline to endpoint were observed in the atomoxetine group: ALT (U/L) decreased by 2.1 ± 4.4 (mean $\pm$ SD, $p<.001$), alkaline phosphatase (U/L) decreased by 15.9 ± 56.5 (mean $\pm$ SD, $p=.021$), total bilirubin (mg/dL) increased by 0.06 ± 0.17 (mean $\pm$ SD, $p=.007$), uric acid (mg/dL) decreased by 0.33 ± 0.96 (mean $\pm$ SD, $p=.006$), calcium (mmol/L) increased by 0.09 ± 0.33 (mean $\pm$ SD, $p=.031$), albumin (g/dL) increased by 0.10 ± 0.23 (mean $\pm$ SD, $p<.001$), and bicarbonate (mEq/L) increased by 1.45 ± 2.39 (mean $\pm$ SD, $p<.001$). In the placebo group, the following statistically significant changes from baseline to endpoint were observed: random glucose (mg/dL) increased by 5.5 ± 13.1 (mean $\pm$ SD, $p=.022$), chloride (mmol/L) increased by 1.1 ± 1.0 (mean $\pm$ SD, $p=.002$), and bicarbonate (mEq/L) decreased by 1.18 ± 2.09 (mean $\pm$ SD, $p=.015$). Statistically significant differences between treatments were observed in the changes from baseline to endpoint of alkaline phosphatase ($p=.029$), GGT ($p=.046$), calcium ($p=.046$), phosphorus ($p=.035$), chloride ($p=.007$), and bicarbonate ($p<.001$). All values that were outside of the normal range were, in the opinion of the treating investigator and the lead clinical research physician, clinically insignificant.

No statistically significant differences were observed between treatments for the following hematological parameters: hemoglobin, hematocrit, platelets, mean cell volume (MCV), red blood cell (RBC) count and white blood cell (WBC) count and differentiation. In the atomoxetine group, the following statistically significant changes from baseline to endpoint were observed: hemoglobin (g/dL) increased by 0.19 ± 0.57 (mean $\pm$ SD, $p=.006$), hematocrit (%) increased by 0.63 ± 1.80 (mean $\pm$ SD, $p=.004$), RBC ($10^6/\text{cmm}$) increased by 0.091 ± 0.187 (mean $\pm$ SD, $p<.001$), and lymphocytes (%) decreased by 2.90 ± 10.08 (mean $\pm$ SD, $p=.025$). Any hematological parameters that were found in subjects to be lower or higher than normal values were deemed clinically insignificant by the treating investigator and the lead clinical research physician.

Urinalysis parameters, including specific gravity, protein, glucose, occult blood, and sediments for RBC, WBC, and epithelial, were also measured at baseline and endpoint and no clinically significant changes were observed.

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Table 22. By-Visit Summary of Systolic Blood Pressure (mmHg) and Change from Baseline

Variable	Visit	Statistics	Atomoxetine	Placebo	Difference	P-value
Systolic BP (mmHg)	Baseline	N	71	34		
		Mean (SD)	95.5 (8.9)	95.4 (10.0)	0.1	
		Median	95.0	96.0		
		Min - Max	79.0 - 125.0	71.0 - 110.0		
		95% CI	93.4 - 97.6	91.9 - 98.9	-3.7 - 3.9	
		P-value				0.941
	Visit 3	N	71	34		
		Mean (SD)	98.4 (10.3)	95.0 (7.9)	3.4	
		Median	98.0	94.0		
		Min - Max	78.0 - 127.0	79.0 - 109.0		
		95% CI	96.0 - 100.8	92.2 - 97.8	-0.5 - 7.4	
	Change from Baseline to Visit 3	N	71	34		
		Mean (SD)	2.9 (10.8)	-0.4 (7.3)	3.3	
		Median	1.0	-2.0		
		Min - Max	-19.0 - 42.0	-18.5 - 16.0		
		95% CI	0.4 - 5.5	-2.9 - 2.1	-0.2 - 6.9	
		P-value	0.026	0.743		0.092
	Visit 4	N	70	34		
		Mean (SD)	95.9 (9.5)	94.1 (7.9)	1.8	
		Median	95.0	95.0		
		Min - Max	70.0 - 123.0	70.0 - 109.0		
		95% CI	93.7 - 98.2	91.4 - 96.9	-1.9 - 5.5	
	Change from Baseline to Visit 4	N	70	34		
		Mean (SD)	0.3 (9.1)	-1.3 (6.1)	1.6	
		Median	0.8	-1.0		
		Min - Max	-18.0 - 38.0	-13.0 - 9.0		
		95% CI	-1.8 - 2.5	-3.4 - 0.9	-1.4 - 4.6	
		P-value	0.753	0.233		0.321

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Table 22. By-Visit Summary of Systolic Blood Pressure (mmHg) and Change from Baseline (concluded)

Variable	Visit	Statistics	Atomoxetine	Placebo	Difference	P-value
Systolic BP (mmHg)	Visit 5	N	69	32		
		Mean (SD)	97.6 (9.0)	96.6 (8.8)	1.1	
		Median	98.0	97.0		
		Min - Max	80.0 - 120.0	71.0 - 112.0		
		95% CI	95.5 - 99.8	93.4 - 99.8	-2.8 - 4.9	
	Change from Baseline to Visit 5	N	69	32		
		Mean (SD)	1.9 (8.7)	1.3 (9.7)	0.6	
		Median	2.0	0.0		
		Min - Max	-22.0 - 23.0	-22.0 - 21.0		
		95% CI	-0.2 - 4.0	-2.2 - 4.8	-3.2 - 4.4	
		P-value	0.074	0.451		0.707
	Visit 6	N	69	29		
		Mean (SD)	97.8 (8.5)	96.7 (6.4)	1.1	
		Median	98.0	99.0		
		Min - Max	79.0 - 122.5	80.0 - 106.0		
		95% CI	95.8 - 99.8	94.3 - 99.2	-2.4 - 4.5	
	Change from Baseline to Visit 6	N	69	29		
		Mean (SD)	2.1 (9.2)	1.0 (8.8)	1.1	
		Median	1.0	-1.0		
		Min - Max	-21.0 - 26.0	-13.5 - 18.0		
		95% CI	-0.1 - 4.3	-2.4 - 4.3	-2.9 - 5.1	
		P-value	0.066	0.554		0.575

N=Number of observations SD=Standard Deviation CI=Confidence Interval BP=Blood Pressure
Baseline is defined as the last value collected prior to first dose of study drug.
Only subjects with a baseline and at least one post-baseline assessment were included.
P-value between treatment groups was using ANOVA with terms of treatment and investigator.
P-value within each treatment group was derived from paired t test.

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Table 23. By-Visit Summary of Diastolic Blood Pressure (mmHg) and Change from Baseline

Variable	Visit	Statistics	Atomoxetine	Placebo	Difference	P-value
Diastolic BP (mmHg)	Baseline	N	71	34		
		Mean (SD)	61.1 (9.5)	60.0 (8.0)	1.1	
		Median	60.0	59.0		
		Min - Max	39.0 - 90.0	46.0 - 80.0		
		95% CI	58.9 - 63.4	57.2 - 62.8	-2.6 - 4.9	
		P-value				0.532
	Visit 3	N	71	34		
		Mean (SD)	65.6 (8.7)	60.5 (10.3)	5.1	
		Median	65.0	60.0		
		Min - Max	37.0 - 90.0	40.0 - 83.0		
		95% CI	63.6 - 67.7	56.9 - 64.1	1.3 - 9.0	
	Change from Baseline to Visit 3	N	71	34		
		Mean (SD)	4.5 (10.6)	0.5 (11.0)	4	
		Median	3.0	-0.3		
		Min - Max	-27.0 - 35.0	-19.0 - 29.5		
		95% CI	2.0 - 7.0	-3.3 - 4.3	-0.4 - 8.4	
		P-value	< 0.001	0.798		0.085
	Visit 4	N	70	34		
		Mean (SD)	65.0 (9.0)	60.9 (9.2)	4.1	
		Median	64.5	59.5		
		Min - Max	40.0 - 85.0	45.0 - 80.0		
		95% CI	62.8 - 67.1	57.7 - 64.1	0.3 - 7.8	
	Change from Baseline to Visit 4	N	70	34		
		Mean (SD)	4.0 (9.4)	0.9 (10.1)	3.1	
		Median	3.8	2.0		
		Min - Max	-15.0 - 30.0	-17.5 - 25.0		
		95% CI	1.7 - 6.2	-2.6 - 4.4	-0.9 - 7.0	
		P-value	< 0.001	0.607		0.129

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Table 23. By-Visit Summary of Diastolic Blood Pressure (mmHg) and Change from Baseline (concluded)

Variable	Visit	Statistics	Atomoxetine	Placebo	Difference	P-value
Diastolic BP (mmHg)	Visit 5	N	69	32		
		Mean (SD)	66.4 (8.4)	62.8 (10.2)	3.6	
		Median	66.0	64.0		
		Min - Max	45.0 - 88.0	35.0 - 82.0		
		95% CI	64.4 - 68.4	59.1 - 66.5	-0.2 - 7.4	
	Change from Baseline to Visit 5	N	69	32		
		Mean (SD)	5.2 (8.8)	2.7 (10.9)	2.5	
		Median	6.0	3.5		
		Min - Max	-20.0 - 25.0	-25.0 - 23.0		
		95% CI	3.0 - 7.3	-1.2 - 6.6	-1.6 - 6.5	
		P-value	< 0.001	0.172		0.249
	Visit 6	N	69	29		
		Mean (SD)	64.9 (9.3)	65.1 (7.6)	-0.1	
		Median	65.0	65.0		
		Min - Max	45.0 - 84.0	45.0 - 80.0		
		95% CI	62.7 - 67.2	62.2 - 67.9	-4.0 - 3.8	
	Change from Baseline to Visit 6	N	69	29		
		Mean (SD)	3.7 (9.0)	5.0 (9.9)	-1.3	
		Median	3.0	8.0		
		Min - Max	-15.0 - 24.0	-13.0 - 22.0		
		95% CI	1.5 - 5.8	1.2 - 8.8	-5.4 - 2.7	
		P-value	0.001	0.011		0.504

N=Number of observations SD=Standard Deviation CI=Confidence Interval BP=Blood Pressure
Baseline is defined as the last value collected prior to first dose of study drug.
Only subjects with a baseline and at least one post-baseline assessment were included.
P-value between treatment groups was using ANOVA with terms of treatment and investigator.
P-value within each treatment group was derived from paired t test.

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Table 24. By-Visit Summary of Heart Rate (bpm) and Change from Baseline

Variable	Visit	Statistics	Atomoxetine	Placebo	Difference	P-value
Heart Rate (bpm)	Baseline	N	71	34		
		Mean (SD)	84.3 (10.8)	82.9 (10.5)	1.5	
		Median	84.0	81.0		
		Min - Max	62.0 - 118.0	68.0 - 116.0		
		95% CI	81.8 - 86.9	79.2 - 86.6	-3.0 - 5.9	
		P-value				0.535
	Visit 3	N	71	34		
		Mean (SD)	87.1 (12.6)	82.4 (9.4)	4.7	
		Median	86.0	83.5		
		Min - Max	62.0 - 118.0	66.0 - 98.0		
		95% CI	84.1 - 90.1	79.1 - 85.7	0.3 - 9.0	
	Change from Baseline to Visit 3	N	71	34		
		Mean (SD)	2.7 (10.7)	-0.5 (10.9)	3.2	
		Median	1.0	1.5		
		Min - Max	-18.0 - 38.0	-24.0 - 20.0		
		95% CI	0.2 - 5.3	-4.3 - 3.3	-1.2 - 7.7	
		P-value	0.035	0.802		0.168
	Visit 4	N	70	34		
		Mean (SD)	85.1 (10.9)	83.6 (10.9)	1.5	
		Median	86.0	82.0		
		Min - Max	58.0 - 106.0	66.0 - 110.0		
		95% CI	82.5 - 87.7	79.8 - 87.4	-3.0 - 6.0	
	Change from Baseline to Visit 4	N	70	34		
		Mean (SD)	0.7 (11.3)	0.7 (12.5)	0	
		Median	2.0	0.5		
		Min - Max	-34.0 - 28.0	-34.0 - 34.0		
		95% CI	-2.0 - 3.4	-3.7 - 5.0	-4.9 - 4.8	
		P-value	0.620	0.755		0.967

(continued)

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Table 24. By-Visit Summary of Heart Rate (bpm) and Change from Baseline (concluded)

Variable	Visit	Statistics	Atomoxetine	Placebo	Difference	P-value
Heart Rate (bpm)	Visit 5	N	69	32		
		Mean (SD)	87.4 (10.8)	85.1 (9.5)	2.3	
		Median	86.0	86.0		
		Min - Max	62.0 - 122.0	72.0 - 106.0		
		95% CI	84.7 - 90.0	81.7 - 88.5	-2.2 - 6.7	
	Change from Baseline to Visit 5	N	69	32		
		Mean (SD)	3.1 (11.2)	2.2 (10.3)	0.9	
		Median	2.5	2.0		
		Min - Max	-22.5 - 28.0	-18.0 - 25.0		
		95% CI	0.4 - 5.7	-1.5 - 5.9	-3.8 - 5.5	
		P-value	0.027	0.237		0.701
	Visit 6	N	69	29		
		Mean (SD)	88.1 (12.1)	86.6 (10.1)	1.5	
		Median	89.0	88.0		
		Min - Max	62.0 - 112.0	66.0 - 110.0		
		95% CI	85.2 - 91.0	82.8 - 90.5	-3.6 - 6.6	
	Change from Baseline to Visit 6	N	69	29		
		Mean (SD)	3.8 (12.5)	2.6 (9.9)	1.2	
		Median	4.5	2.0		
		Min - Max	-31.0 - 36.0	-16.0 - 22.0		
		95% CI	0.8 - 6.8	-1.1 - 6.4	-4.0 - 6.3	
		P-value	0.014	0.165		0.704

N=Number of observations SD=Standard Deviation CI=Confidence Interval BP=Blood Pressure
 Baseline is defined as the last value collected prior to first dose of study drug.
 Only subjects with a baseline and at least one post-baseline assessment were included.
 P-value between treatment groups was using ANOVA with terms of treatment and investigator.
 P-value within each treatment group was derived from paired t test.

Atomoxetine Hydrochloride

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Table 25. By-Visit Summary of Temperature (°C) and Change from Baseline

Variable	Visit	Statistics	Atomoxetine	Placebo	Difference	P-value
Temperature (C)	Baseline	N	71	34		
		Mean (SD)	36.25 (0.67)	36.31 (0.52)	-0.06	
		Median	36.30	36.35		
		Min - Max	34.60 - 37.60	35.30 - 37.20		
		95% CI	36.09 - 36.41	36.13 - 36.49	-0.32 - 0.20	
		P-value				0.533
	Visit 3	N	71	34		
		Mean (SD)	36.24 (0.62)	36.22 (0.67)	0.02	
		Median	36.30	36.30		
		Min - Max	34.50 - 37.30	34.10 - 37.30		
		95% CI	36.09 - 36.39	35.99 - 36.45	-0.24 - 0.28	
	Change from Baseline to Visit 3	N	71	34		
		Mean (SD)	-0.01 (0.59)	-0.09 (0.59)	0.08	
		Median	-0.10	-0.10		
		Min - Max	-1.60 - 1.80	-1.30 - 1.10		
		95% CI	-0.15 - 0.13	-0.29 - 0.12	-0.17 - 0.32	
		P-value	0.920	0.404		0.535
	Visit 4	N	70	34		
		Mean (SD)	36.31 (0.68)	36.26 (0.85)	0.05	
		Median	36.40	36.45		
		Min - Max	34.10 - 39.60	34.30 - 37.90		
		95% CI	36.15 - 36.48	35.97 - 36.56	-0.26 - 0.36	
	Change from Baseline to Visit 4	N	70	34		
		Mean (SD)	0.07 (0.72)	-0.04 (0.80)	0.11	
		Median	0.00	0.00		
		Min - Max	-1.50 - 3.10	-2.20 - 2.40		
		95% CI	-0.10 - 0.24	-0.32 - 0.24	-0.20 - 0.42	
		P-value	0.436	0.751		0.459

(continued)

Atomoxetine Hydrochloride

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Table 25. By-Visit Summary of Temperature (°C) and Change from Baseline (concluded)

Variable	Visit	Statistics	Atomoxetine	Placebo	Difference	P-value
Temperature (C)	Visit 5	N	69	32		
		Mean (SD)	36.26 (0.79)	36.17 (0.52)	0.09	
		Median	36.30	36.30		
		Min - Max	34.00 - 39.50	34.30 - 37.10		
		95% CI	36.07 - 36.45	35.98 - 36.35	-0.17 - 0.36	
	Change from Baseline to Visit 5	N	69	32		
		Mean (SD)	0.02 (0.81)	-0.14 (0.58)	0.16	
		Median	0.00	-0.10		
		Min - Max	-1.90 - 3.20	-1.80 - 0.90		
		95% CI	-0.18 - 0.21	-0.35 - 0.07	-0.12 - 0.44	
		P-value	0.860	0.174		0.258
	Visit 6	N	69	29		
		Mean (SD)	36.22 (0.61)	36.20 (0.54)	0.02	
		Median	36.20	36.20		
		Min - Max	34.40 - 37.70	35.20 - 37.30		
		95% CI	36.07 - 36.37	36.00 - 36.41	-0.24 - 0.28	
	Change from Baseline to Visit 6	N	69	29		
		Mean (SD)	-0.02 (0.65)	-0.10 (0.45)	0.08	
		Median	0.00	-0.10		
		Min - Max	-1.10 - 1.80	-1.10 - 0.90		
		95% CI	-0.18 - 0.13	-0.27 - 0.07	-0.15 - 0.31	
		P-value	0.783	0.244		0.560

N=Number of observations SD=Standard Deviation CI=Confidence Interval BP=Blood Pressure
Baseline is defined as the last value collected prior to first dose of study drug.
Only subjects with a baseline and at least one post-baseline assessment were included.
P-value between treatment groups was using ANOVA with terms of treatment and investigator.
P-value within each treatment group was derived from paired t test.

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Table 26. By-Visit Summary of Weight (kg) and Change from Baseline

Variable	Visit	Statistics	Atomoxetine	Placebo	Difference	P-value
Weight (kg)	Baseline	N	71	34		
		Mean (SD)	31.37 (9.00)	32.30 (9.12)	-0.93	
		Median	29.50	28.50		
		Min - Max	20.00 - 57.60	20.00 - 54.00		
		95% CI	29.24 - 33.50	29.12 - 35.48	-4.66 - 2.81	
		P-value				0.549
	Visit 3	N	71	34		
		Mean (SD)	31.05 (8.81)	32.50 (9.08)	-1.45	
		Median	29.10	28.30		
		Min - Max	20.00 - 56.40	20.00 - 54.50		
		95% CI	28.97 - 33.14	29.33 - 35.67	-5.13 - 2.23	
	Change from Baseline to Visit 3	N	71	34		
		Mean (SD)	-0.32 (0.59)	0.20 (0.54)	-0.52	
		Median	-0.30	0.00		
		Min - Max	-1.90 - 0.80	-0.70 - 1.40		
		95% CI	-0.46 - -0.18	0.01 - 0.39	-0.76 - -0.28	
		P-value	< 0.001	0.038		< 0.001
	Visit 4	N	70	34		
		Mean (SD)	30.91 (8.86)	32.63 (9.25)	-1.72	
		Median	29.10	28.40		
		Min - Max	19.50 - 56.00	20.00 - 54.80		
		95% CI	28.79 - 33.02	29.40 - 35.86	-5.45 - 2.01	
	Change from Baseline to Visit 4	N	70	34		
		Mean (SD)	-0.46 (0.64)	0.33 (0.56)	-0.79	
		Median	-0.55	0.10		
		Min - Max	-2.20 - 1.40	-0.40 - 1.80		
		95% CI	-0.61 - -0.30	0.14 - 0.52	-1.04 - -0.53	
		P-value	< 0.001	0.002		< 0.001

(continued)

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Table 26. By-Visit Summary of Weight (kg) and Change from Baseline (concluded)

Variable	Visit	Statistics	Atomoxetine	Placebo	Difference	P-value
Weight (kg)	Visit 5	N	69	32		
		Mean (SD)	30.62 (8.85)	32.50 (9.23)	-1.88	
		Median	29.00	28.45		
		Min - Max	19.50 - 55.00	20.50 - 54.00		
		95% CI	28.49 - 32.75	29.17 - 35.83	-5.68 - 1.93	
	Change from Baseline to Visit 5	N	69	32		
		Mean (SD)	-0.70 (0.89)	0.48 (0.80)	-1.18	
		Median	-0.60	0.40		
		Min - Max	-3.00 - 1.40	-1.00 - 2.20		
		95% CI	-0.91 - -0.48	0.19 - 0.77	-1.54 - -0.81	
		P-value	< 0.001	0.002		< 0.001
	Visit 6	N	69	29		
		Mean (SD)	30.48 (8.85)	32.84 (9.39)	-2.36	
		Median	28.70	29.00		
		Min - Max	19.80 - 56.00	20.00 - 54.00		
		95% CI	28.35 - 32.60	29.27 - 36.41	-6.32 - 1.60	
	Change from Baseline to Visit 6	N	69	29		
		Mean (SD)	-0.84 (1.02)	0.52 (0.74)	-1.36	
		Median	-0.80	0.40		
		Min - Max	-4.00 - 1.40	-0.60 - 2.20		
		95% CI	-1.08 - -0.59	0.24 - 0.80	-1.73 - -1.00	
		P-value	< 0.001	< 0.001		< 0.001

N=Number of observations SD=Standard Deviation CI=Confidence Interval BP=Blood Pressure
Baseline is defined as the last value collected prior to first dose of study drug.
Only subjects with a baseline and at least one post-baseline assessment were included.
P-value between treatment groups was using ANOVA with terms of treatment and investigator.
P-value within each treatment group was derived from paired t test.

Summary ID# 8226.

Clinical Study Summary: Study B4Z-MC-LYCL

Guiding Dose Increases in Patients Incompletely Responsive to Usual Doses of Atomoxetine by Determining Plasma Atomoxetine Concentrations: A Randomized, Double-Blind Study

Date summary approved by Lilly: 29 March 2006

Brief Summary of Results

Study B4Z-MC-LYCL (LYCL) was a multicenter, double-blind, randomized trial of increased-dose versus continued same-dose atomoxetine in patients who failed to respond optimally to an initial course of atomoxetine at usual doses and whose plasma-atomoxetine levels were below a specified threshold.

The primary objective of this study was to test the hypothesis that patients treated with atomoxetine hydrochloride (hereafter referred to as atomoxetine) at doses of approximately 1.2 mg/kg/day as a single daily dose who have suboptimal clinical responses and peak plasma-atomoxetine levels no higher than 800 ng/mL would benefit from a dose increase to approximately 2.4 mg/kg/day compared to patients continued on a dose of approximately 1.2 mg/kg/day.

It was found that:

- There was no statistically significant difference in symptom improvement between the randomized higher-dose and target-dose groups in the primary efficacy analysis of the Attention Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv).

Secondary efficacy measures demonstrated that:

- There was no statistically significant difference in symptom improvement in the higher-dose group compared with the target-dose group on the ADHDRS-IV-Parent:Inv subscales and Clinical Global Impressions–Attention-Deficit/Hyperactivity Disorder–Severity scale (CGI-ADHD-S).
- Patients who had peak plasma levels that were 800 ng/mL after acute, open-label treatment were statistically significantly more likely to meet the response criterion than patients with peak plasma levels ≤ 800 ng/mL.
- There were no statistically significant differences between the randomized higher- and lower-dose groups with respect to treatment-emergent adverse events (TEAEs) and mean changes in vital signs, weight, or electrocardiogram (ECG) values during double-blind treatment.
- Mean concentrations of atomoxetine for extensive metabolizer (EM) patients increased with increases in dose.

Title of Study: Clinical Study Synopsis: Guiding Dose Increases in Patients Incompletely Responsive to Usual Doses of Atomoxetine by Determining Plasma Atomoxetine Concentrations: A Randomized, Double-Blind Study	
Investigator(s): This multicenter study included 18 principal investigators.	
Study Center(s): This study was conducted at 18 study centers in the United States and Canada.	
Length of Study: 23 months Date first patient enrolled: 29 July 2003 Date last patient completed: 15 June 2005	Phase of Development: 4
Objectives: The primary objective of this study was to test the hypothesis that patients treated with atomoxetine at doses of approximately 1.2 mg/kg/day as a single daily dose who have suboptimal clinical responses and peak plasma-atomoxetine levels no higher than 800 ng/mL would benefit from a dose increase to approximately 2.4 mg/kg/day compared to patients continued on a dose of approximately 1.2 mg/kg/day. This objective was assessed by mean reduction in the total score of the Attention Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv). The secondary objectives of the study are as follows: - to assess the relationship between plasma-atomoxetine concentration levels and Attention-Deficit/Hyperactivity Disorder (ADHD) symptom response, as measured by the ADHDRS-IV-Parent:Inv Total Score - to compare the efficacy of atomoxetine given at a dose of up to 2.4 mg/kg/day with atomoxetine given at a dose of 1.2 mg/kg/day in reducing residual ADHD symptoms, as measured by the mean change in ratings on the Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity scale (CGI-ADHD-S) - to assess the safety and tolerability of atomoxetine at doses up to 2.4 mg/kg/day compared to the standard dose of 1.2 mg/kg/day in patients with peak plasma-atomoxetine concentration levels no higher than 800 ng/mL at usual doses, as assessed by adverse events (AEs) elicited during open-ended questioning.	
Study Design: Study B4Z-MC-LYCL (LYCL) was a multicenter, double-blind, randomized study of increased-dose versus continued same-dose atomoxetine in patients who failed to respond optimally to an initial course of atomoxetine at usual doses and whose plasma-atomoxetine levels were below a specified threshold (see Figure LYCL.1). Study Period I was a 3- to 28-day screening and medication washout period. During Study Period II, approximately 6 weeks, patients received open-label treatment with atomoxetine titrated up to a target dose of approximately 1.2 mg/kg/day, after which response and plasma-atomoxetine levels were measured. During Study Period III, approximately 4 weeks, patients with plasma-atomoxetine concentration levels no higher than 800 ng/mL who failed to achieve adequate ADHD symptom reduction were randomized to continued treatment with either atomoxetine at a dosage of approximately 1.2 mg/kg/day (target-dose group) or atomoxetine increased to approximately 1.8 to 2.4 mg/kg/day (higher-dose group). Patients (nonrandomized responders) who achieved adequate ADHD symptom reduction during Study Period II continued to receive atomoxetine at a dosage of approximately 1.2 mg/kg/day. Nonresponders who had peak plasma-atomoxetine concentrations >800 ng/mL completed the study at Visit 4 after approximately 6 weeks. An addendum to the protocol provided an optional, open-label treatment extension (Study Period IV) for patients enrolled in the study at Canadian sites. This extension permitted Canadian patients to continue receiving open-label treatment until atomoxetine became commercially available in Canada.	

Number of Patients:

Planned: 350 patients to be entered, 300 patients to be enrolled, and 120 patients to be randomized.

Study Period I (Screening): 418 entered, 378 completed (40 screen failures).

Study Period II (Open-Label): 378 patients enrolled (292 completed).

Study Period III (Double-Blind):

Randomized Higher-Dose Group: 63 (57 completed).

Randomized Target-Dose Group: 62 (54 completed).

Nonrandomized US Responders: 99 (93 completed).

Nonrandomized Canadian Patients* (Nonresponders and Responders): 62 (58 completed)

Study Period IV (Open-Label, Canadian Extension): 65 (n=44 completed)

*Patients at sites in the US and Canada were to be randomized to treatment using an Interactive Voice Response System (IVRS). Due to a process error, none of the Canadian patients were randomized.

Nonrandomized Canadian Patients, whether nonresponders or responders, continued at their Study Period II dose.

Diagnosis and Main Criteria for Inclusion: Patients were males or females aged 6 through 16 years at Visit 1. For inclusion, patients had to have met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition™ (DSM-IV) diagnostic criterion for ADHD and scored at least 1.5 standard deviations above the age and gender norm at both Visits 1 and 2 for their diagnostic subtype using published norms (DuPaul et al. 1998) for the ADHDRS-IV-Parent:Inv. Patients must have had an electrocardiogram (ECG) performed at Visit 1.

Test Product, Dose, and Mode of Administration:

Open-Label:

Atomoxetine, titrated to a target dose of approximately 1.2 mg/kg/day given orally once daily using 2.5-, 5-, 10-, 25-, and 40-mg capsules.

Double-Blind:

Randomized Higher-Dose Group: Atomoxetine, at a dose of approximately 1.8 mg/kg/day or, if significant residual ADHD symptoms remained, a maximum dose of approximately 2.4 mg/kg/day, given orally once or twice daily using 2.5-, 5-, 10-, 20-, 25-, and 40-mg capsules.

Randomized Target-Dose Group: Atomoxetine, at a target dose of approximately 1.2 mg/kg/day or, if the dose was not tolerated, a dose of approximately 0.8 mg/kg/day, given orally once or twice daily using 2.5-, 5-, 10-, 20-, 25-, and 40-mg capsules.

Nonrandomized Responders: Atomoxetine, at approximately 1.2 mg/kg/day, given orally once or twice daily using 2.5-, 5-, 10-, 20-, 25-, and 40-mg capsules.

Open-Label Canadian Extension: Atomoxetine, at a dose of approximately 0.8 to 1.8 mg/kg/day, given orally once or twice daily using 2.5-, 5-, 10-, 25-, and 40-mg capsules.

Duration of Treatment:

Open-Label: Approximately 6 weeks.

Double-Blind: Approximately 4 weeks.

Open-Label Canadian Extension: Up to approximately 23 months.

Variables:

Efficacy: Variables included the total score of the 18-item ADHDRS-IV-Parent:Inv and its subscale scores (Inattention and Hyperactivity-Impulsivity), and the secondary measure of CGI-ADHD-S.

Safety: AEs, vital signs, weight, laboratory tests, and ECGs.

Pharmacokinetic: Plasma concentrations of atomoxetine were determined from single blood samples obtained at Visit 3 and at the end of Study Period III (Visit 5 or Visit 6).

Evaluation Methods:

Statistical: During open-label treatment, summary statistics (sample size, mean, standard deviation, minimum, median, maximum scores, and percentages) were computed for efficacy and safety variables. Within-treatment-group changes were assessed using Wilcoxon's signed-rank test. The primary efficacy analysis used analysis of covariance (ANCOVA), with terms for baseline ADHDRS-IV-Parent:Inv Total score, treatment, and investigator included in the model. Baseline was defined as the last measurement obtained on or prior to Visit 4, and endpoint as the last measurement obtained after Visit 4 but on or before Visit 6. The last-observation-carried-forward (LOCF) approach was used to handle missing observations. Changes from baseline to endpoint for vital signs, continuous laboratory values, and ECG parameters were summarized by treatment group, and treatment differences for randomized patients were assessed with analysis of variance (ANOVA) on the ranked data. Categorical safety variables were analyzed by Fisher's exact test.

Patients were assigned to treatment based on ADHD symptom response; the definition of response was detailed in a separate document provided to Institutional Review Boards (IRBs). Throughout the study, investigators and patients remained blinded to this information. Following open-label treatment, incomplete response (nonresponder) was defined as an ADHDRS-IV-Parent:Inv total T-score at Visit 4 at least one standard deviation (SD) above age and gender norms, a value indicating the continuing presence of greater ADHD symptoms than in the normal population.

Pharmacokinetic: Observed plasma concentration data were summarized using a descriptive analysis, and were displayed graphically. No formal pharmacokinetic analysis was performed; however, there were subgroup analyses based on genotype, responder status, and categorical plasma levels (≤ 800 ng/mL versus > 800 ng/mL).

Results:

Patient Demographics

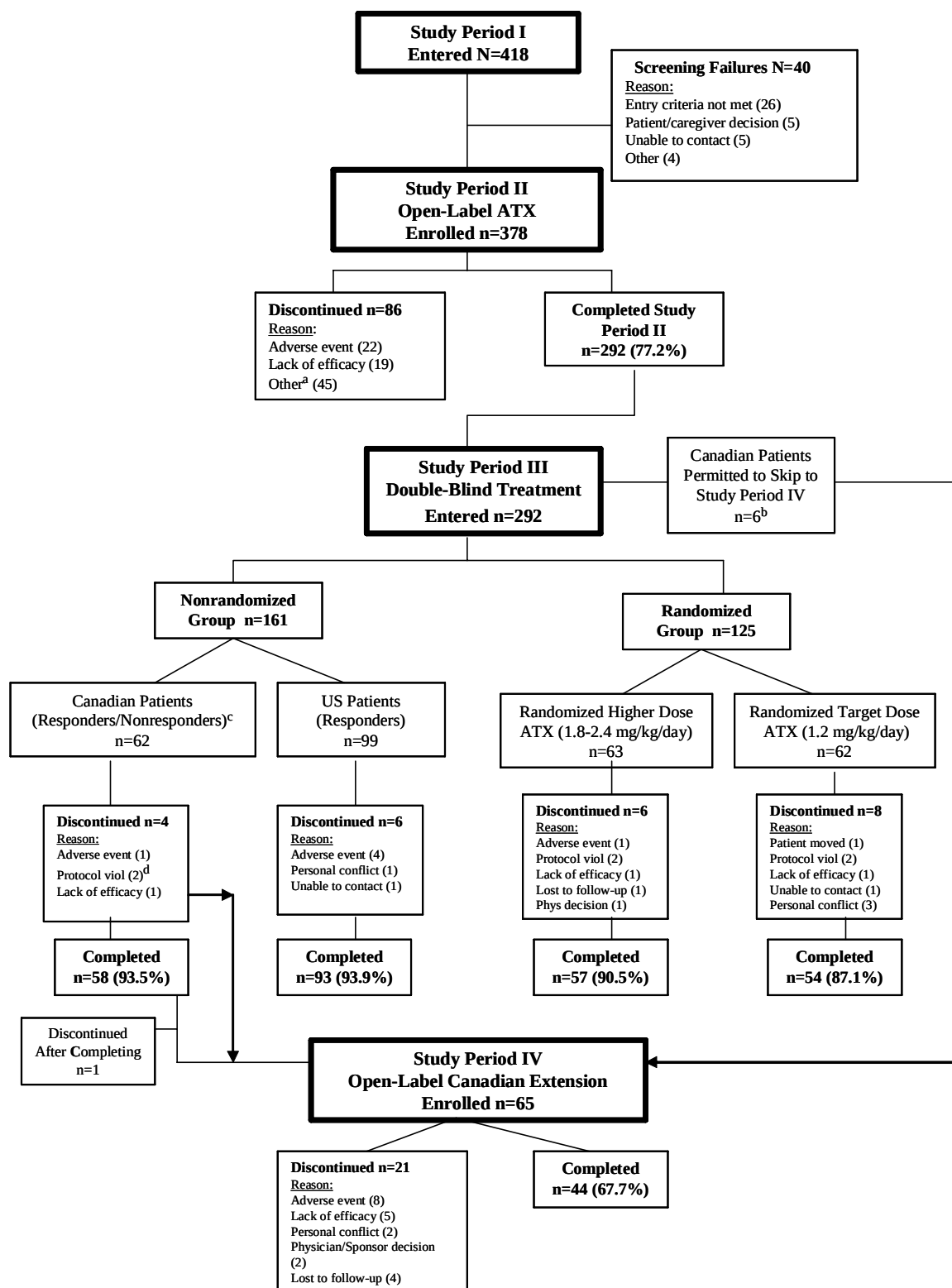
Patients who enrolled in the open-label phase of Study LYCL were predominately Caucasian (81.1%), male (73.9%), with a mean age of 10.9 (SD=2.5; range 6.0 to 16.8 years), and with the Combined ADHD subtype (65.7%). The majority (92.8%) had the extensive metabolizer (EM) genotype for cytochrome P450 2D6 (CYP2D6). During double-blind treatment, the randomized treatment groups were not statistically significantly different with respect to racial origin, sex, age, ADHD subtype, CYP2D6 genotype, and all other characteristics that were measured.

Patient Disposition

A total of 378 patients were enrolled in the approximately 6-week, acute, open-label phase of this study. Two hundred ninety-two patients (77.2%) completed the open-label phase and were enrolled into the double-blind treatment phase. Among the most frequent reasons for discontinuation during open-label treatment were AE (22; 5.8%), lack of efficacy (19; 5.0%), entry criteria for Study Period III not met (15; 4.0%), and lost to follow-up (14; 3.7%). Thirteen out of the 15 patients who did not meet entry criteria for Study Period III were discontinued from the study at Visit 4 due to the combination of a plasma concentration level greater than 800 ng/mL and a failure to meet the blinded response criteria.

Of the 292 patients who continued into the double-blind treatment phase, 125 met the criteria for randomization (plasma concentration levels ≤ 800 ng/mL and inadequate ADHD symptom reduction) and were randomized to receive either higher-dose atomoxetine (n=63) or continue with target-dose atomoxetine (n=62). Six of the randomized higher-dose patients and 8 of the randomized target-dose patients discontinued during double-blind treatment. Three patients in the target-dose group discontinued due to personal conflict and all other categories for both higher- and target-dose patients were not experienced by more than 2 patients. When reasons for study discontinuation were compared for these two randomized groups, there were no statistically significant differences. A total of 161 patients were not randomized, 99 US patients who met the criteria for response and 62 Canadian patients (responders and nonresponders [inadvertently not randomized due to an IVRS programming error]). Study completion rates were high for the double-blind treatment phase, as follows: randomized higher-dose group (90.5%), randomized target-dose group (87.1%), nonrandomized US responders (93.9%), and nonrandomized Canadian patients group (93.5%).

Sixty-five Canadian patients were enrolled in the open-label Canadian extension (Study Period IV). Six of these patients were patients who skipped directly from open-label treatment (Study Period II). Forty-four Canadian patients completed this study period (67.7%). See Figure LYCL.1 for the study disposition.



Abbreviations and footnotes appear on next page.

Figure LYCL.1.

Study disposition.

Abbreviations: ATX = atomoxetine; n = number of patients; phys = physician; protocol viol = protocol violation.

^a The term “other” includes reasons for discontinuation, such as: physician decision, unable to contact/loss to follow-up, personal conflict, or other patient/caregiver decisions.

^b At the end of Study Period II, 6 Canadian patients who met criteria in an addendum to the protocol were permitted to skip Study Period III and enroll in Study Period IV.

^c Due to a process error, Canadian patients were not randomized; all (responders or nonresponders) continued to receive atomoxetine 1.2 mg/kg/day during Study Period III.

^d Two Canadian patients were coded as having discontinued Study Period III due to a "protocol violation". These patients completed Study Period III at Visit 5, instead of Visit 6 (the protocol-defined last visit in Study Period III), then enrolled in the open-label Canadian extension.

Figure LYCL.1. Study disposition (concluded).

Primary Efficacy Endpoint

The primary objective of this study was to test the hypothesis that patients with inadequate clinical response and peak plasma-atomoxetine levels ≤ 800 ng/mL treated with atomoxetine 1.2 mg/kg/day would benefit from an increased atomoxetine dose up to 2.4 mg/kg/day (higher-dose group) compared with patients who continued receiving atomoxetine 1.2 mg/kg/day (target-dose group). This hypothesis was not met, as the analysis did not demonstrate a statistically significant difference between treatment groups (higher-dose versus target-dose). Despite the randomization error that occurred in this study, the primary analysis was adequately powered (82%; 2-sided, 0.05 level) to detect a treatment difference of 6 points on the primary efficacy analysis. Table LYCL.1 summarizes the primary efficacy analysis of the ADHDRS-IV-Parent:Inv total score.

Table LYCL.1. Primary Efficacy Analysis of the ADHDRS-IV-Parent:Inv Total Score

Treatment Group	n	Baseline Mean (SD)	Endpoint Mean (SD)	Change	p-Value
Target-Dose Group	58	32.97 (9.17)	26.81 (11.94)	-6.16	.110
Higher-Dose Group	62	32.40 (8.22)	23.48 (11.00)	-8.92	

Abbreviations: n = number of patients; SD = standard deviation.

Secondary Efficacy Endpoints

The secondary objectives of the study were as follows:

- to assess the relationship between plasma-atomoxetine concentration levels and ADHD symptom response, as measured by the ADHDRS-IV-Parent:Inv Total Score.

- to compare the efficacy of atomoxetine given at a dose of up to 2.4 mg/kg/day with atomoxetine 1.2 mg/kg/day in reducing residual ADHD symptoms, as measured by the mean change in ratings on the Clinical Global Impressions–Attention-Deficit/Hyperactivity Disorder–Severity scale (CGI-ADHD-S).
- to assess the safety and tolerability of atomoxetine at doses up to 2.4 mg/kg/day compared to a standard dose of 1.2 mg/kg/day in patients with peak plasma-atomoxetine concentration levels no higher than 800 ng/mL at usual doses, as assessed by AEs elicited during open-ended questioning.

Table LYCL.2 summarizes the analysis for mean change from baseline to endpoint during open-label treatment for the ADHDRS-IV-Parent:Inv total and subscales and the CGI-ADHD-S score. A statistically significant within-treatment-group reduction (improvement) in mean scores was demonstrated for each scale.

**Table LYCL.2. Mean Change from Baseline to Endpoint
Open-Label Treatment**

ADHDRS-IV-Parent:Inv and CGI-ADHD-S Scores	n^a	Baseline Mean (SD)	Endpoint Mean (SD)	Change	Within-Group p-Value
ADHDRS Total Score	342	39.13 (8.92)	24.79 (12.14)	-14.34	<.001
ADHDRS Total T-Score	342	80.23 (10.34)	64.98 (12.64)	-15.25	<.001
ADHDRS Hyp/Imp Subscale	342	17.15 (6.96)	10.51 (7.02)	-6.64	<.001
ADHDRS Inatt. Subscale	342	21.98 (3.95)	14.28 (6.42)	-7.70	<.001
CGI-ADHD-S Score	343	4.74 (0.79)	3.59 (1.12)	-1.15	<.001

Abbreviations: ADHDRS-IV-Parent:Inv = Attention Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version:Investigator Administered and Scored; CGI-ADHD-S = Clinical Global Impressions–Attention-Deficit/Hyperactivity Disorder–Severity; Hyp/Imp = hyperactivity/impulsivity; Inatt = inattention; n = number of patients; SD = standard deviation.

^a Randomized patients with a baseline and a postbaseline visit.

During open-label treatment, patients had blood drawn to determine their peak plasma-atomoxetine concentrations at Visit 3. The percentage of patients who met the ADHD symptom-response criterion (ADHDRS-IV-Parent:Inv total T-score at least one standard deviation above age and gender norms) was computed by plasma-atomoxetine concentration level (≤ 800 or > 800 ng/mL) and is shown in Table LYCL 3. Patients who had peak plasma levels that were > 800 ng/mL after acute, open-label treatment were statistically significantly associated with response than patients with peak plasma levels ≤ 800 ng/mL.

Table LYCL.3. Response Rates

Response	n (%)	ATX ≤800 ng/mL	ATX >800 ng/mL
Yes	132 (40.0%)	109 (37.3%)	23 (60.5%)
No	198 (60.0%)	183 (62.7%)	15 (39.5%)

Abbreviations: ATX = atomoxetine; n = number of patients.

In the open-label treatment phase, peak plasma-atomoxetine concentration values were correlated with change in the ADHDRS-IV-Parent:Inv total T-score. The Pearson correlation coefficient ($r = -0.12$; $p = .027$) demonstrated a statistically significant negative correlation between these values (plasma concentration and change score).

Table LYCL.4 summarizes the analysis of mean change from baseline to endpoint during double-blind treatment. There were no statistically significant differences between randomized treatment groups on mean ADHDRS-IV-Parent:Inv total T-score and subscale scores and CGI-ADHD-S score.

Table LYCL.4. Mean Change from Baseline to Endpoint

Scales	n	Baseline Mean (SD)	Endpoint Mean (SD)	Change	Between Group-Value
ADHDRS Hyp/Imp Subscale					
Higher-Dose Group	62	14.52 (6.01)	10.34 (6.57)	-4.18	--
Target-Dose Group	58	14.93 (6.63)	11.60 (7.22)	-3.33	.310
ADHDRS Inatt. Subscale					
Higher-Dose Group	62	17.89 (4.46)	13.15 (6.05)	-4.74	--
Target-Dose Group	58	18.03 (4.82)	15.21 (6.48)	-2.83	.060
ADHDRS Total T-Score					
Higher-Dose Group	62	73.61 (8.56)	64.28 (12.31)	-9.33	--
Target-Dose Group	58	73.72 (9.42)	67.81 (13.86)	-5.91	.099
CGI-ADHD-Severity					
Higher-Dose Group	62	4.19 (0.81)	3.34 (1.19)	-0.85	--
Target-Dose Group	58	4.17 (0.92)	3.66 (1.13)	-0.52	.054

Abbreviations: ADHDRS = Attention Deficit/Hyperactivity Disorder Rating Scale; CGI-ADHD-S = Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity; Hyp/Imp = hyperactivity/impulsivity; Inatt = inattention; n = number of patients; SD = standard deviation.

During double-blind treatment, blood was drawn at Visit 6 to determine the peak plasma-atomoxetine concentration level. The Pearson correlation coefficient for the randomized target- and higher-dose groups ($r = 0.04$ and $r = -0.10$, respectively) demonstrated no statistically significant correlation between these values (plasma concentration and change score).

Safety

The mean final prescribed dose during double-blind treatment was 1.13 mg/kg in the randomized target-dose group and 2.10 mg/kg in the randomized higher-dose group.

Adverse Events

One of the objectives of the study was to assess the safety and tolerability of atomoxetine by comparing AEs in the randomized higher-dose group with those in the randomized target-dose group. There were no deaths during this study. One patient reported the serious adverse event (SAE) of “gastroenteritis viral” during open-label treatment, determined by the investigator to be unrelated to study drug. One patient reported the SAE of “hepatitis” during the open-label Canadian extension, which was considered possibly related to study drug by the investigator.

Table LYCL.5 through Table LYCL.9 summarize the reasons for discontinuations by study period. A total of 36 patients who took at least one dose of study drug discontinued due to an AE during the study. By study period, discontinuation due to AE included: 5.9% (22 out of 376) of patients during open-label treatment; 0.8% (1 out of 125) of randomized and 3.1% (5 out of 161) of nonrandomized patients during double-blind treatment (Tables LYCL 7 and 8 combined); and 12.3% (8 out of 65) of patients during the open-label Canadian extension.

**Table LYCL.5. Summary of Discontinuations
Open-Label Treatment**

Preferred Term	TMX (N=376)	
	n	(%)
PATIENTS DISCONTINUED	22	(5.9)
Nausea	4	(1.1)
Abdominal pain upper	2	(0.5)
Dysgeusia	2	(0.5)
Somnolence	2	(0.5)
Vomiting	2	(0.5)
Abdominal pain	1	(0.3)
Alopecia	1	(0.3)
Dyspnoea	1	(0.3)
Fatigue	1	(0.3)
Gastroenteritis viral	1	(0.3)
Irritability	1	(0.3)
Orthostatic hypotension	1	(0.3)
Palpitations	1	(0.3)
Suicidal ideation	1	(0.3)
Tachycardia	1	(0.3)

Abbreviations: TMX = atomoxetine; n = number of patients.

**Table LYCL.6. Summary of Discontinuations
Randomized Population**

Preferred Term	TMX1_2 (N=62) n (%)	TMX1_82 (N=63) n (%)	Total (N=125) n (%)	p-Value*
PATIENTS DISCONTINUED	0	1 (1.6)	1 (0.8)	1.00
Accidental overdose	0	1 (1.6)	1 (0.8)	

Abbreviations: TMX1_2 = atomoxetine lower dose group; TMX1_82 = atomoxetine higher dose group.

**Table LYCL.7. Summary of Discontinuations
Nonrandomized US Population**

Primary Reason for Discontinuation	RESTX1.2 (N = 99) n (%)
Adverse Event	4 (4.0)
Personal conflict or other patient/caregiver decision	1 (1.0)
Protocol completed	93 (93.9)
Unable to contact patient/caregiver	1 (1.0)

Abbreviations: RESTX1.2 = atomoxetine.

**Table LYCL.8. Summary of Discontinuations
Nonrandomized Canadian Population**

Reason for Discont.: Adverse event

Preferred Term	RESTX1_2 (N=62) n (%)
PATIENTS DISCONTINUED	1 (1.6)
Anger	1 (1.6)

Abbreviations: RESTX1_2 = atomoxetine.

**Table LYCL.9. Summary of Discontinuations
Open-Label Canadian Extension**

Primary Reason for Discontinuation	RESTX1_2 (N = 65)
Adv. evt.	8 (12.3)
Lack of efficacy, pat/cargivr & phys per	2 (3.1)
Lack of efficacy, patient/caregiver perc	3 (4.6)
Personal conflict or other pat/carg dec	2 (3.1)
Physician decision	1 (1.5)
Protocol completed	44 (67.7)
Sponsor's decision	1 (1.5)
Unable to contact patient/caregiver	4 (6.2)

Abbreviations: RESTX1-2 = atomoxetine.

Treatment-emergent adverse events (TEAEs) were summarized by study period and treatment group. Table LYCL.10 summarizes TEAEs by study period using MedDRA 7.0 and 8.0 preferred terms.

During open-label treatment, the most commonly reported TEAEs (>10%) were fatigue (17.0%), decreased appetite (15.4%), nausea (15.2%), somnolence (12.2%), and headache (11.2%). The most commonly reported TEAE in the randomized higher-dose group was vomiting (9.5%); in the randomized target-dose group, it was headache (9.7%). Overall, there was a statistically higher proportion of TEAEs in the higher-dose group (41.3%) than in the target-dose group (22.6%; $p=.035$). Among nonrandomized US responders, the most common TEAE reported was vomiting (4.0%); in nonrandomized Canadian patients, it was headache (6.5%). During the open-label Canadian extension, the most commonly reported TEAEs reported were headache (21.5%), fatigue (18.5%), nausea (18.5%), vomiting (16.9%), and decreased appetite (13.8%).

Table LYCL.10. Treatment-Emergent Adverse Events with Greater than 4% Incidence

Preferred Term	n (%)
Open-Label treatment	
Fatigue	64 (17.0%)
Decreased appetite	58 (15.4%)
Nausea	57 (15.2%)
Somnolence	46 (12.2%)
Headache	42 (11.2%)
Abdominal pain upper	32 (8.5%)
Vomiting	31 (8.2%)
Dizziness	20 (5.3%)
Pyrexia	16 (4.3%)
Upper respiratory tract infection	15 (4.0%)
Randomized Treatment	
Higher-Dose Group	
Vomiting	6 (9.5%)
Headache	3 (4.8%)
Abdominal pain upper	3 (4.8%)
Nausea	3 (4.8%)
Upper respiratory tract infection	3 (4.8%)
Somnolence	3 (4.8%)
Cough	3 (4.8%)
Target-Dose Group	
Headache	6 (9.7%)
Abdominal pain upper	3 (4.8%)
Nonrandomized US responders	
Vomiting	4 (4.0%)
Nonrandomized Canadian patients	
Headache	4 (6.5%)
Abdominal pain	3 (4.8%)
Decreased appetite	3 (4.8%)
Canadian patients in open-label extension	
Headache	14 (21.5%)
Fatigue	12 (18.5%)
Nausea	12 (18.5%)
Vomiting	11 (16.9%)
Decreased appetite	9 (13.8%)
Abdominal pain	7 (10.8%)
Pharyngolaryngeal pain	7 (10.8%)

Table LYCL.10. Treatment-Emergent Adverse Events with Greater than 4% Incidence (concluded)

Preferred Term	n (%)
Nasopharyngitis	6 (9.2%)
Upper respiratory tract infection	6 (9.2%)
Irritability	6 (9.2%)
Anxiety	5 (7.7%)
Insomnia	5 (7.7%)
Pyrexia	4 (6.2%)
Dizziness	4 (6.2%)
Varicella	4 (6.2%)
Emotional disorder	4 (6.2%)
Sinusitis	3 (4.6%)
Somnolence	3 (4.6%)
Depressed mood	3 (4.6%)
Cough	3 (4.6%)

Laboratory Values, Vital Signs and ECGs

Frequencies of abnormal laboratory values were compared for the randomized treatment groups (high- vs target-dose) during double-blind treatment, and one analyte was statistically significantly different. A statistically significantly greater percentage of patients in the randomized higher-dose group had an abnormal low cholesterol value at endpoint compared with patients in the randomized target-dose group (10.3% [6 out of 58] versus 0% [0 out of 49], respectively; $p=.030$). Table LYCL.11 presents the frequency of patients with abnormal lab values for randomized patients.

Table LYCL.11. Frequency of Patients with Abnormal Lab Values after Baseline Randomized Population

	TMX1_2 (1)			TMX1_82 (2)			- p-Value * -
Incidence	(Total=62)			(Total=63)			
Group	N	n	(%)	N	n	(%)	Overall
-----	-----	-----	-----	-----	-----	-----	-----
Lab Test: CHOLESTEROL							
LOW	49	0		58	6	(10.3)	.030
HIGH	43	1	(2.3)	58	4	(6.9)	.391

Abbreviations: TMX1_2 = atomoxetine lower dose group; TMX1_82 = atomoxetine higher dose group.

Mean change from baseline to endpoint and categorical change was assessed for vital signs and weight. During open-label treatment, there were statistically significant within-treatment-group differences. There was a mean decrease in weight, 0.76 kg. Categorical changes most commonly noted (>3%) included diastolic (5.3%; 19 out of 357) and systolic blood pressure increase (3.7%; 13 out of 355) and weight decrease (26.6%, 97 out of 364). Table LYCL.12 summarizes the categorical changes in vital signs and weight for the open-label population.

Table LYCL.12. Categorical Changes in Vital Signs and Weight at Endpoint Open-Label Population

Abnormal Vitals		Atomoxetine 1.2		
		N	n	%
-----		-----	-----	-----
Vital	Direction*			
-----		-----	-----	-----
Diastolic Blood Pressure	High	357	19	5.3%
-----		-----	-----	-----
Pulse	High	365	6	1.6%
	-----	-----	-----	-----
	Low	365	1	0.3%
-----		-----	-----	-----
Systolic Blood Pressure	High	355	13	3.7%
-----		-----	-----	-----
Temperature (C)	High	362	0	0.0%
	-----	-----	-----	-----
	Low	362	4	1.1%
-----		-----	-----	-----
Weight (kg)	Decrease	364	97	26.6%

*Criteria: Pulse - High: Increase of at least 25 to a value of at least 110
- Low: Decrease of at least 20 to a value of at most 65
Temperature - High: Increase of at least 1.0 to a value of at least 37.8
- Low: Decrease of at least 1.3 to a value of at most 35.6
Weight - Decrease of at least 3.5%
Blood Pressure - High: Increase of at least 5 mm to above 95% percentile

During double-blind treatment, there were no statistically significant differences between treatment groups in mean change from baseline to endpoint or categorical changes for vital signs or weight. Categorical changes noted in at least 5% of patients included weight decrease (target-dose: 5.2%, 3 out of 58; higher-dose: 11.3%, 7 out of 62). The

mean change in weight was less than 1 kg for either randomized treatment group. Table LYCL.13 summarizes the categorical changes in vital signs and weight at endpoint for the randomized population.

Table LYCL.13. Categorical Changes in Vital Signs and Weight at Endpoint Randomized Population

Abnormal Vitals		Atomoxetine 1.2			Atomoxetine 1.8-2.4			Fisher's Exact
		N	n	%	N	n	%	P-value
Vital	Direction*							
Diastolic Blood Pressure	High	53	1	1.9%	60	0	0.0%	.469
Pulse	High	58	0	0.0%	62	0	0.0%	n/a
	Low	58	0	0.0%	62	0	0.0%	n/a
Systolic Blood Pressure	High	57	1	1.8%	60	1	1.7%	1.00
Temperature (C)	High	58	0	0.0%	62	0	0.0%	n/a
	Low	58	0	0.0%	62	0	0.0%	n/a
Weight (kg)	Decrease	58	3	5.2%	62	7	11.3%	.325

*Criteria: Pulse - High: Increase of at least 25 to a value of at least 110
- Low: Decrease of at least 20 to a value of at most 65
Temperature - High: Increase of at least 1.0 to a value of at least 37.8
- Low: Decrease of at least 1.3 to a value of at most 35.6
Weight - Decrease of at least 3.5%
Blood Pressure - High: Increase of at least 5 mm to above 95% percentile

Abbreviations: TMX1_2 = atomoxetine lower dose group; TMX1_82 = atomoxetine higher dose group.

Categorical changes noted in at least 5% of patients included diastolic blood pressure increase (5.6%, 5 out of 90) and weight decrease (6.1%; 6 out of 98) in nonrandomized US nonresponders, and diastolic increase (5.4%; 3 out of 56) and weight decrease (12.9%; 8 out of 62) in nonrandomized Canadian responders and nonresponders. Mean change in weight was less than 1 kg in either group. Tables LYCL.14 and 15 present the categorical changes in vital signs and weight for the nonrandomized US and Canadian populations.

**Table LYCL.14. Categorical Changes in Vital Signs and Weight at Endpoint
Nonrandomized US Population**

Abnormal Vitals		Atomoxetine 1.2 - Responders		
		N	n	%
Vital	Direction*			
Diastolic Blood Pressure	High	90	5	5.6%
Pulse	High	98	0	0.0%
	Low	98	1	1.0%
Systolic Blood Pressure	High	89	2	2.2%
Temperature (C)	High	98	1	1.0%
	Low	98	0	0.0%
Weight (kg)	Decrease	98	6	6.1%

*Criteria: Pulse - High: Increase of at least 25 to a value of at least 110
- Low: Decrease of at least 20 to a value of at most 65
Temperature - High: Increase of at least 1.0 to a value of at least 37.8
- Low: Decrease of at least 1.3 to a value of at most 35.6
Weight - Decrease of at least 3.5%
Blood Pressure - High: Increase of at least 5 mm to above 95% percentile

**Table LYCL.15. Categorical Changes in Vital Signs and Weight at Endpoint
Nonrandomized Canadian Population**

Abnormal Vitals		Atomoxetine 1.2 - Responders		
		N	n	%
Vital	Direction*			
Diastolic Blood Pressure	High	56	3	5.4%
Pulse	High	62	0	0.0%
	Low	62	2	3.2%
Systolic Blood Pressure	High	59	2	3.4%
Temperature (C)	High	62	0	0.0%
	Low	62	0	0.0%
Weight (kg)	Decrease	62	8	12.9%

*Criteria: Pulse - High: Increase of at least 25 to a value of at least 110
- Low: Decrease of at least 20 to a value of at most 65
Temperature - High: Increase of at least 1.0 to a value of at least 37.8
- Low: Decrease of at least 1.3 to a value of at most 35.6
Weight - Decrease of at least 3.5%
Blood Pressure - High: Increase of at least 5 mm to above 95% percentile

During the open-label Canadian extension, 4 patients met the categorical criterion for a decrease in weight. However, the mean change in weight from baseline to endpoint was a weight increase of 3.19 kg. Table LYCL.16 presents the categorical changes in vital signs and weight for the open-label Canadian extension.

Table LYCL.16. Categorical Changes in Vital Signs and Weight at Endpoint Open-Label Canadian Extension

Abnormal Vitals		TMX_OLEX		
		N	n	%
Vital	Direction*			
Diastolic BP	High	57	1	1.8%
PULSE	High	63	1	1.6%
	Low	63	1	1.6%
Systolic BP	High	57	1	1.8%
Temperature (C)	High	64	0	0.0%
	Low	64	0	0.0%
Weight (kg)	Decrease	64	4	6.3%

*Criteria: Pulse - High: Increase of at least 25 to a value of at least 110
- Low: Decrease of at least 20 to a value of at most 65
Temperature - High: Increase of at least 1.0 to a value of at least 37.8
- Low: Decrease of at least 1.3 to a value of at most 35.6
Weight - Decrease of at least 3.5%
Blood Pressure - High: Increase of at least 5 mm to above 95% percentile

Abbreviations: TMX_OLEX = atomoxetine responders.

Mean change in ECG intervals from baseline to endpoint were summarized by study period and analysis group. A categorical analysis of changes in QT intervals was also conducted using the Committee for Proprietary Medicinal Products (CPMP) criteria for potentially clinically significant changes in corrected QT intervals following baseline. During double-blind treatment, there were no statistically significant differences in the proportion of patients who met the CPMP criteria between the randomized treatment groups.

Pharmacokinetic Outcomes

Blood samples for determination of atomoxetine in plasma were to be drawn 1.0 to 1.5 hours (h) post dose, both at Visit 3 and at the end of Study Period III (Visit 6). At Visit 3, the targeted daily dose was 1.2 mg/kg for all patients. Based upon their Visit 3 plasma concentration results and ADHD symptom reduction, patients were assigned to treatment groups for Study Period III. Patients with adequate ADHD symptom reduction (responders) continued on approximately 1.2 mg/kg/day of atomoxetine into Study Period III. Patients who had peak plasma-atomoxetine concentrations >800 ng/mL and did not achieve adequate ADHD symptom reduction completed the study at Visit 4.

Patients with plasma-atomoxetine concentrations ≤ 800 ng/mL who failed to achieve adequate ADHD symptom reduction (nonresponders) were randomized in a double-blind 1:1 ratio to either remain at their current dose of atomoxetine (target 1.2 mg/kg/day) or be increased up to approximately 1.8 mg/kg/day at Visit 4 and then to approximately 2.4 mg/kg/day at Visit 5 if still symptomatic. Patients were then categorized as responder or nonresponder at the end of Study Period III (Visit 5 or 6).

At Visit 3, 87% of patients (256/294) had concentrations ≤ 800 ng/mL. Of the patients with concentrations ≤ 800 ng/mL, 39% (99/256) achieved adequate ADHD symptom reduction while 55% (21/38) of patients having concentrations > 800 ng/mL were categorized as having adequate ADHD symptom reduction.

Concentrations from CYP2D6 poor metabolizer (PM) patients were generally higher than those from CYP2D6 extensive metabolizer (EM) patients. While 88% (29/33) of all concentrations for PM patients were > 800 ng/mL, only 9% (40/440) of EM patients' concentrations were > 800 ng/mL. At Visit 3, 57% of PM patients were responders, and these observations comprised about 10% of the responder group. At Study Period 3, all PM patients were responders and were receiving 1.2 mg/kg/day; their observations comprised about 14% of the 1.2 mg/kg/day responder group.

Mean concentrations for the 1.8 to 2.4 mg/kg/day groups (only EM patients) increased when compared to the mean concentrations for EM patients taking 1.2 mg/kg/day.

References

DuPaul GJ, Power TJ, Anastopoulos AD, Reid R (1998), ADHD Rating Scale-IV: checklists, norms, and clinical interpretations. New Your: The Guilford Press.

Summary ID# 8619

Clinical Study Summary: Study B4Z-FW-LYCT

A Study to Evaluate Single Dose and Multiple Dose Pharmacokinetics of Atomoxetine Hydrochloride in Chinese Healthy Subjects

Date summary approved by Lilly: 22 September 2006

Brief Summary of Results

The primary objective of this study was to characterise the pharmacokinetics of atomoxetine in Chinese healthy subjects following administration of a single oral dose of 40 mg and multiple oral doses of 80 mg QD.

- Following a single oral dose of 40 mg or multiple once-daily doses of 80 mg for 7 days, atomoxetine was rapidly absorbed with a median $t_{\max}$ of 1.25 and 1.50 hours, respectively, in extensive metabolisers (EM) of cytochrome P450 2D6.
- Atomoxetine concentrations appear to decrease monoexponentially with a mean apparent terminal half-life of approximately 4 hours in EM subjects following both single and multiple doses.
- Mean apparent clearances were similar for single 40 mg and multiple 80 mg doses of atomoxetine.
- *10/*10 homozygous EM subjects have higher mean exposure (approximately 2 times higher) than other EM subjects following single 40 mg and multiple 80-mg doses of atomoxetine.
- There were no deaths or other serious adverse events during this study and no subject discontinued from the study because of an adverse event.

Title of Study: A Study to Evaluate Single Dose and Multiple Dose Pharmacokinetics of Atomoxetine Hydrochloride in Chinese Healthy Subjects.	
Investigator(s): This single-center study included 1 principal investigator.	
Study Center(s): This study was conducted at 1 study center in 1 country.	
Length of Study: 2.5 months Date of first subject visit: 08 July 2004 Date of last subject visit: 16 September 2004	Phase of Development: I
Objectives: Primary Objective: - To characterise the pharmacokinetics of atomoxetine in Chinese healthy subjects following administration of a single oral dose of 40 mg and multiple oral doses of 80 mg QD. Secondary Objective: - To evaluate the tolerability of atomoxetine in Chinese healthy subjects following administration of a single oral dose of 40 mg and multiple oral doses of 80 mg QD.	
Study Design: There were two study designs provided for this study; one for extensive metabolisers (EM) of cytochrome P450 2D6 (CYP2D6) and the other for poor metabolisers (PM) of CYP2D6. Study design for EM: double-blind, randomised, placebo-controlled, single period study where 24 subjects were randomly assigned to receive either atomoxetine 40 mg QD for 3 days followed by atomoxetine 80 mg QD for 7 days, or matching placebo for 10 days. Blood samples for the measurement of atomoxetine in serum were obtained on Day 1 (for single dose pharmacokinetics [PK]), Days 7, 8 and 9 (for trough PK), and Day 10 (for multiple dose PK). Safety data were collected in the form of clinical examinations, clinical laboratory testing, vital sign measurements and a record of adverse events. Study design for PM: open-label, single-period study where enrolled subjects would receive atomoxetine treatment only, 40 mg QD on days 1, 5 and 6 followed by 80 mg QD on days 7 to 14.	
Number of Subjects: Planned: EM subjects: 24; 16 subjects to receive atomoxetine and 8 subjects to receive placebo. PM subjects: number available as determined at the study screening. All subjects were to receive atomoxetine. Randomised/Entered: EM subjects: 24 subjects (16 males; 8 females) PM subjects: none Completed: EM subjects: 16 subjects (11 males; 5 females) on atomoxetine and 8 subjects (5 males; 3 females) on placebo. Total 24. PM subjects: none	
Main Criteria for Inclusion: Overtly healthy males or females as determined by medical history and physical examination, aged between 20 and 45 years, inclusive, within the range of Body Mass Index (BMI) 19.0 – 27.0 kg/m ² , with normal supine blood pressure and pulse rate, with available CYP2D6 genotyping results at study entry, who provided written informed consent.	
Study Drug, Dose, and Mode of Administration: Atomoxetine, 40 mg/day for 3 days, given orally once a day as one 40 mg capsule, followed by 80 mg/day for 7 days, given orally once a day as two 40 mg capsules.	
Comparator, Dose, and Mode of Administration: Placebo, given orally once a day for 3 days as one capsule then given orally once a day for 7 days as two capsules.	

Duration of Treatment:

Atomoxetine: 40 mg QD for 3 days followed by 80 mg QD for 7 days

Placebo: QD for 10 days

Variables:

Safety: Physical examination, safety laboratory tests, vital signs and adverse events.

Bioanalytical: Serum samples were collected for determination of atomoxetine concentration.

Pharmacokinetic: For the single-dose period, parameters determined were the maximum serum concentration (C_{max}), time to maximum serum concentration (t_{max}), the area under the serum concentration vs. time curve from the time of dosing until the time of the last measurable concentration [$AUC(0-t_{last})$], the area under the serum concentration vs. time curve from the time of dosing extrapolated to infinity [$AUC(0-\infty)$], apparent clearance (CL/F), apparent volume of distribution at steady-state (V_{ss}/F), and the terminal half-life ($t_{1/2}$). For the multiple-dose period, parameters determined were the maximum and minimum serum concentrations at steady state ($C_{max,ss}$ and $C_{min,ss}$), time to maximum serum concentrations ($t_{max,ss}$), the average steady-state concentration ($C_{av,ss}$), the area under the serum concentration vs. time curve during one dosing interval at steady-state ($AUC_{\tau,ss}$), apparent clearance at steady-state (CL_{ss}/F), apparent volume of distribution during the terminal phase (V_z/F), peak-trough fluctuation (PTF%) and the accumulation ratio (R_A).

Evaluation Methods:

Safety: Safety laboratory tests and adverse events were listed and summarised.

Bioanalytical: Serum samples were analysed using a LC/APCI/MS/MS method validated over the concentration range 2.50 to 2000.00 ng/mL.

Pharmacokinetic: Non-compartmental pharmacokinetic analyses were performed using WinNonlin Professional, Version 3.1.

Statistical: To study the effect of CYP2D6*10 allele (one of the CYP2D6 allele mutations) on atomoxetine metabolism, comparisons of main pharmacokinetic parameters between *10/*10 homozygous EM subjects and other EM subjects were performed using t-test. Ratio of means and 90% confidence intervals were obtained.

Results:

Subject Demographics

A total of 24 Chinese healthy subjects (16 male, 8 female) enrolled and completed this study. They had a mean ($\pm$ standard deviation, SD) age of 28.0 ± 6.6 years (range 20 – 39 years), and mean BMI ($\pm$ SD) of 22.4 ± 1.6 kg/m². Subject demographics are presented in Table 1. All 24 subjects were CYP2D6 EMs.

Table 1. Subject Demographics

	Age	Gender	Weight (kg)	Height (cm)	BMI (kg/m ²)	Genotype	Predicted Phenotype	Drink	Smoke	Smoking History (years)
	21	M	60.0	170.0	20.8	*2/*10	EM	N	Y	0.5
	24	M	60.0	175.0	19.6	*10/*10	EM	N	N	
	22	M	65.0	179.0	20.3	*2/*10	EM	N	N	
	21	M	57.0	168.0	20.2	*1/*10	EM	N	N	
	22	M	70.0	175.0	22.9	*1/*1	EM	Y	N	
	24	M	70.0	176.0	22.6	*10/*10	EM	N	Y	2.1
	21	M	60.0	168.0	21.3	*1/*10	EM	N	N	
	20	M	70.0	177.0	22.3	*5/*10	EM	N	N	
	24	M	70.0	176.0	22.6	*10/*41	EM	Y	Y	1.5
	21	M	56.5	163.0	21.3	*10/*10	EM	Y	N	
	23	F	59.0	162.0	22.5	*10/*10	EM	N	N	
	20	F	53.0	157.0	21.5	*5/*10	EM	N	N	
	31	F	58.0	160.0	22.7	*1/*10	EM	N	N	
	34	F	54.0	160.0	21.1	*1/*1	EM	N	N	
	33	F	57.0	155.0	23.7	*2/*10	EM	N	N	
	37	F	57.0	156.0	23.4	*1/*10	EM	N	N	
	32	F	57.0	160.0	22.3	*10/*10	EM	N	N	
	30	M	65.0	168.0	23.0	*10/*10	EM	N	N	
	30	M	58.0	164.0	21.6	*10/*10	EM	N	Y	3
	37	M	58.0	163.0	21.8	*1/*1	EM	N	N	
	38	M	65.0	166.0	23.6	*10/*41	EM	N	Y	3.5
	32	M	72.0	172.0	24.3	*1/*10	EM	N	N	
	39	M	69.0	167.0	24.7	*10/*10	EM	N	N	
	35	F	64.0	155.0	26.6	*1/*10	EM	N	N	
Minimum	20.0		53.0	155.0	19.6					
Maximum	39.0		72.0	179.0	26.6					
Average	28.0		61.9	166.3	22.4					
Standard										
Deviation	6.6		5.8	7.5	1.6					

Abbreviations: BMI: body mass index; M: male; F: female; Y: yes; N: no; EM: extensive metaboliser

Subject Disposition

All 24 enrolled subjects (16 on atomoxetine treatment and 8 on placebo treatment) completed the study.

Safety

All 24 subjects who enrolled into the study were included in the safety analyses. There were no deaths or other serious adverse events during this study and no subject discontinued from the study because of an adverse event.

Adverse events occurring on or after the first dose of study drug are presented in Table 2. Fourteen subjects reported a total of 31 adverse events occurring on or after the first dose of drug (28 adverse events were reported by 11 subjects taking atomoxetine and 3 adverse events reported by 3 subjects taking placebo). The most common adverse events were dizziness, nausea and upper abdominal pain. All adverse events were of mild severity and had resolved by the end of the study. All study-drug related adverse events resolved within 10 hours.

Table 2. Adverse Events Occurring on or After the First Dose of Study Drug

MedDRA Term	Atomoxetine						Placebo		
	40 mg			80 mg			Total subject with event	TO	Event possibly/probably related to study drug
	Total subject with event	TO	Event possibly/probably related to study drug	Total subject with event	TO	Event possibly/probably related to study drug			
DIZZINESS	6	6	4	1	1	1	2	2	2
NAUSEA	4	4	4	2	2	2	0	0	0
ABDOMINAL PAIN UPPER	4	4	4	0	0	0	0	0	0
MOTION SICKNESS	0	0	0	2	2	0	0	0	0
NASOPHARYNGITIS	0	0	0	2	2	0	0	0	0
SOMNOLENCE	2	2	2	0	0	0	0	0	0
ANOREXIA	0	0	0	1	1	1	0	0	0
CONSTIPATION	1	1	0	0	0	0	0	0	0
DERMATITIS CONTACT	0	0	0	0	0	0	1	1	0
HYPERHIDROSIS	1	1	0	0	0	0	0	0	0
URINE ABNORMALITY	0	0	0	1	1	0	0	0	0
VOMITING	1	1	1	0	0	0	0	0	0
Total		19	15		9	4		3	2

Abbreviations: TO: total occurrences

There were no clinically significant alterations in laboratory values, abnormal vital signs and ECG recorded during the study.

Pharmacokinetic Outcomes

All atomoxetine serum-concentration data on sampling days 1 and 10 from all 16 enrolled subjects who received atomoxetine treatment were included in the pharmacokinetic evaluation.

Figure 1 illustrates the mean atomoxetine concentration-time profiles for the single- and multiple-dose sampling days, with the single- and multiple-dose PK parameter summary statistics shown in Table 3.

Following a single oral dose of 40 mg or multiple once-daily doses of 80 mg, atomoxetine was rapidly absorbed with a median $t_{\max}$ of 1.25 and 1.50 hours, respectively. Atomoxetine concentrations appear to decrease monoexponentially with a mean $t_{1/2}$ of approximately 4 hours, for both the single and multiple dose regimens. With a $t_{1/2}$ ranging from approximately 2 to 6 hours, almost all atomoxetine was eliminated within 24-hour after dosing. Mean (CV%) accumulation ratio (R_A) was 1.01 (14.9). The steady state parameters of CL_{ss}/F , $t_{1/2}$ and V_z/F after multiple doses parallel the results shown after single-dose administration. The mean (CV%) linearity index (the dose-normalised ratio of $AUC_{\tau,ss}$ after multiple 80 mg doses to $AUC(0-\infty)$ after a single 40-mg dose) was 0.982 (15.3).

Table 4 compares the $t_{1/2}$, AUC and $C_{\max}$ between *10/*10 homozygous and other EM subjects following single dose and multiple doses of atomoxetine. *10/*10 homozygous EM subjects have statistically significantly longer $t_{1/2}$ (approximately 1.5 times), greater AUC (approximately 2 times) and higher $C_{\max}$ (approximately 1.5 times), compared to other EM subjects in the studied Chinese population.

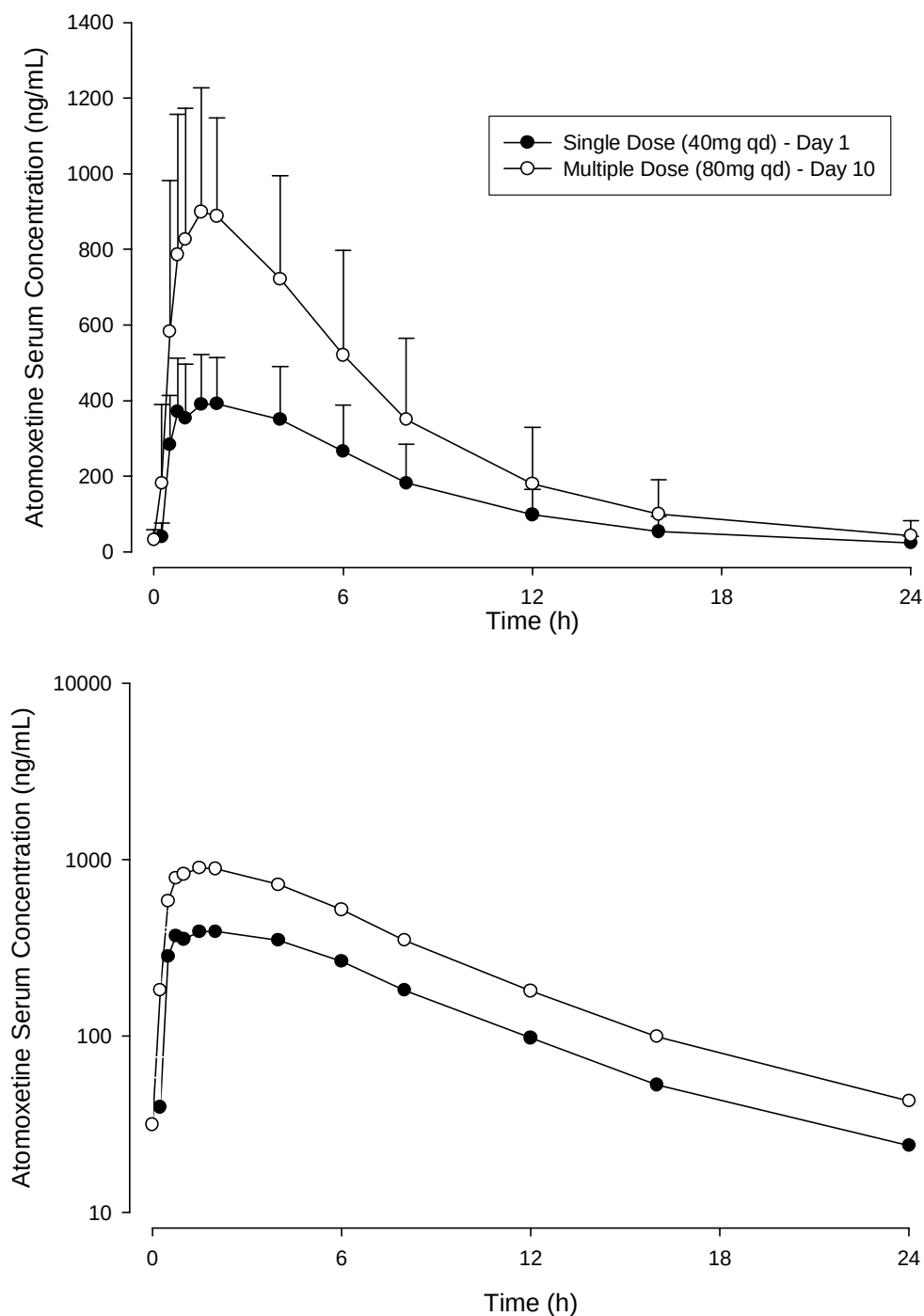


Figure 1.

Arithmetic mean (+SD) serum concentration- time profiles of atomoxetine on day 1 following a single dose of 40 mg (N=16) and on day 10 following multiple doses of 80 mg QD (N=16) (upper panel linear, lower panel log-linear).

Table 3. Summary of Geometric Means (CV%) of Pharmacokinetic Parameters on Day 1 and Day 10 after Single and Multiple Doses of Atomoxetine

Pharmacokinetic Parameters	Single Dose (40 mg)	Multiple Dose (80 mg QD)
N	16	16
C_{max} or C_{max,ss} (ng/mL)	427 (34.0)	965 (36.2)
C_{max,norm} or C_{max,ss,norm} [(ng/mL)/(mg/kg)]	658 (36.7)	744 (39.9)
C_{min,ss}^a (ng/mL)	NC	17.8 (137)
C_{min,ss,norm}^a [(ng/mL)/(mg/kg)]	NC	13.7 (141)
C_{av,ss} (ng/mL)	NC	260 (60.5)
t_{max}^b (h)	1.25 (0.50 – 4.00)	1.50 (0.50 – 4.00)
AUC(0-t_{last}) (h•ng/mL)	3070 (60.1)	NC
AUC(0-∞) (h•ng/mL)	3170 (62.4)	NC
AUC_{τ,ss} (h•ng/mL)	NC	6240 (60.5)
AUC_{τ,ss}/ AUC(0-∞)	NC	0.982 (15.3)
CL/F or CL_{ss}/F (L/h)	12.6 (62.4)	12.8 (60.5)
CL_{ss}/F_{norm} (L/h/kg)	0.204 (62.7)	0.208 (61.4)
V_{ss}/F or V_z/F (L)	84.0 (31.5)	79.8 (38.2)
V_{ss}/F_{norm} or V_z/F_{norm} (L/kg)	1.36 (32.5)	1.29 (41.3)
λ_z (h ⁻¹)	0.167 (33.1)	0.161 (31.8)
t_{1/2}^c (h)	4.15 (2.44 – 5.94)	4.31 (2.22 – 6.39)
PTF^a (%)	NC	365 (28.4)
RA	NC	1.01 (14.9)

Abbreviations: NC = not calculated;

^a Descriptive statistics calculated excluding data where C_{min,ss} = BQL, (N=11)

^b median (range)

^c geomean (range)

Table 4. Comparison of *10/*10 Subjects versus other EM Subjects for C_{max} and AUC

Parameter	Dose	Genotype	Geometric Mean	Ratio (90% CI)	p-Value
AUC(0-t _{last}) (h•ng/mL)	Single 40 mg	*10/*10	4708	2.14 (1.49, 3.08)	0.002
		Other EMs	2202		
AUC(0-∞) (h•ng/mL)		*10/*10	4962	2.21 (1.53, 3.21)	0.002
		Other EMs	2242		
C _{max} (ng/mL)		*10/*10	530	1.47 (1.15, 1.88)	0.014
		Other EMs	360		
t _{1/2} (h)		*10/*10	5.44	1.62 (1.34, 1.96)	0.001
		Other EMs	3.36		
AUC _{τ,ss} (h•ng/mL)	Multiple 80 mg QD	*10/*10	9693	2.19 (1.53, 3.13)	0.002
		Other EMs	4427		
C _{max,ss} (ng/mL)		*10/*10	1199	1.47 (1.13, 1.92)	0.023
		Other EMs	815		
t _{1/2} (h)		*10/*10	5.17	1.38 (1.08, 1.76)	0.034
		Other EMs	3.74		

There were seven *10/*10 subjects and 9 other EM subjects in the analysis dataset.

Abbreviations: EM = extensive metaboliser subjects; CI = confidence interval.

Summary ID# 9040

Clinical Study Summary: Study B4Z-US-LYCU

Efficacy and Safety of Once-Daily Atomoxetine Hydrochloride in Adults with ADHD Over an Extended Period of Time (6 Months): With A Brief Evaluation of Executive Cognition

Date summary approved by Lilly: 05 December 2007

Brief Summary of Results

The primary objective of the acute period was to demonstrate that in the qualified patient subset (defined as those patients who were required to have completed at least 10 weeks of treatment) atomoxetine administered orally, once daily, at doses from 25 mg/day to 100 mg/day given in the morning for 6 months is superior to placebo in adults with attention-deficit hyperactivity disorder (ADHD) as measured by the mean change of the total score of the Adult ADHD Investigator Symptom Rating Scale (AISRS). A reduction of score is indicative of improvement. The objectives of the open-label period were to assess the safety, efficacy, and effect on health outcome measures during 4 months of open-label treatment with atomoxetine.

The results are as follows:

Acute Period - Efficacy:

- The qualified patient atomoxetine treatment group had a statistically significant greater reduction on the AISRS total score compared with placebo after 1 week of treatment, which was statistically significant at every study visit ($p < .001$) as measured by a mixed model repeated measures (MMRM) analysis.
- Similar to the qualified patients subset, total score least squares (LS) mean change for randomized treatment group was statistically significantly greater for the atomoxetine group compared to the placebo group after only 1 week of treatment

(LS Mean difference -1.7 ± 0.8 ; $p=.028$). This pattern continued to be statistically significant for atomoxetine compared to placebo at every visit throughout the double-blind treatment phase with scores being very similar to the qualified patients subset.

- There were statistically significant ($p<.05$) differences between atomoxetine-treated patients and placebo-treated patients on the following variables: Conners' Adult ADHD Index-Investigator Rated Evening (CAARS-O-SV-ADHD Index-I-E) total scores and the Brown ADD adult scale scores from baseline to the last observation carried forward (LOCF) endpoint at 6 months.
- On the State-Trait Anxiety Inventory Scale (STAI) from baseline to LOCF endpoint after 10 weeks of treatment, there was statistically significant reduction in STAI-T (indicating how the patients "generally feel") anxiety score in the atomoxetine group (-8.5 ± 10.4) compared with the placebo group (-6.1 ± 10.6 ; $p=.011$). The mean change differences in the STAI anxiety score associated with STAI-S symptoms (indicating how the patients feel "right now – at this moment") were not different between the 2 treatment groups.
- The mean change in Delis-Kaplan Executive Function System (D-KEFS) global total scores from baseline to LOCF endpoint at 10 weeks demonstrated no statistically significant difference between the atomoxetine and placebo groups though there were reductions from baseline to endpoint within each group. However, the mean change for the Color-Word Interference Test condition which included 4 total scores showed statistically significant greater reduction for the atomoxetine group (-7.7 ± 15.7) compared with the placebo group (-6.2 ± 13.9 ; $p=.024$).
- There were statistically significant ($p<.05$) differences between atomoxetine-treated patients and placebo-treated patients on the following variables: Adult ADHD Self-Report Scale v1.1 Symptom Checklist Evening (ASRS v1.1-Evening), Clinical Global Impression of ADHD-Severity (CGI-ADHD-S), and ADHD Quality of Life (AAQOL) total score from baseline to LOCF endpoint at 10 weeks and 6 months.
- There were no statistically significant differences between treatment groups on the following variables: Resource Utilization (RU), Life Stressors score of the Parent Stress Index, Montgomery-Asberg Depression Rating Scale (MADRS) total score, and Pittsburgh Sleep Quality Index (PSQI) global score or component score at 10 weeks and 6 months.
- The mean change in CAARS-Inv:SV index total scores were statistically significant for the atomoxetine group compared with the placebo group (-4.3 ± 0.4 and -3.1 ± 0.4 , respectively; $p=.032$). The AISRS total score was strongly correlated with the CAARS-Inv-SV total score at baseline ($r=.78$; $p<.001$). The

strong correlation was demonstrated at 10 weeks ($r=.93$; $p<.001$) and 6 months ($r=.94$; $p<.001$).

- The mean change on the CAARS Observer Rated scale for the total ADHD symptom score (-7.9 ± 10.3) and hyperactivity/impulsivity (-3.3 ± 5.0) subscale were statistically significant for the atomoxetine group compared with the placebo group (-5.5 ± 10.0 and -2.4 ± 5.1 ; $p=.012$ and $p=.004$, respectively). There were no statistically significant differences between the groups on the inattentive subscale. The mean change on the ADHD Index subscale for the atomoxetine group (-4.7 ± 6.9) was statistically significant compared with the placebo group (-2.9 ± 7.0 ; $p=.007$).

Acute Period - Safety

- There were no deaths reported in the study. A total of 3 serious adverse events (SAEs) occurred during the double-blind period all of which were from the placebo group. SAEs reported during the study were ectopic pregnancy, gastric outlet obstructive, and food poisoning.
- A total of 57 patients (43 in the atomoxetine group and 14 in the placebo group; $p<.001$) discontinued the study due to adverse events. Statistically significantly more atomoxetine patients discontinued the study due to adverse events of nausea and erectile dysfunction compared with placebo patients.
- Vital sign measures were comparable between the atomoxetine-treated and placebo-treated patients with the following exceptions: there were statistically significant mean change differences in diastolic blood pressure and pulse between the atomoxetine group and the placebo group after 10 weeks of treatment. After 6 months of treatment, only the difference in mean change in pulse was statistically significant. Weight loss in the atomoxetine group was statistically significant compared with the placebo group after 10 weeks and 6 months of treatment.

Open-label Period:

- There were statistically significant differences on the following variables in patients previously randomized to placebo and in patients previously randomized to atomoxetine: AISRS total score, ASRS v1.1-evening total score, and the MADRS total score. The differences between the 2 groups were not statistically significant for any of these variables.
- There were statistically significant differences on the following variables in patients previously randomized to placebo and in patients previously randomized to atomoxetine: the Brown ADD total score, CGI-ADHD-S score, and AAQOL. There were statistically significant differences between the 2 groups for all of these variables.

- At the end of the open-label period, the mean change reduction on the State-Trait anxiety-score was statistically significant in patients who were previously randomized to placebo (-3.4 ± 10.8) but not in patients previously randomized to atomoxetine (-1.5 ± 8.9). The difference in State-trait anxiety-score between the patients who were previously randomized to placebo and patients who were previously randomized to atomoxetine was not statistically significant ($p=.432$).
- At the end of the open-label period, the health care resource utilization measures were similar in patients who were previously randomized to placebo and in patients previously randomized to atomoxetine.
- The parent stress index-life stressor total score was not significant in patients who were previously randomized to placebo ($p=.830$) or atomoxetine ($p=.541$), and the difference in scores between patients previously randomized to atomoxetine and patients previously randomized to placebo was not statistically significant ($p=.893$).
- The mean change in PSQI global score and scores for sleep disturbance and sleep latency were statistically significant ($p=.008$) in patients previously randomized to placebo. The difference for PSQI global score between patients who were previously randomized to atomoxetine and patients previously randomized to placebo was not statistically significant.
- There were no deaths reported during the open-label period or in the study overall. There was 1 SAE reported in a patient previously randomized to placebo and was determined by the investigator to be unrelated to study medication.
- A total of 57 patients (37 patients previously randomized to placebo and 20 patients previously randomized to atomoxetine) discontinued from the study. The primary reasons for discontinuation included nausea and erectile dysfunction.

Title of Study: Efficacy and Safety of Once-Daily Atomoxetine Hydrochloride in Adults with ADHD Over An Extended Period of Time (6 Months): With a Brief Evaluation of Executive Cognition	
Investigator(s): This multicenter study included 20 principal investigators.	
Study Center(s): This study was conducted at 21 study centers in the United States.	
Length of Study: 23 months [from FPV to LPV] Date of first patient enrolled: 04 October 2004 Date of last patient completed (acute): 15 May 2006 Date of last patient completed (open-label): 05 Sep 2006	Phase of Development: IV
Objectives: Acute Period: The primary objective of this study was to demonstrate that atomoxetine administered orally, once daily, at doses from 25 mg/day to 100 mg/day given in the morning for 6 months is superior to placebo in adults with attention-deficit hyperactivity disorder (ADHD) as measured by the mean change of the total score of the Adult ADHD Investigator Symptom Rating Scale (AISRS). The secondary objectives were to demonstrate that atomoxetine is superior in efficacy compared with placebo for the following measures at 6 months: • In the evenings on the total score of the Conners' Adult ADHD Rating Scale-Observer: Screening Version ADHD Index: Investigator Rated-Evening (CAARS-O:SV-ADHD Index-I-E) • In the morning on measures of executive functioning on Brown ADD Scale®: Adult-Total Score • Symptoms of anxiety using the Trait-anxiety score of the State-Trait Anxiety Scale • At 10 weeks, cognitive measures included the following 4 tests from the Delis-Kaplan Executive Functioning System™ (D-KEFS™): Trail Making, Verbal Fluency, Design Fluency, and the Color-Word Interference Test Other secondary objectives were to demonstrate that atomoxetine is superior in efficacy compared to placebo at 10 weeks and 6 months: • Adult ADHD Self-Report Scale-Symptom Checklist version 1.1 (ASRS v1.1-Evening) • Clinical Global Impression of ADHD-Severity (CGI-ADHD-S) • Health outcome measures: Adult ADHD Quality of Life Measure (AAQOL), the Resource Utilization Survey (RUS), and Life Stressor score of the Parent Stress Index • Treatment of symptoms of depression using the Montgomery-Asberg Depression Rating Scale (MADRS) • Sleep functions as measured by the Pittsburgh Sleep Quality Index (PSQI) • The correlations between the Adult ADHD Investigator Symptom Rating Scale (AISRS v1.1), Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV), and CAARS-O-SV at baseline • ADHD Symptom Total Score from the Conners' Adult ADHD Rating Scale-Observer: Screening Version (CAARS-O:SV) at 6 months • Comparison of safety Open-label Period: The objectives of this study were to assess the safety, efficacy, and effect on health outcome measures during 4 months of open-label treatment with atomoxetine.	
Study Design: Study Period II was a placebo-controlled, double-blind, randomized, outpatient study of once-daily dosing of Atomoxetine hydrochloride in adults with ADHD treated for 6 months with either atomoxetine or placebo. Study Period III was an optional, 4-month, open-label, extension phase for those patients completing the double-blind phase. All patients entering Study Period III received atomoxetine. The study design is displayed in Figure 1.	
Number of Patients: Planned: 440 total; 220 atomoxetine and 220 placebo (1:1 randomization)	

Randomized: 250 active drug, 251 placebo Completed – acute phase: 94 active drug, 112 placebo Completed – open-label: 149 (previously randomized to atomoxetine=74, and placebo=75)
Diagnosis and Main Criteria for Inclusion: Adult men and women ages 18 to 54 meeting <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR)</i> criteria for adult ADHD as assessed by the Adult ADHD Clinician Diagnostic Scale (ACDS v1.2) version 1.2
Test Product, Dose, and Mode of Administration: Acute Period: Atomoxetine hydrochloride 25-100 mg/day, given orally once daily in the morning as capsules with strengths of 20, 25, 40, and/or 60 mg. Open-label Period: Atomoxetine hydrochloride 25-100 mg/day, given orally once daily or twice daily in the morning or evening as capsules with strengths of 25, 40, and/or 60 mg.
Comparator, Dose, and Mode of Administration: Placebo was given as capsules in blister cards or packs (Acute Period)
Duration of Treatment: Acute Period: 6 months randomized, double-blind treatment. Open-label Period: 4 months.
Variables: Acute Period: Efficacy: • Primary: mean change of the total score of the AISRS. • Secondary: post-baseline scores for measures: 1) AISRS subscores; 2) Adult ADHD Self Report Scale (ASRS v1.1-Evening); 3) CGI-ADHD-S; 4) CAARS ADHD Index Evening (CAARS-O-SV-ADHD-I-E). • Secondary: change from baseline to endpoint for measures: 1) CAARS Observer: Screening Version Total and subscores; 2) CAARS-Inv-SV Total and subscores; 3) Brown ADD Scale: Adult Total and cluster scores; 4) Montgomery-Asberg Depression Rating Scale (MADRS) Total and item for suicidal ideation; 5) D-KEFS Tests; 6) State-Trait Anxiety of S-Anxiety and T-Anxiety scores. Safety: • Change from baseline scores for: vital signs and weight • Indicator variable for: 1) serious adverse events (SAEs); 2) discontinuations due to adverse events; 3) treatment-emergent adverse events (TEAEs) • Health Outcomes: change from baseline scores for: PSQI, AAQOL, HRUS, and Parent Stress Index Life Stressors Score Open-label Period: Efficacy: • AISRS, ASRS v1.1-Evening, CGI-ADHD-S, Brown ADD Scale, State-Trait Anxiety Scale, and MADRS. Safety: • Adverse events, PSQI. Health Outcomes: • AAQOL, health resource utilization, and life stressor score.

Evaluation Methods:

Statistical: The primary summary measure, the AISRS Total score, was analyzed using a REML-based mixed model repeated measures (MMRM) technique. The analysis included the fixed categorical effects of treatment, investigator, visit, and treatment-by-visit interaction. The analysis also included the continuous, fixed covariate of baseline score. The primary analysis compared atomoxetine dosed in the morning and placebo at Visit 9 using a contrast on the treatment-by-visit interaction term for Visit 9 from the MMRM model. The Kenward-Rogers method was used for the denominator degrees of freedom in the *t*-test at the final visit. This analysis was performed using PROC MIXED on the SAS[®] software system. All patients with a baseline and at least 1 post-baseline AISRS Total Score were included in the analysis.

The first key secondary objective was based on the total score of the CAARS-O-SV-ADHD Index-Investigator Rated Evening using a treatment contrast from the repeated measures mixed effects model at the final post-baseline visit. The repeated measures model included the same terms that were used for the primary efficacy measure.

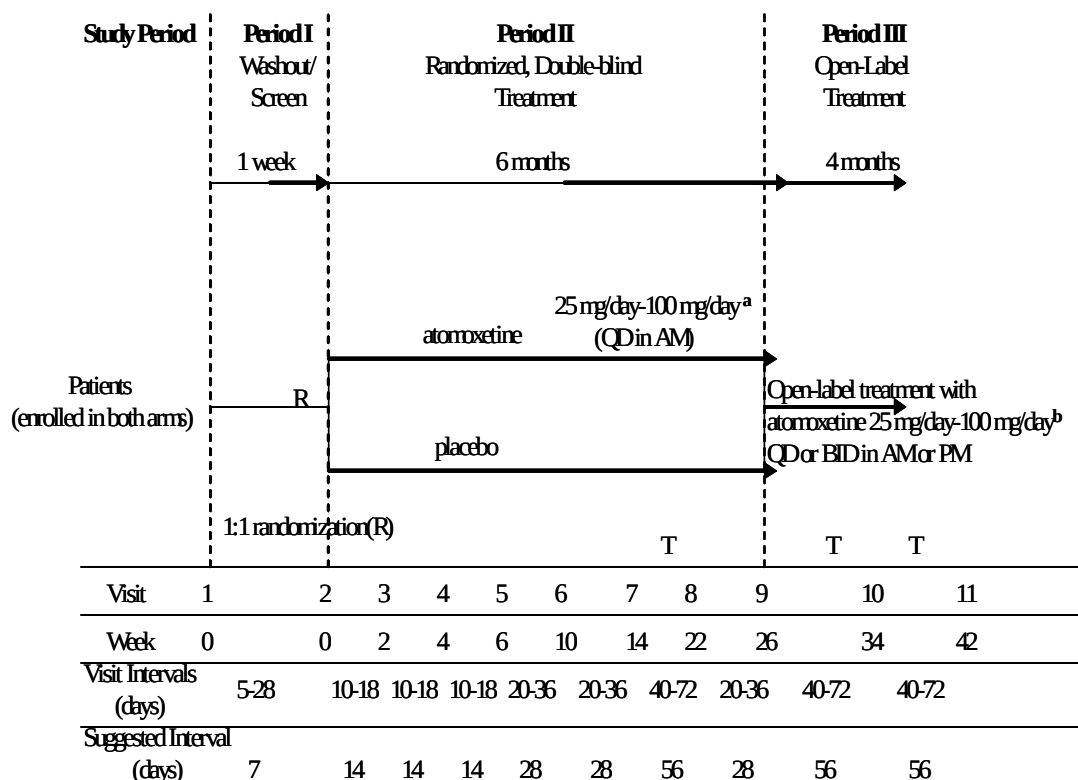
The next key secondary objective measured the executive functioning using the Brown ADD Scale[®]: Adult-Total Score at 6 months. Change from baseline to LOCF endpoint was compared across treatments using an ANCOVA model with terms for baseline, treatment, and investigator.

The third key secondary objective assessed the symptoms of anxiety using the T-anxiety score of the State-Trait Anxiety Scale at 6 months. Change from baseline to LOCF endpoint was compared across treatments using an ANCOVA model with terms for baseline, treatment, and investigator.

The final key secondary objective assessed the measures of cognition. The cognitive measures included the following 4 tests from the Delis-Kaplan Executive Functioning System[™] (D-KEFS[™]): Trail Making, Verbal Fluency, Design Fluency, and the Color-World Interference Test over 10 weeks. Each of the tests were analyzed separately using change from baseline to LOCF endpoint that was compared across treatments using an ANCOVA model with terms for baseline, treatment, and investigator.

For the open-label study, all continuous measures including the AISRS total, CGI-ADHD-S, State-Trait Anxiety Scale, Brown ADD Scale, CAARS, MADRS, AAQOL, PSQ and LSI, etc., were analyzed via the difference between baseline and LOCF endpoint using an ANCOVA model with terms for baseline, treatment, and investigator. Within-group changes were analyzed using paired *t*-tests. Adverse events, reasons for discontinuation, and health resource utilization (Y/N) were analyzed using Fisher's exact test.

Study Design



T=Telephone call to patient to remind them about the next visit

^a **Study Period II Dosing Details:** Beginning the day after Visit 2, 25 mg/day for 7 days minimum, then immediately after the last 25 mg/day dose, 7 days minimum at 40 mg/day. At the end of Visit 3, the dose will be increased to 80 mg/day, unless precluded due to tolerability/adverse events. Beginning the day after Visit 5, the dose will be increased to 100 mg/day unless precluded due to tolerability/adverse events. Dose must remain stable from Visit 6 to Visit 7 and for 14 days immediately following Visit 7 unless a dose decrease is required. Dose increases cannot occur by more than one level at a time. Only one decrease is allowed during SPII. Dose decreases may occur by more than one level, if needed due to tolerability/adverse events. Patients will be discontinued by IVRS if dose decrease less than 25 mg/day requested.

^b **Study Period III Dosing Details:** Beginning the day after Visit 9, 25 mg/day for 7 days minimum, then 7 days minimum at 40 mg/day. Dose increases may occur beginning the day after the last dose of 40 mg/day. Dose increases will be at the discretion of the investigator during the open label period. Dose increases may not occur by more than one dose level at a time. Only one dose decrease is allowed during SPIII. Dose decreases may occur by more than one level.

Figure 1. Illustration of the study design for B4Z-US-LYCU.

Results:

Patient Demographics

Baseline demographic data are provided in Table 1. In this study, 250 patients were randomized to the atomoxetine group and 251 to the placebo group. There were no statistically significant differences between the treatment groups in baseline diagnostic scores.

A total of 206 patients (previously randomized to atomoxetine=94 and placebo=112) entered the open-label period. There were more females (118; 57.9%) than males (88, 42.1%). Mean age was 40.5 years. Height was comparable, and the weight was higher in

patients who entered from the placebo group (for patients previously randomized to atomoxetine=77.1 and placebo=85.7). The majority of the patients were Caucasian (for patients previously randomized to atomoxetine=86.2% and placebo=85.7%). Previous stimulant use was comparable for patients entering from atomoxetine and placebo groups. ADHD subtypes were predominantly mixed subtype (>69%) or inattentive subtype (>28%).

Table 1. Baseline Demographics of All Randomized Patients

Characteristic	ATX (N=250)	PLA (N=251)
Sex (n, %)		
Male	124 (49.6)	130 (51.79)
Female	126 (50.4)	121 (48.21)
Age, y		
Mean (SD)	37.71 (10.39)	37.43 (9.85)
Range	18.21 – 54.93	18.69 – 54.57
Weight		
Mean (SD)	80.86 (18.57)	84.05 (20.76)
Height		
Mean (SD)	170.70 (9.95)	171.92 (10.19)
Ethnic origin, n (%)		
Caucasian	221 (88.40)	219 (87.25)
African Descent	12 (4.80)	16 (6.37)
Hispanic	9 (3.60)	12 (4.78)
Western Asian	4 (1.60)	1 (0.40)
East/Southeast Asian	1 (0.40)	1 (0.40)
Other	3 (1.20)	2 (0.80)
DSM-IV ADHD subtype, n (%)		
Hyperactive/Impulsive	3 (1.20)	4 (1.59)
Inattentive	66 (26.40)	67 (26.69)
Mixed	181 (72.40)	180 (71.71)
Previous stimulant use, n (%)	56 (22.58)	70 (27.89)
Concomitant medication ≥ 1 , n (%)	195 (80.25)	209 (84.27)

Abbreviations: ATX=Atomoxetine, PLA=Placebo, ADHD=Attention Deficit/Hyperactivity Disorder, DSM-IV=Diagnostic and Statistics Manual of Mental Disorders, Fourth Edition.

Patient Disposition

Figure 2 summarizes patient disposition. In this study, 749 patients were screened. There were 501 patients enrolled and randomized to either atomoxetine (250 patients) or placebo (251 patients). Out of the 501 total patients enrolled in the study, 206 patients completed the acute phase of the study; 94 patients were in the atomoxetine group and 112 were in the placebo group.

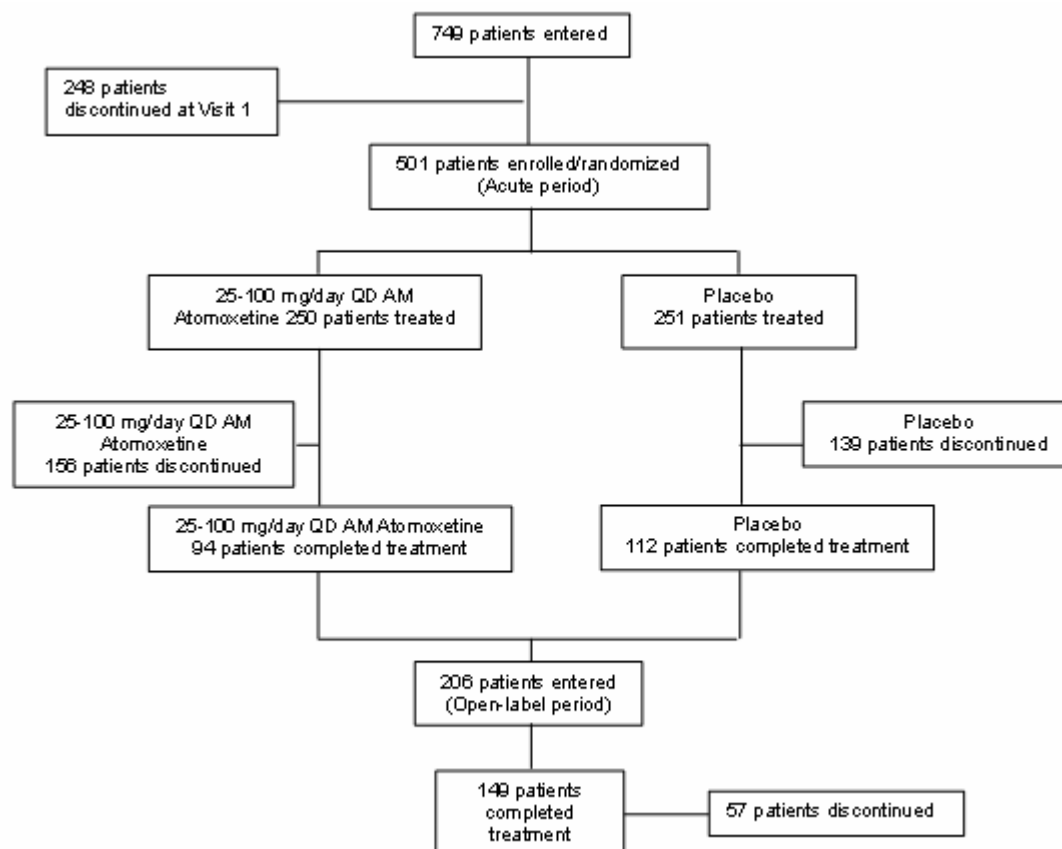


Figure 2. Patient disposition for Study B4Z-US-LYCU.

A total of 206 patients completed the acute phase, and a total of 149 patients completed the open-label phase. During the acute phase, more patients in the atomoxetine group discontinued from the study because of adverse events. In the open-label phase, more patients discontinued from the study compared to other reasons for discontinuation. Reasons for discontinuation from both the acute and open-label phases of the study are summarized in Table 2.

Table 2. Reasons for Discontinuation of Study Periods II and III

Reason for Discontinuation	Acute phase		Open-label phase
	ATX	PLA	
Adverse event	43	14	22
Protocol criteria not met	1	0	0
Lost to follow-up	39	42	15
Patient decision	26	30	9
Protocol violation	18	23	2
Other reasons	17	15	3
Lack of efficacy	12	15	5
Sponsor decision	0	0	1

Abbreviations: ATX=Atomoxetine, PLA=Placebo.

Acute Period

Primary Efficacy Measures - AISRS

A reduction in score indicates improvement.

Table 3 presents the primary analysis, a by-visit repeated measures analysis of the AISRS total score for the qualified patients subset. To be included in this analysis, “qualified patients” were required to have completed at least 10 weeks of treatment. Starting after the first week of treatment (Visit 3), the LS mean change of the total AISRS score was statistically significantly greater for the atomoxetine group compared to the placebo group (LS Mean difference -1.7 ± 0.8 ; $p=.037$). Thereafter, at each visit following the first week of treatment until the end of the double-blind treatment phase, the AISRS total LS Mean change scores for the atomoxetine group continued to demonstrate and remained statistically significant compared to the placebo group. At the end of the treatment phase (Visit 9), the LS Mean change score for the atomoxetine group was -16.2 ± 1.0 and for the placebo group was -11.7 ± 1.0 with a LS Mean difference between the 2 treatment groups of -4.5 ± 1.4 , $p=.001$.

Table 4 presents a by-visit repeated measures analysis of the AISRS total score for all randomized patients. Similar to the qualified patients subset, total score LS mean change was statistically significantly greater for the atomoxetine group compared to placebo after only 1 week of treatment (LS Mean difference -1.7 ± 0.8 ; $p=.028$). This pattern continued to be statistically significant for atomoxetine compared to placebo at every visit throughout the double-blind treatment phase with scores being very similar to the qualified patients subset.

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Table 3. Repeated Measures LS Mean Change in Adult Investigator Symptom Rating Scale (AISRS) - Qualified Patients

VISIT	ATOMOXETINE				PLACEBO				TREATMENT DIFFERENCE		
	N	LSMEAN	SE	P-VAL (A)	N	LSMEAN	SE	P-VAL (A)	LSMEAN	SE	P-VAL (B)
3	204	-7.44	0.61	<.001	215	-5.71	0.59	<.001	-1.73	0.83	.037
4	203	-11.68	0.69	<.001	215	-8.64	0.67	<.001	-3.04	0.94	.001
5	203	-13.93	0.71	<.001	215	-9.39	0.69	<.001	-4.54	0.97	<.001
6	191	-15.65	0.79	<.001	197	-11.00	0.78	<.001	-4.65	1.09	<.001
7	162	-16.29	0.86	<.001	179	-11.54	0.83	<.001	-4.75	1.18	<.001
8	139	-15.60	0.98	<.001	153	-10.99	0.94	<.001	-4.61	1.34	<.001
9	101	-16.22	1.02	<.001	115	-11.68	0.98	<.001	-4.54	1.39	.001
SUMMARY OF MODEL PARAMETERS					F-VALUE		P-VALUE (C)				
BASELINE					27.96		<.001				
TREATMENT					19.35		<.001				
VISIT					34.26		<.001				
INVESTIGATOR					<.001		<.001				
TREATMENT*VISIT					2.07		.056				

ABBREVIATIONS: LSMEAN=LEAST SQUARES MEAN; SE=STANDARD ERROR.

RESULTS BASED ON A MIXED MODEL WITH VISIT, BASELINE, TREATMENT, INVESTIGATOR, AND TREATMENT-BY-VISIT INTERACTION USING AN UNSTRUCTURED COVARIANCE MATRIX TO MODEL CORRELATIONS WITHIN PATIENT ACROSS VISITS
Continued

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Table 3. Repeated Measures LS Mean Change in Adult Investigator Symptom Rating Scale (AISRS) – Qualified Patients (Concluded)

A) P-VALUES ARE FROM TESTS FOR A NONZERO LEAST SQUARES MEAN AT THE GIVEN VISIT

B) P-VALUES ARE FROM TESTS FOR A TREATMENT DIFFERENCE IN LEAST SQUARES MEANS AT THE GIVEN VISIT

C) P-VALUES ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE BASED ON THE MODEL DESCRIBED ABOVE

POPULATION: ALL QUALIFIED PATIENTS – PATIENTS COMPLETED 10 WEEKS TREATMENT

Table 4. Repeated Measures LS Mean Change in Adult Investigator Symptom Rating Scale (AISRS) - Randomized Patients

VISIT	ATOMOXETINE				PLACEBO				TREATMENT DIFFERENCE		
	N	LSMEAN	SE	P-VAL (A)	N	LSMEAN	SE	P-VAL (A)	LSMEAN	SE	P-VAL (B)
3	242	-7.21	0.56	<.001	246	-5.50	0.56	<.001	-1.71	0.77	.028
4	222	-11.12	0.65	<.001	231	-8.28	0.64	<.001	-2.84	0.89	.002
5	210	-13.35	0.68	<.001	225	-8.96	0.67	<.001	-4.39	0.93	<.001
6	191	-15.18	0.77	<.001	197	-10.65	0.76	<.001	-4.52	1.07	<.001
7	162	-15.80	0.84	<.001	179	-11.17	0.82	<.001	-4.63	1.16	<.001
8	139	-15.15	0.96	<.001	153	-10.65	0.93	<.001	-4.50	1.32	<.001
9	101	-15.76	1.00	<.001	115	-11.34	0.96	<.001	-4.42	1.37	.001
continued											

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Table 4. Repeated Measures LS Mean Change in Adult Investigator Symptom Rating Scale (AISRS) - Randomized Patients (Concluded)

SUMMARY OF MODEL PARAMETERS	F-VALUE	P-VALUE (C)
BASELINE	38.99	<.001
TREATMENT	19.66	<.001
VISIT	33.96	<.001
INVESTIGATOR	<.001	<.001
TREATMENT*VISIT	2.11	.051

ABBREVIATIONS: LSMEAN=LEAST SQUARES MEAN; SE+STANDARD ERROR.

RESULTS BASED ON A MIXED MODEL WITH VISIT, BASELINE, TREATMENT, INVESTIGATOR, AND TREATMENT-BY-VISIT INTERACTION USING AN UNSTRUCTURED COVARIANCE MATRIX TO MODEL CORRELATIONS WITHIN PATIENTS ACROSS VISITS

A) P-VALUES ARE FROM TESTS FOR A NONZERO LEAST SQUARES MEAN AT THE GIVEN VISIT

B) P-VALUES ARE FROM TESTS FOR A TREATMENT DIFFERENCE IN LEAST SQUARES MEANS AT THE GIVEN VISIT

C) P-VALUES ARE FROM F-TESTS FOR A NONZERO COEFFICIENT ESTIMATE BASED ON THE MODEL DESCRIBED ABOVE

POPULATION: ALL RANDOMIZED PATIENTS

Secondary Efficacy Measures

A reduction in score indicates improvement.

CAARS-O-SV-ADHD Index-I-E

Table 5 presents mean change in CAARS-O-SV Index total scores from baseline to LOCF endpoint at 6 months for all randomized patients. There was statistically significant reduction in the atomoxetine group (-7.3 ± 8.2) compared with the placebo group (-5.0 ± 7.3 ; $p < .001$).

Brown ADD Scale

A reduction in score indicates improvement.

Table 6 presents mean change in Brown ADD adult scale scores from baseline to LOCF endpoint at the end of the double-blind treatment phase for all randomized patients. There was statistically significant reduction in the atomoxetine group (-27.0 ± 25.4) compared with the placebo group (-19.0 ± 24.7 ; $p < .001$). Furthermore, reductions in the raw scores of individual components of the scale, which included activation, focus, effort, emotion, and memory, were statistically significant in the atomoxetine group compared with the placebo group.

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Table 5. Mean Change in Conners' Adult ADHD Rating Scale Index (CAARS-O-SV-ADHD Index-I-E) Investigator Evening Total Score from Baseline to LOCF Endpoint

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		-----		-----		-----			
		MEAN	SD	MEAN	SD	MEAN	SD		
CAARS-O-SV-ADHD INDEX INV EVENING TOTAL SCORE									
ATX	242	20.71	5.84	13.45	7.68	-7.26	8.21	<.001	<.001
PLA	246	21.25	5.95	16.25	7.66	-5.00	7.34	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-3.79,-1.28)									

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION; ATX=ATOMOXETINE; PLA=PLACEBO

A) P-VALUE IS FROM STUDENT'S T-TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE

POPULATION: ALL RANDOMIZED PATIENTS

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Table 6. Mean Change in Brown ADD Adult Scale from Baseline to LOCF Endpoint

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		MEAN	SD	MEAN	SD	MEAN	SD		
BROWN ADD ADULT TOTAL SCORE									
ATX	188	78.64	17.58	51.60	25.49	-27.04	25.43	<.001	<.001
PLA	195	78.43	17.33	59.42	26.46	-19.02	24.67	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-12.67,-3.25)									
ACTIVATION RAW SCORE									
ATX	189	19.21	4.43	13.15	6.52	-6.05	6.34	<.001	.008
PLA	196	19.19	4.13	14.79	6.73	-4.40	6.40	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-2.85,-0.43)									
FOCUS RAW SCORE									
ATX	188	21.27	3.98	13.78	6.71	-7.49	6.84	<.001	.002
PLA	195	21.26	4.22	15.92	7.09	-5.33	6.73	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-3.41,-0.81)									
EFFORT RAW SCORE									
ATX	189	15.97	5.70	10.31	6.32	-5.66	6.75	<.001	.004
PLA	196	15.91	5.55	11.99	6.62	-3.91	6.24	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-2.85,-0.55)									
EMOTION RAW SCORE									
ATX	189	10.15	4.88	6.47	4.85	-3.68	4.59	<.001	<.001
PLA	195	9.66	4.69	7.47	4.71	-2.18	4.39	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-2.13,-0.57)									
MEMORY RAW SCORE									
ATX	189	12.06	3.63	7.78	4.58	-4.28	4.71	<.001	.001
PLA	196	12.52	3.59	9.43	4.62	-3.08	4.54	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-2.22,-0.55)									
ACTIVATION T-SCORE									
ATX	189	77.68	10.60	65.12	12.88	-12.57	13.18	<.001	.004
PLA	196	77.69	9.83	68.60	13.76	-9.10	12.97	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-5.93,-1.10)									

Continued

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Table 6. Mean Change in Brown ADD Adult Scale from Baseline to LOCF Endpoint (Concluded)

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		MEAN	SD	MEAN	SD	MEAN	SD		
FOCUS T-SCORE									
ATX	188	80.21	8.75	65.43	12.26	-14.79	12.80	<.001	<.001
PLA	195	80.22	9.04	69.82	13.31	-10.40	12.73	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-6.70,-1.92)									
EFFORT T-SCORE									
ATX	189	75.61	13.81	63.15	13.49	-12.46	15.12	<.001	.002
PLA	196	75.56	13.54	67.17	14.50	-8.38	13.89	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-6.49,-1.54)									
EMOTION T-SCORE									
ATX	188	66.02	13.22	57.49	11.30	-8.53	11.31	<.001	.001
PLA	195	64.35	12.76	59.56	10.95	-4.79	11.02	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-4.80,-1.17)									
MEMORY T-SCORE									
ATX	189	75.51	12.13	63.01	12.89	-12.50	13.77	<.001	.001
PLA	196	77.01	12.13	67.84	13.66	-9.16	13.92	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-6.42,-1.62)									

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION; ATX=ATOMOXETINE; PLA=PLACEBO

A) P-VALUE IS FROM STUDENT'S T-TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE

POPULATION: ALL RANDOMIZED PATIENTS

STAI

A reduction in score indicates improvement.

The mean change in State-Trait Anxiety Inventory Scale (STAI) scores from baseline to LOCF endpoint at 6 months for all randomized patients showed that there was statistically significant reduction in STAI-T (indicating how the patients “generally feel”) anxiety score in the atomoxetine group (-8.5 ± 10.4) compared with the placebo group (6.1 ± 10.6 ; $p=.011$). The mean change differences in the STAI anxiety score associated with STAI-S symptoms (indicating how the patients feel “right now – at this moment”) were not statistically significantly different between the 2 treatment groups ($p=.106$).

D-KEFS

A reduction in score indicates improvement.

The mean change in Delis-Kaplan Executive Function System (D-KEFS) scores from baseline to LOCF endpoint at 10 weeks of treatment was statistically significant within treatment groups ($p<.001$), but did not show a statistically significant difference between the 2 treatment groups ($p=.240$).

ASRS

A reduction in score indicates improvement.

Tables 7 and 8 summarize the mean change in Adult ADHD Self-Report Scale v1.1 Symptom Checklist Evening (ASRS v1.1-Evening) from baseline to LOCF endpoint at 10 weeks and 6 months. The mean change in ASRS v1.1-Evening demonstrated statistically significant reduction at both time points in the atomoxetine group compared with the placebo group ($p<.001$ for both time points versus placebo).

CGI-ADHD-S

A reduction in score indicates improvement.

Tables 9 and 10 summarize the mean change in Clinical Global Impression – ADHD-Severity (CGI-ADHD-S) from baseline to LOCF endpoint at 10 weeks and 6 months. The mean change in CGI-ADHD-S demonstrated statistically significant reduction at both time points in the atomoxetine group compared with the placebo group ($p<.001$ and $p=.001$ for 10-week and 6-month periods versus placebo, respectively).

AAQOL

An increase in score indicates improvement.

Tables 11 and 12 summarize the mean change in ADHD Quality of Life (AAQOL) scores from baseline to LOCF endpoint at 10 weeks and 6 months. The mean change in AAQOL demonstrated a statistically significant increase at both time points in the

atomoxetine group compared with the placebo group ($p<.001$ and $p=.004$ for 10-week and 6-month periods versus placebo, respectively).

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Table 7. Mean Change in Adult ADHD Self-Report Scale v1.1 Symptom Checklist Evening from Baseline to LOCF Endpoint at 10 weeks

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		MEAN	SD	MEAN	SD	MEAN	SD		
ASRS V1.1 EVE HYPERACTIVITY IMPUTED									
ATX	242	20.50	7.25	13.83	7.49	-6.67	7.25	<.001	<.001
PLA	245	20.98	7.43	16.85	8.01	-4.13	6.96	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-3.88, -1.58)									
ASRS V1.1 EVE INATTENTIVE IMPUTED									
ATX	242	26.68	5.01	18.80	7.16	-7.88	7.40	<.001	<.001
PLA	245	26.55	5.30	21.70	7.48	-4.85	6.70	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-4.13, -1.76)									
ASRS V1.1 EVE TOTAL SCORE									
ATX	242	47.18	10.41	32.64	13.31	-14.55	13.71	<.001	<.001
PLA	245	47.56	10.84	38.58	14.13	-8.98	12.75	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-7.90, -3.50)									

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION; ATX=ATOMOXETINE; PLA=PLACEBO

A) P-VALUE IS FROM STUDENT'S T-TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE

POPULATION: ALL RANDOMIZED PATIENTS

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Table 8. Mean Change in Adult ADHD Self-Report Scale v1.1 Symptom Checklist Evening from Baseline to LOCF Endpoint at 6 Months

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		MEAN	SD	MEAN	SD	MEAN	SD		
ASRS V1.1 EVE HYPERACTIVITY IMPUTED									
ATX	242	20.50	7.25	13.83	7.89	-6.67	7.70	<.001	<.001
PLA	245	20.98	7.43	16.91	8.10	-4.07	7.70	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-4.06, -1.59)									
ASRS V1.1 EVE INATTENTIVE IMPUTED									
ATX	242	26.68	5.01	19.08	7.77	-7.60	7.88	<.001	<.001
PLA	245	26.55	5.30	22.15	8.20	-4.40	7.36	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-4.44, -1.85)									
ASRS V1.1 EVE TOTAL SCORE									
ATX	242	47.18	10.41	32.94	14.42	-14.25	14.59	<.001	<.001
PLA	245	47.56	10.84	39.07	15.04	-8.49	14.16	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-8.33, -3.53)									

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION; ATX=ATOMOXETINE; PLA=PLACEBO

A) P-VALUE IS FROM STUDENT'S T-TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE

POPULATION: ALL RANDOMIZED PATIENTS

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Table 9. Mean Change in Clinical Global Impression – ADHD-Severity from Baseline to LOCF Endpoint at 10 Weeks

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		-----		-----		-----		-----	-----
		MEAN	SD	MEAN	SD	MEAN	SD		
CGI ADHD SEVERITY SCORE									
ATX	242	4.65	0.65	3.54	1.10	-1.12	1.05	<.001	<.001
PLA	246	4.74	0.62	3.94	1.06	-0.80	1.07	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.53, -0.17)									

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION; ATX=ATOMOXETINE; PLA=PLACEBO

A) P-VALUE IS FROM STUDENT'S T-TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE

POPULATION: ALL RANDOMIZED PATIENTS

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Table 10. Mean Change in Clinical Global Impression – ADHD-Severity from Baseline to LOCF Endpoint at 6 Months

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		-----		-----		-----			
		MEAN	SD	MEAN	SD	MEAN	SD		
CGI ADHD SEVERITY SCORE									
ATX	242	4.65	0.65	3.49	1.24	-1.17	1.21	<.001	.001
PLA	246	4.74	0.62	3.87	1.20	-0.88	1.24	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.55, -0.13)									

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION; ATX=ATOMOXETINE; PLA=PLACEBO

A) P-VALUE IS FROM STUDENT'S T-TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE

POPULATION: ALL RANDOMIZED PATIENTS

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Table 11. Mean Change in Adult ADHD Quality of Life (AAQOL) from Baseline to LOCF Endpoint at 10 Weeks

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		MEAN	SD	MEAN	SD	MEAN	SD		
IMPUTED SUM OF ALL SUBSCALE SCORES									
ATX	214	46.37	14.14	60.23	16.21	13.86	15.48	<.001	<.001
PLA	214	47.32	12.97	54.81	17.13	7.49	14.77	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (3.43, 8.87)									
IMPUTED SCORES FOR LIFE OUTLOOK MEASURE									
ATX	215	50.22	15.82	59.09	16.73	8.87	15.04	<.001	.002
PLA	212	49.40	14.27	54.54	16.78	5.14	15.15	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (1.47, 6.78)									
IMPUTED SCORES FOR LIFE PRODUCTIVITY MEASURE									
ATX	215	40.29	17.04	58.35	19.70	18.06	20.30	<.001	<.001
PLA	213	41.01	16.79	51.24	19.78	10.23	20.07	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (4.16, 11.04)									
IMPUTED SCORES FOR PSYCHOLOGICAL HEALTH									
ATX	215	48.67	21.02	60.99	20.68	12.31	20.36	<.001	.003
PLA	213	51.26	19.08	57.09	22.98	5.83	20.31	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (1.90, 8.98)									
IMPUTED SCORES FOR RELATIONSHIPS MEASURE									
ATX	214	51.76	19.40	65.30	19.07	13.54	19.14	<.001	<.001
PLA	213	53.55	18.59	60.01	20.70	6.46	19.56	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (3.13, 9.59)									

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION; ATX=ATOMOXETINE; PLA=PLACEBO

A) P-VALUE IS FROM STUDENT'S T-TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE

POPULATION: ALL RANDOMIZED PATIENTS

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Table 12. Mean Change in Adult ADHD Quality of Life (AAQOL) from Baseline to LOCF Endpoint at 6 Months

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		MEAN	SD	MEAN	SD	MEAN	SD		
IMPUTED SUM OF ALL SUBSCALE SCORES									
ATX	215	46.44	14.13	59.58	18.04	13.14	16.13	<.001	.004
PLA	216	47.43	12.97	56.05	18.09	8.62	16.92	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (1.41, 7.33)									
IMPUTED SCORES FOR LIFE OUTLOOK MEASURE									
ATX	215	50.22	15.82	59.18	17.77	8.96	16.05	<.001	.032
PLA	215	49.44	14.26	55.80	17.35	6.36	16.44	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (0.27, 5.97)									
IMPUTED SCORES FOR LIFE PRODUCTIVITY MEASURE									
ATX	215	40.29	17.04	57.20	21.72	16.90	21.12	<.001	.003
PLA	215	41.23	16.89	52.21	21.73	10.98	21.99	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (2.02, 9.45)									
IMPUTED SCORES FOR PSYCHOLOGICAL HEALTH									
ATX	216	48.83	21.10	60.90	22.40	12.06	21.25	<.001	.036
PLA	215	51.34	19.04	58.45	22.16	7.10	21.31	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (0.25, 7.56)									
IMPUTED SCORES FOR RELATIONSHIPS MEASURE									
ATX	214	51.76	19.40	64.15	20.66	12.39	18.87	<.001	.037
PLA	215	53.56	18.51	61.71	20.66	8.15	20.56	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (0.21, 6.89)									

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION; ATX=ATOMOXETINE; PLA=PLACEBO

A) P-VALUE IS FROM STUDENT'S T-TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE

POPULATION: ALL RANDOMIZED PATIENTS

Resource Utilization

Tables 13 and 14 summarize the mean change in Resource Utilization (RU) scores from baseline to LOCF endpoint at 10 weeks and 6 months. The mean change in RU did not differ between the 2 treatment groups at 10 weeks or 6 months.

Parent Stress Index

Tables 15 and 16 summarize the mean change in Life Stressors scores from baseline to LOCF endpoint at 10 weeks and 6 months. There were no differences between the atomoxetine and placebo groups in mean change for the Life Stressors score at 10 weeks or 6 months.

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Table 13. Mean Change in Resource Utilization (RU) from Baseline to LOCF Endpoint at 10 weeks

ITEMS OF SCID DIAGNOSES		ATX			PLA			P-VALUE
		TOTAL	N	PERCENT	TOTAL	N	PERCENT	
PRIMARY HEALTH CARE PROV	N	161	118	73.29 %	169	124	73.37 %	1.00
	Y	161	43	26.71 %	169	45	26.63 %	
PSYCHIATRIST	N	247	244	98.79 %	247	245	99.19 %	1.00
	Y	247	2	0.81 %	247	2	0.81 %	
	U	247	1	0.40 %	247	0	0.00 %	
PSYCHOLOGIST/THERAPIST	N	241	235	97.51 %	243	239	98.35 %	.543
	Y	241	6	2.49 %	243	4	1.65 %	
OTHER MENTAL HEALTH WORKER	N	248	248	100.00 %	250	249	99.60 %	1.00
	Y	248	0	0.00 %	250	1	0.40 %	
OTHER SPECIALIST PHYSICIAN	N	198	186	93.94 %	202	183	90.59 %	.262
	Y	198	12	6.06 %	202	19	9.41 %	
OTHER HEALTH WORKER	N	241	240	99.59 %	233	232	99.57 %	1.00
	Y	241	1	0.41 %	233	1	0.43 %	
OTHER SPECIFY	N	225	217	96.44 %	217	207	95.39 %	.636
	Y	225	8	3.56 %	217	10	4.61 %	

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION; ATX=ATOMOXETINE; PLA=PLACEBO
 POPULATION: ALL RANDOMIZED PATIENTS

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Table 14. Mean Change in Resource Utilization (RU) from Baseline to LOCF Endpoint at 6 Months

ITEMS OF SCID DIAGNOSES		ATX			PLA			P-VALUE
		TOTAL	N	PERCENT	TOTAL	N	PERCENT	
PRIMARY HEALTH CARE PROV	N	138	110	79.71 %	143	110	76.92 %	.664
	Y	138	28	20.29 %	143	33	23.08 %	
PSYCHIATRIST	N	246	243	98.78 %	246	244	99.19 %	1.00
	Y	246	2	0.81 %	246	2	0.81 %	
	U	246	1	0.41 %	246	0	0.00 %	
PSYCHOLOGIST/THERAPIST	N	239	235	98.33 %	242	239	98.76 %	.723
	Y	239	4	1.67 %	242	3	1.24 %	
OTHER MENTAL HEALTH WORKER	N	247	247	100.00 %	250	249	99.60 %	1.00
	Y	247	0	0.00 %	250	1	0.40 %	
OTHER SPECIALIST PHYSICIAN	N	191	183	95.81 %	180	170	94.44 %	.632
	Y	191	8	4.19 %	180	10	5.56 %	
OTHER HEALTH WORKER	N	240	239	99.58 %	231	230	99.57 %	1.00
	Y	240	1	0.42 %	231	1	0.43 %	
OTHER SPECIFY	N	214	209	97.66 %	207	200	96.62 %	.570
	Y	214	5	2.34 %	207	7	3.38 %	

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; ATX=ATOMOXETINE; PLA=PLACEBO

POPULATION: ALL RANDOMIZED PATIENTS

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Table 15. Mean Change in Parent Stress Index – Life Stressors Score from Baseline to LOCF Endpoint at 10 weeks

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		-----		-----		-----		-----	-----
		MEAN	SD	MEAN	SD	MEAN	SD		
PARENT STRESS INDEX -LIFE STRESSORS TOTAL SCORE									
ATX	208	37.50	0.99	37.32	1.04	-0.17	1.20	.039	.323
PLA	212	37.44	1.00	37.21	1.20	-0.23	1.30	.010	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.10, 0.31)									

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION; ATX=ATOMOXETINE; PLA=PLACEBO

A) P-VALUE IS FROM STUDENT'S T-TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE

POPULATION: ALL RANDOMIZED PATIENTS

Table 16. Mean Change in Parent Stress Index – Life Stressors Score from Baseline to LOCF Endpoint at 6 Months

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		-----		-----		-----		-----	-----
		MEAN	SD	MEAN	SD	MEAN	SD		
PARENT STRESS INDEX -LIFE STRESSORS TOTAL SCORE									
ATX	210	37.48	1.02	37.29	1.16	-0.19	1.21	.027	.518
PLA	216	37.44	1.00	37.21	1.24	-0.23	1.43	.020	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.15, 0.29)									

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION; ATX=ATOMOXETINE; PLA=PLACEBO

A) P-VALUE IS FROM STUDENT'S T-TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE

POPULATION: ALL RANDOMIZED PATIENTS

MADRS

A decrease in score indicates improvement.

The mean change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline to LOCF endpoint at 10 weeks and 6 months showed no differences between the atomoxetine and placebo groups in mean change for the MADRS total score at 10 weeks (atomoxetine: -1.14 ± 4.82 ; placebo: -0.99 ± 6.05 ; $p=.572$) or 6 months (atomoxetine: -1.53 ± 4.99 ; placebo: -1.65 ± 5.70 ; $p=.972$). The MADRS score for suicidal ideation, which was evaluated separately, did not demonstrate significant differences between the groups at 10 weeks (atomoxetine: 0.01 ± 0.37 ; placebo: -0.02 ± 0.39 ; $p=.637$) or 6 months (atomoxetine: 0.01 ± 0.39 ; placebo: -0.05 ± 0.41 ; $p=.307$).

PSQI

A decrease in score indicates improvement.

Tables 17 and 18 summarize the mean change in Pittsburgh Sleep Quality Index (PSQI) global and component scores from baseline to LOCF endpoint at 10 weeks and 6 months. There were no statistically significant differences ($p>.05$) between the atomoxetine and placebo groups in the PSQI global score or component scores at 10 weeks or 6 months.

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Table 17. Mean Change in Pittsburgh Sleep Quality Index (PSQI) Score from Baseline to LOCF Endpoint at 10 weeks

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		MEAN	SD	MEAN	SD	MEAN	SD		
PSQI - PSQI GLOBAL SCORE									
ATX	189	7.89	3.76	7.31	4.21	-0.58	3.91	.044	.881
PLA	180	7.83	3.86	7.28	4.18	-0.55	3.55	.039	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.76, 0.65)									
PSQI - SLEEP LATENCY SCORE									
ATX	215	2.06	1.81	1.78	1.86	-0.28	1.84	.025	.716
PLA	214	2.02	1.93	1.70	1.80	-0.32	1.71	.007	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.24, 0.35)									
PSQI - SLEEP DURATION SCORE									
ATX	193	1.10	0.74	1.01	0.87	-0.09	0.95	.173	.202
PLA	186	1.04	0.87	1.07	0.96	0.03	0.95	.645	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.28, 0.06)									
PSQI - HABITUAL SLEEP EFFICIENCY SCORE									
ATX	189	0.85	1.11	0.71	1.11	-0.13	1.37	.187	.265
PLA	181	0.69	1.08	0.78	1.11	0.09	1.19	.321	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.34, 0.09)									
PSQI - SLEEP DISTURBANCES SCORE									
ATX	215	1.37	0.60	1.34	0.51	-0.03	0.64	.524	.493
PLA	214	1.39	0.62	1.32	0.61	-0.07	0.63	.084	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.06, 0.13)									
PSQI - USE OF SLEEP MEDICATION SCORE									
ATX	215	0.22	0.71	0.24	0.72	0.02	0.66	.678	.295
PLA	213	0.31	0.77	0.22	0.65	-0.09	0.79	.100	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.05, 0.18)									
PSQI - DAYTIME DYSFUNCTION SCORE									
ATX	215	1.33	0.77	1.12	0.79	-0.22	0.87	<.001	.156
PLA	213	1.27	0.71	1.19	0.75	-0.08	0.86	.155	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.23, 0.04)									

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Table 17. Mean Change in Pittsburgh Sleep Quality Index (PSQI) Score from Baseline to LOCF Endpoint at 10 weeks (Concluded)

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION; ATX=ATOMOXETINE; PLA=PLACEBO
A) P-VALUE IS FROM STUDENT'S T-TEST
B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS
FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE
POPULATION: ALL RANDOMIZED PATIENTS

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Table 18. Mean Change in Pittsburgh Sleep Quality Index (PSQI) Score from Baseline to LOCF Endpoint at 6 Months

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		MEAN	SD	MEAN	SD	MEAN	SD		
PSQI - PSQI GLOBAL SCORE									
ATX	191	7.85	3.77	7.27	4.41	-0.58	4.05	.051	.702
PLA	192	7.90	3.82	7.35	4.13	-0.55	3.72	.043	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.86, 0.58)									
PSQI - SLEEP LATENCY SCORE									
ATX	215	2.06	1.81	1.81	1.87	-0.25	1.90	.055	.687
PLA	216	2.01	1.92	1.72	1.72	-0.29	1.76	.016	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.23, 0.35)									
PSQI - SLEEP DURATION SCORE									
ATX	195	1.10	0.74	1.05	0.88	-0.05	1.01	.525	.793
PLA	197	1.06	0.86	1.06	0.93	0.00	1.02	1.000	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.20, 0.15)									
PSQI - HABITUAL SLEEP EFFICIENCY SCORE									
ATX	191	0.84	1.10	0.75	1.13	-0.09	1.36	.366	.276
PLA	193	0.68	1.07	0.82	1.12	0.13	1.36	.171	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.35, 0.10)									
PSQI - SLEEP DISTURBANCES SCORE									
ATX	215	1.37	0.60	1.30	0.54	-0.07	0.62	.081	.553
PLA	216	1.40	0.63	1.33	0.59	-0.06	0.57	.094	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.12, 0.06)									
PSQI - USE OF SLEEP MEDICATION SCORE									
ATX	215	0.22	0.71	0.27	0.76	0.05	0.72	.302	.289
PLA	215	0.30	0.77	0.23	0.70	-0.07	0.86	.235	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.06, 0.20)									
PSQI - DAYTIME DYSFUNCTION SCORE									
ATX	215	1.33	0.77	1.10	0.78	-0.24	0.89	<.001	.844
PLA	215	1.27	0.71	1.09	0.75	-0.18	0.86	.002	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.15, 0.12)									

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Table 18. Mean Change in Pittsburgh Sleep Quality Index (PSQI) Score from Baseline to LOCF Endpoint at 6 Months (Concluded)

Abbreviations: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION; ATX=ATOMOXETINE; PLA=PLACEBO
A) P-VALUE IS FROM STUDENT'S T-TEST
B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS
FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE
POPULATION: ALL RANDOMIZED PATIENTS

CAARS-O-SV

A decrease in score indicates improvement.

Table 19 summarizes the mean change in Conners' Adult ADHD Rating Scale Screening Version – Observer Rated (CAARS-O:SV) scores from baseline to LOCF endpoint at 6 months. The mean change in the total ADHD symptom score (-7.9 ± 10.3) and hyperactivity/impulsivity (-3.3 ± 5.0) subscale were statistically significant compared with placebo (-5.5 ± 10.0 and -2.4 ± 5.1 ; $p=.012$ and $p=.004$, respectively). There were no statistically significant differences in scores between the groups on the inattentive subscale. The mean change on the ADHD Index subscale for the atomoxetine group (4.7 ± 6.9) was statistically significant compared with placebo (-2.9 ± 7.0 ; $p=.007$).

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Table 19. Mean Change in Conners' Adult ADHD Rating Scale Screening Version – Observer Rated (CAARS-O:SV) Score from Baseline to LOCF Endpoint at 6 Months

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		MEAN	SD	MEAN	SD	MEAN	SD		
TOTAL ADHD SYMPTOM SCORE - OBSERVER									
ATX	171	29.49	10.35	21.56	10.35	-7.93	10.32	<.001	.012
PLA	160	29.47	10.00	23.98	10.47	-5.49	9.99	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-4.32, -0.53)									
INATTENTION SUBSCALE - OBSERVER									
ATX	171	17.27	5.94	12.60	6.26	-4.67	6.33	<.001	.073
PLA	160	16.17	5.61	13.05	6.04	-3.12	5.91	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-2.21, 0.10)									
HYP/IMP SUBSCALE - OBSERVER									
ATX	171	12.22	6.08	8.97	5.52	-3.26	4.95	<.001	.004
PLA	161	13.33	5.73	10.95	5.38	-2.37	5.09	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-2.29, -0.43)									
ADHD INDEX SUBSCALE - OBSERVER									
ATX	171	18.86	6.62	14.13	6.82	-4.72	6.92	<.001	.007
PLA	161	18.82	6.47	15.90	7.24	-2.91	6.96	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-3.12, -0.51)									

Abbreviations: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION; ATX=ATOMOXETINE; PLA=PLACEBO
A) P-VALUE IS FROM STUDENT'S T-TEST
B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS
FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE
POPULATION: ALL RANDOMIZED PATIENTS

Open-Label Phase

Efficacy Measures

All patients entering the open-label period were treated with atomoxetine.

AISRS

At the end of the open-label period, the mean change reduction from open-label period baseline to LOCF endpoint on the AISRS total score was statistically significant in patients previously randomized to placebo (-7.3 ± 10.9 ; $p < .001$) and in patients previously randomized to atomoxetine (-4.0 ± 7.7 ; $p < .001$). The difference in AISRS total score between patients who were previously randomized to atomoxetine and patients who were previously randomized to placebo was not statistically significant ($p = .104$) (Table 20).

The mean change reduction from open-label period baseline to LOCF endpoint for the hyperactive and inattentive scores was statistically significant in patients previously randomized to placebo (-3.2 ± 5.6 ; $p < .001$ and -4.2 ± 6.1 ; $p < .001$, respectively) and in patients who were previously randomized to atomoxetine (-2.0 ± 3.8 ; $p < .001$ and -1.9 ± 4.6 ; $p < .001$, respectively). The difference in inattentive scores between patients who were previously randomized to placebo and atomoxetine was statistically significant ($p = .036$), but was not significant for hyperactive scores ($p = .383$) (Table 20).

Brown ADD

At the end of the open-label period, the mean change reduction from open-label period baseline to LOCF endpoint on the Brown ADD total score was statistically significantly higher in patients who were previously randomized to placebo (-16.6 ± 23.1 ; $p < .001$) compared to patients previously randomized to atomoxetine (-6.6 ± 16.4 ; $p < .001$). The difference in Brown ADD total score between patients who were previously randomized to placebo and patients who were previously randomized to atomoxetine was statistically significant ($p = .006$) (Table 21).

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Table 20. Mean Change in Adult Investigator Symptom Rating Scale (AISRS) from Baseline to LOCF Endpoint - Open-Label Period

TREATMENT GROUP	PREVIOUSLY RANDOMIZED TO	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
			MEAN	SD	MEAN	SD	MEAN	SD		
AISRS TOTAL SCORE										
ATOMOXETINE	ATOMOXETINE	90	21.43	11.98	17.48	11.46	-3.96	7.68	<.001	.104
ATOMOXETINE	PLACEBO	104	25.81	12.68	18.47	11.85	-7.34	10.94	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.45, 4.74)										
AISRS Hyperactive/Impulsive Subscale Imputed										
ATOMOXETINE	ATOMOXETINE	90	8.79	6.30	6.77	6.03	-2.02	3.77	<.001	.383
ATOMOXETINE	PLACEBO	104	10.84	6.38	7.66	5.95	-3.17	5.64	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.74, 1.91)										
AISRS Inattentive Subscale Imputed										
ATOMOXETINE	ATOMOXETINE	90	12.64	6.53	10.71	6.27	-1.93	4.56	<.001	.036
ATOMOXETINE	PLACEBO	104	14.97	7.46	10.81	6.98	-4.16	6.11	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (0.10, 3.02)										

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION

A) P-VALUE IS FROM STUDENT'S T-TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE

POPULATION: ALL PATIENTS WHO ENTERED THE OPEN-LABEL PERIOD

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Table 21. Mean Change in Brown Adult Scale from Baseline to LOCF Endpoint During the Open-label Period

TREATMENT GROUP	PREVIOUSLY RANDOMIZED TO	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
			MEAN	SD	MEAN	SD	MEAN	SD		
BROWN ADD ADULT TOTAL TSCORE										
ATOMOXETINE	ATOMOXETINE	90	46.71	24.34	40.13	25.40	-6.58	16.38	<.001	.006
ATOMXETINE	PLACEBO	104	56.42	27.01	39.82	23.95	-16.61	23.12	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (2.36, 13.60)										

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION

A) P-VALUE IS FROM STUDENT'S T-TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE

POPULATION: ALL PATIENTS WHO ENTERED THE OPEN-LABEL PERIOD

State-Trait Anxiety Scale

At the end of the open-label period, the mean change reduction from open-label period baseline to LOCF endpoint on the STAI-S anxiety score was statistically significant in patients who were previously randomized to placebo (-3.4 ± 10.8 ; $p=.002$), but not in patients previously randomized to atomoxetine (-1.5 ± 8.9 ; $p=.120$). The difference in STAI-S anxiety score between the patients who were previously randomized to placebo and patients who were previously randomized to atomoxetine was not statistically significant ($p=.432$). The mean change reduction from open-label period baseline to LOCF endpoint on the STAI-T score was statistically significant in patients who were previously randomized to placebo (-3.94 ± 8.09 ; $p<.001$) and in patients previously randomized to atomoxetine (-2.56 ± 6.96 ; $p<.001$). (Table 22).

ASRS v.1.1 Symptom Checklist Evening

At the end of the open-label period, the mean change reduction from open-label period baseline to LOCF endpoint on the ASRS v1.1-evening total score was statistically significant in patients who were previously randomized to placebo (-7.6 ± 11.5 ; $p<.001$) and in patients previously randomized to atomoxetine (-4.5 ± 8.7 ; $p<.001$). The difference in ASRS v1.1-evening total score between patients previously randomized to atomoxetine and patients who were previously randomized to placebo was not statistically significant ($p=.095$).

CGI-ADHD-S

At the end of the open-label period, the mean change reduction from open-label period baseline to LOCF endpoint in CGI-ADHD-S score was statistically significantly higher in patients who were previously randomized to placebo (-0.7 ± 1.1 ; $p<.001$) and in patients previously randomized to atomoxetine (-0.3 ± 0.8 ; $p<.001$). The difference in CGI-ADHD-S score between the patients who were previously randomized to placebo and patients who were previously randomized to atomoxetine was statistically significant ($p=.019$).

AAQOL

At the end of the open-label period, the mean change from open-label period baseline to LOCF endpoint on the total subscale score for the AAQOL was statistically significantly higher in patients who were previously randomized to placebo (10.0 ± 12.5 ; $p<.001$) compared with patients previously randomized to atomoxetine (5.5 ± 10.8 ; $p<.001$). The difference in the AAQOL total subscale score between the patients previously randomized to placebo and patients previously randomized to atomoxetine was statistically significant ($p=.025$).

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Table 22. Mean Change in State-Trait Anxiety-Score from Baseline to LOCF Endpoint - Open-label Period

TREATMENT GROUP	PREVIOUSLY RANDOMIZED TO	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
			MEAN	SD	MEAN	SD	MEAN	SD		
STATE-TRAIT ANXIETY-SSCORE										
ATOMOXETINE	ATOMOXETINE	90	34.48	11.30	33.00	12.57	-1.48	8.91	.120	.432
ATOMXETINE	PLACEBO	104	37.13	12.47	33.72	12.10	-3.41	10.84	.002	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-1.65, 3.85)										
STATE-TRAIT ANXIETY-TSCORE										
ATOMOXETINE	ATOMOXETINE	90	38.19	10.84	35.62	11.12	-2.56	6.96	<.001	.265
ATOMOXETINE	PLACEBO	104	41.16	12.45	37.22	12.39	-3.94	8.09	<.001	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.93 ,3.36)										

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION

A) P-VALUE IS FROM STUDENT'S T-TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE

POPULATION: ALL PATIENTS WHO ENTERED THE OPEN-LABEL PERIOD

Resource Utilization

At the end of the open-label period, there were no statistically significant mean changes from open-label period baseline to LOCF endpoint for the health care resource utilization measures in patients who were previously randomized to placebo and in patients previously randomized to atomoxetine and were similar between groups (Table 23).

Parent Stress Index

At the end of the open-label period, the within-group change in the Parent Stress Index-Life Stressor total score was not significant in patients who were previously randomized to placebo ($p=.830$) or atomoxetine ($p=.541$), and the difference in these changes between patients previously randomized to atomoxetine group and patients previously randomized to placebo was not statistically significant ($p=.893$) (Table 24).

MADRS

At the end of the open-label period, the mean change from open-label period baseline to LOCF endpoint in MADRS total score was statistically significant in patients who were previously randomized to placebo (-0.9 ± 4.5 ; $p=.048$), but not in patients previously randomized to atomoxetine (-0.8 ± 4.5 ; $p=.101$). The difference in MADRS total score between the patients who were previously randomized to atomoxetine and patients previously randomized to placebo was not statistically significant ($p=.845$) (Table 25).

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Table 23. Resource Utilization (RU) During the Open-Label Period

VARIABLE	ATOMOXETINE TREATMENT PREVIOUSLY RANDOMIZED TO				TOTAL		FISHERS EXACT P-VALUE (A)
	ATOMOXETINE N	N (%)	PLACEBO N	N (%)	N	N (%)	
OTHER HEALTH WORKER (N)	83	79 (95.2%)	101	98 (97%)	184	177 (96.2%)	.703
OTHER HEALTH WORKER (Y)	83	4 (4.8%)	101	3 (3%)	184	7 (3.8%)	
OTHER MENTAL HEALTH WORKER (N)	83	83 (100%)	101	101 (100%)	184	184 (100%)	
OTHER SPECIALIST PHYSICIAN (N)	83	69 (83.1%)	101	87 (86.1%)	184	156 (84.8%)	.681
OTHER SPECIALIST PHYSICIAN (Y)	83	14 (16.9%)	101	14 (13.9%)	184	28 (15.2%)	
OTHER SPECIFY (N)	83	76 (91.6%)	101	89 (88.1%)	184	165 (89.7%)	.477
OTHER SPECIFY (Y)	83	7 (8.4%)	101	12 (11.9%)	184	19 (10.3%)	
PRIMARY HEALTH CARE PROV (N)	83	63 (75.9%)	101	74 (73.3%)	184	137 (74.5%)	.736
PRIMARY HEALTH CARE PROV (Y)	83	20 (24.1%)	101	27 (26.7%)	184	47 (25.5%)	
PSYCHIATRIST (N)	83	82 (98.8%)	101	99 (98%)	184	181 (98.4%)	1.00
PSYCHIATRIST (Y)	83	1 (1.2%)	101	2 (2%)	184	3 (1.6%)	
PSYCHOLOGIST/THERAPIST (N)	83	83 (100%)	101	99 (98%)	184	182 (98.9%)	.502
PSYCHOLOGIST/THERAPIST (Y)	83	0 (0%)	101	2 (2%)	184	2 (1.1%)	

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION; ATX=ATOMOXETINE; PLA=PLACEBO
 POPULATION: ALL PATIENTS WHO ENTERED THE OPEN-LABEL PERIOD

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Table 24. Mean Change in Parent Stress Index – Life Stressors Score from Baseline to LOCF Endpoint at 4 Months - Open-Label Period

TREATMENT GROUP	PREVIOUSLY RANDOMIZED TO	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
			MEAN	SD	MEAN	SD	MEAN	SD		
PSI-LS TOTAL SCORE										
ATOMOXETINE	ATOMOXETINE	82	37.22	1.11	37.13	1.32	-0.09	1.26	.541	.893
ATOMOXETINE	PLACEBO	100	37.36	1.02	37.33	1.05	-0.03	1.40	.830	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.36, 0.32)										

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION

A) P-VALUE IS FROM PAIRED T-TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE

POPULATION: ALL PATIENTS WHO ENTERED THE OPEN-LABEL PERIOD

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Table 25. Mean Change in Montgomery-Asberg Depression Rating Scale Score from Baseline to LOCF Endpoint at 4 Months During the Open-Label Period

TREATMENT GROUP	PREVIOUSLY RANDOMIZED TO	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
			-----		-----		-----			
			MEAN	SD	MEAN	SD	MEAN	SD		
MADRS TOTAL SCORE										
ATOMOXETINE	ATOMOXETINE	90	5.34	5.11	4.57	5.13	-0.78	4.45	.101	.845
ATOMOXETINE	PLACEBO	104	6.02	5.22	5.13	5.10	-0.88	4.50	.048	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-1.32, 1.08)										

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION

A) P-VALUE IS FROM PAIRED T-TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE

POPULATION: ALL PATIENTS WHO ENTERED THE OPEN-LABEL PERIOD

Safety Evaluation

Acute Period

Adverse events

Safety analyses were conducted using all data from all randomized patients taking at least 1 dose of the study drug. A total of 501 patients were randomized, but only 491 were confirmed to have taken at least 1 dose of study drug. Table 26 presents an overview of adverse events reported during the study.

Table 26. Overview of Adverse Events Reported by All Randomized Patients

Adverse Event ^a	Number (%) of Patients	
	Placebo N=251	Atomoxetine 25-100mg/day N=250
Deaths	0 (0)	0 (0)
Serious adverse events	3 (0.01)	0 (0)
Discontinuations due to an adverse event	14 (5.6)	43 (17.2)
Treatment-emergent adverse events	200 (80.6)	220 (90.5)

^a Patients may be counted in more than 1 category.

Deaths

There were no deaths reported in the study.

Serious adverse events

A total of 3 serious adverse events (SAEs) occurred during the double-blind period all of which were from the placebo group. SAEs reported during the study were ectopic pregnancy, gastric outlet obstructile, and food poisoning.

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Discontinuation due to Adverse Events

Treatment-emergent adverse events (TEAEs) leading to study discontinuation are summarized in Table 27. A total of 57 patients (43 in the atomoxetine group and 14 in the placebo group) discontinued the study due to adverse events. Statistically significantly more atomoxetine patients discontinued the study due to adverse events of nausea and erectile dysfunction compared with placebo patients.

Table 27. Adverse Events Leading to Discontinuation

ADVERSE EVENTS OR DEATH CLASSIFICATION	ATOMOXETINE (N= 250) N (%)	PLACEBO (N= 251) N (%)	P-VALUE FISHER'S EXACT TEST
PATIENTS DISCONTINUED DUE TO AE OR DEATH	43 (17.20)	14 (5.58)	<.001
NAUSEA	6 (2.40)	0	.015
ERECTILE DYSFUNCTION	5 (2.00)	0	.030
SOMNOLENCE	3 (1.20)	0	.124
DEPRESSION	2 (0.80)	1 (0.40)	.623
DIZZINESS	2 (0.80)	0	.249
HEART RATE INCREASED	2 (0.80)	0	.249
HYPERTENSION	2 (0.80)	0	.249
SEDATION	2 (0.80)	0	.249
HEADACHE	1 (0.40)	1 (0.40)	1.000
INSOMNIA	1 (0.40)	1 (0.40)	1.000
MIGRAINE	1 (0.40)	1 (0.40)	1.000
ABDOMINAL PAIN	1 (0.40)	0	.499
ABDOMINAL PAIN UPPER	1 (0.40)	0	.499
ASTHENIA	1 (0.40)	0	.499
CONSTIPATION	1 (0.40)	0	.499
DRUG EXPOSURE DURING PREGNANCY	1 (0.40)	0	.499
DYSPEPSIA	1 (0.40)	0	.499
FATIGUE	1 (0.40)	0	.499
LIBIDO DECREASED	1 (0.40)	0	.499
NERVOUSNESS	1 (0.40)	0	.499
PROSTATITIS	1 (0.40)	0	.499
PRURITUS	1 (0.40)	0	.499
RHINITIS	1 (0.40)	0	.499
SYNCOPE	1 (0.40)	0	.499
URINARY HESITATION	1 (0.40)	0	.499
VERTIGO	1 (0.40)	0	.499
VISION BLURRED	1 (0.40)	0	.499
ANXIETY	0	1 (0.40)	1.000
CHEST DISCOMFORT	0	1 (0.40)	1.000
CHEST PAIN	0	1 (0.40)	1.000
DISORIENTATION	0	1 (0.40)	1.000
KIDNEY INFECTION	0	1 (0.40)	1.000
LETHARGY	0	1 (0.40)	1.000
MEMORY IMPAIRMENT	0	1 (0.40)	1.000
MOOD SWINGS	0	1 (0.40)	1.000
OBSTRUCTION GASTRIC	0	1 (0.40)	1.000
RASH	0	1 (0.40)	1.000

POPULATION: ALL RANDOMIZED PATIENTS

Vital Signs

The analysis of vital signs and mean change in weight from baseline to LOCF after 10 weeks and 6 months of treatment are presented in tables 28 and 29. Vital sign measures were comparable between the atomoxetine-treated and placebo-treated patients with the following exceptions: there were statistically significant mean change differences in diastolic blood pressure and pulse between the atomoxetine group and the placebo group after 10 weeks of treatment. After 6 months of treatment, only the difference in mean change in pulse was statistically significant. The weight loss in the atomoxetine group was statistically significant compared with the placebo group after 6 months of treatment.

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Table 28. Mean Change in Vital Signs from Baseline to LOCF Endpoint After 10 Weeks

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		MEAN	SD	MEAN	SD	MEAN	SD		
SYSTOLIC BP									
ATX	242	117.30	12.23	118.61	11.68	1.31	10.96	.064	.248
PLA	245	117.71	10.93	117.94	11.40	0.23	9.36	.697	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.66, 2.56)									
DIASTOLIC BP									
ATX	242	74.52	8.92	76.21	8.68	1.69	8.52	.002	.022
PLA	245	74.62	8.77	74.87	8.49	0.24	7.28	.599	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (0.21, 2.67)									
PULSE									
ATX	242	72.24	9.77	76.78	11.09	4.53	11.28	<.001	<.001
PLA	245	71.41	10.13	71.84	9.82	0.43	9.29	.467	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (2.97, 6.19)									
WEIGHT (KG)									
ATX	242	81.29	18.76	79.96	18.56	-1.33	2.39	<.001	<.001
PLA	246	84.38	20.60	84.45	20.54	0.08	5.27	.818	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-2.21, -0.76)									

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD, SD=STANDARD DEVIATION.

A) P-VALUE IS FROM STUDENT'S T-TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE

POPULATION: ALL RANDOMIZED PATIENTS

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Table 29. Mean Change in Vital Signs from Baseline to LOCF Endpoint After 6 Months

TREATMENT GROUP	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
		MEAN	SD	MEAN	SD	MEAN	SD		
SYSTOLIC BP									
ATX	242	117.30	12.23	118.92	12.54	1.62	10.42	.016	.107
PLA	245	117.71	10.93	117.94	11.17	0.24	9.07	.683	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.28, 2.82)									
DIASTOLIC BP									
ATX	242	74.52	8.92	75.76	8.53	1.24	8.93	.032	.250
PLA	245	74.62	8.77	75.11	8.17	0.49	7.51	.305	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.51, 1.96)									
PULSE									
ATX	242	72.24	9.77	76.04	10.49	3.79	11.42	<.001	<.001
PLA	245	71.41	10.13	72.87	9.57	1.47	10.06	.023	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (1.26, 4.48)									
WEIGHT (KG)									
ATX	242	81.29	18.76	79.69	18.88	-1.59	3.31	<.001	<.001
PLA	246	84.38	20.60	84.44	20.71	0.06	6.04	.879	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-2.60, -0.85)									

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD, SD=STANDARD DEVIATION.

A) P-VALUE IS FROM STUDENT'S T-TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE

POPULATION: ALL RANDOMIZED PATIENTS

Open-Label Period

Adverse events

Table 30 presents adverse events reported by $\geq 5\%$ of patients during the study.

Table 30. Most Commonly Reported Adverse Events

Adverse Event	Patients (n/N)
Insomnia	11/206
Fatigue	8/206
Dizziness	11/206
Dry mouth	11/206
Irritability	7/206
Nausea	28/206
Decreased appetite	9/206
Ejaculation disorder*	3/88*
Sleep disorder	7/206
Urinary hesitation	7/206

*Based on males only (total=88)

Population: All patients who entered the open-label period and took at least 1 dose of study drug

Deaths

There were no deaths reported in the study.

Serious adverse events

There was 1 patient who continued into the open-label study from the placebo group who reported a SAE that was related to moderate non-cardiac chest pain, which was not related to study medication.

Discontinuation due to adverse events

A total of 22 patients (19 patients previously randomized to placebo and 3 patients who were previously randomized to atomoxetine) discontinued from the study (Table 31).

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Table 31. Adverse Events Leading to Discontinuation - Open-Label Period

TREATMENT WITH ATOMOXETINE PREVIOUSLY RANDOMIZED TO										
	ATOMOXETINE			PLACEBO			TOTAL			FISHER'S EXACT P-VALUE
	N	n	%	N	n	%	N	n	%	
ADVERSE EVENT	94	3	3.19%	112	19	16.96%	206	22	10.68%	.001
PROTOCOL ENTRY CRITERIA NOT MET	94	0	0.00%	112	0	0.00%	206	0	0.00%	
UNABLE TO CONTACT PATIENT (LOST FOLLOW-UP)	94	7	7.45%	112	8	7.14%	206	15	7.28%	1.00
PATIENT DECISION	94	5	5.32%	112	4	3.57%	206	9	4.37%	.735
OTHER	94	1	1.06%	112	2	1.79%	206	3	1.46%	1.00
PROTOCOL VIOLATION	94	2	2.13%	112	0	0.00%	206	2	0.97%	.207
LACK OF EFFICACY	94	2	2.13%	112	3	2.68%	206	5	2.43%	1.00
SPONSOR DECISION	94	0	0.00%	112	1	0.89%	206	1	0.49%	1.00
STUDY PERIOD II COMPLETED	94	0	0.00%	112	0	0.00%	206	0	0.00%	
PROTOCOL COMPLETED	94	74	78.72%	112	75	66.96%	206	149	72.33%	.063

P-VALUES ARE BASED ON FISHERS EXACT TEST
 POPULATION: ALL PATIENTS WHO ENTERED THE OPEN-LABEL PERIOD

Pittsburgh Sleep Quality Index

Table 32 summarizes the mean change in Pittsburgh Sleep Quality Index (PSQI) global and component scores from baseline to LOCF endpoint at 4 months during the open-label period. The mean change from open-label period baseline to LOCF endpoint in PSQI global score was statistically significant in patients previously randomized to placebo ($p=.008$), but not in patients previously randomized to atomoxetine ($p=.890$). The difference for PSQI global score or component scores between patients who were previously randomized to atomoxetine group and patients previously randomized to placebo was not statistically significant ($p=.227$).

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Table 32. Mean Change in Pittsburg Sleep Quality Index from Baseline to LOCF Endpoint After 4 Months - Open-Label Period

TREATMENT GROUP	PREVIOUSLY RANDOMIZED TO	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
			MEAN	SD	MEAN	SD	MEAN	SD		
PSQI GLOBAL SCORE										
ATOMOXETINE	ATOMOXETINE	84	6.39	3.91	6.44	3.75	0.05	3.15	.890	.227
ATOMOXETINE	PLACEBO	101	7.39	3.88	6.39	3.92	-1.00	3.73	.008	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.36, 1.51)										
DAYTIME DYSFUNCTION SCORE										
ATOMOXETINE	ATOMOXETINE	90	1.08	0.80	0.90	0.70	-0.18	0.73	.023	.789
ATOMOXETINE	PLACEBO	105	1.00	0.69	0.90	0.84	-0.10	0.77	.167	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.17, 0.22)										
HABITUAL SLEEP EFFICIENCY SCORE										
ATOMOXETINE	ATOMOXETINE	84	0.57	1.01	0.82	1.15	0.25	1.31	.083	.171
ATOMOXETINE	PLACEBO	102	0.75	1.11	0.58	1.05	-0.17	1.36	.218	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.10, 0.54)										
SLEEP DISTURBANCES SCORE										
ATOMOXETINE	ATOMOXETINE	90	1.27	0.58	1.17	0.48	-0.10	0.50	.060	.943
ATOMOXETINE	PLACEBO	105	1.37	0.56	1.21	0.57	-0.16	0.65	.012	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.14, 0.15)										

(Continued)

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Table 32. Mean Change in Pittsburgh Sleep Quality Index from Baseline to LOCF Endpoint After 4 Months - Open-Label Period (Concluded)

TREATMENT GROUP	PREVIOUSLY RANDOMIZED TO	N	BASELINE		ENDPOINT		CHANGE		P-VALUE (A)	P-VALUE (B)
			MEAN	SD	MEAN	SD	MEAN	SD		
SLEEP DURATION SCORE										
ATOMOXETINE	ATOMOXETINE	84	0.99	0.84	1.06	0.90	0.07	1.07	.543	.727
ATOMOXETINE	PLACEBO	103	1.03	0.83	0.97	0.85	-0.06	0.95	.534	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.20, 0.29)										
SLEEP LATENCY SCORE										
ATOMOXETINE	ATOMOXETINE	90	1.56	1.77	1.31	1.52	-0.24	1.45	.113	.696
ATOMOXETINE	PLACEBO	105	1.69	1.72	1.32	1.52	-0.36	1.49	.015	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.28, 0.42)										
USE OF SLEEP MEDICATION SCORE										
ATOMOXETINE	ATOMOXETINE	90	0.19	0.62	0.16	0.56	-0.03	0.69	.650	.278
ATOMOXETINE	PLACEBO	105	0.33	0.84	0.32	0.79	-0.01	0.95	.918	
95% CONFIDENCE INTERVAL FOR LSMEANS DIFFERENCE: (-0.30, 0.09)										

ABBREVIATIONS: LOCF=LAST OBSERVATION CARRIED FORWARD; SD=STANDARD DEVIATION

A) P-VALUE IS FROM PAIRED T-TEST

B) BETWEEN TREATMENT GROUP P-VALUES ARE FROM BASELINE TO ENDPOINT (LOCF) SCORES USING LEAST SQUARES MEANS FROM AN ANCOVA MODEL WITH TERMS FOR INVESTIGATOR, TREATMENT, AND BASELINE AS A COVARIATE

POPULATION: ALL PATIENTS WHO ENTERED THE OPEN-LABEL PERIOD

Summary ID# 9081

Clinical Study Summary: Study B4Z-MW-LYCZ

Efficacy, Tolerability, and Safety of Once-Daily Atomoxetine Hydrochloride versus Placebo in Russian Children and Adolescents with Attention-Deficit/Hyperactivity Disorder

Date summary approved by Lilly: 01 June 2006

Brief Summary of Results

This study was designed to investigate the efficacy, safety, and tolerability of atomoxetine administered once-daily during a 6-week acute treatment period and a 2-week discontinuation phase in a population of Russian children.

The primary objective was to evaluate and compare efficacy of atomoxetine administered as a single-daily dose with placebo in Russian children and adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD).

The secondary objectives were to compare the improvement in symptoms associated with ADHD in children and adolescents achieved by once-daily dosing of atomoxetine or placebo as defined by a >25% reduction in the ADHDRS-IV-Parent:Inv total score and by mean reductions in the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) and ADHDRS-IV-Parent:Inv subscale scores.

- Ninety nine patients out of 105 (94.3%) completed the protocol in both treatment arms: 67/72 patients (93.1%) – assigned to atomoxetine group and 32/33 (97.0%) assigned to placebo treatment. Six patients discontinued from the study.
- Statistically significant improvement in the ADHDRS total score was observed in both groups of patients, however the atomoxetine treated patients showed greater improvement than patients of placebo arm compared to baseline (differences between the atomoxetine and placebo group were statistically significant, $p=0.013$).

- There was a statistically significant ($p=0.022$) difference between proportions of responders in the two treatment groups: 72.2% for the Active treatment group and 48.5% for the Placebo treatment group with the difference between proportions of 23.7% (95% CI, 3.8% to 43.7%).
- The response was reached statistically significantly earlier in the Active treatment group than in the Placebo treatment group ($p<0.001$): the median time to response was 23 and 50 days in the Active and Placebo treatment groups, respectively. The hazard ratio of the time to response was 0.4 (95% CI, 0.2 to 0.7).
- Secondary analysis of changes in the ADHDRS total score discovered a statistically significant effect of the treatment-by-center interaction. By the end of the Study Period II there was no statistically significant difference in the ADHDRS total score changes between the treatment groups, in all centers except one.
- Thirty three of 72 (45.8%) patients in the Active treatment group and 11/33 (33.3%) patients in the Placebo treatment group had TESS; no effect of the treatment group was observed. The most frequent TESS were anorexia (13/72 18.1% in the Active treatment group and 2/33, 6.1% in the Placebo treatment group) and somnolence (11/72, 15.3% in the Active treatment group and 3/33, 9.1% in the Placebo treatment group). In both treatment groups most TESS were mild in severity. No significant difference in the number of patients who had TESS associated with the use of the Study Drug was noted between the two treatment groups ($p=0.108$). One of 72 (1.4%) patients in the Active treatment group discontinued the treatment due to AE. No deaths or SAEs were reported.
- A clinically significant (7% or more) weight loss was experienced by 9.7% patients in the Active treatment group and by 6.1% patients in the Placebo treatment group; no effect of the treatment group was observed. A statistically significant weight loss was reported in the Active treatment group over the Study Period II; the effect of the treatment group was statistically significant ($p=0.032$). A statistically significant pulse rate increase was reported in the Active treatment group during the Study Period II; the effect of the treatment group was statistically significant ($p=0.054$).
- A statistically significant weight increase was observed in both treatment groups over the Study Period III; the effect of the treatment group was statistically insignificant ($p=0.241$). A statistically significant pulse rate decrease was observed in the Active treatment group over the Study Period III but no significant effect of the treatment group was observed ($p=0.082$).

Title of Study: Efficacy, Tolerability, and Safety of Once-Daily Atomoxetine Hydrochloride versus Placebo in Russian Children and Adolescents with Attention-Deficit/Hyperactivity Disorder	
Investigator(s): This multicenter study included 8 principal investigator(s).	
Study Center(s): This study was conducted at 8 study centers in 1 country	
Length of Study: 6.5 months – 26 Jul 2004 (FPV) through 8 Feb 2005 (LPV) Date of first patient enrolled: 02 Aug 2004 Date of last patient completed: entire study – 8 Feb 2005 treatment phase – 02 Feb 2005	Phase of Development: IIIb
Objectives:	
<u>Primary Objective:</u>	
to evaluate and compare efficacy of atomoxetine administered as a single-daily dose with placebo in Russian children and adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD).	
<u>Secondary Objectives:</u>	
- to compare the improvement in symptoms associated with ADHD in children and adolescents achieved by once-daily dosing of atomoxetine or placebo as defined by a >25% reduction in the ADHDRS-IV-Parent:Inv total score and by mean reductions in the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) and ADHDRS-IV-Parent:Inv subscale scores. - to assess the safety and tolerability of once-daily dosing of atomoxetine in Russian children and adolescents.	
Study Design: Multicenter, randomized, double-blind placebo-controlled outpatient study. The study was comprised of 3 study periods and included an initial randomization of all subjects to acute treatment after an initial screening and washout period (Study period I). Randomization was performed with 2:1 proportions of subjects being assigned to atomoxetine and placebo. During the acute treatment phase (Study Period II), study drug dosage was adjusted by the physician based on assessment of symptom response and tolerability. Following Study Period II, subjects entered a discontinuation phase comprised of 1 follow up visit (Study Period III).	
Number of [Patients/Subjects]:	
Planned: 105	
Randomized/Entered:	72 Atomoxetine Hydrochloride: 63 Male, 9 Female; 33 Placebo: 27 Male, 6 Female.
Completed:	67 Atomoxetine Hydrochloride: 58 Male, 9 Female; 32 Placebo: 26 Male, 6 Female.
Diagnosis: Attention-Deficit/Hyperactivity Disorder [ADHD] that met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV™);	
Main Criteria for Inclusion: Aged 6 to 16 years. Diagnosis assessed by the investigator's clinical evaluation as well as administration of several modules of the K-SADS: PL structured interview, had a total ADHDRS-IV-Parent: Inv score of at least 25 for boys or 22 for girls, or greater than 12 for their diagnostic subtype at both Visit 1 and Visit 2. In addition, they had a CGI-ADHD-S score ≥4 at both Visit 1 and 2.	
Test Product, Dose, and Mode of Administration:	
Atomoxetine Hydrochloride (LY139603) 0.8–1.8 mg/kg/day, maximum total daily dose 100 mg, given in the morning once daily as: 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, or 40 mg capsules.	

Reference Therapy, Dose, and Mode of Administration:

Placebo 0.8–1.8 mg/kg/day, maximum total daily dose 100 mg, given in the morning once daily as: 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, or 40 mg capsules.

Duration of Treatment: Atomoxetine Hydrochloride Frequency: 6 weeks

Placebo Frequency: 6 weeks

Variables:

Efficacy:

Primary Efficacy Measure:

- Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv).

Secondary Efficacy Measures:

- Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S),
- Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S).

Safety: vital signs evaluation, assessments of adverse events collected by discussion, routine laboratory tests, blood sampling, and ECGs.

Evaluation Methods:

Statistical

Efficacy Analysis

Study Period II

Changes in ADHDRS-IV-Parent: Inv total score were determined using an analysis of covariance (ANCOVA) using the last-observation-carried-forward (LOCF) approach to calculating endpoint scores, with terms for baseline score, treatment and investigator. Secondary analyses of changes in the ADHDRS-IV-Parent: Inv total scores included an analysis of variance (ANOVA) (excluding the baseline term from the primary analysis ANCOVA). Analyses of ranked change scores and analyses incorporating other potential covariates such as age and gender were also considered. In addition, the analysis of changes from baseline in the ADHDRS-IV-Parent: Inv total scores was done using a repeated-measures model with visit, treatment, investigator, visit by treatment interaction, and investigator by treatment interaction included in the model.

Secondary efficacy variables, including the ADHDRS-IV-Parent:Inv subscale scores, CGI-ADHD-S and CPRS-R:S were analyzed in a similar fashion as the ADHDRS-IV-Parent:Inv total score.

Treatment differences in binary efficacy measures, such as the percentage of responders (>25% reduction in ADHDRS-IV-Parent:Inv total score), were assessed using the Cochran-Mantel-Haenszel test, stratified by site. Percentages of responders were computed using all randomized subjects with a baseline and at least 1 post-baseline measurement.

Time to onset of sustained response was subjected to Cox's proportional hazards regression model; the validity of the proportional hazards model assumption was tested. The influence of the pre-defined age stratification factor was investigated.

Study Period III

Changes in the ADHDRS-IV-Parent:Inv total and subscale scores, CGI-ADHD-S, CPRS-R:S from Visit 6 (end of Study Period II) to Visit 7 (end of study) were assessed. Because of the sparseness of data expected during this study period due to subjects either discontinuing early or continuing into another atomoxetine study, no treatment comparisons were planned during this period.

Safety Analysis

Study Period II

- Adverse events registered from Visit 3 through Visit 6 were summarized as treatment emergent signs and symptoms (TESS) and were presented by body systems according to the COSTART dictionary. In addition TESS were grouped by intensity and relationship to study drug. TESS were compared across treatment groups using Fisher's exact test for multiple comparing of two-sample binary data.
- Out of range laboratory values were presented by treatment groups. Treatment differences in treatment-emergent out-of-range laboratory values were assessed in a similar fashion as treatment-emergent adverse events.
- Changes from baseline to endpoint for vital signs were computed. Treatment differences were assessed using ANOVA. Within group changes were assessed with paired t-tests or the Wilcoxon signed-rank test.

Study Period III

Summary statistics for safety variables in Study Period III were summarized in a fashion similar to that described above for Study Period II.

Results:

Demographics

All patients enrolled were white/Caucasians, age ranging from 5 to 16 years. Ninety patients (85.7%) were males, 15 patients (14.3%) were females. The two treatment groups did not differ with respect to demographic characteristics. Seventy-four of patients (70.5%) were between 7 and 12 years of age, 20 patients (19.0) were 13 years or older, and 11 children (10.5%) were preschool age.

Table 1 shows the distribution of the patients according to sex and Table 2 shows the distribution of the patients according to age.

Table 1. Demographic Characteristics: Sex

Sex	Active		Placebo		All Patients	
	n	%	n	%	n	%
Female	9	12.5	6	18.2	15	14.3
Male	63	87.5	27	81.8	90	85.7
Fisher's exact p-value: 0.549						

Table 2. Demographic Characteristics: Age

Age	Active		Placebo		Total Patients	
	n	%	n	%	n	%
Preschool age	8	11.1	3	9.1	11	10.5
Junior pupils (7-12)	49	68.1	25	75.8	74	70.5
Adolescents (13+)	15	20.8	5	15.2	20	19.0
Total Patients	72	100.0	33	100.0	105	100.0

Patient Disposition

A total of 105 patients had given written Informed Consent and were randomly assigned to atomoxetine or placebo treatment groups in a 2:1 manner respectively. Ninety nine patients out of 105 (94.3%) completed the protocol in both treatment arms: 67/72 patients (93.1%) assigned to atomoxetine group and 32/33 (97.0%) assigned to placebo treatment. Six patients discontinued from the study. Table 3 provides the list of reasons for patient discontinuation during Study Period II.

Table 3. Patient Disposition for Study Period II

Reason	Active		Placebo		Total Patients	
	n	%	n	%	n	%
Adverse Event	1	1.4	0	0	1	1.0
Personal Conflict or Other Patient/Caregiver Decision	4	5.6	1	3.0	5	4.8
Study Period II Complete	67	93.1	32	97.0	99	94.3
Total Patients	72	100.0	33	100.0	105	100.0

Fisher's exact p-value: >0.999

Primary Outcomes

The change from baseline in total score of the ADHD-DSM-IV scale served as primary outcome measure (Table 4). Statistically significant improvement in the severity of ADHD symptoms was observed in both groups of patients, however the atomoxetine treated patients showed greater improvement than patients of placebo arm compared to baseline (differences between the atomoxetine and placebo group was statistically significant, $p=0.013$).

As is shown in Table 4, mean change from baseline in ADHD Rating Scale - IV: Parent Version - Investigator Scored: Total Score was -15.8 and -11.4 for atomoxetine and placebo treatment groups respectively, resulting in a difference of -4.3 (95% CI, -7.7 to -0.9). Effects of the center and the total score at the baseline in the ANCOVA analysis model were statistically significant as well ($p < 0.001$).

Table 4. Mean Change of ADHD-DSM-IV Scale in Children and Adolescents with the ADHD in the Atomoxetine and Placebo Groups (LOCF)

Variable	Treatment	LS Mean	SE	95% Confidence Limits		LS Mean Difference	95% Confidence Limits		p-values
				Lower	Upper		Lower	Upper	
Hyperactivity-impulsivity subscale score	Atomoxetine	-7.6	0.5	-8.6	-6.6	-2.8	-4.6	-1.1	0.002
	Placebo	-4.8	0.7	-6.2	-3.3				
Inattention subscale score	Atomoxetine	-8.7	0.5	-9.8	-7.6	-2.1	-4.1	-0.2	0.030
	Placebo	-6.5	0.8	-8.1	-5.0				
Total score	Atomoxetine	-15.8	0.9	-17.6	-13.9	-4.3	-7.7	-0.9	0.013
	Placebo	-11.4	1.4	-14.2	-8.7				

Abbreviations: LS = least squares; SE = standard error.

Secondary Efficacy Outcomes

Statistically significantly more patients, 52 patients (72.2%), in the atomoxetine treatment group had more than a 25% improvement in their ADHDRS-IV-Parent:Inv Total Score by the end of Study Period II, which was 23.7% (95% CI, 3.8% to 43.7%) better than in the placebo treatment group (16 patients, 48.5%, $p = 0.022$).

ADHD subtypes and treatment-outcome

An exploratory binary logistic analysis was undertaken to investigate factors influencing the response. Gender, age and ADHD subtypes were used as covariates.

The factors influencing response rate were treatment group ($p=0.012$) and ADHD subtype ($p=0.005$). The adjusted odds of response for the atomoxetine treatment group were 3.2 times higher (95% CI, 1.3 to 8.1) than odds for the placebo treatment group. The adjusted odds of response for combined ADHD subtype patients were 5.4 times higher (95% CI, = 1.9 to 14.9) than odds for inattentive ADHD subtype patients. The response rates of hyperactive and inattentive ADHD subtype patients as well as the response rates of combined and hyperactive ADHD subtype patients were not statistically significantly different.

The effect size of atomoxetine was 0.6 as measured by change from baseline in ADHDRS-IV-Parent:Inv (LOCF).

Changes in CGI-S

Changes in the ADHD **CGI-S** showed results similar to the data assessed by ADHD Rating Scale.

Atomoxetine treated children showed a statistically significantly greater reduction in CGI-ADHD-S score compared to placebo [(-1.5 (95% CI -1.7 to -1.3) and -1.1 (95% CI -1.4 to -0.7), $p=0.035$, LOCF].

Outcomes Assessed by Parents: Conner's Parent Rating Scale Short Form (CPRS-R:S)

An ANCOVA analysis was used to estimate the difference between atomoxetine and placebo treatment. The mean changes (SE) of CPRS-R:S from baseline-to-endpoint: -5.1 (0.4) and -3.2 (0.6) in the atomoxetine group and placebo group respectively were statistically significant on the hyperactivity subscale score ($p = 0.014$). Changes in the

CPRS-R:S index subscale score : -10.7 (0.8) and -7.5 (1.2) respectively were statistically significant (p=0.028).

There was no statistically significant difference between groups as measured by the Cognitive problems subscale of CPRS-R:S [-4.8 (0.4) and -3.3 (0.6), p=0.065]. There was no difference measured by the oppositional subscale of CPRS-R:S [-1.3(0.4) and -0.6 (0.6) respectively, p=0.326].

Safety

The mean exposure to treatment with atomoxetine was 41.6±8.0 days. The mean exposure to treatment with placebo was 43.5±6.8 days. The difference between the treatment groups in study drug exposure was not statistically significant.

Forty-four out of 105 patients (41.9%) presented treatment emergent adverse events (TESS): 33/72 (45.8%) in the atomoxetine treatment group and 11/33 (33.3%) in the placebo treatment group. The most frequent TESS were anorexia (13 /72 [18.1%] in the atomoxetine group and 2/33 [6.1%] in the placebo group), somnolence (11/72 [15.3%] and 3/33 [9.1%], respectively) and nausea (8/72 [11.1%] and 1/33 [3.0%], respectively) (Table 5). No statistically significant difference in the number of patients who had TESS was noted between the two groups.

Table 5. Number (%) of Patients with Treatment Emergent Signs and Symptoms

				Treatment Groups				p-value
		Total Patients Number		Atomoxetine		Placebo		
Body System	COSTART Class Term	n	%	n	%	n	%	
BODY AS WHOLE	Patients with at least one TESS	26	24.8	19	26.4	7	21.2	0.934
	ABDOMINAL PAIN	10	9.5	9	12.5	1	3.0	
	ALLERGIC REACTION	1	1.0	1	1.4	0	0.0	
	ASTHENIA	3	2.9	3	4.2	0	0.0	
	FLU SYNDROME	2	1.9	0	0.0	2	6.1	
	HEADACHE	7	6.7	5	6.9	2	6.1	
	INFECTION	5	4.8	3	4.2	2	6.1	
	PAIN	1	1.0	1	1.4	0	0.0	
(continued)								

Table 5. Number (%) of Patients with Treatment Emergent Signs and Symptoms (continued)

Body System	COSTART Class Term	Total Patients Number		Treatment Groups				p-value
				Atomoxetine		Placebo		
		n	%	n	%	n	%	
	Patients with at least one TESS	1	1.0	0	0.0	1	3.0	
CARDIOVASCULAR								0.748
	SYNCOPE	1	1.0	0	0.0	1	3.0	

Table 5. Number (%) of Patients with Treatment Emergent Signs and Symptoms (concluded)

		Treatment Groups						p-value
		Total Patients Number		Atomoxetine		Placebo		
Body System	COSTART Class Term	n	%	n	%	n	%	
SKIN AND APPENDAGES	Patients with at least one TESS	2	1.9	2	2.8	0	0.0	> 0.999
	PRURITUS	2	1.9	2	2.8	0	0.0	
	RASH	2	1.9	2	2.8	0	0.0	
SPECIAL SENSES	Patients with at least one TESS	3	2.9	3	4.2	0	0.0	0.919
	CONJUNCTIVITIS	1	1.0	1	1.4	0	0.0	
	MYDRIASIS	1	1.0	1	1.4	0	0.0	
	TASTE PERVERSION	1	1.0	1	1.4	0	0.0	

Table 6 lists a summary of patients who had TESS possibly related to study drug.

Table 6. Treatment Emergent Signs and Symptoms Possibly Related to Study Drug

Was TESS Possibly Related to Study Drug?	Atomoxetine		Placebo		All Patients	
	n	%	n	%	n	%
No	47	65.3	27	81.8	74	70.5
Yes	25	34.7	6	18.2	31	29.5

Fisher's exact p-value: 0.108

Analysis of Adverse Events (Study Period II)

Eighty-five mild TESS, 25 moderate, and 4 severe TESS were reported during the study in both treatment groups (Table 7).

Table 7. TESS Severity (Study Period II)

Severity	Atomoxetine		Placebo		All Patients	
	n	%	n	%	n	%
Mild	68	72.3	17	85.0	85	74.6
Moderate	23	24.5	2	10.0	25	21.9
Severe	3	3.2	1	5.0	4	3.5

Clinically significant weight change (defined as 7% or more) was observed in 11 patients during Study Period II. Among them, a clinically significant weight loss was experienced by 7 (9.7%) patients in the atomoxetine treatment group and by 2 (6.1%) patients in the placebo group.

No adverse events were reported during Study Period III.

No SAEs were reported during the study and there were no deaths reported during the study.

Summary ID# 9496

Clinical Study Summary: Study B4Z-SB-LYDD

An Open-label Study on Effectiveness and Tolerability of Atomoxetine as Perceived by Patients, Parents, and Physicians in Children with Attention-Deficit/Hyperactivity Disorder in Germany

Date summary approved by Lilly: 08 February 2007

Brief Summary of Results

The primary objective of this study was to compare the perception of general effectiveness and tolerability of atomoxetine between children with Attention-Deficit/Hyperactivity Disorder (ADHD), their parents/primary caregivers, and their physicians, as measured by the newly devised Global Impression of Perceived Difficulties (GIPD) instrument.

The Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHDRS-IV-Parent:Inv) Scale and Clinical Global Impression (CGI) Scales were also used to assess the baseline severity of ADHD and to evaluate the effectiveness of atomoxetine. The effect of atomoxetine on evening and morning behavior was assessed with the Weekly Ratings of Evening and Morning Behavior - Revised - Investigator Rated (WREMB-R-Inv) evening and morning scores, and Items 1 (morning) and 4 (evening) of the newly devised GIPD instrument. The O'Brien Sleep Questionnaire (OBSQ) was used to assess sleep quality.

The results of this open-label study (Screening and Washout [Study Period I], 8-week Treatment Period [Study Period II], followed by a 16-week Extension Period [Study Period III]) were as follows:

- Patients gave the lowest ratings for ADHD-related difficulties, parents higher ratings, and physicians the highest ratings. The mean baseline ratings for the GIPD total score differed statistically significantly as shown by non-overlapping 95% confidence intervals (CIs): patients

13.4±5.8 (95% CI: 12.6;14.1); parents 19.4±5.9 (95% CI: 18.7;20.1); physicians 21.1±5.7 (95% CI: 20.4;21.8).

- The mean scores per rater group for the GIPD total score decreased statistically significantly from baseline to Week 8, and decreases were maintained at Week 24. This improvement was smallest for the patients' rating, greater for the parents' rating, and greatest for the physicians' rating. The mean decrease from baseline to Week 8 for the physician-rated score of -6.5±7.9 (95% CI: -7.4;-5.5) was statistically significantly greater than the corresponding mean change for the patient-rated score of -2.8±6.5 (95% CI: -3.6;-2.0) and the mean change for the parent-rated score of -4.6±7.6 (95% CI: -5.6;-3.7).
- There was a higher degree of agreement between the mean parent- and physician-rated scores than between the mean patient- and parent- or patient- and physician-rated scores (Cohen's kappa [95% CI]: parent-physician 0.50 [0.44;0.57]; patient-parent 0.12 [0.07;0.17]; patient-physician 0.11 [0.08;0.15]).
- All effectiveness scores used, including the ADHDRS-IV-Parent:Inv, CGI-S-ADHD, and WREMB-R-Inv scores, improved consistently and statistically significantly (non-overlapping 95% CIs) from baseline to Week 8. Improvements were maintained at Week 24.
- Evening and morning behavior of ADHD patients both improved consistently during the study, as shown by statistically significant decreases (non-overlapping 95% CIs) in the mean WREMB-R-Inv evening (e.g., from 14.7±5.1 to 8.5±6.0 at Week 8) and morning subscores (e.g., from 4.5±2.5 to 2.5±2.4 at Week 8). All changes from baseline to Week 24 were also statistically significant. Corresponding statistically significant decreases (non-overlapping 95% CIs) were found for the ADHD-related morning and evening difficulties (GIPD Items 1 and 4) at Week 8 and Week 24 as perceived by patients, parents, and physicians.
- For 21 of 23 different sleep-related items assessed in the OBSQ, the proportion of patients affected by the problem decreased from baseline to Week 8.
- No patients died during the study, and no serious adverse events were rated as possibly related to study drug. Adverse events possibly related to study drug were reported in 47.7% of patients overall, with fatigue (19.8%), nausea (13.4%), headache (8.0%), upper abdominal pain (7.3%), decreased appetite (5.7%), and anorexia (5.3%) reported most frequently. Treatment-emergent adverse events led to atomoxetine discontinuation in 12 (4.6%) patients.

Title of Study: An Open-label Study on Effectiveness and Tolerability of Atomoxetine as Perceived by Patients, Parents, and Physicians in Children with Attention-Deficit/Hyperactivity Disorder in Germany	
Investigator(s): This multicenter study included 58 principal investigators (1 investigator recruited patients at 2 different sites).	
Study Center(s): This study was conducted at 59 study centers in one country.	
Length of Study: 1 year and 4 months Date first patient entered: 28 October 2004 Date first patient enrolled: 02 November 2004 Date last patient completed: 24 February 2006	Phase of Development: 3
Objectives: The primary objective of this study was to compare the perception of general effectiveness and tolerability of atomoxetine between children with ADHD, their parents/primary caregivers, and their physicians, based on scores on the newly devised GIPD Scale at baseline, Week 8, and Week 24. Secondary objectives : – To assess differences in the perception of ADHD severity (ADHD-related difficulties as assessed by the GIPD Scale) between rater groups at baseline and over the course of atomoxetine treatment. – To assess the effectiveness of atomoxetine in the treatment of children as measured by the ADHDRS-IV-Parent:Inv. – To assess the effectiveness of atomoxetine in the treatment of children as measured by the Clinical Global Impression-Severity-ADHD (CGI-S-ADHD) and Clinical Global Impression-Improvement-ADHD (CGI-I-ADHD). – To assess the effect of atomoxetine on evening and morning behavior of children as measured by the WREMB-R-Inv. – To assess sleep characteristics of children treated with atomoxetine as measured by the OBSQ. – To assess the tolerability of atomoxetine in the treatment of children as assessed by treatment-emergent adverse events (TEAEs) elicited by open-ended questioning. – To assess solicited tolerability parameters as rated by the patients, their parents/primary caregivers and physicians, measured by the Pediatric Adverse Events Rating Scale (PAERS). – To assess parameters reflecting attitudes towards ADHD and representing common clinical practice in Germany (e.g., pretreatment, concomitant treatment, treatment by pediatricians or child and adolescent psychiatrists, family setting) and their impact on effectiveness and tolerability of atomoxetine (not included in Statistical Analysis Plan, to be reported separately). – To assess specific safety and sleep parameters as measured by the PAERS and the OBSQ in subgroups (i.e., type of pretreatment) of patients at screening (not included in Statistical Analysis Plan, to be reported separately). – To evaluate effectiveness and tolerability of atomoxetine in the treatment of children and adolescents (accomplished by a pooled analysis of data from the studies B4Z-SB-LYDD [children] and B4Z-SB-LYDE [adolescents; CT#7233]).	
Study Design: Single-arm, open-label, phase 3, multicenter study to evaluate the effectiveness and tolerability of atomoxetine (once daily, target dose 1.2 mg/kg/day), as perceived by patients, parents, and physicians, and its impact on quality of sleep in children with ADHD treated as outpatients in Germany (aged 6–11 years). After an initial Screening and Washout Period (Study Period I), there was an 8-week Treatment Period (Study Period II), followed by a 16-week Extension Period (Study Period III). At the end of Study Period II, the physician decided whether the patient was to be continued into Study Period III.	
Number of Patients: Planned: 257 Screened: 265 Enrolled: 262 Completed: 149	

Diagnosis and Main Criteria for Inclusion: ADHD according to the <i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition™</i> (DSM-IV™) criteria, confirmed by the German instrument “Diagnose-Checkliste Hyperkinetische Störungen” (Diagnostic checklist for hyperkinetic disorders) routinely used for ADHD diagnosis in Germany. Patients had to be children aged between 6 and 11 years. They had to be of normal intelligence (likely to achieve an IQ test score of ≥ 70). Patients were to be excluded if they had any significantly abnormal laboratory findings, any acute or unstable medical conditions, cardiovascular diseases, history of seizure disorder, bipolar disorder, psychosis or pervasive developmental disorder, any medical condition that would markedly increase sympathetic nervous system activity, or were likely to need psychotropic medication other than the study drug.
Test Product, Dose, and Mode of Administration: Atomoxetine capsules. Recommended dosing according to German Summary of Product Characteristics (SmPC): initial dose approx. 0.5 mg/kg/day for 7 days, titrated to a target of approx. 1.2 mg/kg/day for the remainder of Study Period II. During Study Period II, dose reductions to a minimum of 0.5 mg/kg were allowed for safety reasons only. During Study Period III, the investigator was allowed to titrate the dose between 0.5 and 1.2 mg/kg/day according to clinical effectiveness and tolerability.
Duration of Treatment: An 8-week treatment period (Study Period II) was followed by a 16-week Extension Period (Study Period III).
Variables: <u>Effectiveness:</u> Primary - comparison of the perception of general effectiveness and tolerability (ADHD-related difficulties) of atomoxetine between patients, parents, and their physicians at baseline, and after 8 and 24 weeks of treatment based on the GIPD Scale completed by all rater groups at each visit. Secondary - application of the ADHDRS-IV-Parent:Inv Scale, CGI-S-ADHD Scale, CGI-I-ADHD Scale, WREMB-R-Inv Scale, and the OBSQ to observe effectiveness, compare ratings, and assess sleep quality. <u>Safety:</u> Standard adverse event reporting, laboratory safety investigations, and application of the Pediatric Adverse Events Rating Scale (PAERS).
Evaluation Methods: <u>Statistical:</u> Analyses of effectiveness parameters were based on the full analysis set. Different imputation rules for missing values were applied, including “last observation carried forward” (LOCF) and “observed cases” (OC) approaches. For all instruments used, the scores at each visit and the respective changes from baseline were presented using descriptive statistics. In addition, exploratory 95% confidence intervals (CIs) were calculated. For the primary analysis, the agreement between patient, parent, and physician GIPD ratings was assessed using Cohen’s kappa. Subgroup analyses by gender and by type of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis were provided.

Results:

Patient Demographics

Of the 262 patients enrolled, 213 (81.3%) patients were boys and 49 (18.7%) were girls. Table 1 shows the DSM-IV diagnostic subtypes of ADHD by gender.

**Table 1. Diagnostic Subtypes According to DSM-IV by Gender
Full Analysis Set**

DSM-IV ADHD diagnosis	Number (%) of patients					
	Female N=49 (100%)		Male N=213 (100%)		Total N=262 (100%)	
Combined type	26	(53.1)	171	(80.3)	197	(75.2)
Predominantly inattentive type	18	(36.7)	33	(15.5)	51	(19.5)
Predominantly hyperactive-impulsive type	2	(4.1)	4	(1.9)	6	(2.3)
ADHD not otherwise specified	3	(6.1)	5	(2.3)	8	(3.1)

Abbreviations: ADHD=Attention-Deficit/Hyperactivity Disorder; DSM-IV=*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*TM; N = total number of patients.

Combined type ADHD was the most frequent DSM-IV diagnosis (197, 75.2%), followed by predominantly inattentive type ADHD (51, 19.5%). There were very small numbers (6 [2.3%] and 8 [3.1%], respectively) of predominantly hyperactive-impulsive type patients and patients in whom the ADHD subtype was not otherwise specified (not further reported). The proportion of combined type ADHD patients was 80.3% in boys (171/213) and 53.1% in girls (26/49). The proportion of predominantly inattentive type ADHD patients was 36.7% in girls (18/49) and 15.5% in boys (33/213).

The patients' mean age ($\pm$ SD) at baseline was 9.3 $\pm$ 1.5 years. Symptoms of ADHD first occurred at a mean age of 3.8 $\pm$ 1.9 years, and ADHD was first diagnosed at a mean age of 7.1 $\pm$ 1.8 years. A mean interval of 3.2 $\pm$ 1.9 years had elapsed between the first occurrence of ADHD symptoms and the first diagnosis of ADHD. Details on age characteristics by gender and DSM-IV diagnostic subtypes can be found in Table 2 and Table 3, respectively.

Table 2. Age of Patients at Baseline, First Occurrence of ADHD Symptoms and First Diagnosis of ADHD, and Time Difference between First Occurrence and Diagnosis by Gender, Full Analysis Set

Variable (years)	Female N=49	Male N=213	Total N=262
Age at baseline			
Median	10.0	9.5	9.5
Mean ± standard deviation	9.7±1.6	9.3±1.4	9.3±1.5
95% confidence interval	[9.2;10.1]	[9.1;9.5]	[9.2;9.5]
Age at first occurrence			
Median	3.6	4.0	4.0
Mean ± standard deviation	3.8 ± 2.2	3.9 ± 1.8	3.8 ± 1.9
95% confidence interval	[3.2;4.4]	[3.6;4.1]	[3.6;4.1]
Age at first diagnosis			
Median	7.4	7.0	7.2
Mean ± standard deviation	7.6 ± 1.6	6.9 ± 1.9	7.1 ± 1.8
95% confidence interval	[7.1;8.0]	[6.7;7.2]	[6.8;7.3]
Time difference			
Median	3.8	3.0	3.0
Mean ± standard deviation	3.8 ± 2.2	3.1 ± 1.9	3.2 ± 1.9
95% confidence interval	[3.1;4.4]	[2.8;3.3]	[3.0;3.5]

Abbreviations: ADHD=Attention-Deficit/Hyperactivity Disorder; N = total number of patients.

Table 3. Age of Patients at Baseline, First Occurrence of ADHD Symptoms and First Diagnosis of ADHD, and Time Difference between First Occurrence and Diagnosis by DSM-IV Diagnosis, Full Analysis Set

Variable (years)	Combined type ADHD N=197	Predominantly inattentive type ADHD N=51
Age at baseline		
Median	9.3	9.9
Mean ± standard deviation	9.2 ± 1.5	9.8 ± 1.2
95% confidence interval	[9.0;9.4]	[9.5;10.2]
Age at first occurrence		
Median	3.7	5.0
Mean ± standard deviation	3.6 ± 1.8	4.9 ± 1.8
95% confidence interval	[3.3;3.8]	[4.4;5.4]
Age at first diagnosis		
Median	6.9	7.9
Mean ± standard deviation	6.8 ± 1.8	8.0 ± 1.5
95% confidence interval	[6.5;7.0]	[7.6;8.5]
Time difference		
Median	3.0	3.0
Mean ± standard deviation	3.2 ± 1.9	3.1 ± 1.9
95% confidence interval	[2.9;3.5]	[2.6;3.7]

Abbreviations: ADHD=Attention-Deficit/Hyperactivity Disorder; DSM-IV=*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*TM; N = total number of patients.

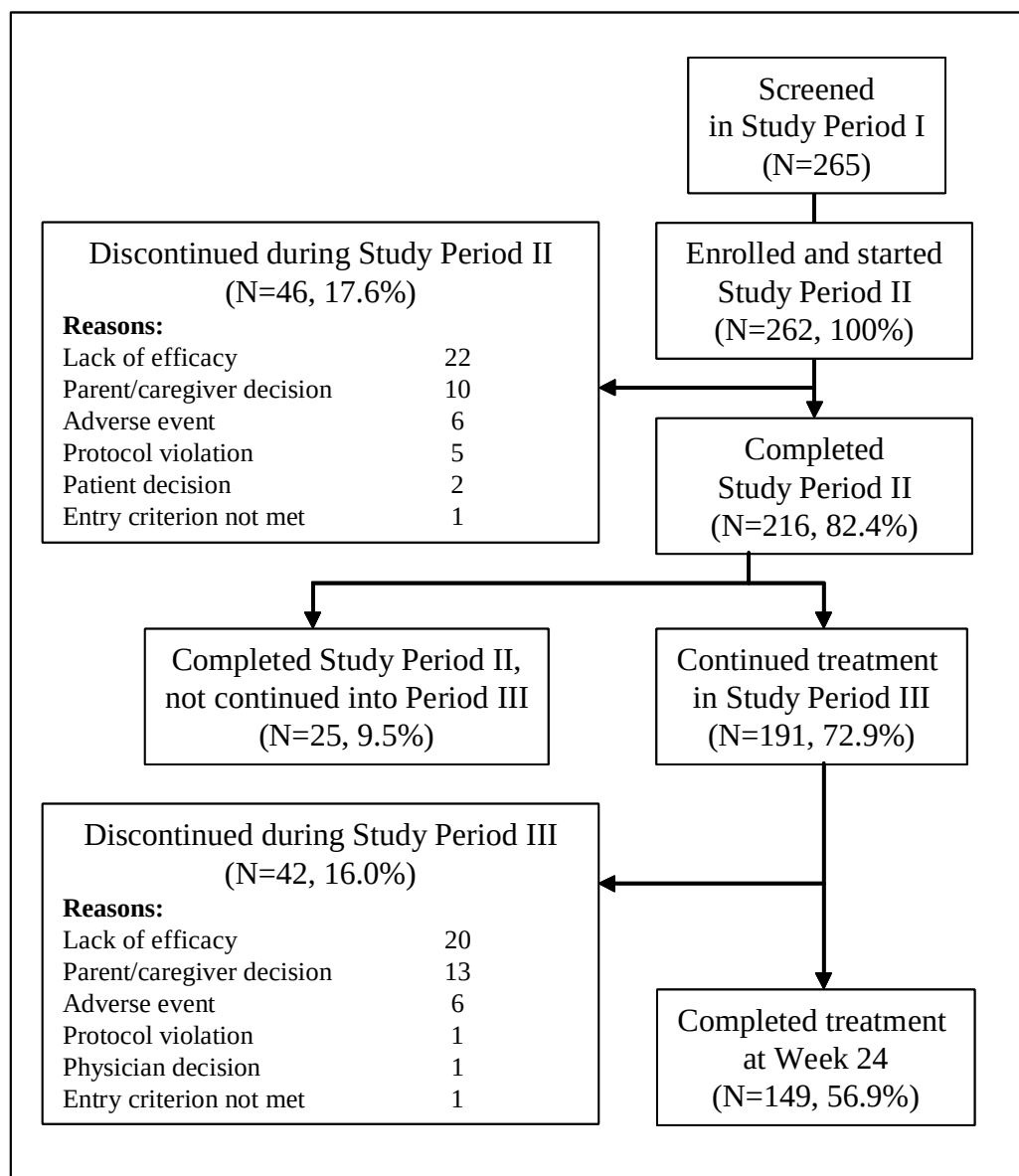
Overall, 212 (80.9%) patients had had previous treatment for ADHD (boys 173, 81.2%; girls 39, 79.6%). A total of 164 (83.2%) patients with combined type ADHD and 36 (70.6%) patients with predominantly inattentive type ADHD had been treated previously for ADHD.

Overall, 173 (66.0%) patients were given any concomitant therapy, most frequently pharmacological therapy. Concomitant medications used in more than 5% of all patients included paracetamol (37; 14.1%), ambroxol (32; 12.2%), xylometazoline (25; 9.5%), ibuprofen (23; 8.8%), acetylcysteine (14; 5.3%), and Hedera helix (14; 5.3%).

The mean daily prescribed dose of atomoxetine remained in the same range of 1.16 mg/kg/day after the first week of up-titration, up to the final prescription at Week 16 (for the last visit interval, i.e., Weeks 17–24). The mean final prescribed dose at Week 16 was 1.16 ± 0.19 mg/kg/day. A total of 18 (6.9%) patients were noncompliant with respect to medication at some time during the study.

Patient Disposition

Of the 262 patients enrolled, 191 (72.9%) patients continued into Study Period III and 149 (56.9%) completed treatment at Week 24. Figure 1 summarizes patient disposition, including the reasons for discontinuation.



Abbreviation: N = total number of patients.

Note: At the end of the Study Period II (Visit 7), it was decided whether the patient should continue into the Extension Period (Study Period III). This decision was at the investigator's discretion, based on the effectiveness and tolerability of treatment as well as parents' and patients' wishes.

Figure 1. Patient disposition and reasons for discontinuation.

For 25 (9.5%) patients who completed Study Period II, the physician decided they should not continue into Study Period III. In addition, 46 (17.6%) patients were withdrawn during Study Period II, 42 (16.0%) patients were withdrawn during Study Period III. The main reason for withdrawal was lack of efficacy, for 42 (16.0%) patients overall,

followed by patient/caregiver decision for 23 (8.8%), and treatment-emergent adverse events for 12 (4.6%) patients overall.

Primary Effectiveness Measure

The primary objective of this study was to compare the perception of general effectiveness and tolerability (ADHD-related difficulties) of atomoxetine between patients, their parents/primary caregivers, and their physicians. The GIPD Scale was used to assess ADHD-related difficulties, and was completed by all three rater groups. The degree of agreement between the mean scores was also assessed using Cohen's kappa. The primary assessment timepoints were baseline, Week 8, and Week 24.

Table 4 shows details of the GIPD Total Score, the GIPD Score Item 1 (ADHD-related difficulties in the morning), and GIPD Score Item 4 (ADHD-related difficulties in the evening).

**Table 4. GIPD Scores at Baseline, Week 8, and Week 24
Full Analysis Set (LOCF)**

Time-point	Patient			Parent ^a			Physician		
	N	Mean ± SD	95% CI	N	Mean ± SD	95% CI	N	Mean ± SD	95% CI
<i>GIPD Total Score (Sum of Items 1-5)</i>									
BL	259	13.4±5.8	12.6;14.1	257	19.4±5.9	18.7;20.1	259	21.1±5.7	20.4;21.8
Wk 8	260	10.5±5.8	9.8;11.3	253	14.9±6.9	14.0;15.7	261	14.8±7.2	13.9;15.6
Wk 24	260	10.6±5.8	9.9;11.3	255	15.6±7.3	14.7;16.5	261	16.0±7.6	15.1;16.9
<i>GIPD Score Item 1 (ADHD-related difficulties in the morning)</i>									
BL	260	2.5±1.6	2.3;2.7	261	3.6±1.7	3.4;3.8	261	3.9±1.6	3.7;4.0
Wk 8	261	1.9±1.3	1.7;2.1	254	2.6±1.6	2.4;2.8	261	2.5±1.6	2.3;2.7
Wk 24	261	1.9±1.4	1.7;2.1	256	2.7±1.7	2.5;2.9	261	2.8±1.7	2.6;3.0
<i>GIPD Score Item 4 (ADHD-related difficulties in the evening)</i>									
BL	260	2.6±1.8	2.4;2.8	261	4.0±1.6	3.8;4.2	261	4.3±1.4	4.2;4.5
Wk 8	261	1.9±1.3	1.8;2.1	254	2.8±1.6	2.6;3.0	261	2.9±1.6	2.7;3.1
Wk 24	261	1.9±1.4	1.8;2.1	256	3.0±1.7	2.7;3.2	261	3.1±1.8	2.9;3.3

^a LOCF-BR for parent-rated scores, i.e., LOCF for all ratings made by the same parent.

Abbreviations: ADHD=Attention-Deficit/Hyperactivity Disorder; BL=Baseline; CI=Confidence interval; GIPD=Global Impression of Perceived Difficulties; LOCF=Last observation carried forward; LOCF-BR=Last observation carried forward, baseline rater; N = total number of patients; SD=standard deviation; Wk=Week.

At baseline, the mean patient-rated total score (±SD) was the lowest at 13.4±5.8, the parent-rated score was intermediate at 19.4±5.9, and the physician-rated score was highest at 21.1±5.7. All three ratings for the total score differed statistically significantly at baseline (non-overlapping 95% CIs), but the parent- and physician-rated scores did not differ statistically significantly at Week 8 or Week 24. All scores improved statistically significantly up to Week 8; this improvement was maintained at Week 24 (Table 4).

Patients gave similar ratings for their ADHD-related difficulties in the morning and evening, whereas parents and physicians gave higher ratings for the evening problems than for the morning problems (Table 4). However, all 3 ratings improved statistically significantly from baseline to Week 8 (non-overlapping 95% CIs), and the improvement was maintained at Week 24.

Further, parents and physicians gave statistically significantly higher ratings for ADHD-related difficulties in combined type ADHD patients than in predominantly inattentive type ADHD patients (e.g., GIPD total score, physician-rated at baseline: combined type ADHD 22.4 ± 5.4 ; 95% CI [21.7;23.2]; predominantly inattentive type 17.3 ± 4.4 ; 95% CI [16.8;18.5]).

Analysis of agreement between rater groups for GIPD scores: The agreement was highest between parent- and physician-rated scores (kappa for agreement at baseline [95% CI]: 0.50 [0.44;0.57]) and low between patient- and parent- (0.12 [0.07;0.17]) and patient- and physician-rated (0.11 [0.08;0.15]) scores. Table 5 shows details of the degree of agreement between each rater group at baseline, Week 8, and Week 24 for the GIPD Total Score, GIPD Item 1 (Morning) Score, and GIPD Item 4 (Evening) Score.

Table 5. Agreement Between Each Rater Group at Baseline, Week 8 and Week 24 for GIPD Total Score, GIPD Item 1 (Morning) Score and GIPD Item 4 (Evening) Score, Weighted Kappa Statistics, Full Analysis Set

Timepoint	Kappa statistic, 95% Confidence interval								
	Patient–Parent			Patient–Physician			Parent–Physician		
	N	K ^a	95% CI	N	K ^a	95% CI	N	K ^a	95% CI
<i>GIPD Total Score</i>									
Baseline	256	0.12	0.07;0.17	257	0.11	0.08;0.15	256	0.50	0.44;0.57
Week 8	177	0.30	0.21;0.39	198	0.29	0.20;0.37	176	0.69	0.64;0.74
Week 24	138	0.19	0.11;0.27	148	0.24	0.17;0.31	139	0.66	0.59;0.73
<i>GIPD Score Item 1 (ADHD-related difficulties in the morning)</i>									
Baseline	260	0.14	0.07;0.21	260	0.13	0.06;0.19	261	0.56	0.49;0.62
Week 8	183	0.22	0.12;0.33	201	0.23	0.14;0.33	183	0.58	0.50;0.66
Week 24	142	0.13	0.03;0.23	149	0.24	0.14;0.33	142	0.62	0.52;0.71
<i>GIPD Score Item 4 (ADHD-related difficulties in the evening)</i>									
Baseline	260	0.16	0.09;0.22	260	0.14	0.09;0.20	261	0.50	0.41;0.55
Week 8	183	0.24	0.14;0.35	201	0.20	0.11;0.28	183	0.64	0.56;0.71
Week 24	142	0.12	0.02;0.22	149	0.20	0.10;0.31	142	0.63	0.55;0.72

^a K: weighted Kappa coefficient; analysis based on OC data for patient- and physician-ratings, and OC-BR for parents.

Abbreviations: ADHD=Attention-Deficit/Hyperactivity Disorder; CI=confidence interval; GIPD=Global Impression of Perceived Difficulties; N = total number of patients; OC=last observed value within a visit interval was taken for this visit interval; OC-BR=values not rated by the baseline rater were deleted and then the last value from the baseline rater within a visit interval was chosen, if present, otherwise the value was dropped.

Changes in GIPD scores over time: Changes in GIPD scores over time are presented in Figures 2–4 (observed cases, vertical bars indicate 95% CIs). Mean GIPD total scores decreased statistically significantly (non-overlapping 95% CIs) in all three rater groups from baseline to Week 8. The smallest improvements were given by patients, greater improvements by parents, and the greatest improvement by physicians (LOCF/LOCF-baseline rater (BR), mean changes in GIPD total scores: patients, LOCF, -2.8 ± 6.5 ; parents, LOCF-BR, -4.6 ± 7.6 ; physicians, LOCF, -6.5 ± 7.9). The improvements were maintained at Week 24 (Figure 2). Morning and evening problems also decreased statistically significantly from baseline to Week 8 in all three rater groups. Again, this improvement was maintained at Week 24 (Figures 3 and 4).

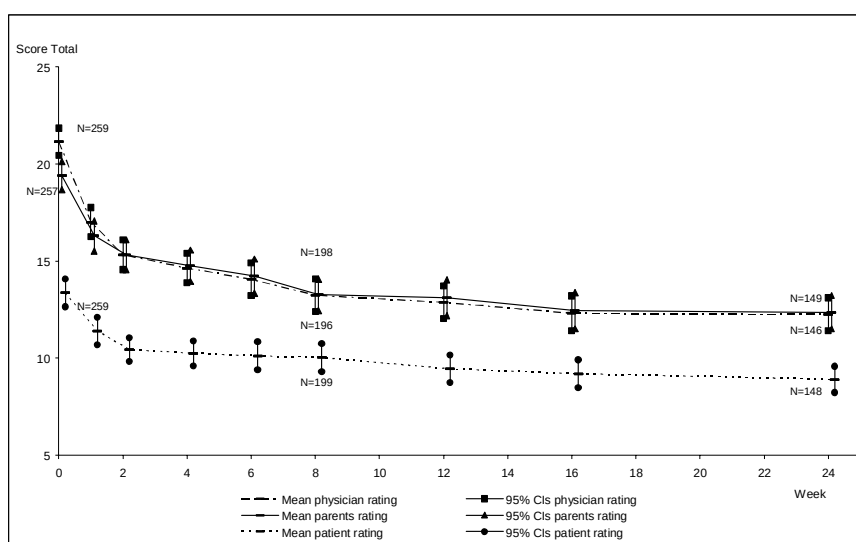


Figure 2. GIPD mean total scores over time for the full analysis set; OC analysis.

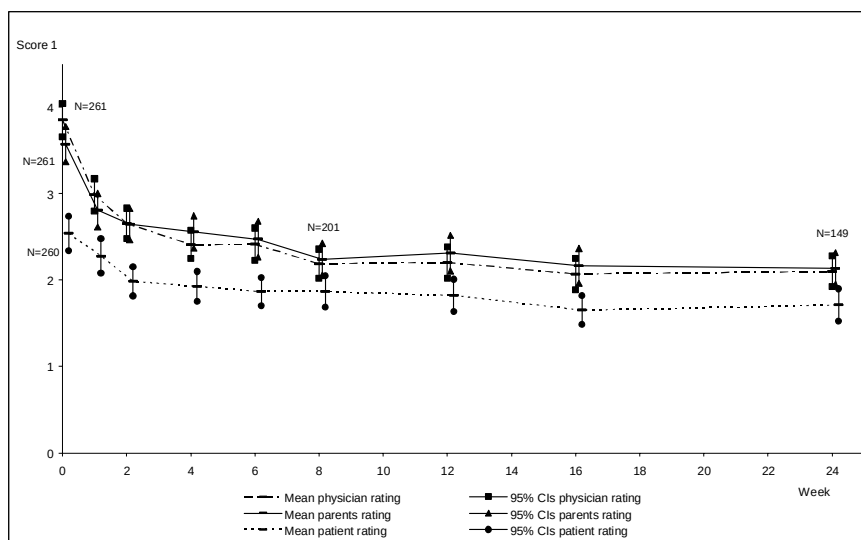


Figure 3. GIPD mean scores for Item 1 (morning) over time for the full analysis set; OC analysis.

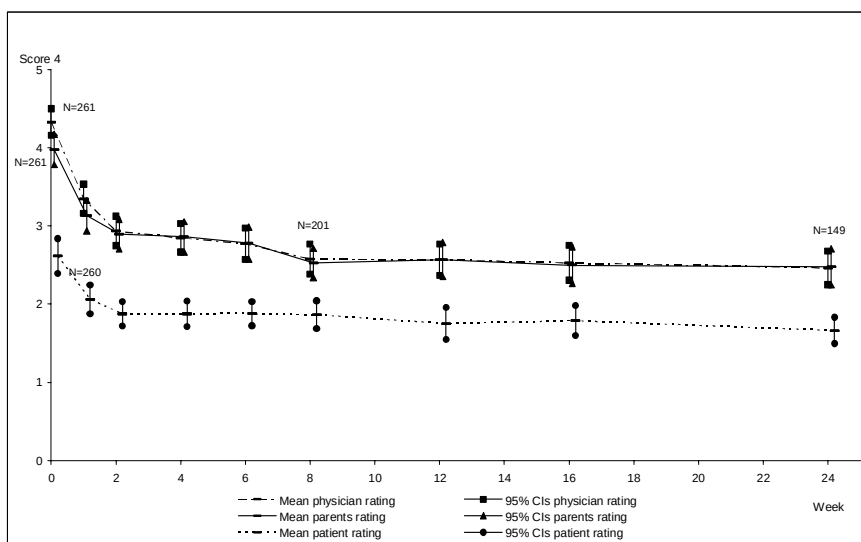


Figure 4. GIPD mean scores for Item 4 (evening) over time for the full analysis set; OC analysis.

Abbreviations in Figures 2–4: CI=confidence interval; GIPD=Global Impression of Perceived Difficulties; N= total number of patients; OC=observed cases, last observed value within a visit interval was taken for this visit interval.

Secondary Effectiveness Measures

The ADHDRS-IV-Parent:Inv, CGI-S-ADHD, and WREMB-R-Inv evening and morning scores all improved statistically significantly and consistently from baseline to Week 8 (non-overlapping 95% CIs, Table 6). The improvements were maintained at Week 24. On the CGI-S-ADHD Scale, the proportion of patients rated as at least “markedly ill” decreased from 218 (83.5%) at baseline to 96 (36.6%) at Week 8 and 115 (43.9%) at Week 24. In terms of CGI-I-ADHD, 126 (48.1%) patients were rated as “much or very much improved” at Week 8, compared with 112 (42.7%) at Week 24. With all instruments, combined type ADHD patients had higher ratings than predominantly inattentive type ADHD patients at baseline, Week 8 and Week 24, but statistically significant improvements from baseline to Week 8 were found in both subgroups (Table 6). In terms of CGI-I-ADHD, 47.7% of combined type and 52.9% of predominantly inattentive type ADHD patients were rated as “much or very much improved” at Week 8 (41.7% and 52.9% at Week 24).

Table 6. ADHDRS-IV-Parent:Inv, CGI-ADHD, and WREMB-R-Inv Scores at Baseline, Week 8 and 24 Full Analysis Set (LOCF)

Time-point	Total			ADHD subtype					
	N	Mean ± SD	95% CI	Combined			Predom. inattentive		
				N	Mean ± SD	95% CI	N	Mean ± SD	95% CI
ADHDRS-IV-Parent:Inv Score									
BL	260	35.2±10.6	33.9;36.4	196	38.2±9.3	36.9;39.5	51	26.0±8.2	23.7;28.3
Wk 8	261	21.5±13.1	19.9;23.1	197	23.8±13.2	22.0;25.7	50	14.5±9.8	11.7;17.3
Wk 24	261	22.8±13.9	21.1;24.5	197	25.3±13.8	23.3;27.2	50	13.8±10.1	10.9;16.7
CGI-S-ADHD Score									
BL	261	5.1±0.8	5.0;5.2	197	5.3±0.7	5.2;5.4	51	4.5±0.6	4.3;4.7
Wk 8	262	4.0±1.3	3.8;4.1	197	4.2±1.3	4.0;4.3	51	3.4±1.1	3.0;3.7
Wk 24	262	4.1±1.4	3.9;4.2	197	4.3±1.4	4.1;4.4	51	3.3±1.2	3.0;3.7
CGI-I-ADHD Score									
Wk 8	262	3.0±1.5	2.8;3.2	197	3.1±1.6	2.9;3.4	51	2.6±1.3	2.3;3.0
Wk 24	262	3.2±1.7	3.0;3.4	197	3.3±1.7	3.1;3.5	51	2.6±1.4	2.2;3.0
WREMB-R-Inv – Evening Score (8 items)									
BL	260	14.7±5.1	14.0;15.3	196	16.0±4.7	15.3;16.6	51	10.8±3.8	9.8;11.9
Wk 8	261	8.5±6.0	7.8;9.2	197	9.3±6.2	8.5;10.2	50	5.8±4.5	4.5;7.0
Wk 24	261	9.4±6.3	8.6;10.2	197	10.2±6.4	9.4;11.1	50	5.9±4.9	4.5;7.3
WREMB-R-Inv – Morning Score (3 items)									
BL	261	4.5±2.5	4.2;4.8	197	5.0±2.4	4.6;5.3	51	3.5±2.0	2.9;4.1
Wk 8	261	2.5±2.4	2.2;2.8	197	2.7±2.4	2.4;3.1	50	1.8±2.2	1.2;2.4
Wk 24	261	2.7±2.5	2.4;3.0	197	3.0±2.5	2.6;3.3	50	1.8±2.1	1.2;2.4

Abbreviations: ADHDRS-IV-Parent:Inv=Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored; BL=Baseline; CGI-I-ADHD=Clinical Global Impression – Improvement – Attention Deficit/Hyperactivity Disorder; CGI-S-ADHD=Clinical Global Impression – Severity – Attention Deficit/Hyperactivity Disorder; CI=confidence interval; LOCF=Last observation carried forward; N = total number of patients; Predom = predominately; SD=standard deviation; Wk=Week; WREMB-R-INV=Weekly Ratings of Evening and Morning Behavior-Revised.

The ADHDRS-IV-Parent:Inv mean score over time by gender is shown in Figure 5.

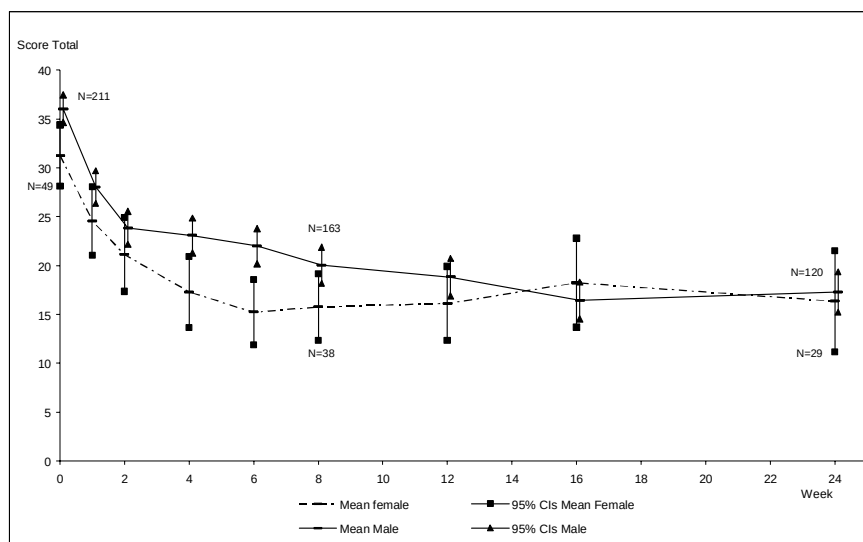


Figure 5. ADHDRS-IV-Parent:Inv mean score over time by gender for the full analysis set; OC analysis.

Note: Vertical bars indicate 95% confidence intervals.

Abbreviations: ADHDRS-IV-Parent:Inv=Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored; CI = confidence interval; N = total number of patients; OC=observed cases, last observed value within a visit interval was taken for this visit interval.

Quality of Sleep (OBSQ): For 21 of 23 different sleep-related items assessed in the OBSQ, the proportion of patients affected by the problem decreased from baseline to Week 8. For the sleep-related problems reported most frequently at baseline, the proportion of patients affected decreased as follows:

- Problems with going to bed willingly:
baseline, 57.6%; Week 8, 31.3%; Week 24, 35.9%;
- Problems with falling asleep easily:
baseline, 53.4%; Week 8, 32.1%; Week 24, 40.1%;
- Child complains of difficulties going to sleep:
baseline, 50.4%; Week 8, 20.2%; Week 24, 26.3%;
- Restless sleeper:
baseline, 45.4%; Week 8, 24.0%; Week 24, 27.5%;
- Patient is easy to wake up:
baseline, 44.7%; Week 8, 24.8%; Week 24, 20.6%.

Increases in the proportion of patients affected were observed for two problems: 'sleepiness during daytime' (baseline, 22.9%; Week 8, 27.5%; Week 24, 23.7%) and 'falls asleep watching television' (baseline, 4.6%; Week 8, 9.5%; Week 24, 8.0%).

Safety

Treatment-emergent adverse events (TEAEs) were reported in 207/262 (79.0%) patients and were considered as possibly related to study drug in 125/262 (47.7%) patients. Table 7 shows an overview of adverse events reported during the study. Serious adverse events were reported in 3 patients, none was rated as related to study drug (1 forearm fracture; 1 fall, abdominal injury, forearm fracture and head injury; 1 appendicitis). In 12 (4.6%) patients, adverse events led to discontinuation from the study (3 nausea, 2 aggression, 2 fatigue; 1 each for: headache, psychotic disorder, sleep disorder, upper abdominal pain, suicidal ideation).

Table 7. Overview of Adverse Events, Full Analysis Set

Type of adverse event	Number (%) of patients N=262 (100%)	
Deaths	0	(0)
Serious adverse events	3	(1.1)
Serious adverse events (possibly, probably, or definitely related to study drug as judged by the investigator)	0	(0)
Discontinuations due to an adverse event	12	(4.6)
Treatment-emergent adverse events (TEAEs)	207	(79.0)
Adverse reactions (TEAEs possibly, probably, or definitely related to study drug as judged by the investigator)	125	(47.7)

Abbreviation: N = total number of patients.

Table 8 presents the TEAEs reported in at least 5% of patients.

Table 8. Treatment-Emergent Adverse Events Occurring in ≥5% of Patients by Preferred Term, Full Analysis Set

Adverse Event	Number (%) of patients N=262 (100%)	
Fatigue	61	(23.3)
Headache	48	(18.3)
Nausea	47	(17.9)
Vomiting	31	(11.8)
Abdominal pain upper	30	(11.5)
Nasopharyngitis	20	(7.6)
Upper respiratory tract infection	20	(7.6)
Diarrhea	18	(6.9)
Cough	17	(6.5)
Decreased appetite	17	(6.5)
Abdominal pain	16	(6.1)
Anorexia	15	(5.7)
Rhinitis	15	(5.7)

Abbreviation: N = total number of patients.

The most common spontaneously reported TEAEs were fatigue (23.3%), headache (18.3%), nausea (17.9%), vomiting (11.8%), and upper abdominal pain (11.5%).

Table 9 shows the TEAEs considered at least as possibly related to study drug by the investigator, reported in at least 3% of patients.

Table 9. Treatment-Emergent Adverse Events Classified as Related To Study Drug Occurring in $\geq 3\%$ of Patients by Preferred Term, Full Analysis Set

Adverse Event	Number (%) of patients	
	N=262 (100%)	
Fatigue	52	(19.8)
Nausea	35	(13.4)
Headache	21	(8.0)
Abdominal pain, upper	19	(7.3)
Decreased appetite	15	(5.7)
Anorexia	14	(5.3)
Vomiting	12	(4.6)
Hypersomnia	11	(4.2)
Weight decreased	10	(3.8)
Abdominal pain	9	(3.4)

Abbreviation: N = total number of patients.

The most common TEAEs classified as related to study drug by the investigator were fatigue (19.8%), nausea (13.4%), headache (8.0%), upper abdominal pain (7.3%), decreased appetite (5.7%), and anorexia (5.3%).

Clinical laboratory measurements and changes in vital signs were unremarkable; there were no clinically relevant changes and their evaluation gave no cause for any safety concerns.

PAERS: The PAERS questionnaire assesses the frequency and severity of 48 solicited events frequently observed in pediatric patient populations under treatment with psychotropic medication. Because several items represent symptoms of ADHD, the patient-, physician-, and parent-rated PAERS total scores were high at baseline and decreased over time (e.g., mean total patient-rated score: Baseline, 20.6 ± 14.4 ; Week 8, 10.9 ± 10.3 ; Week 24, 11.3 ± 11.2).

Pooled Analysis of Studies B4Z-SB-LYDD and B4Z-SB-LYDE

Parallel to this study B4Z-SB-LYDD in children, a similarly designed study in adolescents (B4Z-SB-LYDE; CT#7233) was performed. The pooled dataset from Studies LYDD and LYDE comprised a sample of 421 patients aged 6–17 years. In the pooled sample, the mean patient-rated GIPD total score ($\pm$ SD) was the lowest at 13.1 ± 5.8 , the parent-rated score was intermediate at 18.6 ± 6.1 , and the physician-rated score was highest at 20.3 ± 5.9 . All 3 ratings differed statistically significantly at baseline

(non-overlapping 95% CIs), but the parent- and physician-rated scores did not differ statistically significantly at Week 8 and Week 24. The analysis of agreement by Cohen kappa statistics also showed that agreement was highest between parent- and physician-rated scores (Cohen's kappa for agreement at baseline [95% CI]: 0.52 [0.47;0.57]), and low between patient- and parent-rated scores (0.16 [0.12;0.21]) or between patient- and physician-rated scores (0.14 [0.11;0.18]). All effectiveness scores used, including the ADHDRS-IV-Parent:Inv, CGI-S-ADHD and WREMB-R-Inv scores, improved consistently and statistically significantly from baseline to Week 8. Improvements were maintained at Week 24.

In the pooled sample, treatment-emergent adverse events were reported in 331/421 (76.3%) patients, which were considered as possibly related to study drug in 207/421 (49.2%) patients. The most common spontaneously reported adverse events were fatigue (25.2%, related 22.3%), headache (20.4%, related 8.6%), nausea (18.3%, related 13.5%), vomiting (12.4%, related 5.0%), and upper abdominal pain (10.0%, related 7.1%). Laboratory investigations and vital signs were clinically not relevant and gave no cause for concern.

Summary ID# 9586

Clinical Study Summary: Study H8V-FW-LTBD

An Exploratory Study, using Atomoxetine, on Central Nervous System (CNS) Biomarkers

Date summary approved by Lilly: 17 October 2006

Brief Summary of Results

The primary objective of this open-label, Phase 1 study was to collect cerebrospinal fluid (CSF) and blood samples from healthy subjects before and after atomoxetine treatment, for subsequent exploratory assessment of the effect of atomoxetine treatment on change from baseline in CSF protein profile.

- A total of 9 full (Day 1 and Day 18, via needle and catheter) and 2 partial (Day 1 and Day 18 needle) sets of CSF samples were collected from this study for subsequent exploratory assessment.
- The statistically significant changes observed in CSF catecholamine biomarkers [decreased 3,4-dihydroxyphenylglycol (DHPG) and increased norepinephrine (NE)] post- atomoxetine treatment indicate a pharmacological effect of atomoxetine treatment.
- Observations from this study suggest that sample collection technique is a potentially important variable in the design and interpretation of studies involving CSF analytes.
- The tolerability profile of atomoxetine in this study and the adverse event profile attributable to the study procedures appear to be comparable to previous experience.

- There were no deaths. The most common adverse events (classified as study-drug related) reported in this study were: headache, nausea, erectile dysfunction, paraesthesia, somnolence and dizziness.

Title of Study: An Exploratory Study, using Atomoxetine, on Central Nervous System (CNS) Biomarkers	
Investigator(s): This study had one principal investigator.	
Study Center(s): This study was conducted at one study center.	
Length of Study: 4 months Date of first patient visit: 20 September 2004 Date of last patient visit: 18 January 2005	Phase of Development: 1
Objectives: Primary objective: • To collect cerebrospinal fluid (CSF) and blood samples from healthy subjects before and after atomoxetine treatment, for subsequent exploratory assessment of the effect of atomoxetine treatment on change from baseline in CSF protein profile Secondary objectives: • To explore the effect of different collection techniques on CSF protein profile • To explore the effect of atomoxetine on potential biomarkers such as brain-derived neurotrophic factor (BDNF) in CSF • To explore the potential relationships between atomoxetine concentrations and protein profile changes • To evaluate, in an exploratory manner, markers of CSF blood contamination	
Study Design: This was an open-label single-period study.	
Number of Subjects: Planned: This study targeted to achieve the collection of 9 analysable sets of CSF samples (<u>i.e., CSF samples collected on Day 1 and Day 18</u>). Randomized/Entered: Of the 15 male subjects who entered the study, 12 were enrolled. Completed: Nine subjects completed the entire study.	
Main Criteria for Inclusion: Healthy adult male subjects aged between 21 and 45 years.	
Study Drug, Dose, and Mode of Administration: Atomoxetine 40 mg capsule: 40 mg Atomoxetine orally, once a day, for 3 consecutive days (Days 1 to 3) followed by 80 mg Atomoxetine, once a day, for the next 15 consecutive days (Days 4 to 18).	
Duration of Treatment: Atomoxetine was given once a day for 18 consecutive days.	
Variables: <u>Safety:</u> physical examination, vital signs, adverse events, and clinical laboratory evaluations. <u>Bioanalytical:</u> Sequential blood and CSF samples were collected for the analysis of plasma and CSF concentration of atomoxetine and metabolites. CSF samples were assayed for DHPG and NE concentrations.	
Evaluation Methods: <u>Bioanalytical:</u> Plasma and CSF concentrations of atomoxetine and metabolites were measured using validated liquid chromatography/atmospheric pressure chemical ionisation/mass spectrometry/mass spectrometry (LC/APCI/MS/MS). <u>Pharmacokinetic:</u> Day 18 CSF:plasma concentration ratios of atomoxetine and LY424478 were calculated. <u>Biomarker:</u> CSF concentrations of DHPG and NE were analysed by a high-performance liquid chromatographic method with electrochemical detection (HPLC-EC). DHPG and NE concentrations and the DHPG:NE concentration ratio were examined by tabular representations of the data. <u>Statistical:</u> Mixed effect models appropriate for repeated measurements were used to analyse pharmacokinetic parameters and biomarkers. Log-transformation was applied to observed values prior to statistical analysis.	

Results:

Subject Demographics

A total of 12 healthy male subjects were enrolled in this study. The average age of subjects was 28.4 years (range: 22-45 years), with an average height of 169.9 cm (range: 164.0-177.5 cm), and an average weight of 65.1 kg (range: 54.7-84.1 kg). The body mass index (BMI) ranged between 19.2-27.9 kg/m² with a mean of 22.6 kg/m². The majority (10/12) of subjects were Chinese. There was one Malay subject and one Indian subject. Table 1 lists subject demographics.

Table 1. Subject Demographics

Age (yr)	Height (cm)	Weight (kg)	BMI (kg/m ²)	CYP2D6 Predicted Phenotype	CYP2D6 Genotype
36	173.5	84.1	27.9	extensive metaboliser	*10/wt
28	164.8	69.0	25.4	extensive metaboliser	*10/wt
28	177.5	64.1	20.3	extensive metaboliser	*10/wt
22	175.3	65.1	21.2	extensive metaboliser	*10/*10
25	171.5	58.4	19.9	extensive metaboliser	*10/wt
23	164.0	61.9	23.0	extensive metaboliser	*10/wt
25	169.0	54.7	19.2	extensive metaboliser	*10/*10
23	165.5	57.4	21.0	extensive metaboliser	*5/wt
27	170.2	74.1	25.6	extensive metaboliser	*10/wt
24	174.0	61.0	20.1	extensive metaboliser	*10/wt
35	168.0	67.2	23.8	extensive metaboliser	*10/wt
45	165.0	63.8	23.4	extensive metaboliser	*5/*10

Abbreviations: BMI = body mass index

Subject Disposition

Of the 15 subjects who entered the study, 12 were enrolled. Three subjects entered the study but did not receive treatment. Nine subjects completed the entire study. Two subjects were discontinued by investigator on Day 18 after collection of the Day 18 CSF needle sample. Neither subject received the final (Day 18) dose of atomoxetine as the subarachnoid catheterisation procedure could not be completed, for technical reasons, in each case. Another subject discontinued on Day 16 for personal reasons, after receiving 15 days of study drug treatment.

Safety

Data for all 12 enrolled subjects were included in this safety analysis. No deaths occurred during this study. There were two serious adverse events recorded by two subjects during the study. Both subjects were hospitalised for epidural blood patch treatment for further management of post dural puncture headache. Both subjects recovered fully after the epidural blood-patch.

Of the 129 adverse events that occurred on or after study Day 1 (treatment-emergent), 71 were classified as study-drug related by the investigator, and 41 were classified as related to protocol procedure by the investigator. The most common adverse events (classified as study-drug related) reported in this study were: headache, nausea, erectile dysfunction, paraesthesia, somnolence and dizziness. The distribution of the events by baseline severity was mild (98/129), moderate (23/129), and severe (8/129). All treatment-emergent adverse events, except two (cannula site reaction and tension headache), had resolved at time of discharge from the study.

There were no clinically significant alterations in vital sign values and laboratory values during the study.

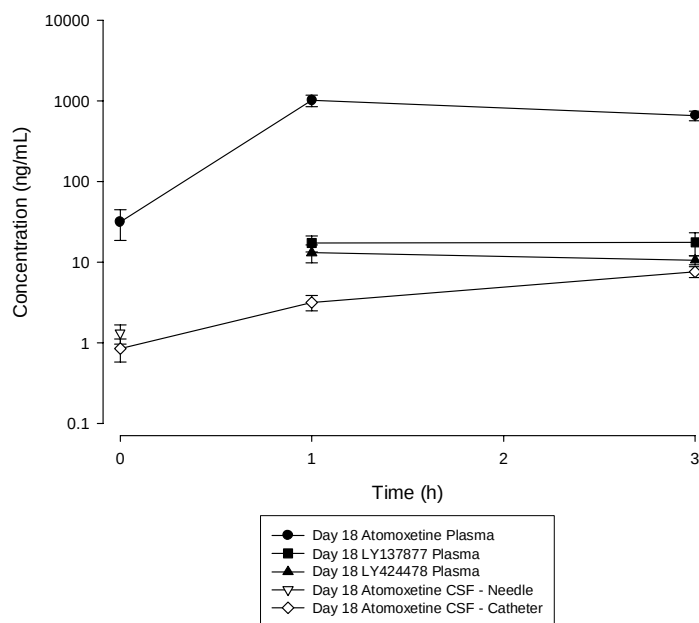
Pharmacokinetics Outcomes

Figure 1 shows the atomoxetine, N-desmethyatomoxetine (LY137877), and 4-hydroxyatomoxetine (LY424478) plasma and CSF concentration-time profiles on Day 18. Table 2 presents the plasma and CSF atomoxetine concentrations on Day 18. At predose, the mean atomoxetine plasma concentration was approximately 32 ng/mL, whereas LY137877 and LY424478 plasma concentrations were undetectable (<1.0 ng/mL). Atomoxetine plasma concentrations remained greater than LY137877 and LY424478 following dosing on Day 18.

The Day 18 pre-dose atomoxetine CSF concentrations measured following needle sampling were greater than atomoxetine concentrations measured following catheter sampling in almost all individuals. The ratio of geometric means of needle to catheter sampling was 1.95 with 95% confidence interval (1.30, 2.92). These samples were collected after 17 days of atomoxetine dosing, and were collected approximately 1 hour apart.

The average atomoxetine CSF:plasma concentration ratios at predose (Day 18), 1 hour (h), and 3 h postdose were approximately 0.04, 0.003 and 0.01, respectively. In most subjects, LY137877 and LY424478 CSF concentrations were undetectable.

The elimination half life ($t_{1/2}$) of atomoxetine in CSF and plasma could not be estimated because of the limited duration of sampling and number of samples collected on Day 18.



Abbreviation: CSF = cerebrospinal fluid.

Figure 1. Atomoxetine, LY137877 and LY424478 concentration-time profiles (arithmetic mean $\pm$ SEM) on Day 18.

Table 2. Summary of Day 18 Plasma and CSF Atomoxetine Concentrations

Day 18 Atomoxetine Concentrations (ng/mL)							
	Plasma			CSF			
	Predose	1h	3h	Predose (needle)	Predose (catheter)	1h	3h
N	11	8	9	11	8	9	9
Mean	31.8	1020	661	1.33	0.851	3.18	7.69
SD	43.7	490	280	1.18	0.771	2.10	3.45
Min	4.42	139	183	0.500	<0.250	0.650	1.27
Max	147	1840	1170	4.34	2.46	7.46	14.3

Abbreviations: CSF = cerebrospinal fluid; h = hour; Max = maximum; Min = minimum; N = number of observations; SD = standard deviation.

Biomarkers Outcomes

Table 3 shows the geometric mean CSF concentrations of DHPG and NE, and the ratio of DHPG/NE, obtained via needle and catheter on Day 1 and Day 18. Significant changes in DHPG and NE were observed after treatment with atomoxetine. For Day 18 CSF samples collected via a needle, a 27% decrease in the mean DHPG concentration and a 72% increase in the mean NE concentration was observed when compared to Day 1. In addition, the mean DHPG/NE ratio was decreased 63%. On Day 18, the mean predose DHPG concentration was 13% higher in the catheter samples compared to those obtained via a needle.

Table 3. Statistical Comparison of Geometric Means of CSF DHPG (pg/mL), NE (pg/mL), and DHPG/NE Ratio

Method	Day / Time	N	LS GeoMean (95% C.I.)	Ratio to Needle Day 1 (95% C.I.)	Ratio to Needle Day 18 (95% C.I.)
DHPG					
Needle	Day 1 / 0 h	8	1663 (1389, 1992)		
	Day 18 / 0 h	11	1206 (1008, 1443)	0.73 (0.69, 0.76)	
Catheter	Day 18 / 0 h	8	1360 (1125, 1645)	0.82 (0.75, 0.89)	1.13 (1.04, 1.22)
	Day 18 / 1 h	8	1356 (1122, 1639)	0.82 (0.75, 0.89)	1.12 (1.04, 1.22)
	Day 18 / 2 h	8	1387 (1147, 1677)	0.83 (0.77, 0.91)	1.15 (1.06, 1.25)
	Day 18 / 3 h	8	1306 (1081, 1579)	0.79 (0.72, 0.85)	1.08 (1.00, 1.18)
NE					
Needle	Day 1 / 0 h	11	65.7 (48.5, 89.0)		
	Day 18 / 0 h	11	113 (83.4, 153)	1.72 (1.50, 1.97)	
Catheter	Day 18 / 0 h	9	141 (109, 181)	2.15 (1.65, 2.79)	1.25 (0.96, 1.62)
	Day 18 / 1 h	9	153 (119, 197)	2.33 (1.79, 3.03)	1.35 (1.04, 1.76)
	Day 18 / 2 h	9	152 (118, 196)	2.32 (1.78, 3.02)	1.35 (1.03, 1.75)
	Day 18 / 3 h	9	142 (111, 183)	2.17 (1.66, 2.82)	1.26 (0.97, 1.64)
DHPG/NE					
Needle	Day 1 / 0 h	8	28.9 (23.3, 36.0)		
	Day 18 / 0 h	11	10.7 (8.67, 13.1)	0.37 (0.32, 0.43)	
Catheter	Day 18 / 0 h	8	9.87 (7.61, 12.8)	0.34 (0.25, 0.46)	0.93 (0.69, 1.24)
	Day 18 / 1 h	8	9.81 (6.79, 11.4)	0.30 (0.23, 0.41)	0.83 (0.62, 1.10)
	Day 18 / 2 h	8	9.00 (6.94, 11.7)	0.31 (0.23, 0.42)	0.84 (0.63, 1.13)
	Day 18 / 3 h	8	9.02 (6.95, 11.7)	0.31 (0.23, 0.42)	0.85 (0.63, 1.13)

Abbreviations: C.I. = confidence interval; DHPG = 3,4-dihydroxyphenylglycol; h = hour; LS GeoMean = least square geometric mean; N = number of observations; NE = norepinephrine.

The exploratory evaluation of markers of CSF blood contamination was not performed.

Summary ID# 9684

Clinical Study Summary: Study B4Z-CA-S012

A 3-Month, Open-Label Study of Atomoxetine in Children with Attention-Deficit/Hyperactivity Disorder; Symptomatic and Functional Outcomes

Date summary approved by Lilly: 03 June 2007

Brief Summary of Results

This Phase 4, multicenter, single-arm, open-label study was designed to examine the change in efficacy measures, functional outcomes, and health-related quality of life measures in children aged 6 – 11 years with Attention-Deficit/Hyperactivity Disorder (ADHD) treated with open-label, flexible doses of atomoxetine for approximately 3 months.

- A total of 212 patients were enrolled in this study (stimulant-naïve, n=116; non-stimulant-naïve, n=96). Of these, 150 (70.8%) completed the study.
- The correlation in change from baseline to 3 months between the Attention Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) total score and the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) overall score was 0.403 ($p<.001$).
- At 3 months, the correlations in change from baseline between ADHDRS-IV-Parent:Inv subscale scores and the Child Health and Illness Profile – Child Edition – Parent Rated (CHIP-CE) domain scores that were statistically significant ($p<.05$) ranged between -0.410 to -0.207.

- At 3 months, the mean change from baseline in ADHDRS-IV-Parent:Inv total score was -23.0 (95% CI: -25.0, -21.1; $p < .001$). At 3 months, the mean change from baseline in the Clinical Global Impression-ADHD-Severity (CGI-ADHD-S) score was -2.1 (95% CI: -2.3, -1.8; $p < .001$).
- At 3 months, mean change from baseline in WFIRS-P overall score was -0.48 (95% CI: -0.54, -0.42; $p < .001$).
- At 3 months, the mean changes from baseline in the CHIP-CE domains were as follows: Satisfaction, 7.0 (95% CI: 5.0, 9.1); Comfort, 7.4 (95% CI: 5.6, 9.2); Resilience, 5.8 (95% CI: 3.9, 7.7); Risks Avoidance, 9.9 (95% CI: 8.2, 11.6); Achievement, 9.0 (95% CI: 7.2, 10.8); all with $p < .001$.
- Psychometric properties of WFIRS-P were explored.
- No deaths occurred during this study. Three serious adverse events occurred during this study. The five most commonly occurring treatment-emergent adverse events were headache, decreased appetite, nausea, upper abdominal pain, and cough.

Title of Study: A 3-Month, Open-Label Study of Atomoxetine in Children with Attention-Deficit/Hyperactivity Disorder; Symptomatic and Functional Outcomes	
Investigator(s): This multicenter study included 22 principal investigators.	
Study Center(s): This study was conducted at 22 study centers in one country.	
Length of Study: 14.5 months Date of first patient enrolled: 06 April 2005 Date of last patient completed: 30 June 2006	Phase of Development: 4

Objectives:

Primary Objective: The primary objective of this study was to assess the correlation of change from baseline to approximately 3 months in the core symptoms of ADHD as measured by the Attention Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored, total score, (ADHDRS-IV-Parent:Inv) with change from baseline in functional outcome as assessed by the average score of the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) in children with ADHD, treated with open-label flexible doses of atomoxetine.

Secondary Objectives: The secondary objectives of the study were as follows:

1. To assess the relationships of change from baseline to approximately 1, 2, and 3 months, or endpoint in the core symptoms of ADHD with the changes in functional outcomes, as assessed by the WFIRS-P, and QoL, as assessed by the Child Health and Illness Profile – Child Edition – Parent Rated (CHIP – CE) in the total sample and in the subgroups of stimulant-naïve and non-stimulant-naïve patients.
2. To explore the time course of changes in ADHD symptomatology, functional outcomes, and QoL over the approximately 3 months of atomoxetine treatment in the total sample, the subgroups of stimulant-naïve and non-stimulant-naïve patients, and the diagnostic subtypes of ADHD.
3. To assess the efficacy of open-label flexible doses of atomoxetine after approximately 1, 2, and 3 months, or endpoint as measured by the change from baseline in the ADHDRS-IV-Parent:Inv (total score) and the Clinical Global Impression-ADHD-Severity (CGI-ADHD-S), in the total sample and in the subgroups of stimulant-naïve and non-stimulant-naïve patients.
4. To explore the impact of data collection time points on efficacy, quality of life, and functional outcome in four groups: 1) both baseline and endpoint collected during school year, 2) baseline during school year and endpoint during summer vacation, 3) baseline during summer vacation and endpoint during the school year, and 4) both baseline and endpoint collected during summer vacations.
5. To use the data collected in this study to examine the WFIRS-P questionnaire's psychometric properties including internal consistency, convergent validity, and responsiveness to change.

Study Design: This was a Phase 4, multicenter, single-arm, open-label study of atomoxetine in outpatients aged 6 – 11 years diagnosed with ADHD. This study was conducted over a 3-month period, and consisted of two study periods: a screening and washout period (approximately 7 days), and an open-label, atomoxetine treatment period (approximately 91 days).

Number of Patients:

Planned: 200

Entered: 212

Completed: 150

Diagnosis and Main Criteria for Inclusion: Male and female outpatients weighing at least 20 kg and aged 6 – 11 years meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for ADHD (any subtype), and who met a symptom severity threshold of at least 1.5 standard deviations above the age and gender norm of the ADHDRS-IV-Parent:Inv total score were enrolled in this study.

Study Drug, Dose, and Mode of Administration: Atomoxetine hydrochloride 0.5 – 1.2 mg/day, given orally once daily (or twice daily, if the patient experienced tolerability issues). Atomoxetine was prescribed based on the weight and titration schedule as recommended by the approved product label in Canada. Flexible doses between the recommended dose range of the study drug were permitted if judged appropriate by the investigator, based on tolerability and response to the medication.

Comparator, Dose, and Mode of Administration: Not applicable

Duration of Treatment: 3 months

Variables:

Efficacy: Core ADHD symptoms and efficacy were assessed by the ADHDRS-IV-Parent:Inv. Efficacy was also measured by the CGI-ADHD-S. Health-related quality of life was assessed by the CHIP-CE. Functional outcomes were measured by the WFIRS-P, and the Global Assessment of Functioning (GAF). WFIRS-P is a parent-completed questionnaire that measures the impact of ADHD on their child's functioning in 6 domains: Home; School; Self-concept; Social; Activities of Daily Living; and Risk Taking.

Safety: Assessment of adverse events and vital signs.

Evaluation Methods:

Statistical: For the primary analysis, endpoint was defined as measurement obtained at Visit 7 (3 months). For all secondary analyses, unless otherwise specified, endpoint was defined as the last post-baseline measurement obtained in Study Period II (i.e., on or before Visit 7). Any change to the endpoint analyses was performed using both the completer population as defined above, and the last observation carried forward (LOCF) approach. Baseline was defined as the measurement obtained on Visit 2. The primary outcome for this study was the Pearson's correlation between the change from baseline to 3 months of the ADHDRS-IV-Parent:Inv and that of WFIRS-P. In subgroup analyses, within group differences were performed using a paired t-test. Between group differences were analyzed using ANOVA. Changes from baseline between groups were analyzed using ANCOVA, with pooled sites and baseline as covariates. Investigative sites with 5 or fewer enrolled patients were to be pooled with other small investigative sites by region. The effect size between the stimulant naïve and non stimulant naïve groups was calculated, by taking the difference in the mean change from baseline between the two groups and dividing it by the average standard deviation of the two samples.

All tests of hypotheses were tested at a two-sided alpha level of 0.05. All patients who had taken at least one dose of study drug were included in the safety analysis.

Since the power of the study was on the primary endpoint and not on individual subgroups, it was planned that the sample size of each subgroup would be assessed before statistical comparisons were conducted.

Sample size calculation: No previous data for a similar objective were available. A conservative estimate of a correlation of 0.3 was assumed, between the change from baseline to 3 months in the total scores of ADHDRS-IV-Parent:Inv and that of the WFIRS-P. In order to have 90% power at a two-sided significance level of 0.05, a sample of 113 patients completing the study was required. Assuming a 40% drop out rate, about 200 patients were planned for enrollment.

Results:

Patient Demographics

Table 1 summarizes the baseline demographic characteristics of all patients who were enrolled in this study.

**Table 1. Baseline Demographics
All Enrolled Patients**

Variable	Stimulant-Naïve (N=116)	Non-Stimulant-Naïve (N=96)	Total (N=212)
Age (years)			
N	116	96	212
Mean (SD)	8.2 (1.55)	8.9 (1.57)	8.5 (1.59)
Median (Min – Max)	8.0 (6 - 11)	9.0 (6 - 11)	8.0 (6 - 11)
Ethnic Origin [n (%)]			
Caucasian	109 (94.0)	84 (87.5)	193 (91.0)
African	3 (2.6)	6 (6.3)	9 (4.2)
Hispanic	0 (0.0)	2 (2.1)	2 (0.9)
Native American/Inuit	0 (0.0)	1 (1.0)	1(0.5)
East Asian	4 (3.4)	2 (2.1)	6 (2.8)
Western Asian	0 (0.0)	1 (1.0)	1 (0.5)
Gender [n (%)]			
Male	90 (77.6)	67 (69.8)	157 (74.1)
Female	26 (22.4)	29 (30.2)	55 (25.9)

Abbreviations: Max = maximum; Min = minimum; N = total number of patients; n = number of patients;
SD = standard deviation.

Of the 212 enrolled patients, 116 (54.7%) were stimulant-naïve with the remainder (n=96, 45.3%) non-stimulant-naïve. The majority of patients were diagnosed with ADHD combined subtype (n=166, 78.3%), while 20.3% (n=43) and 1.4% (n=3) of patients were diagnosed with ADHD Inattentive subtype and Hyperactive/Impulsive subtype, respectively.

Patient Disposition

A total of 212 patients were enrolled in this study. A total of 206 patients received at least one dose of study drug. Of these, 150 (70.8%) completed the study. The reasons for discontinuation are summarized in Table 2.

**Table 2. Patient Disposition
All Enrolled Patients**

PRIMARY REASON	PATIENTS ENROLLED (N=212)	
	N	(%)
Protocol Completed	150	(70.8%)
Adverse Event	14	(6.6%)
Death	0	
Lack of efficacy	19	(9.0%)
Unable to contact patient	2	(0.9%)
Personal conflict	11	(5.2%)
Protocol entry criteria not met	1	(0.5%)
Protocol violation	6	(2.8%)
Physician decision	8	(3.8%)
Sponsor decision	1	(0.5%)
Other (resulting in Screen Failure)	0	

Abbreviations: N = number of patients.

Primary Outcome Measure

As shown in Table 3, the correlation in change from baseline to 3 months (Day 91, study completers) between ADHDRS-IV-Parent:Inv total score and WFIRS-P overall score was 0.403 (95% CI: 0.259 - 0.529; $p < .001$). In both scales, a decrease in score indicates an improvement.

Secondary Outcome Measures

1a) Relationship of Change in Core ADHD Symptoms (ADHDRS-IV-Parent:Inv) with Change in Functional Outcomes (WFIRS-P)

The correlations in change from baseline between ADHDRS-IV-Parent:Inv total score and WFIRS-P overall score at 1, 2, and 3 months (study completers) and LOCF endpoint for the total patient sample are presented in Table 3. These data are presented by stimulant-naïve and non-stimulant-naïve patient subgroups in Table 4.

1b) Relationship of Change in Core ADHD Symptoms (ADHDRS-IV-Parent:Inv) with Change in Health-Related Quality of Life (CHIP-CE)

The correlations in change from baseline between ADHDRS-IV-Parent:Inv subscale scores and CHIP-CE domain scores at 1, 2, and 3 months (study completers) and LOCF endpoint for the total patient sample are presented in Table 5. These data are presented by stimulant-naïve and non-stimulant-naïve patient subgroups in Table 6. An increase in CHIP-CE domain score (mean of norm=50; SD=10) indicates an improvement.

Table 3. Correlation in Change from Baseline Between ADHDRS-IV-Parent:Inv (Total Score) and WFIRS-P (Overall) All Enrolled Patients

ADHDRS-IV-PARENT-INV (TOTAL)						
VISIT	WFIRS-P	N	CORR	95 % CI		P-VALUE[1]
				LOWER	UPPER	
Day 35	WFIRS-P (Overall)	175	0.368	0.232	0.490	<.001
Day 63	WFIRS-P (Overall)	153	0.372	0.226	0.501	<.001
Day 91	WFIRS-P (Overall)	150	0.403	0.259	0.529	<.001
LOCF	WFIRS-P (Overall)	198	0.576	0.475	0.662	<.001

Abbreviations: ADHDRS-IV-Parent:Inv = Attention Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CI = confidence interval; CORR = Pearson's correlation coefficient; LOCF = last observation carried forward; N = number of patients; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

[1] The p-value is under the null hypothesis of zero correlation.

Table 4. Correlation in Change from Baseline Between ADHDRS-IV-Parent:Inv (Total Score) and WFIRS-P (Overall) All Enrolled Patients by Prior Stimulant Use

Visit	ADHDRS-IV-PARENT-INV (TOTAL)					
	SUBGROUP	N	CORR	95 % CI		P-VALUE [1]
				LOWER	UPPER	
35	Stimulant Naive (N=116)	94	0.403	0.218	0.560	<.001
	Non - Stimulant Naive (N=96)	81	0.331	0.121	0.512	0.002
63	Stimulant Naive (N=116)	87	0.452	0.267	0.605	<.001
	Non - Stimulant Naive (N=96)	66	0.258	0.017	0.470	0.036
91	Stimulant Naive (N=116)	84	0.467	0.280	0.619	<.001
	Non - Stimulant Naive (N=96)	66	0.319	0.083	0.521	0.009
LOCF	Stimulant Naive (N=116)	107	0.620	0.488	0.725	<.001
	Non - Stimulant Naive (N=96)	91	0.524	0.357	0.659	<.001

Abbreviations: ADHDRS-IV-Parent:Inv = Attention Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CI = confidence interval; CORR = Pearson's correlation coefficient; LOCF = last observation carried forward; N = total number of patients (column 2); N = number of patients (column 3); WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

[1] The p-value is under the null hypothesis of zero correlation.

Table 5. Correlation in Change from Baseline Between ADHDRS-IV-Parent:Inv Subscale Scores and CHIP-CE (Domains) All Enrolled Patients.

Visit	CHIP-CE Domain	ADHDRS-IV-PARENT-INV									
		INATTENTION					HYPERACTIVE/IMPULSIVE				
		95 % CI					95 % CI				
		N	CORR	LOWER	UPPER	P-VALUE[1]	N	CORR	LOWER	UPPER	P-VALUE[1]
35	Satisfaction	169	-0.237	-0.375	-0.089	0.002	169	-0.188	-0.330	-0.038	0.014
	Comfort	175	-0.122	-0.265	0.027	0.109	175	-0.074	-0.220	0.075	0.330
	Resilience	175	-0.080	-0.226	0.069	0.290	175	-0.065	-0.211	0.084	0.394
	Risks	175	-0.251	-0.385	-0.106	<.001	175	-0.324	-0.450	-0.184	<.001
	Avoidance										
	Achievement	165	-0.359	-0.485	-0.219	<.001	165	-0.231	-0.371	-0.081	0.003
63	Satisfaction	148	-0.232	-0.379	-0.073	0.004	148	-0.245	-0.391	-0.087	0.003
	Comfort	153	-0.166	-0.316	-0.007	0.041	153	-0.149	-0.300	0.010	0.066
	Resilience	153	-0.167	-0.318	-0.009	0.039	153	-0.087	-0.242	0.073	0.288
	Risks	153	-0.339	-0.473	-0.191	<.001	153	-0.425	-0.547	-0.286	<.001
	Avoidance										
	Achievement	147	-0.514	-0.624	-0.384	<.001	147	-0.384	-0.514	-0.236	<.001
91	Satisfaction	144	-0.269	-0.415	-0.111	0.001	144	-0.246	-0.394	-0.086	0.003
	Comfort	150	-0.207	-0.355	-0.048	0.011	150	-0.151	-0.304	0.010	0.066
	Resilience	150	-0.119	-0.274	0.042	0.148	150	-0.053	-0.211	0.108	0.522
	Risks	150	-0.392	-0.519	-0.247	<.001	150	-0.410	-0.535	-0.267	<.001
	Avoidance										
	Achievement	140	-0.378	-0.512	-0.227	<.001	140	-0.241	-0.392	-0.079	0.004
LOCF	Satisfaction	193	-0.341	-0.460	-0.210	<.001	193	-0.299	-0.422	-0.164	<.001
	Comfort	198	-0.306	-0.427	-0.174	<.001	198	-0.308	-0.429	-0.176	<.001
	Resilience	198	-0.185	-0.316	-0.047	0.009	198	-0.144	-0.278	-0.005	0.043
	Risks	198	-0.466	-0.568	-0.349	<.001	198	-0.508	-0.605	-0.397	<.001
	Avoidance										
	Achievement	194	-0.497	-0.596	-0.383	<.001	194	-0.377	-0.492	-0.249	<.001

Abbreviations: ADHDRS-IV-Parent:Inv = Attention Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CHIP-CE = Child Health and Illness Profile – Child Edition – Parent Rated; CI = confidence interval; CORR = Pearson’s correlation coefficient; LOCF = last observation carried forward; N = number of patients.

[1] The p-value is under the null hypothesis of zero correlation.

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Table 6. Correlation in Change from Baseline Between ADHDRS-IV-Parent:Inv (Subscale Scores) and CHIP-CE (Domains) by Visit. All Enrolled Patients by Prior Stimulant Use

CHIP-CE Domain	Visit	SUBGROUP	ADHDRS-IV-PARENT-INV									
			INATTENTION					HYPERACTIVE/IMPULSIVE				
			95 % CI					95 % CI				
			N	CORR	LOWER	UPPER	P-VALUE[1]	N	CORR	LOWER	UPPER	P-VALUE[1]
Satisfaction	35	Stimulant Naive (N=116)	92	-0.207	-0.395	-0.003	0.047	92	-0.210	-0.398	-0.005	0.044
		Non - Stimulant Naive (N=96)	77	-0.272	-0.468	-0.051	0.016	77	-0.161	-0.372	0.065	0.161
	63	Stimulant Naive (N=116)	85	-0.282	-0.467	-0.074	0.009	85	-0.291	-0.475	-0.083	0.007
		Non - Stimulant Naive (N=96)	63	-0.168	-0.400	0.083	0.188	63	-0.190	-0.418	0.060	0.136
	91	Stimulant Naive (N=116)	82	-0.283	-0.471	-0.070	0.010	82	-0.313	-0.496	-0.103	0.004
		Non - Stimulant Naive (N=96)	62	-0.245	-0.466	0.005	0.055	62	-0.137	-0.374	0.117	0.289
Comfort	35	Stimulant Naive (N=116)	106	-0.398	-0.547	-0.224	<.001	106	-0.408	-0.556	-0.236	<.001
		Non - Stimulant Naive (N=96)	87	-0.257	-0.444	-0.049	0.016	87	-0.150	-0.350	0.062	0.165
	63	Stimulant Naive (N=116)	94	-0.088	-0.286	0.117	0.400	94	-0.049	-0.249	0.155	0.641
		Non - Stimulant Naive (N=96)	81	-0.182	-0.385	0.038	0.104	81	-0.135	-0.344	0.086	0.229
	91	Stimulant Naive (N=116)	87	-0.266	-0.451	-0.058	0.013	87	-0.192	-0.387	0.019	0.074
		Non - Stimulant Naive (N=96)	66	-0.021	-0.261	0.223	0.870	66	-0.095	-0.330	0.150	0.448
	LOCF	Stimulant Naive (N=116)	84	-0.353	-0.528	-0.150	<.001	84	-0.289	-0.474	-0.079	0.007
		Non - Stimulant Naive (N=96)	66	-0.008	-0.250	0.234	0.947	66	0.023	-0.220	0.264	0.854
	35	Stimulant Naive (N=116)	107	-0.368	-0.521	-0.191	<.001	107	-0.394	-0.543	-0.220	<.001
		Non - Stimulant Naive (N=96)	91	-0.235	-0.421	-0.031	0.024	91	-0.215	-0.403	-0.009	0.041
	63	Stimulant Naive (N=116)	94	-0.032	-0.233	0.171	0.758	94	-0.062	-0.262	0.142	0.552
		Non - Stimulant Naive (N=96)	81	-0.137	-0.345	0.084	0.223	81	-0.071	-0.285	0.150	0.532
Resilience	35	Stimulant Naive (N=116)	87	-0.206	-0.399	0.005	0.056	87	-0.133	-0.334	0.080	0.219
		Non - Stimulant Naive (N=96)	66	-0.094	-0.328	0.152	0.456	66	-0.006	-0.247	0.237	0.965
	63	Stimulant Naive (N=116)	84	-0.144	-0.348	0.073	0.191	84	-0.083	-0.292	0.134	0.456
		Non - Stimulant Naive (N=96)	66	-0.081	-0.317	0.164	0.518	66	-0.011	-0.252	0.232	0.933
	91	Stimulant Naive (N=116)	107	-0.237	-0.408	-0.049	0.014	107	-0.224	-0.397	-0.035	0.020
		Non - Stimulant Naive (N=96)	91	-0.115	-0.314	0.093	0.277	91	-0.045	-0.249	0.162	0.670

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Table 6. Correlation in Change from Baseline Between ADHDRS-IV-Parent:Inv (Subscale Scores) and CHIP-CE (Domains). All Enrolled Patients by Prior Stimulant Use (concluded)

CHIP-CE Domain	Visit	SUBGROUP	ADHDRS-IV-PARENT-INV							
			INATTENTION					HYPERACTIVE/IMPULSIVE		
			95 % CI					95 % CI		
			N	CORR	LOWER	UPPER	P-VALUE[1]	N	CORR	P-VALUE[1]
Risks Avoidance	35	Stimulant Naive (N=116)	94	-0.220	-0.404	-0.018	0.033	94	-0.308	0.002
		Non - Stimulant Naive (N=96)	81	-0.288	-0.476	-0.074	0.009	81	-0.310	0.005
	63	Stimulant Naive (N=116)	87	-0.319	-0.497	-0.117	0.002	87	-0.478	<.001
		Non - Stimulant Naive (N=96)	66	-0.391	-0.578	-0.165	0.001	66	-0.349	0.004
Achievement	91	Stimulant Naive (N=116)	84	-0.417	-0.580	-0.223	<.001	84	-0.461	<.001
		Non - Stimulant Naive (N=96)	66	-0.340	-0.538	-0.107	0.005	66	-0.317	0.009
	LOCF	Stimulant Naive (N=116)	107	-0.471	-0.607	-0.309	<.001	107	-0.555	<.001
		Non - Stimulant Naive (N=96)	91	-0.452	-0.602	-0.271	<.001	91	-0.433	<.001
	35	Stimulant Naive (N=116)	89	-0.452	-0.604	-0.270	<.001	89	-0.309	0.003
		Non - Stimulant Naive (N=96)	76	-0.236	-0.438	-0.011	0.040	76	-0.099	0.394
	63	Stimulant Naive (N=116)	84	-0.615	-0.733	-0.462	<.001	84	-0.432	<.001
		Non - Stimulant Naive (N=96)	63	-0.389	-0.581	-0.156	0.001	63	-0.330	0.008
	91	Stimulant Naive (N=116)	82	-0.433	-0.594	-0.239	<.001	82	-0.272	0.013
		Non - Stimulant Naive (N=96)	58	-0.269	-0.493	-0.012	0.041	58	-0.170	0.203
LOCF		Stimulant Naive (N=116)	105	-0.546	-0.668	-0.396	<.001	105	-0.388	<.001
		Non - Stimulant Naive (N=96)	89	-0.418	-0.576	-0.229	<.001	89	-0.349	<.001

Abbreviations: ADHDRS-IV-Parent:Inv = Attention Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CHIP-CE = Child Health and Illness Profile – Child Edition – Parent Rated; CI = confidence interval; CORR = Pearson’s correlation coefficient; LOCF = last observation carried forward; N = total number of patients (column 3); N = number of patients (columns 4 and 9).

[1] The p-value is under the null hypothesis of zero correlation.

2) Changes in ADHDRS-IV-Parent:Inv, WFIRS-P, and CHIP-CE Over Time

The change from baseline in ADHDRS-IV-Parent:Inv total score over time for the total patient sample is presented in Table 7. No statistically significant differences were found between the stimulant-naïve and non-stimulant-naïve patient subgroups ($p > .05$).

The change from baseline in WFIRS-P overall score over time for the total patient sample is presented in Table 8. There was a statistically significant difference between the stimulant-naïve and non-stimulant-naïve patient subgroups in the “Learning and School” domain at LOCF endpoint [mean change: -0.63 (stimulant-naïve), -0.44 (non-stimulant-naïve); $p = .048$].

The change from baseline in CHIP-CE domain and subdomain scores over time for the total patient sample is presented in Table 9. These data are presented by stimulant-naïve and non-stimulant-naïve patient subgroups in Table 10.

The ADHD diagnostic subgroup analyses were deemed statistically inappropriate because of the disproportionate number of patients diagnosed with the different ADHD subtypes [Combined: 78.3% ($n=166$); Inattentive: 20.3% ($n=43$); Hyperactive/Impulsive: 1.4% ($n=3$)].

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**Table 7. Visit-wise Mean Score and Change from Baseline in ADHDRS-IV-Parent-Inv (Total and Subscales)
All Patients Enrolled**

ADHDRS-IV-PARENT-INV	VISIT	N	MEAN (SD)	95% CI	MIN,MAX	CHANGE			
						MEAN (SD)	95% CI	MIN,MAX	P-VALUE [1]
Total	Baseline	209	40.5 (7.51)	39.5, 41.5	21, 54				
	Day 35	175	22.1 (11.72)	20.4, 23.9	0, 54	-18.5 (12.06)	-20.3, -16.7	-51, 15	<.001
	Day 63	153	19.8 (10.69)	18.1, 21.5	0, 48	-21.3 (11.70)	-23.2, -19.5	-54, 6	<.001
	Day 91	150	18.1 (11.13)	16.3, 19.9	0, 49	-23.0 (12.17)	-25.0, -21.1	-52, 13	<.001
	LOCF	209	22.6 (13.46)	20.7, 24.4	0, 54	-18.9 (13.83)	-20.9, -17.0	-52, 14	<.001
Inattention	Baseline	209	22.0 (3.74)	21.5, 22.5	12, 27				
	Day 35	175	12.0 (6.41)	11.1, 13.0	0, 27	-10.1 (6.76)	-11.1, -9.0	-27, 8	<.001
	Day 63	153	10.8 (5.65)	9.9, 11.7	0, 25	-11.3 (6.64)	-12.4, -10.2	-27, 5	<.001
	Day 91	150	9.9 (5.73)	9.0, 10.8	0, 25	-12.3 (6.60)	-13.3, -11.2	-27, 6	<.001
	LOCF	209	12.4 (7.16)	11.5, 13.4	0, 27	-10.1 (7.69)	-11.2, -9.0	-27, 9	<.001
Hyperactive/Impulsive	Baseline	209	18.5 (6.09)	17.7, 19.3	1, 27				
	Day 35	175	10.1 (6.36)	9.1, 11.0	0, 27	-8.4 (6.29)	-9.4, -7.5	-24, 13	<.001
	Day 63	153	9.0 (5.97)	8.0, 9.9	0, 24	-10.0 (6.40)	-11.0, -9.0	-27, 6	<.001
	Day 91	150	8.2 (6.11)	7.3, 9.2	0, 25	-10.8 (6.43)	-11.8, -9.7	-25, 7	<.001
	LOCF	209	10.1 (7.21)	9.2, 11.1	0, 27	-8.8 (7.06)	-9.8, -7.8	-25, 8	<.001

Abbreviations: ADHDRS-IV-Parent:Inv = Attention Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CI = confidence interval; LOCF = last observation carried forward; Max = maximum; Min = minimum; N = number of patients; SD = standard deviation.

[1] The p-value is based on paired t-test.

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**Table 8. Visit-wise Mean Score and Change from Baseline in WFIRS-P (Overall and Subscales)
All Patients Enrolled**

WFIRS-P	VISIT	N	MEAN(SD)	95% CI	MIN,MAX	CHANGE			
						MEAN(SD)	95% CI	MIN,MAX	P-VALUE [1]
Overall	Baseline	209	1.10 (0.431)	1.04, 1.16	0.32, 2.38				
	Day 35	176	0.72 (0.388)	0.66, 0.78	0.12, 2.26	-0.38 (0.333)	-0.43, -0.33	-1.33, 0.38	<.001
	Day 63	153	0.63 (0.345)	0.58, 0.69	0.10, 2.08	-0.46 (0.339)	-0.51, -0.41	-1.50, 0.42	<.001
	Day 91	150	0.62 (0.374)	0.56, 0.68	0.00, 2.06	-0.48 (0.354)	-0.54, -0.42	-1.84, 0.40	<.001
	LOCF	210	0.73 (0.441)	0.67, 0.79	0.00, 2.11	-0.40 (0.384)	-0.45, -0.34	-1.84, 0.74	<.001
A: Family	Baseline	209	1.30 (0.731)	1.20, 1.40	0.00, 2.80				
	Day 35	176	0.83 (0.602)	0.74, 0.92	0.00, 2.60	-0.47 (0.550)	-0.55, -0.39	-2.40, 0.89	<.001
	Day 63	153	0.75 (0.582)	0.65, 0.84	0.00, 2.90	-0.56 (0.527)	-0.64, -0.47	-1.80, 0.70	<.001
	Day 91	150	0.76 (0.644)	0.66, 0.87	0.00, 2.80	-0.55 (0.559)	-0.64, -0.46	-2.11, 0.90	<.001
	LOCF	210	0.88 (0.704)	0.79, 0.98	0.00, 2.80	-0.44 (0.599)	-0.52, -0.36	-2.11, 1.50	<.001
B: Learning and School	Baseline	207	1.37 (0.570)	1.29, 1.45	0.10, 2.75				
	Day 35	166	0.86 (0.577)	0.78, 0.95	0.00, 3.00	-0.50 (0.561)	-0.58, -0.41	-1.96, 1.20	<.001
	Day 63	141	0.75 (0.486)	0.67, 0.83	0.00, 2.63	-0.60 (0.562)	-0.70, -0.51	-2.36, 0.70	<.001
	Day 91	142	0.70 (0.503)	0.62, 0.79	0.00, 2.75	-0.64 (0.608)	-0.75, -0.54	-2.30, 0.95	<.001
	LOCF	210	0.87 (0.599)	0.78, 0.95	0.00, 2.75	-0.54 (0.621)	-0.63, -0.45	-2.30, 1.00	<.001
C: Life Skills	Baseline	209	1.22 (0.538)	1.15, 1.30	0.10, 2.70				
	Day 35	176	0.81 (0.458)	0.74, 0.88	0.00, 2.30	-0.43 (0.476)	-0.50, -0.35	-2.00, 0.80	<.001
	Day 63	153	0.75 (0.431)	0.69, 0.82	0.00, 2.00	-0.46 (0.463)	-0.53, -0.39	-2.00, 0.80	<.001
	Day 91	150	0.72 (0.425)	0.65, 0.79	0.00, 2.50	-0.49 (0.456)	-0.56, -0.42	-2.20, 0.70	<.001
	LOCF	210	0.82 (0.476)	0.75, 0.88	0.00, 2.50	-0.43 (0.478)	-0.49, -0.36	-2.20, 0.70	<.001
D: Child's Self-concept	Baseline	209	1.21 (0.865)	1.09, 1.33	0.00, 3.00				
	Day 35	176	0.87 (0.663)	0.77, 0.97	0.00, 3.00	-0.36 (0.767)	-0.48, -0.25	-2.33, 2.00	<.001
	Day 63	153	0.68 (0.617)	0.58, 0.78	0.00, 3.00	-0.57 (0.682)	-0.68, -0.46	-2.33, 1.33	<.001
	Day 91	150	0.67 (0.616)	0.57, 0.77	0.00, 3.00	-0.55 (0.700)	-0.66, -0.44	-2.33, 1.00	<.001

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**Table 8. Visit-wise Mean Score and Change from Baseline in WFIRS-P (Overall and Subscales)
All Patients Enrolled (concluded)**

WFIRS-P	VISIT	N	MEAN (SD)	95% CI	MIN,MAX	CHANGE			
						MEAN (SD)	95% CI	MIN,MAX	P-VALUE [1]
D: Child's Self-concept	LOCF	210	0.80 (0.666)	0.71, 0.89	0.00, 3.00	-0.44 (0.732)	-0.54, -0.33	-2.33, 1.33	<.001
E: Social Activities	Baseline	209	1.04 (0.681)	0.95, 1.14	0.00, 3.00				
	Day 35	176	0.73 (0.561)	0.65, 0.81	0.00, 2.57	-0.31 (0.477)	-0.38, -0.24	-2.14, 0.71	<.001
	Day 63	153	0.61 (0.480)	0.54, 0.69	0.00, 1.86	-0.42 (0.573)	-0.51, -0.33	-2.43, 1.00	<.001
	Day 91	150	0.60 (0.496)	0.52, 0.68	0.00, 2.14	-0.44 (0.527)	-0.53, -0.36	-2.29, 0.71	<.001
	LOCF	210	0.70 (0.598)	0.61, 0.78	0.00, 3.00	-0.37 (0.554)	-0.45, -0.29	-2.29, 1.43	<.001
F: Risky Activities	Baseline	209	0.52 (0.367)	0.47, 0.57	0.00, 1.80				
	Day 35	176	0.35 (0.302)	0.30, 0.39	0.00, 1.60	-0.16 (0.246)	-0.20, -0.13	-1.10, 0.70	<.001
	Day 63	153	0.31 (0.292)	0.26, 0.36	0.00, 1.90	-0.21 (0.255)	-0.25, -0.17	-1.10, 0.40	<.001
	Day 91	150	0.30 (0.271)	0.26, 0.34	0.00, 1.50	-0.22 (0.249)	-0.26, -0.18	-1.20, 0.30	<.001
	LOCF	210	0.36 (0.328)	0.31, 0.40	0.00, 1.90	-0.17 (0.267)	-0.21, -0.14	-1.20, 0.80	<.001

Abbreviations: CI = confidence interval; LOCF = last observation carried forward; Max = maximum; Min = minimum; N = number of patients; SD = standard deviation; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

[1] The p-value is based on paired t-test.

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**Table 9. Visit-wise Mean Score and Change from Baseline in CHIP-CE (Domains)
All Patients Enrolled**

CHIP-CE	VISIT	N	MEAN (SD)	95% CI	MIN,MAX	CHANGE			
						MEAN (SD)	95% CI	MIN,MAX	P-VALUE [1]
Satisfaction Domain	Baseline	204	33.8(14.18)	31.8, 35.8	-6.9, 64.2				
	Day 35	175	37.5(13.32)	35.5, 39.5	-4.8, 66.3	4.3(11.20)	2.6, 6.0	-25.1, 37.6	<.001
	Day 63	152	40.0(12.61)	37.9, 42.0	3.6, 66.3	6.9(10.80)	5.2, 8.7	-31.4, 37.6	<.001
	Day 91	149	40.5(13.33)	38.3, 42.7	1.5, 66.3	7.0(12.37)	5.0, 9.1	-29.3, 41.8	<.001
	LOCF	210	38.8(13.44)	36.9, 40.6	-0.6, 66.3	5.2(12.58)	3.4, 7.0	-29.3, 46.0	<.001
Comfort Domain	Baseline	209	41.1(11.60)	39.5, 42.7	1.9, 67.2				
	Day 35	176	46.6(9.26)	45.2, 47.9	22.6, 66.1	5.5(9.42)	4.1, 6.9	-17.4, 41.4	<.001
	Day 63	153	48.1(9.10)	46.6, 49.5	23.6, 66.1	7.6(9.93)	6.0, 9.2	-14.2, 32.7	<.001
	Day 91	150	48.0(10.37)	46.3, 49.6	18.2, 67.2	7.4(11.12)	5.6, 9.2	-22.9, 43.6	<.001
	LOCF	210	45.9(11.35)	44.4, 47.5	13.8, 67.2	5.0(11.93)	3.4, 6.7	-29.0, 43.6	<.001
Resilience Domain	Baseline	209	37.6(12.78)	35.9, 39.3	-2.2, 69.0				
	Day 35	176	41.2(11.74)	39.4, 42.9	3.5, 64.7	4.1(10.77)	2.5, 5.7	-28.5, 38.4	<.001
	Day 63	153	42.7(11.39)	40.9, 44.5	12.1, 70.4	5.4(10.43)	3.7, 7.1	-18.5, 35.6	<.001
	Day 91	150	43.4(12.14)	41.4, 45.3	7.8, 70.4	5.8(11.62)	3.9, 7.7	-25.6, 37.0	<.001
	LOCF	210	42.2(12.25)	40.5, 43.8	3.5, 70.4	4.9(11.51)	3.3, 6.5	-25.6, 37.0	<.001
Risk Avoidance Domain	Baseline	209	34.5(13.22)	32.7, 36.3	-4.0, 57.9				
	Day 35	176	42.8(12.11)	41.0, 44.6	14.9, 61.0	8.2(9.25)	6.8, 9.6	-21.5, 36.9	<.001
	Day 63	153	44.3(12.35)	42.3, 46.3	10.3, 62.5	10.1(9.54)	8.6, 11.7	-15.4, 50.7	<.001
	Day 91	150	44.0(11.74)	42.1, 45.9	13.6, 62.5	9.9(10.69)	8.2, 11.6	-24.3, 50.7	<.001
	LOCF	210	42.0(12.74)	40.3, 43.8	5.7, 62.5	8.1(10.89)	6.5, 9.6	-24.3, 50.7	<.001
Achievement Domain	Baseline	205	30.8(9.47)	29.5, 32.1	7.5, 59.8				
	Day 35	169	37.8(10.86)	36.2, 39.5	5.7, 64.2	7.7(9.80)	6.2, 9.2	-12.4, 35.4	<.001
	Day 63	149	39.4(10.61)	37.6, 41.1	5.7, 65.9	8.9(10.74)	7.1, 10.6	-19.5, 39.4	<.001
	Day 91	142	39.0(10.33)	37.3, 40.7	12.8, 64.2	9.0(10.71)	7.2, 10.8	-19.5, 39.4	<.001
	LOCF	210	37.0(11.08)	35.5, 38.5	11.0, 64.2	6.9(11.15)	5.3, 8.5	-19.5, 39.4	<.001

Abbreviations: CHIP-CE = Child Health and Illness Profile – Child Edition – Parent Rated; CI = confidence interval; LOCF = last observation carried forward; Max = maximum; Min = minimum; N = number of patients; SD = standard deviation.

[1] The p-value is based on paired t-test.

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**Table 10. Visit-wise Change from Baseline in CHIP-CE (Domains)
All Patients Enrolled by Prior Stimulant Use**

CHIP-CE Domain	Visit			N	MEAN (SD)	95% CI		MIN,MAX	P[1]	P[2]	EFFECT
											SIZE
											[3]
Satisfaction	35	Change	Stimulant Naive (N=116)	92	4.5(11.26)	2.2,	6.8	-25.1, 31.4	<.001		
			Non - Stimulant Naive (N=96)	78	4.1(11.19)	1.6,	6.6	-25.1, 37.6	0.002	0.317	0.034
	63	Change	Stimulant Naive (N=116)	85	7.3(10.20)	5.1,	9.5	-17.1, 37.6	<.001		
			Non - Stimulant Naive (N=96)	63	6.5(11.62)	3.6,	9.5	-31.4, 29.3	<.001	0.186	0.066
	91	Change	Stimulant Naive (N=116)	82	7.3(13.36)	4.3,	10.2	-29.3, 41.8	<.001		
			Non - Stimulant Naive (N=96)	62	6.7(11.01)	3.9,	9.5	-23.0, 35.6	<.001	0.551	0.051
	LOCF	Change	Stimulant Naive (N=116)	106	5.3(13.32)	2.7,	7.8	-29.3, 41.8	<.001		
			Non - Stimulant Naive (N=96)	88	5.1(11.70)	2.6,	7.5	-23.0, 46.0	<.001	0.331	0.016
Comfort	35	Change	Stimulant Naive (N=116)	94	4.9(10.06)	2.8,	6.9	-17.4, 41.4	<.001		
			Non - Stimulant Naive (N=96)	82	6.3(8.64)	4.4,	8.2	-13.1, 28.3	<.001	0.775	0.148
	63	Change	Stimulant Naive (N=116)	87	7.0(9.78)	4.9,	9.1	-10.9, 32.7	<.001		
			Non - Stimulant Naive (N=96)	66	8.4(10.16)	5.9,	10.9	-14.2, 29.4	<.001	0.580	0.138
	91	Change	Stimulant Naive (N=116)	84	6.1(11.57)	3.6,	8.6	-22.9, 43.6	<.001		
			Non - Stimulant Naive (N=96)	66	9.0(10.39)	6.4,	11.5	-15.2, 30.5	<.001	0.442	0.261
	LOCF	Change	Stimulant Naive (N=116)	107	4.5(12.17)	2.1,	6.8	-22.9, 43.6	<.001		
			Non - Stimulant Naive (N=96)	92	5.7(11.69)	3.3,	8.1	-29.0, 30.5	<.001	0.814	0.103
Resilience	35	Change	Stimulant Naive (N=116)	94	4.1(10.73)	1.9,	6.3	-28.5, 28.5	<.001		
			Non - Stimulant Naive (N=96)	82	4.0(10.87)	1.7,	6.4	-18.5, 38.4	0.001	0.563	0.009
	63	Change	Stimulant Naive (N=116)	87	5.9(11.57)	3.5,	8.4	-18.5, 32.7	<.001		
			Non - Stimulant Naive (N=96)	66	4.7(8.73)	2.6,	6.8	-18.5, 35.6	<.001	0.376	0.120
	91	Change	Stimulant Naive (N=116)	84	6.0(11.60)	3.5,	8.6	-24.2, 37.0	<.001		
			Non - Stimulant Naive (N=96)	66	5.5(11.74)	2.6,	8.3	-25.6, 34.2	<.001	0.815	0.050
	LOCF	Change	Stimulant Naive (N=116)	107	5.2(11.52)	3.0,	7.4	-24.2, 37.0	<.001		
			Non - Stimulant Naive (N=96)	92	4.5(11.56)	2.1,	6.9	-25.6, 37.0	<.001	0.453	0.058
Risks Avoidance	35	Change	Stimulant Naive (N=116)	94	10.0(10.53)	7.8,	12.1	-21.5, 36.9	<.001		
			Non - Stimulant Naive (N=96)	82	6.2(7.05)	4.6,	7.7	-10.8, 29.2	<.001	0.048	0.431
	63	Change	Stimulant Naive (N=116)	87	11.2(10.43)	9.0,	13.4	-15.4, 50.7	<.001		
			Non - Stimulant Naive (N=96)	66	8.8(8.09)	6.8,	10.8	-12.3, 29.2	<.001	0.541	0.258
	91	Change	Stimulant Naive (N=116)	84	11.0(11.92)	8.4,	13.6	-24.3, 50.7	<.001		
			Non - Stimulant Naive (N=96)	66	8.4(8.76)	6.3,	10.6	-12.3, 36.9	<.001	0.478	0.251
	LOCF	Change	Stimulant Naive (N=116)	107	9.4(12.13)	7.1,	11.7	-24.3, 50.7	<.001		
			Non - Stimulant Naive (N=96)	92	6.5(9.05)	4.6,	8.4	-12.3, 36.9	<.001	0.140	0.276

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**Table 10. Visit-wise Change from Baseline in CHIP-CE (Domains)
All Patients Enrolled by Prior Stimulant Use (concluded)**

CHIP-CE Domain	Visit			N	MEAN (SD)	95% CI	MIN,MAX	P[1]	P[2]	EFFECT SIZE [3]
Achievement	35	Change	Stimulant Naive (N=116)	89	9.1 (9.64)	7.1, 11.1	-8.9, 33.7	<.001		
			Non - Stimulant Naive (N=96)	77	6.2 (9.81)	3.9, 8.4	-12.4, 35.4	<.001	0.050	0.303
	63	Change	Stimulant Naive (N=116)	84	10.0 (10.28)	7.7, 12.2	-14.2, 39.4	<.001		
			Non - Stimulant Naive (N=96)	63	7.4 (11.22)	4.5, 10.2	-19.5, 39.0	<.001	0.040	0.243
	91	Change	Stimulant Naive (N=116)	82	9.9 (11.37)	7.4, 12.4	-19.5, 39.4	<.001		
			Non - Stimulant Naive (N=96)	58	7.7 (9.66)	5.2, 10.3	-15.9, 31.9	<.001	0.107	0.206
	LOCF	Change	Stimulant Naive (N=116)	105	8.2 (11.68)	6.0, 10.5	-19.5, 39.4	<.001		
			Non - Stimulant Naive (N=96)	90	5.4 (10.35)	3.2, 7.5	-15.9, 39.0	<.001	0.035	0.260

Abbreviations: ANCOVA = analysis of covariance; CHIP-CE = Child Health and Illness Profile – Child Edition – Parent Rated; CI = confidence interval; LOCF = last observation carried forward; Max = maximum; Min = minimum; N = total number of patients (column 4); N = number of patients (column 5); SD = standard deviation.

[1] The p-value within group is based on paired t-test.

[2] The p-value between groups is based on ANCOVA using pooled sites and baseline as covariates.

[3] The effect size is calculated by taking the difference in the mean change from baseline between the two groups and dividing it by the average standard deviation of the two samples.

3) Efficacy: Change in ADHDRS-IV-Parent:Inv Total Score and CGI-ADHD-S Score

The change from baseline in ADHDRS-IV-Parent:Inv total score at 1, 2, and 3 months (study completers) and LOCF endpoint for the total patient sample is presented in Table 7. No statistically significant differences were found between the stimulant-naïve and non-stimulant-naïve patient subgroups.

The change from baseline in CGI-ADHD-S score at 1, 2, and 3 months (study completers) and LOCF endpoint for the total patient sample is presented in Table 11. There was a statistically significant difference between the stimulant-naïve and non-stimulant-naïve patient subgroups at Day 35 [mean change: -1.8 (stimulant-naïve), -1.4 (non-stimulant-naïve); p=.027].

Table 11. Change in CGI-ADHD-S Score from Baseline Over Time All Patients Enrolled

VISIT	N	MEAN (SD)	95% CI	MIN,MAX	CHANGE			
					MEAN (SD)	95% CI	MIN,MAX	P-VALUE [1]
Baseline	209	4.8 (0.87)	4.7, 5.0	3.0, 7.0				
Day 35	176	3.3 (1.16)	3.1, 3.4	1.0, 6.0	-1.6 (1.39)	-1.8, -1.4	-6.0, 1.0	<.001
Day 63	153	2.9 (1.20)	2.7, 3.1	1.0, 6.0	-1.9 (1.50)	-2.2, -1.7	-6.0, 1.0	<.001
Day 91	150	2.8 (1.23)	2.6, 3.0	1.0, 6.0	-2.1 (1.50)	-2.3, -1.8	-6.0, 1.0	<.001
LOCF	209	3.2 (1.37)	3.0, 3.4	1.0, 7.0	-1.7 (1.58)	-1.9, -1.5	-6.0, 2.0	<.001

Abbreviations: CGI-ADHD-S = Clinical Global Impressions – ADHD- Severity; CI = confidence interval; Max = maximum; Min = minimum; N = number of patients; SD = standard deviation.

[1] The p-value is based on paired t-test.

4) Impact of Data Collection Time Points on Efficacy, Functional Outcome, and QoL

The impact of data collection time points subgroup analyses were deemed statistically inappropriate because of the disproportionate number of patients in the subgroup with both baseline and endpoint occurring during the school year. At 3 months, the numbers in the four patient subgroups were: 1) both baseline and endpoint occurring during the school year (n=97); 2) baseline during the school year and endpoint during summer vacation (n=32); 3) baseline during summer vacation and endpoint during the school year (n=13); 4) both baseline and endpoint occurring during summer vacation (n=0). For eight patients it was unknown whether the endpoints occurred during the school year or summer vacation.

5) Evaluation of Psychometric Properties of the WFIRS-P

Internal consistency: The Cronbach's coefficient alpha on WFIRS-P variables within the same domain are presented in Table 12.

Convergent validity: The correlation between WFIRS-P and the Global Assessment of Functioning (GAF) score at each visit are presented in Table 13 (WFIRS-P: overall) and

Table 14 (WFIRS-P: domains). The correlation on change from baseline are presented in Table 15 (WFIRS-P: overall) and Table 16 (WFIRS-P: domains).

Discriminant analysis: The change in WFIRS-P (overall and domains) by change in ADHDRS-IV-Parent:Inv (total), ADHDRS-IV-Parent:Inv (Inattention), and ADHDRS-IV-Parent:Inv (Hyperactive/Impulsive) by visit are presented in Table 17, Table 18, and Table 19, respectively.

The change in WFIRS-P (overall and domains) by change in CGI-ADHD-S by visit is presented in Table 20 (improvement: CGI-ADHD-S score reduction by at least 1 point) and Table 21 (improvement: CGI-ADHD-S score reduction by at least 2 points).

**Table 12. Cronbach's Coefficient Alpha on WFIRS-P
All Patients Enrolled**

VISIT	WFIRS-P	N	CRONBACH'S COEFFICIENT ALPHA	
			RAW	STANDARDISED
Baseline	A: Family	154	0.910	0.910
	B: Learning and School	186	0.769	0.763
	C: Life Skills	202	0.749	0.747
	D: Child's Self-concept	208	0.875	0.875
	E: Social Activities	190	0.848	0.846
	F: Risky Activities	207	0.736	
	All Items	127	0.921	
Day 35	A: Family	136	0.911	0.911
	B: Learning and School	155	0.822	0.824
	C: Life Skills	156	0.746	0.753
	D: Child's Self-concept	176	0.805	0.807
	E: Social Activities	162	0.806	0.814
	F: Risky Activities	173	0.748	
	All Items	105	0.939	
Day 63	A: Family	121	0.926	0.927
	B: Learning and School	130	0.768	0.768
	C: Life Skills	138	0.715	0.709
	D: Child's Self-concept	153	0.808	0.810
	E: Social Activities	137	0.767	0.786
	F: Risky Activities	149	0.773	
	All Items	96	0.934	
Day 91	A: Family	125	0.937	0.937
	B: Learning and School	132	0.818	0.818
	C: Life Skills	138	0.749	0.752
	D: Child's Self-concept	150	0.827	0.828
Day 91	E: Social Activities	141	0.804	0.821
	F: Risky Activities	149	0.760	
	All Items	99	0.938	
LOCF	A: Family	175	0.939	0.939
	B: Learning and School	206	0.837	0.836
	C: Life Skills	210	0.764	0.763
	D: Child's Self-concept	210	0.832	0.832
	E: Social Activities	206	0.851	0.854
	F: Risky Activities	210	0.794	
	All Items	170	0.950	

Abbreviations: LOCF = last observation carried forward; N = number of patients; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

Note: Some standardized Cronbach's coefficients could not be calculated due to missing scores.

**Table 13. Correlation in Scores between GAF and WFIRS-P (Overall)
All Patients Enrolled by Visit**

		GAF				
		95 % CI				
VISIT	WFIRS-P	N	CORR	LOWER	UPPER	P-VALUE [1]
Day 35	WFIRS-P (Overall)	176	-0.368	-0.489	-0.232	<.001
Day 63	WFIRS-P (Overall)	153	-0.521	-0.628	-0.395	<.001
Day 91	WFIRS-P (Overall)	150	-0.580	-0.678	-0.463	<.001
LOCF	WFIRS-P (Overall)	209	-0.603	-0.683	-0.509	<.001

Abbreviations: CI = confidence interval; CORR = Pearson's correlation coefficient; GAF = Global Assessment of Functioning; LOCF = last observation carried forward; N = number of patients; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

[1] The p-value is under the null hypothesis of zero correlation.

**Table 14. Correlation in Raw Scores between GAF and WFIRS-P
(Domains) by Visit
All Patients Enrolled**

		GAF				
		95 % CI				
VISIT	WFIRS-P	N	CORR	LOWER	UPPER	P-VALUE [1]
Day 35	A: Family	176	-0.291	-0.421	-0.150	<.001
	B: Learning and School	166	-0.333	-0.462	-0.191	<.001
	C: Life Skills	176	-0.285	-0.416	-0.143	<.001
	D: Child's Self-concept	176	-0.255	-0.388	-0.111	<.001
	E: Social Activities	176	-0.242	-0.376	-0.097	0.001
	F: Risky Activities	176	-0.249	-0.383	-0.105	<.001
Day 63	A: Family	153	-0.461	-0.577	-0.326	<.001
	B: Learning and School	141	-0.427	-0.553	-0.282	<.001
	C: Life Skills	153	-0.355	-0.486	-0.208	<.001
	D: Child's Self-concept	153	-0.365	-0.495	-0.219	<.001
	E: Social Activities	153	-0.271	-0.412	-0.117	<.001
	F: Risky Activities	153	-0.398	-0.524	-0.256	<.001
Day 91	A: Family	150	-0.535	-0.641	-0.410	<.001
	B: Learning and School	142	-0.437	-0.562	-0.294	<.001
	C: Life Skills	150	-0.425	-0.548	-0.284	<.001
	D: Child's Self-concept	150	-0.402	-0.528	-0.258	<.001
	E: Social Activities	150	-0.452	-0.571	-0.315	<.001
	F: Risky Activities	150	-0.400	-0.527	-0.257	<.001
LOCF	A: Family	209	-0.509	-0.603	-0.401	<.001
	B: Learning and School	209	-0.547	-0.636	-0.445	<.001
	C: Life Skills	209	-0.455	-0.556	-0.340	<.001
LOCF	D: Child's Self-concept	209	-0.479	-0.577	-0.367	<.001
	E: Social Activities	209	-0.438	-0.541	-0.321	<.001
	F: Risky Activities	209	-0.467	-0.567	-0.354	<.001

Abbreviations: CI = confidence interval; CORR = Pearson's correlation coefficient; GAF = Global Assessment of Functioning; LOCF = last observation carried forward; N = number of patients; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

[1] The p-value is under the null hypothesis of zero correlation.

Table 15. Correlation in Change from Baseline between GAF and WFIRS-P (Overall) by Visit All Patients Enrolled

		GAF				
		95 % CI				
VISIT	WFIRS-P	N	CORR	LOWER	UPPER	P-VALUE [1]
Day 35	WFIRS-P (Overall)	176	-0.255	-0.389	-0.112	<.001
Day 63	WFIRS-P (Overall)	153	-0.220	-0.366	-0.063	0.006
Day 91	WFIRS-P (Overall)	150	-0.216	-0.364	-0.058	0.008
LOCF	WFIRS-P (Overall)	198	-0.370	-0.484	-0.243	<.001

Abbreviations: CI = confidence interval; CORR = Pearson's correlation coefficient; GAF = Global Assessment of Functioning; LOCF = last observation carried forward; N = number of patients; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

[1] The p-value is under the null hypothesis of zero correlation.

Table 16. Correlation in Change from Baseline between GAF and WFIRS-P (Domains) by Visit All Patients Enrolled

		GAF				
		95 % CI				
VISIT	WFIRS-P	N	CORR	LOWER	UPPER	P-VALUE [1]
Day 35	A: Family	176	-0.223	-0.359	-0.077	0.003
	B: Learning and School	165	-0.255	-0.393	-0.107	<.001
	C: Life Skills	176	-0.106	-0.250	0.042	0.161
	D: Child's Self-concept	176	-0.086	-0.231	0.063	0.258
	E: Social Activities	176	-0.154	-0.295	-0.006	0.042
	F: Risky Activities	176	-0.113	-0.257	0.036	0.136
Day 63	A: Family	153	-0.194	-0.342	-0.036	0.016
	B: Learning and School	140	-0.285	-0.431	-0.125	<.001
	C: Life Skills	153	-0.147	-0.298	0.012	0.071
	D: Child's Self-concept	153	-0.023	-0.181	0.136	0.781
	E: Social Activities	153	-0.067	-0.223	0.093	0.413
	F: Risky Activities	153	-0.035	-0.193	0.124	0.667
Day 91	A: Family	150	-0.144	-0.298	0.016	0.078
	B: Learning and School	141	-0.309	-0.452	-0.152	<.001
	C: Life Skills	150	-0.108	-0.264	0.053	0.189
	D: Child's Self-concept	150	-0.056	-0.215	0.105	0.494
	E: Social Activities	150	-0.174	-0.325	-0.014	0.033
	F: Risky Activities	150	0.041	-0.120	0.200	0.616
LOCF	A: Family	198	-0.285	-0.408	-0.152	<.001
	B: Learning and School	195	-0.400	-0.512	-0.275	<.001
	C: Life Skills	198	-0.249	-0.375	-0.113	<.001
LOCF	D: Child's Self-concept	198	-0.147	-0.281	-0.008	0.038
	E: Social Activities	198	-0.268	-0.393	-0.133	<.001
	F: Risky Activities	198	-0.128	-0.263	0.012	0.073

Abbreviations: CI = confidence interval; CORR = Pearson's correlation coefficient; GAF = Global Assessment of Functioning; LOCF = last observation carried forward; N = number of patients; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

[1] The p-value is under the null hypothesis of zero correlation.

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**Table 17. Change in WFIRS-P (Overall and Domains) by Change in ADHDRS-IV-Parent:Inv (Total) by Visit
All Patients Enrolled**

WFIRS-P	VISIT	CHANGE IN ADHDRS [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	IMPROVED	NO CHANGE	WORSENERD
Overall	Day 35	Improved (N=137)	137	0.64 (0.344)	-0.42 (0.326)	<.001	—	<.001	<.001
		No Change (N=29)	29	0.98 (0.321)	-0.21 (0.303)	<.001	<.001	—	0.804
		Worsened (N=9)	9	1.05 (0.570)	-0.21 (0.348)	0.108	<.001	0.804	—
	Day 63	Improved (N=131)	131	0.57 (0.288)	-0.49 (0.340)	<.001	—	<.001	<.001
		No Change (N=15)	15	1.00 (0.337)	-0.29 (0.256)	<.001	<.001	—	0.386
		Worsened (N=7)	7	1.04 (0.582)	-0.22 (0.293)	0.096	<.001	0.386	—
	Day 91	Improved (N=129)	129	0.54 (0.296)	-0.52 (0.354)	<.001	—	<.001	0.006
		No Change (N=15)	15	1.17 (0.440)	-0.14 (0.174)	0.006	<.001	—	0.248
		Worsened (N=6)	6	0.90 (0.442)	-0.35 (0.199)	0.008	0.006	0.248	—
	LOCF	Improved (N=144)	144	0.57 (0.343)	-0.51 (0.354)	<.001	—	<.001	<.001
		No Change (N=34)	34	1.06 (0.420)	-0.12 (0.185)	<.001	<.001	—	0.524
		Worsened (N=20)	20	1.12 (0.405)	-0.02 (0.361)	0.824	<.001	0.524	—
A: Family	Day 35	Improved (N=137)	137	0.72 (0.553)	-0.53 (0.535)	<.001	—	<.001	0.005
		No Change (N=29)	29	1.21 (0.545)	-0.27 (0.537)	0.013	<.001	—	0.711
		Worsened (N=9)	9	1.18 (0.790)	-0.22 (0.690)	0.357	0.005	0.711	—
	Day 63	Improved (N=131)	131	0.66 (0.507)	-0.60 (0.522)	<.001	—	0.008	<.001
		No Change (N=15)	15	1.18 (0.591)	-0.46 (0.381)	<.001	0.008	—	0.029
		Worsened (N=7)	7	1.42 (1.025)	0.05 (0.535)	0.810	<.001	0.029	—
	Day 91	Improved (N=129)	129	0.66 (0.541)	-0.60 (0.554)	<.001	—	<.001	0.047
		No Change (N=15)	15	1.18 (0.591)	-0.46 (0.381)	<.001	0.008	—	0.029
		Worsened (N=7)	7	1.42 (1.025)	0.05 (0.535)	0.810	<.001	0.029	—
	Day 35	Improved (N=137)	137	0.72 (0.553)	-0.53 (0.535)	<.001	—	<.001	0.005
		No Change (N=29)	29	1.21 (0.545)	-0.27 (0.537)	0.013	<.001	—	0.711
		Worsened (N=9)	9	1.18 (0.790)	-0.22 (0.690)	0.357	0.005	0.711	—

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**Table 17. Change in WFIRS-P (Overall and Domains) by Change in ADHDRS-IV-Parent:Inv (Total) by Visit
All Patients Enrolled**

WFIRS-P	VISIT	CHANGE IN ADHDRS [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	IMPROVED	NO CHANGE	WORSENER
A: Family	Day 91	No Change (N=15)	15	1.55 (0.778)	-0.21 (0.458)	0.103	<.001	—	0.479
		Worsened (N=6)	6	1.08 (0.960)	-0.32 (0.598)	0.247	0.047	0.479	—
	LOCF	Improved (N=144)	144	0.69 (0.582)	-0.58 (0.555)	<.001	—	<.001	<.001
		No Change (N=34)	34	1.27 (0.783)	-0.14 (0.389)	0.042	<.001	—	0.331
		Worsened (N=20)	20	1.42 (0.748)	0.13 (0.687)	0.420	<.001	0.331	—
B: Learning and School	Day 35	Improved (N=137)	131	0.77 (0.519)	-0.56 (0.569)	<.001	—	<.001	0.018
		No Change (N=29)	25	1.24 (0.612)	-0.27 (0.462)	0.008	<.001	—	0.948
		Worsened (N=9)	9	1.20 (0.792)	-0.06 (0.299)	0.606	0.018	0.948	—
	Day 63	Improved (N=131)	120	0.68 (0.444)	-0.64 (0.561)	<.001	—	<.001	0.462
		No Change (N=15)	15	1.19 (0.448)	-0.38 (0.592)	0.027	<.001	—	0.671
		Worsened (N=7)	6	1.03 (0.755)	-0.36 (0.297)	0.053	0.462	0.671	—
	Day 91	Improved (N=129)	121	0.61 (0.430)	-0.72 (0.604)	<.001	—	<.001	0.209
		No Change (N=15)	15	1.29 (0.623)	-0.11 (0.318)	0.189	<.001	—	0.233
		Worsened (N=6)	6	1.08 (0.467)	-0.34 (0.550)	0.239	0.209	0.233	—
	LOCF	Improved (N=144)	144	0.65 (0.467)	-0.71 (0.594)	<.001	—	<.001	<.001
		No Change (N=34)	34	1.32 (0.615)	-0.09 (0.362)	0.168	<.001	—	1.000
		Worsened (N=20)	20	1.33 (0.521)	-0.07 (0.589)	0.622	<.001	1.000	—
C: Life Skills	Day 35	Improved (N=137)	137	0.72 (0.397)	-0.46 (0.457)	<.001	—	<.001	0.007
		No Change (N=29)	29	1.07 (0.494)	-0.28 (0.490)	0.005	<.001	—	0.824

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**Table 17. Change in WFIRS-P (Overall and Domains) by Change in ADHDRS-IV-Parent:Inv (Total) by Visit
All Patients Enrolled (continued)**

WFIRS-P	VISIT	CHANGE IN ADHDRS [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	IMPROVED	NO CHANGE	WORSENERD
C: Life Skills	Day 35	Worsened (N=9)	9	1.29 (0.602)	-0.31 (0.666)	0.204	0.007	0.824	—
	Day 63	Improved (N=131)	131	0.70 (0.397)	-0.50 (0.455)	<.001	—	0.010	<.001
		No Change (N=15)	15	1.05 (0.427)	-0.31 (0.497)	0.031	0.010	—	0.296
		Worsened (N=7)	7	1.23 (0.566)	-0.13 (0.390)	0.395	<.001	0.296	—
	Day 91	Improved (N=129)	129	0.65 (0.361)	-0.53 (0.459)	<.001	—	<.001	0.041
		No Change (N=15)	15	1.16 (0.637)	-0.22 (0.260)	0.006	<.001	—	0.838
		Worsened (N=6)	6	0.98 (0.354)	-0.32 (0.549)	0.210	0.041	0.838	—
	LOCF	Improved (N=144)	144	0.68 (0.393)	-0.53 (0.463)	<.001	—	<.001	<.001
		No Change (N=34)	34	1.12 (0.493)	-0.22 (0.334)	<.001	<.001	—	0.380
		Worsened (N=20)	20	1.22 (0.494)	-0.04 (0.483)	0.719	<.001	0.380	—
D: Child's Self-concept	Day 35	Improved (N=137)	137	0.78 (0.608)	-0.43 (0.744)	<.001	—	0.095	0.001
		No Change (N=29)	29	1.02 (0.556)	-0.14 (0.654)	0.247	0.095	—	0.104
		Worsened (N=9)	9	1.56 (0.957)	-0.07 (1.267)	0.865	0.001	0.104	—
	Day 63	Improved (N=131)	131	0.60 (0.552)	-0.60 (0.676)	<.001	—	0.002	0.048
		No Change (N=15)	15	1.16 (0.744)	-0.29 (0.765)	0.166	0.002	—	0.997
		Worsened (N=7)	7	1.19 (0.858)	-0.57 (0.535)	0.030	0.048	0.997	—
	Day 91	Improved (N=129)	129	0.58 (0.534)	-0.57 (0.678)	<.001	—	<.001	0.963
		No Change (N=15)	15	1.44 (0.793)	-0.36 (0.811)	0.112	<.001	—	0.045
		Worsened (N=6)	6	0.61 (0.491)	-0.50 (0.913)	0.237	0.963	0.045	—

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**Table 17. Change in WFIRS-P (Overall and Domains) by Change in ADHDRS-IV-Parent:Inv (Total) by Visit
All Patients Enrolled (continued)**

WFIRS-P	VISIT	CHANGE IN ADHDRS [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	IMPROVED	NO CHANGE	WORSENER
D: Child's Self-concept	LOCF	Improved (N=144)	144	0.62 (0.566)	-0.53 (0.687)	<.001	—	<.001	0.001
		No Change (N=34)	34	1.30 (0.679)	-0.20 (0.809)	0.167	<.001	—	0.770
		Worsened (N=20)	20	1.10 (0.659)	-0.16 (0.797)	0.386	0.001	0.770	—
E: Social Activities	Day 35	Improved (N=137)	137	0.66 (0.522)	-0.35 (0.477)	<.001	—	0.004	0.547
		No Change (N=29)	29	0.93 (0.537)	-0.11 (0.432)	0.163	0.004	—	0.665
		Worsened (N=9)	9	0.96 (0.733)	-0.36 (0.541)	0.081	0.547	0.665	—
	Day 63	Improved (N=131)	131	0.58 (0.467)	-0.43 (0.560)	<.001	—	0.033	0.984
		No Change (N=15)	15	0.95 (0.454)	-0.20 (0.439)	0.093	0.033	—	0.251
		Worsened (N=7)	7	0.59 (0.560)	-0.70 (0.930)	0.092	0.984	0.251	—
	Day 91	Improved (N=129)	129	0.51 (0.421)	-0.49 (0.526)	<.001	—	<.001	0.396
		No Change (N=15)	15	1.25 (0.573)	0.01 (0.391)	0.914	<.001	—	0.043
		Worsened (N=6)	6	0.83 (0.576)	-0.62 (0.194)	<.001	0.396	0.043	—
	LOCF	Improved (N=144)	144	0.54 (0.470)	-0.48 (0.531)	<.001	—	<.001	<.001
		No Change (N=34)	34	1.03 (0.604)	-0.01 (0.388)	0.859	<.001	—	0.566
		Worsened (N=20)	20	0.93 (0.648)	-0.12 (0.561)	0.354	<.001	0.566	—
F: Risky Activities	Day 35	Improved (N=137)	137	0.31 (0.257)	-0.18 (0.244)	<.001	—	0.003	0.229
		No Change (N=29)	29	0.48 (0.386)	-0.09 (0.269)	0.080	0.003	—	0.916
		Worsened (N=9)	9	0.48 (0.427)	-0.16 (0.188)	0.038	0.229	0.916	—
	Day 63	Improved (N=131)	131	0.26 (0.211)	-0.23 (0.258)	<.001	—	<.001	<.001

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**Table 17. Change in WFIRS-P (Overall and Domains) by Change in ADHDRS-IV-Parent:Inv (Total) by Visit
All Patients Enrolled (concluded)**

WFIRS-P	VISIT	CHANGE IN ADHDRS [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	IMPROVED	NO CHANGE	WORSENERD
F: Risky Activities	Day 63	No Change (N=15)	15	0.58 (0.420)	-0.09 (0.179)	0.063	<.001	—	0.132
		Worsened (N=7)	7	0.69 (0.616)	-0.03 (0.240)	0.776	<.001	0.132	—
	Day 91	Improved (N=129)	129	0.25 (0.227)	-0.23 (0.252)	<.001	—	<.001	0.008
		No Change (N=15)	15	0.59 (0.381)	-0.07 (0.175)	0.127	<.001	—	0.938
		Worsened (N=6)	6	0.57 (0.280)	-0.20 (0.253)	0.111	0.008	0.938	—
	LOCF	Improved (N=144)	144	0.27 (0.261)	-0.22 (0.256)	<.001	—	<.001	<.001
		No Change (N=34)	34	0.50 (0.402)	-0.06 (0.174)	0.071	<.001	—	0.100
		Worsened (N=20)	20	0.67 (0.373)	0.01 (0.334)	0.895	<.001	0.100	—

Abbreviations: ADHDRS-IV-Parent:Inv = Attention Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; LOCF = last observation carried forward; N = total number of patients (column 3); N = number of patients (column 4); SD = standard deviation; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

[1] Change in ADHDRS-IV-Parent:Inv: Improved = when percent change $\leq$ -25%; No Change = when percent change is $>$ -25% and $\leq$ 0%; Worsened = when percent change is $>$ 0%.

[2] The p-value within group is based on paired t-test.

[3] The p-value between groups is based on ANCOVA using pooled sites and baseline as covariates.

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Table 18. Change in WFIRS-P (Overall and Domains) by Change in ADHDRS-IV-Parent:Inv (Inattention) by Visit All Patients Enrolled

WFIRS-P	VISIT	CHANGE IN ADHDRS [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	IMPROVED	NO CHANGE	WORSENER
Overall	Day 35	Improved (N=140)	140	0.64 (0.318)	-0.42 (0.328)	<.001	—	<.001	<.001
		No Change (N=23)	23	0.97 (0.448)	-0.24 (0.305)	<.001	<.001	—	0.763
		Worsened (N=12)	12	1.10 (0.523)	-0.15 (0.332)	0.135	<.001	0.763	—
	Day 63	Improved (N=128)	128	0.57 (0.293)	-0.49 (0.342)	<.001	—	<.001	<.001
		No Change (N=20)	20	0.93 (0.362)	-0.33 (0.274)	<.001	<.001	—	0.043
		Worsened (N=5)	5	1.10 (0.580)	-0.12 (0.217)	0.297	<.001	0.043	—
	Day 91	Improved (N=131)	131	0.55 (0.302)	-0.51 (0.354)	<.001	—	<.001	0.004
		No Change (N=13)	13	1.11 (0.516)	-0.25 (0.299)	0.010	<.001	—	0.952
		Worsened (N=6)	6	1.02 (0.452)	-0.30 (0.280)	0.048	0.004	0.952	—
	LOCF	Improved (N=144)	144	0.58 (0.348)	-0.50 (0.350)	<.001	—	<.001	<.001
		No Change (N=36)	36	1.00 (0.433)	-0.14 (0.262)	0.003	<.001	—	0.208
		Worsened (N=18)	18	1.17 (0.406)	-0.01 (0.354)	0.916	<.001	0.208	—
A: Family	Day 35	Improved (N=140)	140	0.75 (0.546)	-0.52 (0.534)	<.001	—	0.031	<.001
		No Change (N=23)	23	1.08 (0.662)	-0.38 (0.600)	0.006	0.031	—	0.256
		Worsened (N=12)	12	1.30 (0.707)	-0.07 (0.516)	0.663	<.001	0.256	—
	Day 63	Improved (N=128)	128	0.67 (0.521)	-0.61 (0.517)	<.001	—	<.001	<.001
		No Change (N=20)	20	1.10 (0.606)	-0.33 (0.424)	0.002	<.001	—	0.124
		Worsened (N=5)	5	1.40 (1.071)	-0.00 (0.683)	0.995	<.001	0.124	—
	Day 91	Improved (N=131)	131	0.67 (0.547)	-0.58 (0.543)	<.001	—	0.002	0.004
		No Change (N=13)	13	1.11 (0.516)	-0.25 (0.299)	0.010	<.001	—	0.952
		Worsened (N=6)	6	1.02 (0.452)	-0.30 (0.280)	0.048	0.004	0.952	—
	LOCF	Improved (N=144)	144	0.58 (0.348)	-0.50 (0.350)	<.001	—	<.001	<.001
		No Change (N=36)	36	1.00 (0.433)	-0.14 (0.262)	0.003	<.001	—	0.208
		Worsened (N=18)	18	1.17 (0.406)	-0.01 (0.354)	0.916	<.001	0.208	—

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**Table 18. Change in WFIRS-P (Overall and Domains) by Change in ADHDRS-IV-Parent:Inv (Inattention) by Visit
All Patients Enrolled (continued)**

WFIRS-P	VISIT	CHANGE IN ADHDRS [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	IMPROVED	NO CHANGE	WORSENER
A: Family	Day 91	No Change (N=13)	13	1.36 (0.828)	-0.42 (0.575)	0.021	0.002		0.696
		Worsened (N=6)	6	1.50 (1.086)	-0.18 (0.776)	0.588	0.004	0.696	
	LOCF	Improved (N=144)	144	0.72 (0.613)	-0.57 (0.545)	<.001		<.001	<.001
		No Change (N=36)	36	1.12 (0.712)	-0.18 (0.523)	0.042	<.001		0.049
		Worsened (N=18)	18	1.52 (0.804)	0.15 (0.659)	0.363	<.001	0.049	
B: Learning and School	Day 35	Improved (N=140)	134	0.77 (0.503)	-0.55 (0.563)	<.001		<.001	0.027
		No Change (N=23)	20	1.25 (0.717)	-0.26 (0.503)	0.033	<.001		0.981
		Worsened (N=12)	11	1.25 (0.767)	-0.17 (0.437)	0.261	0.027	0.981	
	Day 63	Improved (N=128)	118	0.67 (0.445)	-0.64 (0.581)	<.001		<.001	0.174
		No Change (N=20)	18	1.16 (0.399)	-0.44 (0.421)	<.001	<.001		0.987
		Worsened (N=5)	5	1.10 (0.837)	-0.23 (0.263)	0.186	0.174	0.987	
	Day 91	Improved (N=131)	123	0.63 (0.439)	-0.71 (0.605)	<.001		<.001	0.222
		No Change (N=13)	13	1.26 (0.669)	-0.21 (0.435)	0.111	<.001		0.444
		Worsened (N=6)	6	1.08 (0.467)	-0.22 (0.517)	0.395	0.222	0.444	
	LOCF	Improved (N=144)	144	0.65 (0.467)	-0.71 (0.584)	<.001		<.001	<.001
		No Change (N=36)	36	1.33 (0.618)	-0.06 (0.424)	0.383	<.001		0.921
		Worsened (N=18)	18	1.32 (0.502)	-0.10 (0.586)	0.485	<.001	0.921	
C: Life Skills	Day 35	Improved (N=140)	140	0.71 (0.375)	-0.47 (0.458)	<.001		<.001	<.001
		No Change (N=23)	23	1.08 (0.522)	-0.28 (0.477)	0.011	<.001		0.364

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Table 18. Change in WFIRS-P (Overall and Domains) by Change in ADHDRS-IV-Parent:Inv (Inattention) by Visit All Patients Enrolled (continued)

WFIRS-P	VISIT	CHANGE IN ADHDRS [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	IMPROVED	NO CHANGE	WORSENERD
C: Life Skills	Day 35	Worsened (N=12)	12	1.38 (0.579)	-0.14 (0.579)	0.409	<.001	0.364	—
	Day 63	Improved (N=128)	128	0.70 (0.407)	-0.50 (0.455)	<.001	—	0.008	<.001
		No Change (N=20)	20	0.99 (0.432)	-0.35 (0.448)	0.002	0.008	—	0.034
		Worsened (N=5)	5	1.28 (0.455)	0.07 (0.379)	0.687	<.001	0.034	—
	Day 91	Improved (N=131)	131	0.66 (0.359)	-0.52 (0.456)	<.001	—	<.001	0.373
		No Change (N=13)	13	1.17 (0.726)	-0.24 (0.443)	0.076	<.001	—	0.519
		Worsened (N=6)	6	0.90 (0.352)	-0.47 (0.375)	0.027	0.373	0.519	—
	LOCF	Improved (N=144)	144	0.69 (0.391)	-0.52 (0.459)	<.001	—	<.001	<.001
		No Change (N=36)	36	1.10 (0.520)	-0.20 (0.398)	0.005	<.001	—	0.612
		Worsened (N=18)	18	1.19 (0.523)	-0.09 (0.474)	0.413	<.001	0.612	—
D: Child's Self-concept	Day 35	Improved (N=140)	140	0.77 (0.585)	-0.42 (0.743)	<.001	—	0.013	0.002
		No Change (N=23)	23	1.16 (0.576)	-0.25 (0.683)	0.098	0.013	—	0.485
		Worsened (N=12)	12	1.36 (1.010)	0.07 (1.081)	0.828	0.002	0.485	—
	Day 63	Improved (N=128)	128	0.61 (0.543)	-0.57 (0.667)	<.001	—	0.330	<.001
		No Change (N=20)	20	0.92 (0.794)	-0.55 (0.826)	0.008	0.330	—	0.018
		Worsened (N=5)	5	1.67 (0.667)	-0.60 (0.548)	0.070	<.001	0.018	—
	Day 91	Improved (N=131)	131	0.60 (0.535)	-0.56 (0.689)	<.001	—	0.043	0.363
		No Change (N=13)	13	1.26 (0.983)	-0.56 (0.762)	0.020	0.043	—	0.959
		Worsened (N=6)	6	0.94 (0.647)	-0.33 (0.894)	0.403	0.363	0.959	—

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**Table 18. Change in WFIRS-P (Overall and Domains) by Change in ADHDRS-IV-Parent:Inv (Inattention) by Visit
All Patients Enrolled (continued)**

WFIRS-P	VISIT	CHANGE IN ADHDRS [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	IMPROVED	NO CHANGE	WORSENERD
D: Child's Self-concept	LOCF	Improved (N=144)	144	0.62 (0.551)	-0.52 (0.695)	<.001	—	<.001	<.001
		No Change (N=36)	36	1.19 (0.710)	-0.30 (0.788)	0.030	<.001	—	0.456
		Worsened (N=18)	18	1.31 (0.709)	0.01 (0.755)	0.959	<.001	0.456	—
E: Social Activities	Day 35	Improved (N=140)	140	0.65 (0.497)	-0.33 (0.481)	<.001	—	0.024	0.513
		No Change (N=23)	23	0.96 (0.628)	-0.15 (0.366)	0.059	0.024	—	0.722
		Worsened (N=12)	12	1.06 (0.699)	-0.37 (0.608)	0.058	0.513	0.722	—
	Day 63	Improved (N=128)	128	0.58 (0.476)	-0.44 (0.558)	<.001	—	0.251	0.347
		No Change (N=20)	20	0.80 (0.476)	-0.27 (0.679)	0.087	0.251	—	0.853
		Worsened (N=5)	5	0.79 (0.471)	-0.49 (0.525)	0.108	0.347	0.853	—
	Day 91	Improved (N=131)	131	0.52 (0.423)	-0.46 (0.520)	<.001	—	<.001	0.081
		No Change (N=13)	13	1.19 (0.576)	-0.20 (0.592)	0.247	<.001	—	0.794
		Worsened (N=6)	6	1.07 (0.722)	-0.46 (0.474)	0.065	0.081	0.794	—
	LOCF	Improved (N=144)	144	0.54 (0.474)	-0.46 (0.528)	<.001	—	<.001	<.001
		No Change (N=36)	36	0.94 (0.591)	-0.13 (0.469)	0.096	<.001	—	0.872
		Worsened (N=18)	18	1.04 (0.688)	-0.04 (0.591)	0.758	<.001	0.872	—
F: Risky Activities	Day 35	Improved (N=140)	140	0.31 (0.238)	-0.18 (0.245)	<.001	—	0.012	0.041
		No Change (N=23)	23	0.51 (0.467)	-0.14 (0.287)	0.033	0.012	—	0.978
		Worsened (N=12)	12	0.46 (0.408)	-0.08 (0.160)	0.133	0.041	0.978	—
	Day 63	Improved (N=128)	128	0.26 (0.213)	-0.22 (0.254)	<.001	—	<.001	0.001

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Table 18. Change in WFIRS-P (Overall and Domains) by Change in ADHDRS-IV-Parent:Inv (Inattention) by Visit All Patients Enrolled (concluded)

WFIRS-P	VISIT	CHANGE IN ADHDRS [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	IMPROVED	NO CHANGE	WORSENERD
F: Risky Activities	Day 63	No Change (N=20)	20	0.55 (0.405)	-0.14 (0.245)	0.016	<.001	—	0.293
		Worsened (N=5)	5	0.70 (0.689)	-0.02 (0.268)	0.876	0.001	0.293	—
	Day 91	Improved (N=131)	131	0.26 (0.229)	-0.23 (0.253)	<.001	—	<.001	0.025
		No Change (N=13)	13	0.56 (0.425)	-0.09 (0.180)	0.089	<.001	—	0.986
		Worsened (N=6)	6	0.58 (0.279)	-0.20 (0.253)	0.111	0.025	0.986	—
	LOCF	Improved (N=144)	144	0.28 (0.264)	-0.22 (0.256)	<.001	—	<.001	<.001
		No Change (N=36)	36	0.48 (0.396)	-0.05 (0.187)	0.100	<.001	—	0.082
		Worsened (N=18)	18	0.69 (0.375)	0.02 (0.328)	0.832	<.001	0.082	—

Abbreviations: ADHDRS-IV-Parent:Inv = Attention Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; LOCF = last observation carried forward; N = total number of patients (column 3); N = number of patients (column 4); SD = standard deviation; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

[1] Change in ADHDRS-IV-Parent:Inv: Improved = when percent change $\leq$ -25%; No Change = when percent change is $>$ -25% and $\leq$ 0%; Worsened = when percent change is $>$ 0%.

[2] The p-value within group is based on paired t-test.

[3] The p-value between groups is based on ANCOVA using pooled sites and baseline as covariates.

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Table 19. Change in WFIRS-P (Overall and Domains) by Change in ADHDRS-IV-Parent:Inv (Hyperactive/Impulsive) by Visit All Patients Enrolled

WFIRS-P	VISIT	CHANGE IN ADHDRS [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	IMPROVED	NO CHANGE	WORSENERD
Overall	Day 35	Improved (N=134)	134	0.63 (0.329)	-0.41 (0.336)	<.001	—	0.001	<.001
		No Change (N=30)	30	0.96 (0.350)	-0.29 (0.269)	<.001	0.001	—	0.135
		Worsened (N=11)	11	1.11 (0.554)	-0.13 (0.346)	0.248	<.001	0.135	—
	Day 63	Improved (N=127)	127	0.58 (0.303)	-0.49 (0.349)	<.001	—	0.002	0.001
		No Change (N=19)	19	0.87 (0.351)	-0.32 (0.214)	<.001	0.002	—	0.418
		Worsened (N=7)	7	0.97 (0.592)	-0.25 (0.297)	0.067	0.001	0.418	—
	Day 91	Improved (N=128)	128	0.55 (0.306)	-0.52 (0.361)	<.001	—	<.001	0.004
		No Change (N=15)	15	1.06 (0.536)	-0.24 (0.219)	<.001	<.001	—	0.968
		Worsened (N=7)	7	0.90 (0.374)	-0.28 (0.197)	0.009	0.004	0.968	—
	LOCF	Improved (N=148)	148	0.58 (0.347)	-0.49 (0.365)	<.001	—	<.001	<.001
		No Change (N=32)	32	1.08 (0.485)	-0.17 (0.233)	<.001	<.001	—	0.580
		Worsened (N=18)	18	1.06 (0.356)	-0.01 (0.350)	0.869	<.001	0.580	—
A: Family	Day 35	Improved (N=134)	134	0.71 (0.547)	-0.51 (0.544)	<.001	—	0.062	<.001
		No Change (N=30)	30	1.16 (0.524)	-0.45 (0.462)	<.001	0.062	—	0.022
		Worsened (N=11)	11	1.33 (0.768)	-0.00 (0.694)	0.985	<.001	0.022	—
	Day 63	Improved (N=127)	127	0.68 (0.521)	-0.60 (0.515)	<.001	—	0.048	0.001
		No Change (N=19)	19	1.02 (0.646)	-0.47 (0.517)	<.001	0.048	—	0.174
		Worsened (N=7)	7	1.14 (1.063)	-0.08 (0.570)	0.725	0.001	0.174	—
	Day 91	Improved (N=128)	128	0.68 (0.572)	-0.59 (0.572)	<.001	—	0.003	0.021
		No Change (N=15)	15	1.06 (0.536)	-0.24 (0.219)	<.001	<.001	—	0.968
		Worsened (N=7)	7	0.90 (0.374)	-0.28 (0.197)	0.009	0.004	0.968	—
	LOCF	Improved (N=148)	148	0.58 (0.347)	-0.49 (0.365)	<.001	—	<.001	<.001
		No Change (N=32)	32	1.08 (0.485)	-0.17 (0.233)	<.001	<.001	—	0.580
		Worsened (N=18)	18	1.06 (0.356)	-0.01 (0.350)	0.869	<.001	0.580	—

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Table 19. Change in WFIRS-P (Overall and Domains) by Change in ADHDRS-IV-Parent:Inv (Hyperactive/Impulsive) by Visit All Patients Enrolled (continued)

WFIRS-P	VISIT	CHANGE IN ADHDRS [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	IMPROVED	NO CHANGE	WORSENERD
A: Family	Day 91	No Change (N=15)	15	1.32 (0.855)	-0.40 (0.440)	0.004	0.003		0.905
		Worsened (N=7)	7	1.04 (0.838)	-0.26 (0.451)	0.178	0.021	0.905	—
	LOCF	Improved (N=148)	148	0.70 (0.592)	-0.55 (0.567)	<.001		<.001	<.001
		No Change (N=32)	32	1.37 (0.833)	-0.18 (0.470)	0.034	<.001		0.508
		Worsened (N=18)	18	1.27 (0.666)	0.09 (0.652)	0.558	<.001	0.508	—
B: Learning and School	Day 35	Improved (N=134)	128	0.75 (0.508)	-0.57 (0.577)	<.001		<.001	<.001
		No Change (N=30)	27	1.20 (0.580)	-0.29 (0.374)	<.001	<.001		0.381
		Worsened (N=11)	10	1.45 (0.753)	0.02 (0.356)	0.856	<.001	0.381	—
	Day 63	Improved (N=127)	116	0.71 (0.462)	-0.65 (0.558)	<.001		0.278	0.304
		No Change (N=19)	19	0.89 (0.483)	-0.39 (0.600)	0.010	0.278		0.837
		Worsened (N=7)	6	1.17 (0.734)	-0.38 (0.311)	0.053	0.304	0.837	—
	Day 91	Improved (N=128)	120	0.62 (0.439)	-0.72 (0.610)	<.001		<.001	0.024
		No Change (N=15)	15	1.15 (0.608)	-0.16 (0.460)	0.204	<.001		0.987
		Worsened (N=7)	7	1.17 (0.591)	-0.40 (0.311)	0.014	0.024	0.987	—
	LOCF	Improved (N=148)	148	0.67 (0.474)	-0.67 (0.603)	<.001		<.001	<.001
		No Change (N=32)	32	1.33 (0.617)	-0.16 (0.470)	0.078	<.001		0.934
		Worsened (N=18)	18	1.31 (0.582)	-0.09 (0.538)	0.491	<.001	0.934	—
C: Life Skills	Day 35	Improved (N=134)	134	0.73 (0.400)	-0.44 (0.478)	<.001		0.127	0.009
		No Change (N=30)	30	1.00 (0.494)	-0.41 (0.377)	<.001	0.127	—	0.286

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Table 19. Change in WFIRS-P (Overall and Domains) by Change in ADHDRS-IV-Parent:Inv (Hyperactive/Impulsive) by Visit
All Patients Enrolled (continued)

WFIRS-P	VISIT	CHANGE IN ADHDRS [1]	N	MEAN (SD)	ADHDRS [2]		CT CHANGE [3]		
					MEAN (SD)	P [2]	IMPROVED	NO CHANGE	WORSENERD
C: Life Skills	Day 35	Worsened (N=11)	11	1.20 (0.663)	-0.26 (0.694)	0.245	0.009	0.286	—
		Improved (N=127)	127	0.68 (0.396)	-0.49 (0.476)	<.001	—	0.010	0.006
		No Change (N=19)	19	1.07 (0.384)	-0.36 (0.347)	<.001	0.010	—	0.547
	Day 63	Worsened (N=7)	7	1.17 (0.589)	-0.18 (0.389)	0.272	0.006	0.547	—
		Improved (N=128)	128	0.66 (0.369)	-0.52 (0.465)	<.001	—	<.001	0.034
		No Change (N=15)	15	1.11 (0.656)	-0.33 (0.299)	<.001	<.001	—	0.999
	Day 91	Worsened (N=7)	7	0.95 (0.236)	-0.20 (0.445)	0.269	0.034	0.999	—
		Improved (N=148)	148	0.70 (0.406)	-0.51 (0.468)	<.001	—	<.001	<.001
		No Change (N=32)	32	1.11 (0.558)	-0.29 (0.368)	<.001	<.001	—	0.398
	LOCF	Worsened (N=18)	18	1.15 (0.434)	0.01 (0.442)	0.930	<.001	0.398	—
		Improved (N=134)	134	0.76 (0.590)	-0.43 (0.732)	<.001	—	0.024	0.001
		No Change (N=30)	30	1.08 (0.682)	-0.17 (0.834)	0.283	0.024	—	0.237
D: Child's Self-concept	Day 35	Worsened (N=11)	11	1.48 (0.736)	-0.15 (0.959)	0.612	0.001	0.237	—
		Improved (N=127)	127	0.63 (0.594)	-0.59 (0.693)	<.001	—	0.347	0.069
		No Change (N=19)	19	0.88 (0.621)	-0.47 (0.612)	0.003	0.347	—	0.464
	Day 63	Worsened (N=7)	7	1.10 (0.833)	-0.38 (0.705)	0.203	0.069	0.464	—
		Improved (N=128)	128	0.58 (0.548)	-0.59 (0.687)	<.001	—	<.001	0.594
		No Change (N=15)	15	1.33 (0.745)	-0.24 (0.718)	0.208	<.001	—	0.161
	Day 91	Worsened (N=7)	7	0.90 (0.659)	-0.52 (0.836)	0.148	0.594	0.161	—

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Table 19. Change in WFIRS-P (Overall and Domains) by Change in ADHDRS-IV-Parent:Inv (Hyperactive/Impulsive) by Visit All Patients Enrolled (continued)

WFIRS-P	VISIT	CHANGE IN ADHDRS [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	IMPROVED	NO CHANGE	WORSENERD
D: Child's Self-concept	LOCF	Improved (N=148)	148	0.64 (0.587)	-0.52 (0.701)	<.001	—	<.001	0.002
		No Change (N=32)	32	1.23 (0.664)	-0.16 (0.812)	0.285	<.001	—	0.910
		Worsened (N=18)	18	1.20 (0.658)	-0.23 (0.721)	0.191	0.002	0.910	—
E: Social Activities	Day 35	Improved (N=134)	134	0.66 (0.516)	-0.34 (0.471)	<.001	—	0.025	0.438
		No Change (N=30)	30	0.90 (0.555)	-0.18 (0.516)	0.070	0.025	—	0.884
		Worsened (N=11)	11	0.94 (0.732)	-0.29 (0.441)	0.054	0.438	0.884	—
	Day 63	Improved (N=127)	127	0.58 (0.467)	-0.44 (0.569)	<.001	—	0.026	0.758
		No Change (N=19)	19	0.88 (0.502)	-0.17 (0.350)	0.051	0.026	—	0.089
		Worsened (N=7)	7	0.52 (0.477)	-0.77 (0.895)	0.063	0.758	0.089	—
	Day 91	Improved (N=128)	128	0.52 (0.445)	-0.48 (0.533)	<.001	—	<.001	0.155
		No Change (N=15)	15	1.08 (0.632)	-0.09 (0.392)	0.371	<.001	—	0.574
		Worsened (N=7)	7	0.90 (0.428)	-0.39 (0.404)	0.043	0.155	0.574	—
	LOCF	Improved (N=148)	148	0.56 (0.492)	-0.46 (0.545)	<.001	—	<.001	0.004
		No Change (N=32)	32	0.98 (0.672)	-0.06 (0.385)	0.360	<.001	—	0.898
		Worsened (N=18)	18	0.92 (0.513)	-0.11 (0.539)	0.389	0.004	0.898	—
F: Risky Activities	Day 35	Improved (N=134)	134	0.29 (0.246)	-0.18 (0.241)	<.001	—	0.001	0.121
		No Change (N=30)	30	0.54 (0.377)	-0.12 (0.283)	0.028	0.001	—	0.919
		Worsened (N=11)	11	0.50 (0.388)	-0.13 (0.205)	0.061	0.121	0.919	—
	Day 63	Improved (N=127)	127	0.27 (0.235)	-0.23 (0.260)	<.001	—	0.002	<.001

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Table 19. Change in WFIRS-P (Overall and Domains) by Change in ADHDRS-IV-Parent:Inv (Hyperactive/Impulsive) by Visit All Patients Enrolled (concluded)

WFIRS-P	VISIT	CHANGE IN ADHDRS [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	IMPROVED	NO CHANGE	WORSENERD
F: Risky Activities	Day 63	No Change (N=19)	19	0.48 (0.335)	-0.13 (0.196)	0.009	0.002		0.195
		Worsened (N=7)	7	0.63 (0.644)	-0.03 (0.240)	0.776	<.001	0.195	—
	Day 91	Improved (N=128)	128	0.26 (0.228)	-0.23 (0.256)	<.001		0.010	0.001
		No Change (N=15)	15	0.54 (0.455)	-0.19 (0.217)	0.005	0.010		0.342
		Worsened (N=7)	7	0.49 (0.157)	-0.07 (0.125)	0.182	0.001	0.342	—
	LOCF	Improved (N=148)	148	0.27 (0.250)	-0.21 (0.256)	<.001		<.001	<.001
		No Change (N=32)	32	0.58 (0.459)	-0.13 (0.205)	0.001	<.001		0.050
		Worsened (N=18)	18	0.58 (0.349)	0.08 (0.301)	0.257	<.001	0.050	—

Abbreviations: ADHDRS-IV-Parent:Inv = Attention Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; LOCF = last observation carried forward; N = total number of patients (column 3); N = number of patients (column 4); SD = standard deviation; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

[1] Change in ADHDRS-IV-Parent:Inv: Improved = when percent change $\leq$ -25%; No Change = when percent change is $>$ -25% and $\leq$ 0%; Worsened = when percent change is $>$ 0%.

[2] The p-value within group is based on paired t-test.

[3] The p-value between groups is based on ANCOVA using pooled sites and baseline as covariates.

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**Table 20. Change in WFIRS-P (Overall and Domains) by Change in CGI-ADHD-S (First Set) by Visit
All Patients Enrolled**

WFIRS-P	VISIT	CHANGE IN CGI-S [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	GRP1	GRP2	GRP3
Overall	Day 35	Group 1 (N=139)	139	0.69 (0.394)	-0.41 (0.336)	<.001	—	0.004	0.030
		Group 2 (N=34)	34	0.81 (0.319)	-0.25 (0.289)	<.001	0.004	—	0.333
		Group 3 (N=3)	3	1.22 (0.483)	-0.21 (0.349)	0.399	0.030	0.333	—
	Day 63	Group 1 (N=128)	128	0.60 (0.325)	-0.48 (0.337)	<.001	—	0.079	0.003
		Group 2 (N=22)	22	0.74 (0.308)	-0.39 (0.346)	<.001	0.079	—	0.069
		Group 3 (N=3)	3	1.23 (0.778)	-0.13 (0.158)	0.280	0.003	0.069	—
	Day 91	Group 1 (N=126)	126	0.56 (0.353)	-0.52 (0.359)	<.001	—	<.001	0.044
		Group 2 (N=23)	23	0.85 (0.339)	-0.28 (0.256)	<.001	<.001	—	0.300
		Group 3 (N=1)	1				0.044	0.300	—
	LOCF	Group 1 (N=150)	150	0.61 (0.389)	-0.48 (0.381)	<.001	—	<.001	<.001
		Group 2 (N=50)	50	0.97 (0.437)	-0.17 (0.284)	<.001	<.001	—	0.049
		Group 3 (N=6)	6	1.42 (0.354)	-0.05 (0.221)	0.607	<.001	0.049	—
A: Family	Day 35	Group 1 (N=139)	139	0.79 (0.588)	-0.52 (0.552)	<.001	—	0.005	0.559
		Group 2 (N=34)	34	1.00 (0.651)	-0.25 (0.498)	0.007	0.005	—	0.995
		Group 3 (N=3)	3	1.09 (0.417)	-0.49 (0.553)	0.268	0.559	0.995	—
	Day 63	Group 1 (N=128)	128	0.71 (0.552)	-0.58 (0.505)	<.001	—	0.555	0.013
		Group 2 (N=22)	22	0.88 (0.577)	-0.48 (0.588)	0.001	0.555	—	0.059
		Group 3 (N=3)	3	1.53 (1.306)	-0.02 (0.828)	0.977	0.013	0.059	—
	Day 91	Group 1 (N=126)	126	0.69 (0.602)	-0.61 (0.544)	<.001	—	0.001	0.018
		Group 2 (N=23)	23	1.09 (0.702)	-0.27 (0.552)	0.029	0.001	—	0.140

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**Table 20. Change in WFIRS-P (Overall and Domains) by Change in CGI-ADHD-S (First Set) by Visit
All Patients Enrolled (continued)**

WFIRS-P	VISIT	CHANGE IN CGI-S[1]	N	MEAN (SD)	CHANGE		P-VALUE[3]		
					MEAN (SD)	P[2]	GRP1	GRP2	GRP3
A: Family	Day 91	Group 3 (N=1)	1				0.018	0.140	—
	LOCF	Group 1 (N=150)	150	0.75 (0.634)	-0.56 (0.586)	<.001	—	<.001	<.001
		Group 2 (N=50)	50	1.16 (0.786)	-0.12 (0.507)	0.107	<.001	—	0.152
		Group 3 (N=6)	6	1.78 (0.515)	0.14 (0.323)	0.344	<.001	0.152	—
B: Learning and School	Day 35	Group 1 (N=139)	133	0.83 (0.584)	-0.54 (0.584)	<.001	—	0.052	0.328
		Group 2 (N=34)	30	0.99 (0.525)	-0.29 (0.406)	<.001	0.052	—	0.859
		Group 3 (N=3)	3	1.20 (0.700)	-0.40 (0.400)	0.225	0.328	0.859	—
	Day 63	Group 1 (N=128)	118	0.70 (0.425)	-0.63 (0.574)	<.001	—	0.040	0.826
		Group 2 (N=22)	20	0.95 (0.632)	-0.47 (0.485)	<.001	0.040	—	0.941
		Group 3 (N=3)	3	1.37 (1.026)	-0.15 (0.212)	0.500	0.826	0.941	—
	Day 91	Group 1 (N=126)	118	0.66 (0.508)	-0.71 (0.619)	<.001	—	0.041	—
		Group 2 (N=23)	23	0.88 (0.386)	-0.33 (0.435)	0.002	0.041	—	—
		Group 3 (N=1)	1						
	LOCF	Group 1 (N=150)	150	0.72 (0.544)	-0.66 (0.618)	<.001	—	<.001	0.007
		Group 2 (N=50)	50	1.18 (0.600)	-0.17 (0.467)	0.016	<.001	—	0.442
		Group 3 (N=6)	6	1.60 (0.341)	-0.31 (0.690)	0.439	0.007	0.442	—
C: Life Skills	Day 35	Group 1 (N=139)	139	0.77 (0.449)	-0.47 (0.472)	<.001	—	0.058	0.038
		Group 2 (N=34)	34	0.92 (0.450)	-0.29 (0.460)	<.001	0.058	—	0.221
		Group 3 (N=3)	3	1.40 (0.529)	-0.10 (0.608)	0.803	0.038	0.221	—

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**Table 20. Change in WFIRS-P (Overall and Domains) by Change in CGI-ADHD-S (First Set) by Visit
All Patients Enrolled (continued)**

WFIRS-P	VISIT	CHANGE IN CGI-S[1]	N	MEAN (SD)	CHANGE		P-VALUE[3]		
					MEAN (SD)	P[2]	GRP1	GRP2	GRP3
C: Life Skills	Day 63	Group 1 (N=128)	128	0.72 (0.417)	-0.50 (0.448)	<.001	—	0.091	0.060
		Group 2 (N=22)	22	0.85 (0.411)	-0.29 (0.535)	0.019	0.091	—	0.397
		Group 3 (N=3)	3	1.37 (0.777)	-0.21 (0.184)	0.185	0.060	0.397	—
	Day 91	Group 1 (N=126)	126	0.67 (0.404)	-0.51 (0.476)	<.001	—	0.013	0.459
		Group 2 (N=23)	23	0.97 (0.437)	-0.37 (0.310)	<.001	0.013	—	0.855
		Group 3 (N=1)	1				0.459	0.855	—
	LOCF	Group 1 (N=150)	150	0.72 (0.433)	-0.48 (0.490)	<.001	—	<.001	<.001
		Group 2 (N=50)	50	1.02 (0.486)	-0.29 (0.375)	<.001	<.001	—	0.031
		Group 3 (N=6)	6	1.52 (0.496)	-0.13 (0.627)	0.630	<.001	0.031	—
D: Child's Self-concept	Day 35	Group 1 (N=139)	139	0.84 (0.661)	-0.42 (0.757)	<.001	—	0.353	0.017
		Group 2 (N=34)	34	0.92 (0.641)	-0.20 (0.792)	0.158	0.353	—	0.060
		Group 3 (N=3)	3	1.67 (0.667)	0.33 (0.333)	0.225	0.017	0.060	—
	Day 63	Group 1 (N=128)	128	0.67 (0.624)	-0.56 (0.681)	<.001	—	0.786	0.884
		Group 2 (N=22)	22	0.76 (0.619)	-0.62 (0.715)	<.001	0.786	—	0.983
		Group 3 (N=3)	3	0.67 (0.333)	-0.44 (0.694)	0.383	0.884	0.983	—
	Day 91	Group 1 (N=126)	126	0.60 (0.579)	-0.61 (0.701)	<.001	—	<.001	0.927
		Group 2 (N=23)	23	1.06 (0.686)	-0.20 (0.609)	0.124	<.001	—	0.869
		Group 3 (N=1)	1				0.927	0.869	—
	LOCF	Group 1 (N=150)	150	0.65 (0.595)	-0.54 (0.712)	<.001	—	<.001	<.001
		Group 2 (N=50)	50	1.17 (0.674)	-0.15 (0.723)	0.160	<.001	—	0.285

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**Table 20. Change in WFIRS-P (Overall and Domains) by Change in CGI-ADHD-S (First Set) by Visit
All Patients Enrolled (continued)**

WFIRS-P	VISIT	CHANGE IN CGI-S [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	GRP1	GRP2	GRP3
D: Child's Self-concept	LOCF	Group 3 (N=6)	6	1.56 (0.807)	0.00 (0.632)	1.000	<.001	0.285	—
E: Social Activities	Day 35	Group 1 (N=139)	139	0.70 (0.569)	-0.33 (0.484)	<.001	—	0.345	0.004
		Group 2 (N=34)	34	0.74 (0.405)	-0.25 (0.458)	0.003	0.345	—	0.019
		Group 3 (N=3)	3	1.95 (0.459)	-0.05 (0.330)	0.826	0.004	0.019	—
	Day 63	Group 1 (N=128)	128	0.57 (0.470)	-0.45 (0.590)	<.001	—	0.032	0.058
		Group 2 (N=22)	22	0.77 (0.476)	-0.26 (0.411)	0.007	0.032	—	0.490
		Group 3 (N=3)	3	1.19 (0.502)	-0.38 (0.861)	0.524	0.058	0.490	—
	Day 91	Group 1 (N=126)	126	0.52 (0.458)	-0.49 (0.545)	<.001	—	<.001	0.074
		Group 2 (N=23)	23	0.94 (0.493)	-0.19 (0.338)	0.011	<.001	—	0.415
		Group 3 (N=1)	1				0.074	0.415	—
	LOCF	Group 1 (N=150)	150	0.56 (0.499)	-0.47 (0.564)	<.001	—	<.001	0.001
		Group 2 (N=50)	50	0.99 (0.666)	-0.09 (0.447)	0.160	<.001	—	0.393
		Group 3 (N=6)	6	1.40 (0.805)	-0.18 (0.246)	0.136	0.001	0.393	—
F: Risky Activities	Day 35	Group 1 (N=139)	139	0.34 (0.304)	-0.16 (0.234)	<.001	—	0.758	0.457
		Group 2 (N=34)	34	0.34 (0.290)	-0.18 (0.294)	0.001	0.758	—	0.609
		Group 3 (N=3)	3	0.57 (0.351)	-0.17 (0.252)	0.370	0.457	0.609	—
	Day 63	Group 1 (N=128)	128	0.29 (0.268)	-0.20 (0.247)	<.001	—	0.997	0.016
		Group 2 (N=22)	22	0.35 (0.232)	-0.23 (0.285)	0.001	0.997	—	0.026
		Group 3 (N=3)	3	0.87 (0.925)	-0.10 (0.453)	0.748	0.016	0.026	—

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**Table 20. Change in WFIRS-P (Overall and Domains) by Change in CGI-ADHD-S (First Set) by Visit
All Patients Enrolled (concluded)**

WFIRS-P	VISIT	CHANGE IN CGI-S [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	GRP1	GRP2	GRP3
F: Risky Activities	Day 91	Group 1 (N=126)	126	0.28 (0.264)	-0.21 (0.249)	<.001	—	0.472	0.308
		Group 2 (N=23)	23	0.36 (0.259)	-0.22 (0.257)	<.001	0.472	—	0.461
		Group 3 (N=1)	1				0.308	0.461	—
	LOCF	Group 1 (N=150)	150	0.31 (0.286)	-0.20 (0.255)	<.001	—	0.004	<.001
		Group 2 (N=50)	50	0.46 (0.389)	-0.12 (0.282)	0.007	0.004	—	0.055
		Group 3 (N=6)	6	0.77 (0.398)	0.02 (0.366)	0.915	<.001	0.055	—

Abbreviations: CGI-ADHD-S = Clinical Global Impressions – ADHD – Severity; GRP = group; LOCF = last observation carried forward; N = total number of patients (column 3); N = number of patients (column 4); SD = standard deviation; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

[1] Change in CGI-S (first set): Group 1 = reduction of at least 1 point; Group 2 = no change; Group 3 = worsened.

[2] The p-value within group is based on paired t-test.

[3] The p-value between groups is based on ANCOVA using pooled sites and baseline as covariates.

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**Table 21. Change in WFIRS-P (Overall and Domains) by Change in CGI-ADHD-S (Second Set) by Visit
All Patients Enrolled**

WFIRS-P	VISIT	CHANGE IN CGI-S [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	GRP1	GRP2	GRP3
Overall	Day 35	Group 1 (N=75)	75	0.63 (0.373)	-0.45 (0.358)	<.001	—	0.098	0.042
		Group 2 (N=98)	98	0.78 (0.379)	-0.32 (0.304)	<.001	0.098	—	0.165
		Group 3 (N=3)	3	1.22 (0.483)	-0.21 (0.349)	0.399	0.042	0.165	—
	Day 63	Group 1 (N=84)	84	0.54 (0.311)	-0.53 (0.352)	<.001	—	<.001	<.001
		Group 2 (N=66)	66	0.73 (0.316)	-0.38 (0.305)	<.001	<.001	—	0.024
		Group 3 (N=3)	3	1.23 (0.778)	-0.13 (0.158)	0.280	<.001	0.024	—
	Day 91	Group 1 (N=91)	91	0.53 (0.348)	-0.54 (0.371)	<.001	—	0.003	0.044
		Group 2 (N=58)	58	0.73 (0.362)	-0.38 (0.309)	<.001	0.003	—	0.175
		Group 3 (N=1)	1				0.044	0.175	—
	LOCF	Group 1 (N=100)	100	0.57 (0.395)	-0.53 (0.372)	<.001	—	<.001	<.001
		Group 2 (N=100)	100	0.83 (0.424)	-0.27 (0.350)	<.001	<.001	—	0.006
		Group 3 (N=6)	6	1.42 (0.354)	-0.05 (0.221)	0.607	<.001	0.006	—
A: Family	Day 35	Group 1 (N=75)	75	0.73 (0.559)	-0.60 (0.580)	<.001	—	0.107	0.611
		Group 2 (N=98)	98	0.90 (0.630)	-0.37 (0.510)	<.001	0.107	—	0.955
		Group 3 (N=3)	3	1.09 (0.417)	-0.49 (0.553)	0.268	0.611	0.955	—
	Day 63	Group 1 (N=84)	84	0.61 (0.473)	-0.66 (0.505)	<.001	—	0.005	0.002
		Group 2 (N=66)	66	0.88 (0.619)	-0.45 (0.512)	<.001	0.005	—	0.044
		Group 3 (N=3)	3	1.53 (1.306)	-0.02 (0.828)	0.977	0.002	0.044	—
	Day 91	Group 1 (N=91)	91	0.63 (0.577)	-0.63 (0.566)	<.001	—	0.019	0.019

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**Table 21. Change in WFIRS-P (Overall and Domains) by Change in CGI-ADHD-S (Second Set) by Visit
All Patients Enrolled (continued)**

WFIRS-P	VISIT	CHANGE IN CGI-S [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	GRP1	GRP2	GRP3
A: Family	Day 91	Group 2 (N=58)	58	0.94 (0.674)	-0.44 (0.528)	<.001	0.019	—	0.072
		Group 3 (N=1)	1				0.019	0.072	—
	LOCF	Group 1 (N=100)	100	0.68 (0.618)	-0.62 (0.554)	<.001	—	<.001	<.001
		Group 2 (N=100)	100	1.03 (0.729)	-0.29 (0.595)	<.001	<.001	—	0.033
		Group 3 (N=6)	6	1.78 (0.515)	0.14 (0.323)	0.344	<.001	0.033	—
B: Learning and School	Day 35	Group 1 (N=75)	73	0.73 (0.539)	-0.63 (0.608)	<.001	—	0.069	0.275
		Group 2 (N=98)	90	0.96 (0.586)	-0.39 (0.505)	<.001	0.069	—	0.703
		Group 3 (N=3)	3	1.20 (0.700)	-0.40 (0.400)	0.225	0.275	0.703	—
	Day 63	Group 1 (N=84)	80	0.65 (0.410)	-0.73 (0.603)	<.001	—	0.001	0.534
		Group 2 (N=66)	58	0.86 (0.515)	-0.45 (0.462)	<.001	0.001	—	1.000
		Group 3 (N=3)	3	1.37 (1.026)	-0.15 (0.212)	0.500	0.534	1.000	—
	Day 91	Group 1 (N=91)	86	0.60 (0.425)	-0.76 (0.593)	<.001	—	<.001	—
		Group 2 (N=58)	55	0.85 (0.561)	-0.46 (0.590)	<.001	<.001	—	—
		Group 3 (N=1)	1						
	LOCF	Group 1 (N=100)	100	0.64 (0.471)	-0.76 (0.588)	<.001	—	<.001	0.003
		Group 2 (N=100)	100	1.03 (0.638)	-0.32 (0.578)	<.001	<.001	—	0.186
		Group 3 (N=6)	6	1.60 (0.341)	-0.31 (0.690)	0.439	0.003	0.186	—
C: Life Skills	Day 35	Group 1 (N=75)	75	0.71 (0.413)	-0.48 (0.497)	<.001	—	0.568	0.067
		Group 2 (N=98)	98	0.87 (0.470)	-0.39 (0.455)	<.001	0.568	—	0.120

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**Table 21. Change in WFIRS-P (Overall and Domains) by Change in CGI-ADHD-S (Second Set) by Visit
All Patients Enrolled (continued)**

WFIRS-P	VISIT	CHANGE IN CGI-S[1]	N	MEAN (SD)	CHANGE		P-VALUE[3]		
					MEAN (SD)	P[2]	GRP1	GRP2	GRP3
C: Life Skills	Day 35	Group 3 (N=3)	3	1.40 (0.529)	-0.10 (0.608)	0.803	0.067	0.120	—
	Day 63	Group 1 (N=84)	84	0.62 (0.372)	-0.53 (0.459)	<.001	—	<.001	0.007
		Group 2 (N=66)	66	0.90 (0.419)	-0.38 (0.463)	<.001	<.001	—	0.226
		Group 3 (N=3)	3	1.37 (0.777)	-0.21 (0.184)	0.185	0.007	0.226	—
	Day 91	Group 1 (N=91)	91	0.65 (0.416)	-0.51 (0.473)	<.001	—	0.151	0.488
		Group 2 (N=58)	58	0.82 (0.414)	-0.45 (0.428)	<.001	0.151	—	0.704
		Group 3 (N=1)	1	—	—	—	0.488	0.704	—
	LOCF	Group 1 (N=100)	100	0.68 (0.445)	-0.53 (0.475)	<.001	—	0.002	<.001
		Group 2 (N=100)	100	0.91 (0.457)	-0.34 (0.453)	<.001	0.002	—	0.007
		Group 3 (N=6)	6	1.52 (0.496)	-0.13 (0.627)	0.630	<.001	0.007	—
D: Child's Self-concept	Day 35	Group 1 (N=75)	75	0.77 (0.600)	-0.41 (0.839)	<.001	—	0.881	0.030
		Group 2 (N=98)	98	0.93 (0.691)	-0.35 (0.711)	<.001	0.881	—	0.036
		Group 3 (N=3)	3	1.67 (0.667)	0.33 (0.333)	0.225	0.030	0.036	—
	Day 63	Group 1 (N=84)	84	0.60 (0.626)	-0.56 (0.686)	<.001	—	0.579	0.813
		Group 2 (N=66)	66	0.78 (0.606)	-0.58 (0.685)	<.001	0.579	—	0.960
		Group 3 (N=3)	3	0.67 (0.333)	-0.44 (0.694)	0.383	0.813	0.960	—
	Day 91	Group 1 (N=91)	91	0.56 (0.594)	-0.60 (0.689)	<.001	—	0.082	0.932
		Group 2 (N=58)	58	0.83 (0.625)	-0.46 (0.717)	<.001	0.082	—	0.999
		Group 3 (N=1)	1	—	—	—	0.932	0.999	—

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**Table 21. Change in WFIRS-P (Overall and Domains) by Change in CGI-ADHD-S (Second Set) by Visit
All Patients Enrolled (continued)**

WFIRS-P	VISIT	CHANGE IN CGI-S[1]	N	MEAN (SD)	CHANGE		P-VALUE[3]		
					MEAN (SD)	P[2]	GRP1	GRP2	GRP3
D: Child's Self-concept	LOCF	Group 1 (N=100)	100	0.61 (0.615)	-0.57 (0.713)	<.001		0.003	0.001
		Group 2 (N=100)	100	0.95 (0.651)	-0.33 (0.736)	<.001	0.003		0.051
		Group 3 (N=6)	6	1.56 (0.807)	0.00 (0.632)	1.000	0.001	0.051	
E: Social Activities	Day 35	Group 1 (N=75)	75	0.61 (0.504)	-0.36 (0.529)	<.001		0.276	0.003
		Group 2 (N=98)	98	0.78 (0.557)	-0.28 (0.435)	<.001	0.276		0.011
		Group 3 (N=3)	3	1.95 (0.459)	-0.05 (0.330)	0.826	0.003	0.011	
	Day 63	Group 1 (N=84)	84	0.57 (0.479)	-0.47 (0.618)	<.001		0.636	0.072
		Group 2 (N=66)	66	0.64 (0.468)	-0.37 (0.504)	<.001	0.636		0.137
		Group 3 (N=3)	3	1.19 (0.502)	-0.38 (0.861)	0.524	0.072	0.137	
	Day 91	Group 1 (N=91)	91	0.50 (0.467)	-0.55 (0.534)	<.001		0.005	0.082
		Group 2 (N=58)	58	0.73 (0.488)	-0.28 (0.479)	<.001	0.005		0.269
		Group 3 (N=1)	1				0.082	0.269	
	LOCF	Group 1 (N=100)	100	0.55 (0.526)	-0.53 (0.565)	<.001		<.001	0.001
		Group 2 (N=100)	100	0.77 (0.603)	-0.22 (0.512)	<.001	<.001		0.104
		Group 3 (N=6)	6	1.40 (0.805)	-0.18 (0.246)	0.136	0.001	0.104	
F: Risky Activities	Day 35	Group 1 (N=75)	75	0.33 (0.326)	-0.17 (0.251)	<.001		0.516	0.377
		Group 2 (N=98)	98	0.36 (0.280)	-0.16 (0.244)	<.001	0.516		0.571
		Group 3 (N=3)	3	0.57 (0.351)	-0.17 (0.252)	0.370	0.377	0.571	
	Day 63	Group 1 (N=84)	84	0.27 (0.282)	-0.23 (0.265)	<.001		0.060	0.004

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**Table 21. Change in WFIRS-P (Overall and Domains) by Change in CGI-ADHD-S (Second Set) by Visit
All Patients Enrolled (concluded)**

WFIRS-P	VISIT	CHANGE IN CGI-S [1]	N	MEAN (SD)	CHANGE		P-VALUE [3]		
					MEAN (SD)	P [2]	GRP1	GRP2	GRP3
F: Risky Activities	Day 63	Group 2 (N=66)	66	0.34 (0.233)	-0.18 (0.235)	<.001	0.060		0.036
		Group 3 (N=3)	3	0.87 (0.925)	-0.10 (0.453)	0.748	0.004	0.036	—
	Day 91	Group 1 (N=91)	91	0.27 (0.265)	-0.22 (0.259)	<.001		0.566	0.310
		Group 2 (N=58)	58	0.33 (0.261)	-0.21 (0.235)	<.001	0.566		0.412
		Group 3 (N=1)	1				0.310	0.412	—
	LOCF	Group 1 (N=100)	100	0.29 (0.292)	-0.22 (0.254)	<.001		0.003	<.001
		Group 2 (N=100)	100	0.40 (0.339)	-0.14 (0.266)	<.001	0.003		0.021
		Group 3 (N=6)	6	0.77 (0.398)	0.02 (0.366)	0.915	<.001	0.021	—

Abbreviations: CGI-ADHD-S = Clinical Global Impressions – ADHD – Severity; GRP = group; LOCF = last observation carried forward; N = total number of patients (column 3); N = number of patients (column 4); SD = standard deviation; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

[1] Change in CGI-S (second set): Group 1 = reduction of at least 2 points; Group 2 = no change or reduction of 1 point; Group 3 = worsened.

[2] The p-value within group is based on paired t-test.

[3] The p-value between groups is based on ANCOVA using pooled sites and baseline as covariates.

Safety

No deaths occurred during this study. Three serious adverse events were reported during this study, as follows: 1) one patient with “suicidal ideation/suicidal thoughts” which was reported by the investigator as not related to study drug. This event did not lead to study discontinuation. 2) one patient with “aggressive hostile behaviour” which was reported by the investigator as related to study drug. This event did not lead to study discontinuation. 3) one patient with “depression/suicidal ideation” which was reported by the investigator as related to study drug. This event did lead to study discontinuation.

A total of 14/206 patients (6.6%) discontinued due to at least one adverse event. A total of 175 patients (84.95%) reported 853 treatment-emergent adverse events (TEAEs) during this study. The most commonly reported TEAEs (occurring in $\geq 5\%$ of patients) are summarized in Table 22.

**Table 22. TEAEs Occurring In $\geq 5\%$ Of Patients
MedDRA Preferred Term (Version 8.0)
Patients Who Received At Least One Dose of Study Drug**

TEAE^a	Number of Patients [n (%)]
MedDRA Preferred Term	(N=206)
Total number of patients experiencing TEAE(s)	175 (84.95)
Headache	48 (23.30)
Decreased appetite	32 (15.53)
Nausea	30 (14.56)
Abdominal pain upper	30 (14.56)
Cough	28 (13.59)
Vomiting	26 (12.62)
Pharyngolaryngeal pain	25 (12.14)
Therapeutic response unexpected	23 (11.17)
Aggression	23 (11.17)
Pyrexia	22 (10.68)
Abdominal pain	22 (10.68)
Fatigue	20 (9.71)
Nasopharyngitis	18 (8.74)
Emotional disorder	15 (7.28)
Irritability	14 (6.80)
Diarrhoea	14 (6.80)
Mood altered	13 (6.31)
Somnolence	12 (5.83)
Negativism	11 (5.34)

Abbreviations: TEAE = treatment emergent adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients; n = number of patients.

^a This table contains adverse events that occurred on and after the first dose. Multiple occurrences of an adverse event within a patient are counted only once.

Vital Signs, Height, and Weight

Change in vital signs, height and weight from baseline to endpoint are summarized in Table 23.

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**Table 23. Change in Vital Signs, Height and Weight from Baseline to Study Discontinuation by Age Group
All Patients Who Received At Least One Dose of Study Drug**

AGE GROUP	VARIABLE	VISIT	N	MEAN (SD)	MEDIAN	CHANGE		P[1]
						MEAN (SD)	MEDIAN	
6-8 years (N=107)	Systolic Blood Pressure (mm Hg)	Baseline	106	96.2 (8.69)	95			
		Day 91	99	97.2 (9.38)	98	0.9 (8.74)	0	0.334
	Diastolic Blood Pressure (mm Hg)	Baseline	106	60.7 (7.43)	60			
		Day 91	99	62.5 (6.89)	62	1.8 (7.94)	1	0.031
	Heart Rate (bpm)	Baseline	106	81.8 (9.83)	84			
		Day 91	99	85.7 (13.58)	84	3.8 (11.40)	2	0.001
9-10 years (N=76)	Weight (kg)	Baseline	107	27.62 (5.447)	27.1			
		Day 91	99	27.35 (5.260)	26.6	-0.33 (1.595)	-0.2	0.042
	Height (cm)	Baseline	107	126.28 (7.143)	127			
		Day 91	98	127.75 (7.032)	128	1.37 (1.658)	1	<.001
	BMI (kg/m ²)	Baseline	107	17.21 (2.246)	16.8			
		Day 91	98	16.65 (2.067)	16.3	-0.56 (0.989)	-0.4	<.001
9-10 years (N=76)	Systolic Blood Pressure (mm Hg)	Baseline	76	100.3 (9.84)	100			
		Day 91	74	99.7 (9.66)	100	-0.7 (9.88)	0	0.566
	Diastolic Blood Pressure (mm Hg)	Baseline	76	60.8 (8.24)	60			
		Day 91	74	63.6 (7.80)	65	2.7 (10.15)	3	0.024
	Heart Rate (bpm)	Baseline	76	80.4 (11.56)	80			
		Day 91	74	86.4 (12.73)	88	6.3 (14.26)	5	<.001
	Weight (kg)	Baseline	76	36.06 (10.816)	33.5			

(continued)

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**Table 23. Change in Vital Signs, Height and Weight from Baseline to Study Discontinuation by Age Group
All Patients Who Received At Least One Dose of Study Drug (concluded)**

AGE GROUP	VARIABLE	VISIT	N	MEAN (SD)	MEDIAN	CHANGE		P[1]
						MEAN (SD)	MEDIAN	
9-10 years (N=76)	Weight (kg)	Day 91	74	35.23 (10.228)	33.3	-0.84 (1.779)	-0.9	<.001
	Height (cm)	Baseline	76	138.79 (7.955)	139			
		Day 91	73	140.19 (7.989)	140	1.49 (2.066)	1	<.001
	BMI (kg/m ²)	Baseline	76	18.49 (4.236)	17.1			
		Day 91	73	17.61 (3.826)	16.2	-0.80 (1.101)	-0.7	<.001
11-12 years (N=23)	Systolic Blood Pressure (mm Hg)	Baseline	23	105.9 (10.38)	104			
		Day 91	20	104.4 (8.21)	103	-0.9 (7.77)	-2	0.630
	Diastolic Blood Pressure (mm Hg)	Baseline	23	67.4 (8.22)	68			
		Day 91	20	67.2 (5.52)	68	0.4 (9.79)	0	0.857
	Heart Rate (bpm)	Baseline	23	76.7 (12.33)	78			
		Day 91	19	80.4 (12.60)	80	6.3 (12.47)	2	0.042
	Weight (kg)	Baseline	23	43.67 (10.206)	40			
		Day 91	20	42.35 (10.752)	39	-0.23 (2.031)	-0.3	0.618
	Height (cm)	Baseline	23	147.34 (5.476)	147.3			
		Day 91	19	149.36 (5.732)	149.8	2.32 (2.609)	1.8	0.001
	BMI (kg/m ²)	Baseline	23	19.99 (3.904)	19.1			
		Day 91	19	18.90 (4.066)	18.4	-0.76 (0.778)	-0.9	<.001

Abbreviations: BMI = body mass index; bpm = beats per minute; N = total number of patients (column 1); N = number of patients (column 4); SD = standard deviation.

[1] The p-value within group is based on paired t-test.

Summary ID# 9721

Clinical Study Summary: Study B4Z-CA-S013

An Open-Label Pilot Study of Atomoxetine Hydrochloride to Evaluate Neuropsychological Function in Children Ages 6 to 10 Years with Attention-Deficit/Hyperactivity Disorder

Date summary approved by Lilly: 25 May 2007

Brief Summary of Results

The primary objective of this Phase 4 pilot study was to evaluate the neuropsychological status in five domains as measured by the change in a Developmental Neuropsychological Assessment (NEPSY®) from baseline to 6 months post initiation of atomoxetine treatment in children aged 6.0 to 10.5 years who were diagnosed with attention-deficit/hyperactivity disorder (ADHD). The results of the study are as follows:

- The p-values should be interpreted with caution due to the small sample size of this pilot study.
- A total of 21 ADHD patients were enrolled in the study, of which 16 patients (76.2%) completed the study. Five patients (23.8%) discontinued prior to completion due to lack of efficacy (n=3; 14.3%) and adverse event (n=2; 9.5%).
- Age- and gender-matched control subjects (without any psychiatric disorder) were assessed using the NEPSY and the Behavior Rating Inventory of Executive Function™ (BRIEF™)-Parent Version to allow for assessment of changes in the atomoxetine versus control group from baseline to 6 months. A total of 20 control subjects were enrolled, and all (100.0%) completed the study.
- Change from baseline in the “Memory and Learning” domain of the NEPSY for ADHD patients was 10.6 (baseline=93.6, p=.006) following 6 months of atomoxetine treatment.

- Improvement ($p \leq .05$) in executive function of ADHD patients was observed at 6 months compared to baseline, as measured by scores for “Global Executive Composite” (mean change = -31.6, baseline = 168.8) and clinical scales of BRIEF-Parent Version, and “Global Executive Composite” (mean change = -14.9, baseline = 145.6), “Metacognition,” and the following clinical scales, “Working Memory,” “Plan/Organize,” “Organization of Materials,” and “Monitor” of the BRIEF-Teacher Version.
- Improvement ($p \leq .05$) in attention of ADHD patients was observed, as revealed by change from baseline to 6 months (mean changes $\leq |3.1|$, baseline ranging from 3.9 to 11.0) for all subtests of Test of Everyday Attention for Children (TEA-Ch), excluding “Sky Search Targets Found” and “Score!” subtests.
- Improvement ($p \leq .05$) in ADHD symptoms of patients was observed, as revealed by change from baseline at 2 months, 6 months, and last observation carried forward (LOCF) endpoint in Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) and Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Teacher Version: Investigator Administered and Scored (ADHDRS-IV-Teacher:Inv) scores; and at all visits with the exception of Visit 3 (14 days) for Clinical Global Impressions-Severity (CGI-S) scores.
- Improvement ($p \leq .05$) in functional outcomes was observed in ADHD patients as revealed by change from baseline at 2 months, 6 months and LOCF endpoint in “Overall,” “Family,” “Learning & School,” and “Life Skills” subscale scores of Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P).
- The differences between ADHD patients and control subjects in change from baseline to 6 months in each subtest (with the exception of “Tower”) of the NEPSY were not statistically significant ($p > .05$). The differences between ADHD patients and control subjects in change from baseline to 6 months in all subscales of the BRIEF-Parent Version, were statistically significant ($p < .01$).
- At 6 months, the correlation of change from baseline to endpoint in ADHD symptoms, as measured by ADHDRS-IV-Parent:Inv and ADHDRS-IV-Teacher:Inv, with change from baseline in each of the subtests of NEPSY as well as subsets of TEA-Ch was not statistically significant ($p > .05$).
- At 6 months, the correlation of change in ADHDRS-IV-Parent:Inv with BRIEF-Parent Version ranged from 0.31 to 0.84 ($p \leq .05$) for all clinical scales, excluding the “Inhibit” and “Emotional Control” subscales. The correlation of change in ADHDRS-IV-Teacher:Inv with BRIEF-Teacher Version ranged from 0.43 to 0.85 ($p \leq .05$) for all subscales excluding the “Shift” and “Initiate” clinical scales.

- Using LOCF, the correlations of change in ADHDRS-IV-Parent:Inv and ADHDRS-IV-Teacher: Inv with WFIRS-P were approximately 0.62 ($p \leq .05$) for “Learning and School” subscale at endpoint.
- Psychometric properties of the French language version of WFIRS-P were explored.
- No serious adverse events were reported during the study, and no deaths occurred during the study. Twenty patients (95.2%) reported at least 1 treatment-emergent adverse event.

Title of Study: An Open-Label Pilot Study of Atomoxetine Hydrochloride to Evaluate Neuropsychological Function in Children Ages 6 to 10 Years with Attention-Deficit/Hyperactivity Disorder	
Investigator: This single-center study included one principal investigator.	
Study Center: This study was conducted at one study center in one country.	
Length of Study: 10 months Date of first patient enrolled: 19 September 2005 Date of last patient completed: 1 June, 2006 Date of first control subject enrolled: 11 October 2005 Date of last control subject completed: 26 July 2006	Phase of Development: 4
Objectives: The primary objective of this study was to evaluate the neuropsychological status in five domains as measured by the change in the NEPSY® (Korkman et al. 1998) from baseline to 6 months post initiation of atomoxetine treatment in children aged 6.0 to 10.5 years diagnosed with attention-deficit/hyperactivity disorder (ADHD). The secondary objectives were: • To assess changes in executive function and attention using the Behavior Rating Inventory of Executive Function™ (BRIEF™; parent and teacher forms; Gioia et al. 2000) and the Test of Everyday Attention for Children (TEA-Ch) battery in atomoxetine-treated patients. • To assess and compare changes in neuropsychological status in a normal control group, gender- and age-matched with the atomoxetine-treated patients, at baseline and 6 months using the NEPSY and the BRIEF (parent form). • To assess the efficacy of open-label flexible doses of atomoxetine after approximately 2 and 6 months, or endpoint, as measured by the change from baseline in the Attention-Deficit/Hyperactivity Disorder Rating Scale: Investigator Administered and Scored, total scores of the ADHDRS-IV-Parent:Inv and ADHDRS-IV-Teacher:Inv scales, total scores, and at each visit as measured by the Clinical Global Impressions-Severity (CGI-S) scale. • To assess the correlation of change from baseline to 6 months, or at study discontinuation, in ADHD symptoms as measured by the ADHDRS-IV-Parent:Inv and ADHDRS-IV-Teacher:Inv with change from baseline in each of the neuropsychological subtests of the NEPSY, the BRIEF (parent and teacher forms) and the TEA-Ch battery. • To assess the relationships of change from baseline to approximately 2 and 6 months, or endpoint, in the core symptoms of ADHD with the changes in <i>functional outcomes</i> as assessed by the parent-completed questionnaire: Weiss Functional Impairment Rating Scale (WFIRS-P). • To use the data collected in this study to examine the French language version of the WFIRS-P questionnaire’s psychometric properties including internal consistency and responsiveness to change.	
Study Design: This was a single-center, single-arm, open-label, Phase 4 study in outpatient children with	

ADHD. The study consisted of two study periods. Study Period I involved screening for eligibility and wash-out of any psychoactive agents for treatment of ADHD or other psychiatric illness. In Study Period II, patients received atomoxetine and underwent neuropsychological testing at various time points for 6 months from baseline. Patients who discontinued the study before completing at least 114 days of treatment did not do the BRIEF (parent and teacher), NEPSY, and TEA-Ch as part of the study discontinuation procedures. Figure 1 represents the study design schematically. Age- and gender-matched control subjects who completed selected neuropsychological testing at baseline and 6 months were also enrolled.

Number of Participants:

Planned: 20 patients with ADHD; 20 control subjects.
Entered: 21 patients with ADHD; 20 control subjects.
Completed: 16 patients with ADHD; 20 control subjects.

Diagnosis and Main Criteria for Inclusion: Outpatients of both sexes aged 6.0 to 10.5 years who weighed at least 20 kg and were able to swallow drug capsules were included in this study. The patients had a diagnosis of ADHD that met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision*TM (DSM-IV-TRTM) criteria for ADHD and was confirmed through the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version: Behavioral Disorders Supplement (KSADS-PL:Behavioral). Patients may or may not have been treated previously with medications for ADHD. Other inclusion criteria were that patients met a symptom severity threshold of at least 1.5 standard deviations above the age and gender norms on the total score for the ADHDRS-IV-Parent:Inv at Visit 2; were of normal intelligence in the judgment of the investigator, and on the 2 subtest version of the Wechsler Abbreviated Scale of IntelligenceTM (WASITM). The control subjects did not have any psychiatric disorder and were of normal intelligence in the judgment of the investigator and on the 2 subtest version of WASI.

Study Drug, Dose, and Mode of Administration: Atomoxetine was administered in a flexible dosing of 0.5, 0.8, 1.2 or 1.4 mg/kg given orally once per day as capsules. Atomoxetine was prescribed based on the weight and titration schedule as recommended by the approved product label in Canada. Flexible doses between the recommended dose range of the study drug were permitted if judged appropriate by the investigator, based on tolerability and response to the medication.

Duration of Treatment: Patients were followed up for 6 months after study enrollment.

Variables:

Efficacy: Neuropsychological status during the course of treatment was determined using NEPSY (Korkman et al. 1998); symptom severity was assessed using the ADHDRS-IV-Parent:Inv (DuPaul et al. 1998; Faries et al. 2001), ADHDRS-IV-Teacher:Inv (DuPaul et al. 1998), and CGI-S (Guy 1976; NIMH 1985); attention was assessed using the TEA-Ch battery (Manly et al. 2001); functioning was assessed using the BRIEF (Gioia et al. 2000) and WFIRS-P.

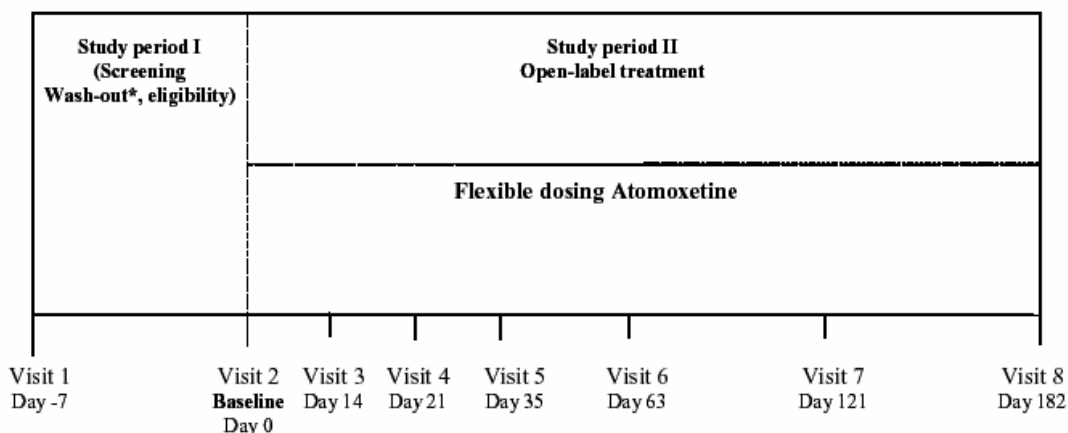
Safety: Safety was assessed by the incidence of adverse events (AEs), including serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs).

Evaluation Methods:

Statistical: The primary efficacy analysis population included patients who completed Visit 8 (6 months) who were still on medication. Changes from baseline to endpoint (6 months) in the five NEPSY domain scores were assessed using paired t-tests or Wilcoxon signed rank test. Endpoint for all secondary analyses was Visit 8. When Visit 8 data was missing, a last observation carried forward (LOCF) approach was used. Analyses of changes from baseline to endpoint in ADHD symptoms included all enrolled patients, while only completers were included for other efficacy measures. Comparisons with the control group were conducted for Visit 8 completers only, using paired t-test or Wilcoxon signed rank test. Correlations of change from baseline in ADHD symptoms and other measures utilized Pearson's correlation. Raw scores were used in change analyses where available. Corresponding T-scores or percentiles were presented where appropriate. For continuous variables, 95% confidence intervals for the mean change from baseline were calculated. Internal consistency of WFIRS-P was analyzed using Cronbach's alpha. All statistical tests were evaluated based on a two-sided significance level of 0.05. All patients who had taken at least one dose of study drug were included in the safety analyses.

Study Design:

Figure 1 represents the study design schematically.



- * For participation in the study, all patients should have been free of any excluded medications according to the following guidelines for medication wash-out:
- Patients taking any medication excluded by the protocol at Visit 1 that had a half-life of >24 hours must have a wash-out period equal to a minimum of 5 half-lives of the parent compound and any active metabolite of the parent compound prior to Visit 2.
 - Patients taking any health food supplements that, in the investigator's opinion, may have central nervous system activity (for example, St. John's Wort, melatonin, ephedrine) must have a wash-out period equal to a minimum of 5 half-lives of that supplement prior to Visit 2. If the half-life of the supplement is unknown, then the patient should have a 28-day wash-out period.

Figure 1. Study design.

Results:

Patient Demographics

Table 1 summarizes the baseline demographics of attention-deficit/hyperactivity disorder (ADHD) patients and control subjects.

Table 1. Baseline Demographics

Variable	ADHD Group (N = 21)	Control Group (N = 20)
Age (years), Mean (SD)	8.0 (1.28)	8.0 (1.49)
Gender (n, %)		
Male	16 (76.2)	15 (75.0)
Female	5 (23.8)	5 (25.0)
Race (n, %)		
Caucasian	20 (95.2)	20 (100.0)
East Asian	1 (4.8)	0 (0.0)
Education, current grade (n, %)		
Kindergarten	0 (0.0)	1 (5.0)
Grade 1	2 (9.5)	4 (20.0)
Grade 2	10 (47.6)	5 (25.0)
Grade 3	4 (19.0)	4 (20.0)
Grade 4	4 (19.0)	5 (25.0)
Grade 5	1 (4.8)	1 (5.0)
Full Scale IQ Score, Mean (SD)		
WASI ^a	98.2 (12.53)	118.5 (12.32)
ADHD subtype (n, %)		
Inattentive	15 (71.4)	-
Combined	6 (28.6)	-

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; IQ = intelligence quotient; N = sample size; n = number of patients; SD = standard deviation; WASI = Wechsler Abbreviated Scale of Intelligence.

^a Information on WASI scores available in 20/21 ADHD patients.

Patient Disposition

A total of 21 ADHD patients entered the screening phase (Study Period I) of the study. All 21 patients received the study drug and were enrolled in the study (Study Period II). Of these, 16 patients (76.2%) completed the study, and 5 patients (23.8%) discontinued prior to completion. The reasons for discontinuation included lack of efficacy in 3 patients (14.3%) and adverse event in 2 patients (9.5%).

A total of 20 control subjects were screened and enrolled in Study Period II. All 20 control subjects (100.0%) completed the study.

Primary Efficacy Analysis

Table 2 summarizes the baseline to endpoint changes in the five core domains of NEPSY (norm mean = 100, SD = 15) for ADHD patients who completed Visit 8 (6 months) and were still on medication.

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Table 2. Change in Core Domain Scores of NEPSY® (ADHD Patients who Completed the Study)

NEPSY Domain		n	Mean (SD)	Median	Min, Max	95% CI	p-value		
							(a)	(b)	(c)
Attention/Executive Functions	Baseline	16	99.8 (17.17)	96.5	74, 142	90.6 - 108.9			
	Endpoint	16	103.1 (13.29)	103.0	69, 129	96.0 - 110.1			
	Change from Baseline	16	3.3 (16.98)	4.0	-40, 28	-5.7 - 12.4	0.321	0.447	0.397
Language	Baseline	16	99.1 (18.05)	97.5	69, 129	89.4 - 108.7			
	Endpoint	16	100.9 (15.56)	101.0	72, 135	92.6 - 109.2			
	Change from Baseline	16	1.9 (12.88)	2.5	-16, 23	-5.0 - 8.7	0.213	0.569	0.715
Visual-spatial Processing	Baseline	16	103.6 (22.03)	106.0	50, 139	91.8 - 115.3			
	Endpoint	16	105.8 (18.88)	109.0	70, 136	95.7 - 115.8			
	Change from Baseline	16	2.2 (13.62)	1.5	-34, 20	-5.1 - 9.4	0.134	0.530	0.309
Sensorimotor	Baseline	16	96.7 (12.92)	95.0	75, 127	89.8 - 103.6			
	Endpoint	16	98.0 (15.29)	99.0	66, 132	89.9 - 106.1			
	Change from Baseline	16	1.3 (16.66)	-3.0	-25, 37	-7.6 - 10.2	0.644	0.757	0.910
Memory and Learning	Baseline	16	93.6 (17.43)	103.0	63, 123	84.3 - 102.9			
	Endpoint	16	104.1 (16.02)	110.5	74, 123	95.6 - 112.7			
	Change from Baseline	16	10.6 (13.34)	13.0	-18, 33	3.5 - 17.7	0.469	0.006	0.010

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CI = confidence interval; Max = maximum; Min = minimum; n = number of patients; SD = standard deviation.

a p-value using Shapiro-Wilk normality test.

b p-value using paired t-test comparing mean change to zero.

c p-value using Wilcoxon signed rank test.

Secondary Efficacy Analyses

The baseline to endpoint changes in Behavior Rating Inventory of Executive Function (BRIEF)-Parent Version and BRIEF-Teacher Version scores for ADHD patients who completed Visit 8 (6 months) are summarized in Table 3 and Table 4 respectively. A decrease in score indicates an improvement.

Table 5 summarizes the baseline to endpoint changes in the Test of Everyday Attention for Children (TEA-Ch) for ADHD patients who completed Visit 8 (6 months). Other than the “Timing” and the “Sky Search Attention” scores, an increase in score indicates an improvement.

The changes from baseline in ADHDRS-IV-Parent:Inv and ADHDRS-IV-Teacher:Inv scores for ADHD patients who received at least one dose of study drug are summarized in Table 6 and Table 7 respectively. Table 8 summarizes the changes from baseline in CGI-S scores. A decrease in score indicates an improvement.

The changes from baseline to 2 months (Visit 6), 6 months (Visit 8), and LOCF endpoint in total and subscale scores of the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) are summarized in Table 9, Table 10 and Table 11 respectively. A decrease in score indicates an improvement.

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Table 3. Change in Raw Scores from the BRIEF™-Parent Version (ADHD Patients who Completed the Study)

BRIEF: Raw Scores		n	Mean (SD)	Median	Min, Max	95% CI	p-value		
							(a)	(b)	(c)
Parent:	Global Executive Composite	Baseline	16 168.8 (14.44)	167.0	145, 197	161.1 - 176.5			
		Endpoint	16 137.2 (27.06)	132.0	87, 201	122.8 - 151.6			
		Change from Baseline	16 -31.6 (24.19)	-29.0	-81, 4	-44.5 - -18.7	0.696	<.001	<.001
	Behavioral Regulation	Baseline	16 61.8 (8.53)	61.5	45, 74	57.2 - 66.3			
		Endpoint	16 51.5 (11.69)	50.0	30, 73	45.3 - 57.7			
		Change from Baseline	16 -10.3 (6.93)	-9.0	-25, 1	-13.9 - -6.6	0.838	<.001	<.001
	Metacognition	Baseline	16 107.1 (10.70)	105.5	91, 124	101.4 - 112.8			
		Endpoint	16 85.7 (17.79)	90.5	57, 128	76.2 - 95.2			
		Change from Baseline	16 -21.4 (19.21)	-17.0	-66, 4	-31.6 - -11.1	0.333	<.001	<.001
Inhibit	Baseline	16 22.5 (4.08)	22.5	15, 30	20.3 - 24.7				
	Endpoint	16 17.9 (4.95)	17.5	10, 29	15.2 - 20.5				
	Change from Baseline	16 -4.6 (3.26)	-4.0	-13, 0	-6.4 - -2.9	0.104	<.001	<.001	
Shift	Baseline	16 16.3 (3.16)	15.5	11, 24	14.6 - 18.0				
	Endpoint	16 14.1 (3.19)	14.0	10, 24	12.4 - 15.8				
	Change from Baseline	16 -2.3 (2.32)	-2.5	-7, 2	-3.5 - -1.0	0.730	0.002	0.002	
Emotional Control	Baseline	16 22.9 (5.09)	23.0	12, 30	20.2 - 25.7				
	Endpoint	16 19.6 (5.25)	18.5	10, 30	16.8 - 22.4				
	Change from Baseline	16 -3.4 (3.74)	-3.0	-11, 2	-5.4 - -1.4	0.508	0.003	0.002	
Initiate	Baseline	16 17.0 (2.85)	17.5	11, 21	15.5 - 18.5				
	Endpoint	16 14.1 (3.51)	14.5	8, 22	12.2 - 15.9				
	Change from Baseline	16 -2.9 (3.34)	-3.0	-10, 2	-4.7 - -1.2	0.663	0.003	0.003	

(continued)

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Table 3. Change in Raw Scores from the BRIEF™-Parent Version (ADHD Patients who Completed the Study) (concluded)

BRIEF: Raw Scores		n	Mean (SD)	Median	Min, Max	95% CI	p-value		
							(a)	(b)	(c)
Parent:	Working Memory	Baseline	16 26.7 (2.77)	27.0	22, 30	25.2 - 28.2			
		Endpoint	16 20.7 (5.03)	21.5	13, 30	18.0 - 23.4			
		Change from Baseline	16 -6.0 (4.05)	-4.5	-15, 0	-8.2 - -3.8	0.255	<.001	<.001
	Plan/Organize	Baseline	16 28.6 (4.38)	28.0	22, 36	26.2 - 30.9			
		Endpoint	16 22.3 (5.35)	22.5	13, 34	19.5 - 25.2			
		Change from Baseline	16 -6.3 (7.09)	-5.5	-23, 5	-10.0 - -2.5	0.749	0.003	0.003
	Organization of Materials	Baseline	16 15.5 (2.80)	17.0	11, 18	14.0 - 17.0			
		Endpoint	16 13.3 (3.13)	14.0	7, 18	11.6 - 14.9			
		Change from Baseline	16 -2.3 (3.36)	-1.0	-10, 2	-4.0 - -0.5	0.070	0.017	0.017
	Monitor	Baseline	16 19.3 (2.21)	19.0	16, 23	18.1 - 20.5			
		Endpoint	16 15.2 (3.31)	14.5	11, 24	13.4 - 17.0			
		Change from Baseline	16 -4.1 (3.72)	-4.0	-10, 2	-6.1 - -2.1	0.410	<.001	<.001

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; BRIEF™ = Behavior Rating Inventory of Executive Function™; CI = confidence interval; Max = maximum; Min = minimum; n = number of patients; SD = standard deviation.

a p-value using Shapiro-Wilk normality test.

b p-value using paired t-test comparing mean change to zero.

c p-value using Wilcoxon signed rank test.

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Table 4. Change in Raw Scores from the BRIEF™-Teacher Version (ADHD Patients who Completed the Study)

BRIEF: Raw Scores			n	Mean (SD)	Median	Min, Max	95% CI	p-value		
								(a)	(b)	(c)
Teacher:	Global Executive Composite	Baseline	16	145.6 (34.87)	156.5	86, 207	127.0 - 164.2			
		Endpoint	16	130.8 (30.77)	130.5	92, 213	114.4 - 147.1			
		Change from Baseline	16	-14.9 (26.05)	-18.0	-61, 42	-28.8 - -1.0	0.964	0.037	0.043
	Behavioral Regulation	Baseline	16	48.8 (15.66)	49.0	30, 86	40.5 - 57.2			
		Endpoint	16	45.6 (13.44)	45.0	29, 87	38.5 - 52.8			
		Change from Baseline	16	-3.2 (10.88)	-0.5	-23, 15	-9.0 - 2.6	0.623	0.260	0.349
	Metacognition	Baseline	16	96.8 (23.17)	106.0	54, 127	84.5 - 109.2			
		Endpoint	16	85.1 (20.61)	82.5	58, 126	74.1 - 96.1			
		Change from Baseline	16	-11.7 (17.64)	-13.0	-46, 27	-21.1 - -2.3	0.990	0.018	0.016
	Inhibit	Baseline	16	19.8 (7.27)	21.0	10, 30	15.9 - 23.6			
		Endpoint	16	17.8 (4.92)	18.0	10, 30	15.1 - 20.4			
		Change from Baseline	16	-2.0 (5.43)	-1.0	-10, 8	-4.9 - 0.9	0.504	0.161	0.192
	Shift	Baseline	16	15.9 (5.44)	15.0	10, 30	13.0 - 18.8			
		Endpoint	16	16.0 (4.97)	16.0	10, 30	13.4 - 18.6			
		Change from Baseline	16	0.1 (4.40)	0.0	-12, 8	-2.2 - 2.5	0.045	0.911	0.854
	Emotional Control	Baseline	16	13.2 (4.82)	11.5	9, 27	10.6 - 15.8			
		Endpoint	16	11.9 (4.73)	10.5	9, 27	9.4 - 14.4			
		Change from Baseline	16	-1.3 (2.60)	-0.5	-7, 2	-2.7 - 0.1	0.244	0.062	0.077
	Initiate	Baseline	16	15.5 (4.53)	15.0	7, 21	13.1 - 17.9			
		Endpoint	16	14.8 (4.09)	15.0	8, 21	12.6 - 17.0			
		Change from Baseline	16	-0.7 (2.80)	0.0	-5, 6	-2.2 - 0.8	0.259	0.341	0.298

(continued)

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Table 4. Change in Raw Scores from the BRIEF™-Teacher Version (ADHD Patients who Completed the Study) (concluded)

BRIEF: Raw Scores		n	Mean (SD)	Median	Min, Max	95% CI	p-value		
							(a)	(b)	(c)
Teacher:	Working Memory	Baseline	16 23.4 (5.51)	25.0	11, 29	20.5 - 26.4			
		Endpoint	16 20.7 (4.91)	19.0	14, 28	18.1 - 23.3			
		Change from Baseline	16 -2.8 (4.99)	-2.5	-10, 8	-5.4 - -0.1	0.650	0.043	0.051
	Plan/Organize	Baseline	16 21.8 (5.94)	23.5	11, 30	18.6 - 25.0			
		Endpoint	16 19.2 (5.31)	19.5	12, 29	16.4 - 22.0			
		Change from Baseline	16 -2.6 (4.43)	-3.0	-9, 8	-5.0 - -0.3	0.486	0.031	0.027
	Organization of Materials	Baseline	16 14.1 (5.02)	14.0	7, 21	11.5 - 16.8			
		Endpoint	16 11.3 (3.77)	10.5	7, 19	9.2 - 13.3			
		Change from Baseline	16 -2.9 (3.88)	-2.5	-13, 3	-4.9 - -0.8	0.285	0.010	0.007
	Monitor	Baseline	16 21.9 (5.30)	23.5	13, 30	19.1 - 24.8			
		Endpoint	16 19.2 (5.05)	19.5	12, 30	16.5 - 21.9			
		Change from Baseline	16 -2.8 (4.61)	-3.5	-13, 5	-5.2 - -0.3	0.840	0.031	0.029

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; BRIEF™ = Behavior Rating Inventory of Executive Function™; CI = confidence interval; Max = maximum; Min = minimum; n = number of patients; SD = standard deviation.

- a p-value using Shapiro-Wilk normality test.
- b p-value using paired t-test comparing mean change to zero.
- c p-value using Wilcoxon signed rank test.

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Table 5. Change in TEA-Ch (ADHD Patients who Completed the Study)

TEA-Ch: Raw Score		n	Mean (SD)	Median	Min, Max	95% CI	p-value		
							(a)	(b)	(c)
Sky Search Targets Found	Baseline Raw Score	16	18.7 (1.70)	19.0	15, 20	17.8 - 19.6			
	Endpoint Raw Score	16	18.0 (1.90)	18.5	15, 20	17.0 - 19.0			
	Change from Baseline	16	-0.7 (2.30)	-0.5	-5, 4	-1.9 - 0.5	0.609	0.251	0.240
Sky Search Time per Target	Baseline Raw Score	16	8.2 (4.53)	6.1	4, 18	5.8 - 10.6			
	Endpoint Raw Score	16	6.4 (3.40)	5.3	4, 15	4.6 - 8.2			
	Change from Baseline	16	-1.8 (2.13)	-1.2	-8, 1	-3.0 - -0.7	0.034	0.004	<.001
Sky Search Attention Score	Baseline Raw Score	16	6.4 (3.86)	4.6	3, 15	4.3 - 8.4			
	Endpoint Raw Score	16	4.8 (2.50)	4.1	2, 12	3.4 - 6.1			
	Change from Baseline	16	-1.6 (2.31)	-1.1	-7, 2	-2.8 - -0.4	0.025	0.014	0.004
Score!	Baseline Raw Score	16	6.6 (2.94)	7.0	0, 10	5.0 - 8.1			
	Endpoint Raw Score	16	7.3 (2.62)	8.0	0, 10	5.9 - 8.6			
	Change from Baseline	16	0.7 (2.09)	0.0	-2, 6	-0.4 - 1.8	0.063	0.208	0.267
Creature Counting Accuracy	Baseline Raw Score	16	3.9 (2.13)	5.0	0, 6	2.7 - 5.0			
	Endpoint Raw Score	16	5.0 (2.31)	5.5	0, 7	3.8 - 6.2			
	Change from Baseline	16	1.1 (1.75)	1.0	-2, 6	0.2 - 2.1	0.029	0.021	0.021
Creature Counting Timing Score	Baseline Raw Score	13	7.5 (3.25)	6.2	4, 14	5.6 - 9.5			
	Endpoint Raw Score	15	5.7 (2.33)	5.1	4, 13	4.4 - 7.0			
	Change from Baseline	13	-2.4 (3.45)	-0.7	-9, 2	-4.5 - -0.3	0.232	0.028	0.048
Walk, Don't Walk	Baseline Raw Score	15	11.0 (5.22)	12.0	0, 20	8.1 - 13.9			
	Endpoint Raw Score	16	14.1 (4.34)	14.5	6, 20	11.7 - 16.4			
	Change from Baseline	15	3.1 (4.73)	4.0	-4, 14	0.4 - 5.7	0.494	0.025	0.024

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CI = confidence interval; Max = maximum; Min = minimum; n = number of patients; SD = standard deviation; TEA-Ch = Test of Everyday Attention for Children.

a p-value using Shapiro-Wilk normality test.

b p-value using paired t-test comparing mean change to zero.

c p-value using Wilcoxon signed rank test.

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Table 6. Change in ADHDRS-IV-Parent:Inv at 2 Months, 6 Months, and LOCF Endpoint (Enrolled ADHD Patients who Received At Least One Dose of Study Drug)

CGI-S and ADHDRS-IV	Visit		n	Mean (SD)	Median	Min, Max	95% CI	p-value		
								(a)	(b)	(c)
ADHDRS-IV-Parent	Visit 6	Score at Visit	18	24.1 (8.64)	22.5	12, 41	19.8 - 28.4			
		Change from Baseline	18	-11.6 (10.32)	-12.0	-34, 3	-16.7 - -6.5	0.598	<.001	<.001
	Visit 8	Score at Visit	16	15.9 (9.22)	14.5	3, 37	11.0 - 20.9			
		Change from Baseline	16	-19.5 (11.14)	-21.5	-43, 0	-25.4 - -13.6	0.792	<.001	<.001
	LOCF	Score at Visit	20	18.8 (10.13)	16.5	3, 37	14.0 - 23.5			
		Change from Baseline	20	-17.3 (10.95)	-18.0	-43, 0	-22.4 - -12.1	0.489	<.001	<.001

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CI = confidence interval; LOCF = last observation carried forward; Max = maximum; Min = minimum; n = number of patients; SD = standard deviation.

- a p-value using Shapiro-Wilk normality test.
- b p-value using paired t-test comparing mean change to zero.
- c p-value using Wilcoxon signed rank test.

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Table 7. Change in ADHDRS-IV-Teacher:Inv at 2 Months, 6 Months, and LOCF Endpoint (Enrolled ADHD Patients who Received At Least One Dose of Study Drug)

CGI-S and ADHDRS-IV	Visit		n	Mean (SD)	Median	Min, Max	95% CI	p-value		
								(a)	(b)	(c)
ADHDRS-IV-Teacher	Visit 6	Score at Visit	18	20.8 (10.55)	20.0	8, 39	15.6 - 26.1			
		Change from Baseline	18	-7.6 (11.70)	-7.0	-34, 14	-13.4 - -1.8	0.498	0.013	0.008
	Visit 8	Score at Visit	16	14.2 (7.89)	12.5	5, 32	10.0 - 18.4			
		Change from Baseline	16	-13.1 (11.11)	-12.5	-35, 5	-19.0 - -7.2	0.704	<.001	<.001
	LOCF	Score at Visit	19	17.8 (11.21)	13.0	5, 39	12.4 - 23.2			
		Change from Baseline	19	-10.6 (11.79)	-11.0	-35, 6	-16.3 - -5.0	0.426	<.001	<.001

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ADHDRS-IV-Teacher:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Teacher Version: Investigator Administered and Scored; CI = confidence interval; LOCF = last observation carried forward; Max = maximum; Min = minimum; n = number of patients; SD = standard deviation.

- a p-value using Shapiro-Wilk normality test.
- b p-value using paired t-test comparing mean change to zero.
- c p-value using Wilcoxon signed rank test.

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Table 8. Change in CGI-S (Enrolled ADHD Patients who Received At Least One Dose of Study Drug)

CGI-S and ADHDRS-IV	Visit		n	Mean (SD)	Median	Min, Max	95% CI	p-value		
								(a)	(b)	(c)
CGI-S	Visit 3	Score at Visit	20	4.8 (0.52)	5.0	4, 6	4.6 - 5.0			
		Change from Baseline	20	0.0 (0.32)	0.0	-1, 1	-0.2 - 0.2	<.001	1.000	1.000
	Visit 4	Score at Visit	20	4.5 (0.51)	4.5	4, 5	4.3 - 4.7			
		Change from Baseline	20	-0.3 (0.47)	0.0	-1, 0	-0.5 - -0.1	<.001	0.010	0.031
	Visit 5	Score at Visit	19	4.2 (0.42)	4.0	4, 5	4.0 - 4.4			
		Change from Baseline	19	-0.6 (0.51)	-1.0	-1, 0	-0.8 - -0.3	<.001	<.001	<.001
	Visit 6	Score at Visit	18	4.1 (0.54)	4.0	3, 5	3.8 - 4.3			
		Change from Baseline	18	-0.7 (0.57)	-1.0	-2, 0	-1.0 - -0.4	<.001	<.001	<.001
	Visit 7	Score at Visit	16	3.1 (0.57)	3.0	2, 4	2.8 - 3.4			
		Change from Baseline	16	-1.7 (0.79)	-2.0	-3, 0	-2.1 - -1.3	<.001	<.001	<.001
	Visit 8	Score at Visit	16	2.7 (0.79)	3.0	2, 5	2.3 - 3.1			
		Change from Baseline	16	-2.1 (0.85)	-2.0	-3, 0	-2.5 - -1.6	0.008	<.001	<.001
	LOCF	Score at Visit	21	3.2 (1.22)	3.0	2, 5	2.7 - 3.8			
		Change from Baseline	21	-1.6 (1.12)	-2.0	-3, 0	-2.1 - -1.1	0.004	<.001	<.001

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CGI-S = Clinical Global Impressions-Severity; CI = confidence interval; LOCF = last observation carried forward; Max = maximum; Min = minimum; n = number of patients; SD = standard deviation.

a p-value using Shapiro-Wilk normality test.

b p-value using paired t-test comparing mean change to zero.

c p-value using Wilcoxon signed rank test.

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Table 9. Change in Total and Subscales of WFIRS-P at 2 Months (Enrolled ADHD Patients who Received At Least One Dose of Study Drug)

Visit	WFIRS - Parent		n	Mean (SD)	Median	Min, Max	95% CI	p-value		
								(a)	(b)	(c)
Visit 6	Overall	Score at Visit	18	0.64 (0.266)	0.66	0.20, 1.04	0.51 - 0.77			
		Change from Baseline	18	-0.22 (0.270)	-0.20	-0.96, 0.17	-0.35 - -0.08	0.183	0.003	0.002
	Family	Score at Visit	18	0.71 (0.436)	0.60	0.00, 1.70	0.49 - 0.92			
		Change from Baseline	18	-0.30 (0.401)	-0.20	-1.40, 0.20	-0.50 - -0.10	0.006	0.005	<.001
	Learning and School	Score at Visit	18	0.82 (0.363)	0.80	0.30, 1.50	0.64 - 1.00			
		Change from Baseline	18	-0.24 (0.459)	-0.10	-1.20, 0.50	-0.47 - -0.02	0.114	0.037	0.029
	Life Skills	Score at Visit	18	0.64 (0.410)	0.65	0.00, 1.40	0.43 - 0.84			
		Change from Baseline	18	-0.34 (0.448)	-0.25	-1.30, 0.20	-0.57 - -0.12	0.178	0.005	0.007
	Child Self Concept	Score at Visit	18	0.93 (0.672)	1.00	0.00, 2.67	0.59 - 1.26			
		Change from Baseline	18	0.04 (0.694)	0.00	-1.00, 1.67	-0.31 - 0.38	0.605	0.824	1.000
	Social Activities	Score at Visit	18	0.64 (0.416)	0.64	0.14, 1.86	0.44 - 0.85			
		Change from Baseline	18	-0.25 (0.429)	-0.21	-1.00, 0.43	-0.46 - -0.03	0.280	0.026	0.063
	Risky Activities	Score at Visit	18	0.32 (0.280)	0.25	0.00, 0.90	0.18 - 0.46			
		Change from Baseline	18	-0.03 (0.247)	0.00	-0.70, 0.30	-0.15 - 0.09	0.095	0.639	0.886

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CI = confidence interval; Max = maximum; Min = minimum; n = number of patients; SD = standard deviation; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

a p-value using Shapiro-Wilk normality test.

b p-value using paired t-test comparing mean change to zero.

c p-value using Wilcoxon signed rank test.

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Table 10. Change in Total and Subscales of WFIRS-P at 6 Months (Enrolled ADHD Patients who Received At Least One Dose of Study Drug)

Visit	WFIRS - Parent		n	Mean (SD)	Median	Min, Max	95% CI	p-value		
								(a)	(b)	(c)
Visit 8	Overall	Score at Visit	16	0.61 (0.331)	0.49	0.28, 1.60	0.43 - 0.78			
		Change from Baseline	16	-0.26 (0.306)	-0.22	-1.10, 0.36	-0.43 - -0.10	0.050	0.004	0.002
	Family	Score at Visit	16	0.77 (0.535)	0.70	0.10, 2.20	0.48 - 1.05			
		Change from Baseline	16	-0.25 (0.351)	-0.30	-0.90, 0.30	-0.44 - -0.07	0.579	0.012	0.014
	Learning and School	Score at Visit	16	0.58 (0.399)	0.45	0.20, 1.70	0.36 - 0.79			
		Change from Baseline	16	-0.46 (0.456)	-0.50	-1.20, 0.50	-0.70 - -0.21	0.738	0.001	0.002
	Life Skills	Score at Visit	16	0.67 (0.494)	0.55	0.10, 2.20	0.41 - 0.93			
		Change from Baseline	16	-0.36 (0.545)	-0.25	-1.50, 0.50	-0.65 - -0.07	0.765	0.020	0.025
	Child Self Concept	Score at Visit	16	0.60 (0.389)	0.67	0.00, 1.00	0.40 - 0.81			
		Change from Baseline	16	-0.33 (0.404)	-0.33	-1.00, 0.33	-0.55 - -0.12	0.083	0.005	0.006
	Social Activities	Score at Visit	16	0.75 (0.488)	0.71	0.14, 2.29	0.49 - 1.01			
		Change from Baseline	16	-0.13 (0.453)	-0.14	-1.14, 0.71	-0.38 - 0.11	0.612	0.256	0.266
	Risky Activities	Score at Visit	16	0.31 (0.296)	0.20	0.00, 1.00	0.15 - 0.47			
		Change from Baseline	16	-0.06 (0.231)	0.00	-0.80, 0.10	-0.19 - 0.06	<.001	0.295	0.418

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CI = confidence interval; Max = maximum; Min = minimum; n = number of patients; SD = standard deviation; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

a p-value using Shapiro-Wilk normality test.

b p-value using paired t-test comparing mean change to zero.

c p-value using Wilcoxon signed rank test.

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Table 11. Change in Total and Subscales of WFIRS-P at Endpoint Using LOCF (Enrolled ADHD Patients who Received At Least One Dose of Study Drug)

Visit	WFIRS - Parent		n	Mean (SD)	Median	Min, Max	95% CI	p-value		
								(a)	(b)	(c)
LOCF	Overall	Score at Visit	20	0.67 (0.354)	0.61	0.28, 1.60	0.50 - 0.83			
		Change from Baseline	20	-0.23 (0.322)	-0.22	-1.10, 0.36	-0.38 - -0.08	0.212	0.004	0.003
	Family	Score at Visit	19	0.78 (0.501)	0.70	0.10, 2.20	0.54 - 1.02			
		Change from Baseline	19	-0.27 (0.327)	-0.40	-0.90, 0.30	-0.43 - -0.11	0.643	0.002	0.003
	Learning and School	Score at Visit	20	0.74 (0.486)	0.50	0.20, 1.70	0.51 - 0.96			
		Change from Baseline	20	-0.38 (0.501)	-0.45	-1.20, 0.50	-0.61 - -0.14	0.361	0.003	0.004
	Life Skills	Score at Visit	20	0.67 (0.506)	0.45	0.10, 2.20	0.43 - 0.90			
		Change from Baseline	20	-0.34 (0.514)	-0.25	-1.50, 0.50	-0.58 - -0.10	0.722	0.008	0.012
	Child Self Concept	Score at Visit	20	0.73 (0.491)	0.67	0.00, 2.00	0.50 - 0.96			
		Change from Baseline	20	-0.17 (0.557)	-0.17	-1.00, 1.00	-0.43 - 0.09	0.116	0.196	0.193
	Social Activities	Score at Visit	20	0.76 (0.440)	0.71	0.14, 2.29	0.55 - 0.96			
		Change from Baseline	20	-0.17 (0.465)	-0.14	-1.14, 0.71	-0.39 - 0.05	0.758	0.116	0.141
	Risky Activities	Score at Visit	20	0.38 (0.370)	0.20	0.00, 1.40	0.20 - 0.55			
		Change from Baseline	20	-0.04 (0.292)	0.00	-0.80, 0.70	-0.17 - 0.10	0.017	0.599	0.636

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CI = confidence interval; LOCF = last observation carried forward; Max = maximum; Min = minimum; n = number of patients; SD = standard deviation; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

a p-value using Shapiro-Wilk normality test.

b p-value using paired t-test comparing mean change to zero.

c p-value using Wilcoxon signed rank test.

Change in Neuropsychological Status: Comparison between ADHD Patients and Control Subjects

Table 12 summarizes the differences between ADHD patients and control subjects in change from baseline to endpoint in each subtest of the NEPSY as well as all clinical scales of the BRIEF-Parent Version.

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Table 12. Comparison of Changes in NEPSY® and BRIEF™-Parent Version between ADHD Patients and Control Subjects (Enrolled ADHD Patients who Completed the Study and Matched Control Group)

Domain	Change from Baseline to Endpoint														p-value (a)
	Completed Enrolled ADHD Patients (N = 16)						Matched Normal Control Subjects (N = 16)								
	n	Mean (SD)	Median	Min, Max	95% CI	n	Mean (SD)	Median	Min, Max	95% CI					
NEPSY - Core Domain Score:															
Attention/Executive Functions	16	3.3 (16.98)	4.0	-40, 28	-5.7 - 12.4	16	0.8 (14.78)	0.5	-33, 22	-7.1 - 8.7	0.640				
Language	16	1.9 (12.88)	2.5	-16, 23	-5.0 - 8.7	15	4.9 (8.13)	2.0	-9, 21	0.4 - 9.4	0.284				
Visual-spatial Processing	16	2.2 (13.62)	1.5	-34, 20	-5.1 - 9.4	16	1.1 (11.64)	0.0	-18, 27	-5.1 - 7.3	0.817				
Sensorimotor	16	1.3 (16.66)	-3.0	-25, 37	-7.6 - 10.2	16	-2.1 (11.90)	-1.5	-31, 18	-8.5 - 4.2	0.458				
Memory and Learning	16	10.6 (13.34)	13.0	-18, 33	3.5 - 17.7	16	10.5 (13.29)	12.5	-20, 34	3.4 - 17.6	0.988				
NEPSY Subtest (Raw score)															
Attention/Executive Functions Domain:															
Tower	16	2.1 (3.50)	1.0	-2, 11	0.3 - 4.0	16	0.3 (2.38)	0.5	-5, 4	-1.0 - 1.5	0.026				
Auditory Attention & Response Set	16	15.3 (19.28)	15.5	-22, 45	5.0 - 25.5	16	5.3 (13.52)	7.5	-24, 23	-1.9 - 12.5	0.102				
Visual Attention	16	1.9 (4.11)	1.0	-5, 10	-0.3 - 4.1	16	2.4 (4.80)	2.5	-10, 10	-0.1 - 5.0	0.758				
Language Domain:															
Phonological Processing	16	0.9 (3.01)	1.5	-3, 6	-0.7 - 2.5	16	2.4 (2.37)	2.0	-1, 7	1.2 - 3.7	0.177				
Speeded Naming	16	3.0 (10.62)	1.0	-16, 27	-2.7 - 8.7	16	0.4 (4.77)	3.0	-11, 6	-2.2 - 2.9	0.425				
Comprehension of Instructions	16	1.4 (2.73)	2.0	-3, 5	-0.1 - 2.8	16	1.2 (1.94)	1.0	-2, 5	0.2 - 2.2	0.847				
Visual-spatial Processing Domain:															
Design Copy	16	1.8 (6.86)	2.0	-18, 11	-1.8 - 5.5	16	-0.2 (3.97)	-0.5	-7, 8	-2.3 - 1.9	0.368				
Arrows	16	1.9 (3.03)	1.0	-2, 8	0.3 - 3.5	16	1.5 (2.90)	1.5	-5, 7	-0.0 - 3.0	0.754				
Sensorimotor Domain:															
Finger Tapping	16	-2.3 (26.84)	-2.0	-34, 78	-16.6 - 12.1	16	-8.3 (17.83)	-8.0	-32, 32	-17.7 - 1.2	0.490				
Imitating Hand Positions	16	0.9 (1.59)	0.0	-1, 4	0.0 - 1.7	16	0.3 (2.30)	0.0	-4, 5	-0.9 - 1.5	0.488				
Visuomotor Precision	16	2.3 (9.71)	0.5	-11, 26	-2.9 - 7.4	16	0.9 (5.25)	1.0	-10, 9	-1.9 - 3.7	0.664				

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Table 12. Comparison of Changes in NEPSY® and BRIEF™-Parent Version between ADHD Patients and Control Subjects (Enrolled ADHD Patients who Completed the Study and Matched Control Group) (Concluded)

Domain	Change from Baseline to Endpoint														p-value (a)
	Completed Enrolled ADHD Patients (N = 16)						Matched Normal Control Subjects (N = 16)								
	n	Mean (SD)	Median	Min, Max	95% CI		n	Mean (SD)	Median	Min, Max	95% CI				
Memory and Learning Domain:															
Memory for Faces	16	1.7 (4.67)	2.0	-13, 10	-0.8	- 4.2	16	3.1 (2.90)	4.0	-1, 11	1.6	- 4.7	0.412		
Memory for Names	16	6.1 (3.42)	6.0	0, 13	4.2	- 7.9	16	4.7 (3.72)	3.0	-1, 12	2.7	- 6.7	0.270		
Narrative Memory	16	4.0 (5.18)	2.5	-7, 13	1.2	- 6.8	16	2.9 (5.58)	2.0	-8, 12	-0.0	- 5.9	0.518		
BRIEF (Parent) - Raw Score:															
Global Executive Composite	16	-31.6 (24.19)	-29.0	-81, 4	-44.5	- -18.7	16	7.1 (16.27)	0.0	-6, 56	-1.5	- 15.8	<.001		
Behavioral Regulation	16	-10.3 (6.93)	-9.0	-25, 1	-13.9	- -6.6	16	1.6 (6.54)	0.0	-6, 21	-1.9	- 5.1	<.001		
Metacognition	16	-21.4 (19.21)	-17.0	-66, 4	-31.6	- -11.1	16	5.5 (10.27)	2.5	-4, 35	0.0	- 11.0	<.001		
Inhibit	16	-4.6 (3.26)	-4.0	-13, 0	-6.4	- -2.9	16	0.4 (2.87)	0.0	-3, 9	-1.2	- 1.9	<.001		
Shift	16	-2.3 (2.32)	-2.5	-7, 2	-3.5	- -1.0	16	0.5 (1.93)	1.0	-3, 4	-0.5	- 1.5	0.004		
Emotional Control	16	-3.4 (3.74)	-3.0	-11, 2	-5.4	- -1.4	16	0.8 (3.21)	0.0	-6, 8	-1.0	- 2.5	<.001		
Initiate	16	-2.9 (3.34)	-3.0	-10, 2	-4.7	- -1.2	16	0.9 (2.36)	0.5	-2, 6	-0.4	- 2.1	<.001		
Working Memory	16	-6.0 (4.05)	-4.5	-15, 0	-8.2	- -3.8	16	1.4 (3.14)	0.5	-3, 11	-0.2	- 3.1	<.001		
Plan/Organize	16	-6.3 (7.09)	-5.5	-23, 5	-10.0	- -2.5	16	1.3 (3.00)	1.0	-2, 10	-0.3	- 2.8	0.001		
Organization of Materials	16	-2.3 (3.36)	-1.0	-10, 2	-4.0	- -0.5	16	1.1 (1.81)	1.5	-2, 4	0.1	- 2.0	0.003		
Monitor	16	-4.1 (3.72)	-4.0	-10, 2	-6.1	- -2.1	16	0.9 (2.78)	0.0	-3, 6	-0.6	- 2.4	<.001		
Inconsistency	16	-0.1 (2.17)	0.0	-3, 5	-1.2	- 1.1	16	1.1 (1.77)	1.0	-2, 5	0.1	- 2.0	0.123		
Negativity	16	-1.3 (1.53)	-1.0	-5, 1	-2.1	- -0.4	16	0.0 (0.52)	0.0	-1, 1	-0.3	- 0.3	0.002		

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; BRIEF™ = Behavior Rating Inventory of Executive Function™; CI = confidence interval; Max = maximum; Min = minimum; N = sample size; n = number of patients; SD = standard deviation.

Note: The normal control population included only the subjects who were matches for the completed ADHD patients.

a p-value using paired t-test.

Correlation between the Outcome Measures

The correlation of change from baseline to endpoint in ADHD symptoms (as measured by ADHDRS-IV-Parent:Inv and ADHDRS-IV-Teacher:Inv scores) with change from baseline in: each of the subtest scores of NEPSY (Table 13); BRIEF clinical scale scores (Table 14); each of the subtest scores of the TEA-Ch (Table 15), and in total and subscale scores of WFIRS-P at 2 months (Table 16), 6 months (Table 17), and LOCF endpoint (Table 18) is displayed.

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Table 13. Correlation of Change from Baseline to Endpoint in NEPSY® Subtests with Change from Baseline to Endpoint in ADHDRS-IV-Parent:Inv and ADHDRS-IV-Teacher:Inv (ADHD Patients who Completed the Study)

NEPSY Subtests	ADHDRS-IV-Parent					ADHDRS-IV-Teacher				
	n	r	95% CI		p-value (a)	n	r	95% CI		p-value (a)
Attention/Executive Functions Domain:										
Tower	16	0.0410	-0.4641	- 0.5260	0.880	16	0.2387	-0.2915	- 0.6567	0.373
Auditory Attention & Response Set	16	0.3476	-0.1790	- 0.7193	0.187	16	-0.2049	-0.6360	- 0.3237	0.446
Visual Attention	16	-0.3433	-0.7170	- 0.1836	0.193	16	0.1762	-0.3501	- 0.6179	0.514
Language Domain:										
Phonological Processing	16	-0.2049	-0.6360	- 0.3237	0.447	16	0.1770	-0.3494	- 0.6185	0.512
Speeded Naming	16	0.0406	-0.4645	- 0.5257	0.881	16	0.1203	-0.3992	- 0.5814	0.657
Comprehension of Instructions	16	0.1710	-0.3548	- 0.6146	0.527	16	-0.2248	-0.6483	- 0.3049	0.403
Visual-spatial Processing Domain:										
Design Copy	16	-0.4687	-0.7826	- 0.0352	0.067	16	-0.1673	-0.6123	- 0.3581	0.536
Arrows	16	-0.1580	-0.6062	- 0.3664	0.559	16	-0.0460	-0.5297	- 0.4602	0.866
Sensorimotor Domain:										
Finger Tapping	16	0.0475	-0.4590	- 0.5307	0.861	16	0.2380	-0.2922	- 0.6563	0.375
Imitating Hand Positions	16	0.3093	-0.2202	- 0.6980	0.244	16	-0.0009	-0.4964	- 0.4950	0.997
Visuomotor Precision	16	0.2464	-0.2840	- 0.6614	0.358	16	0.1856	-0.3415	- 0.6239	0.491
Memory and Learning Domain:										
Memory for Faces	16	-0.4335	-0.7649	- 0.0792	0.093	16	-0.1112	-0.5752	- 0.4069	0.682
Memory for Names	16	-0.3005	-0.6930	- 0.2294	0.258	16	-0.0806	-0.5542	- 0.4324	0.767
Narrative Memory	16	0.3930	-0.1276	- 0.7438	0.132	16	0.1611	-0.3636	- 0.6082	0.551

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; ADHDRS-IV-Teacher:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Teacher Version: Investigator Administered and Scored; CI = confidence interval; n = number of patients.

a p-value comparing the Pearson's correlation between changes in NEPSY subtests and change in ADHDRS-IV-Parent:Inv or ADHDRS-IV-Teacher:Inv to zero.

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Table 14. Correlation of Change from Baseline to Endpoint in Raw Scores from BRIEF™-Parent Version with Change from Baseline to Endpoint in ADHDRS-IV-Parent:Inv and ADHDRS-IV-Teacher:Inv (ADHD Patients who Completed the Study)

BRIEF: Raw Score	ADHDRS-IV-Parent					ADHDRS-IV-Teacher				
	n	r	95% CI	p-value (a)		n	r	95% CI	p-value (a)	
Parent:										
Global Executive Composite	16	0.8131	0.5316 - 0.9328	<.001		16	0.2078	-0.3210 - 0.6378	0.440	
Behavioral Regulation	16	0.4971	0.0019 - 0.7965	0.050		16	-0.0402	-0.5255 - 0.4647	0.882	
Metacognition	16	0.8443	0.5994 - 0.9446	<.001		16	0.2761	-0.2544 - 0.6789	0.301	
Inhibit	16	0.3135	-0.2157 - 0.7004	0.237		16	-0.0593	-0.5392 - 0.4496	0.827	
Shift	16	0.5382	0.0579 - 0.8161	0.032		16	0.3370	-0.1906 - 0.7135	0.202	
Emotional Control	16	0.3136	-0.2156 - 0.7004	0.237		16	-0.2323	-0.6528 - 0.2977	0.387	
Initiate	16	0.7847	0.4730 - 0.9218	<.001		16	0.2197	-0.3098 - 0.6451	0.414	
Working Memory	16	0.7565	0.4173 - 0.9107	<.001		16	0.3897	-0.1314 - 0.7420	0.136	
Plan/Organize	16	0.8274	0.5623 - 0.9383	<.001		16	0.3607	-0.1644 - 0.7265	0.170	
Organization of Materials	16	0.5562	0.0835 - 0.8246	0.025		16	-0.0724	-0.5484 - 0.4391	0.790	
Monitor	16	0.8184	0.5429 - 0.9348	<.001		16	0.1576	-0.3668 - 0.6060	0.560	
Teacher:										
Global Executive Composite	16	0.2823	-0.2482 - 0.6825	0.290		16	0.8015	0.5074 - 0.9284	<.001	
Behavioral Regulation	16	0.1674	-0.3580 - 0.6123	0.535		16	0.5958	0.1421 - 0.8426	0.015	
Metacognition	16	0.3136	-0.2156 - 0.7004	0.237		16	0.8162	0.5383 - 0.9340	<.001	
Inhibit	16	0.0849	-0.4289 - 0.5571	0.755		16	0.5825	0.1220 - 0.8366	0.018	
Shift	16	0.0912	-0.4237 - 0.5615	0.737		16	0.4331	-0.0797 - 0.7647	0.094	
Emotional Control	16	0.3693	-0.1547 - 0.7312	0.159		16	0.5454	0.0681 - 0.8195	0.029	
Initiate	16	0.3368	-0.1907 - 0.7134	0.202		16	0.4517	-0.0568 - 0.7741	0.079	
Working Memory	16	0.2496	-0.2809 - 0.6632	0.351		16	0.8477	0.6071 - 0.9459	<.001	
Plan/Organize	16	0.1988	-0.3294 - 0.6322	0.461		16	0.6830	0.2832 - 0.8806	0.004	
Organization of Materials	16	0.3023	-0.2275 - 0.6940	0.255		16	0.6423	0.2150 - 0.8632	0.007	
Monitor	16	0.2803	-0.2502 - 0.6813	0.293		16	0.7358	0.3779 - 0.9024	0.001	

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; ADHDRS-IV-Teacher:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Teacher Version: Investigator Administered and Scored; BRIEF™ = Behavior Rating Inventory of Executive Function™; CI = confidence interval; n = number of patients.
a p-value comparing the Pearson's correlation between changes in BRIEF and change in ADHDRS-IV-Parent:Inv or ADHDRS-IV-Teacher:Inv to zero.

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Table 15. Correlation of Change from Baseline to Endpoint in TEA-Ch Subtests with Change from Baseline to Endpoint in ADHDRS-IV-Parent:Inv and ADHDRS-IV-Teacher:Inv (ADHD Patients who Completed the Study)

TEA-Ch: Raw Score	ADHDRS-IV-Parent					ADHDRS-IV-Teacher				
	n	r	95% CI	p-value (a)		n	r	95% CI	p-value (a)	
Sky Search Targets Found	16	-0.2119	-0.6404 - 0.3171	0.431		16	-0.3947	-0.7447 - 0.1256	0.130	
Sky Search Time per Target	16	-0.3715	-0.7323 - 0.1523	0.157		16	0.0733	-0.4383 - 0.5491	0.787	
Sky Search Attention Score	16	-0.4336	-0.7649 - 0.0791	0.093		16	0.1134	-0.4051 - 0.5767	0.676	
Score!	16	0.0816	-0.4315 - 0.5549	0.764		16	0.1648	-0.3603 - 0.6106	0.542	
Creature Counting Accuracy	16	-0.3974	-0.7461 - 0.1224	0.127		16	0.1383	-0.3837 - 0.5933	0.610	
Creature Counting Timing Score	13	0.3752	-0.2216 - 0.7675	0.206		13	0.1837	-0.4087 - 0.6671	0.548	
Walk, Don't Walk	15	-0.0796	-0.5686 - 0.4511	0.778		15	-0.0891	-0.5751 - 0.4434	0.752	

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; ADHDRS-IV-Teacher:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Teacher Version: Investigator Administered and Scored; CI = confidence interval; n = number of patients; TEA-Ch = Test of Everyday Attention for Children.

a p-value comparing the Pearson's correlation between changes in TEA-Ch and change in ADHDRS-IV-Parent:Inv or ADHDRS-IV-Teacher:Inv to zero.

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Table 16. Correlation of Change in Total and Subscales of WFIRS-P at 2 Months with Change in ADHDRS-IV-Parent:Inv or ADHDRS-IV-Teacher:Inv (Enrolled ADHD Patients who Received At Least One Dose of Study Drug)

Visit	WFIRS-P	ADHDRS-IV-Parent				ADHDRS-IV-Teacher			
		n	r	95% CI	p-value (Pearson)	n	r	95% CI	p-value (Pearson)
Visit 6	Overall	18	0.2649	-0.2305 - 0.6512	0.288	18	-0.0981	-0.5403 - 0.3864	0.698
	Family	18	0.3039	-0.1899 - 0.6750	0.220	18	-0.2072	-0.6146 - 0.2875	0.409
	Learning and School	18	0.3997	-0.0826 - 0.7303	0.100	18	0.3412	-0.1495 - 0.6970	0.166
	Life Skills	18	0.1137	-0.3730 - 0.5513	0.653	18	-0.1354	-0.5665 - 0.3538	0.592
	Child Self Concept	18	0.2726	-0.2226 - 0.6560	0.274	18	-0.0592	-0.5119 - 0.4193	0.816
	Social Activities	18	-0.2407	-0.6361 - 0.2548	0.336	18	-0.3489	-0.7015 - 0.1409	0.156
	Risky Activities	18	0.0661	-0.4135 - 0.5171	0.794	18	-0.1208	-0.5563 - 0.3668	0.633

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; ADHDRS-IV-Teacher:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Teacher Version: Investigator Administered and Scored; CI = confidence interval; n = number of patients; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

p-value comparing the Pearson's correlation between changes in WFIRS-P and change in ADHDRS-IV-Parent:Inv or ADHDRS-IV-Teacher:Inv to zero.

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Table 17. Correlation of Change in Total and Subscales of WFIRS-P at 6 Months with Change in ADHDRS-IV-Parent:Inv or ADHDRS-IV-Teacher:Inv (Enrolled ADHD Patients who Received At Least One Dose of Study Drug)

Visit	WFIRS-P	ADHDRS-IV-Parent				ADHDRS-IV-Teacher			
		n	r	95% CI	p-value (Pearson)	n	r	95% CI	p-value (Pearson)
Visit 8	Overall	16	0.4813	-0.0190 - 0.7888	0.059	16	0.0936	-0.4217 - 0.5632	0.730
	Family	16	0.2250	-0.3047 - 0.6484	0.402	16	-0.0377	-0.5236 - 0.4667	0.890
	Learning and School	16	0.6305	0.1960 - 0.8580	0.009	16	0.4946	-0.0015 - 0.7953	0.051
	Life Skills	16	0.3726	-0.1510 - 0.7329	0.155	16	-0.1872	-0.6249 - 0.3401	0.487
	Child Self Concept	16	0.1729	-0.3530 - 0.6158	0.522	16	0.0545	-0.4535 - 0.5357	0.841
	Social Activities	16	0.2650	-0.2656 - 0.6724	0.321	16	0.0797	-0.4331 - 0.5535	0.769
	Risky Activities	16	0.2699	-0.2607 - 0.6753	0.312	16	0.0046	-0.4923 - 0.4991	0.987

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; ADHDRS-IV-Teacher:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Teacher Version: Investigator Administered and Scored; CI = confidence interval; n = number of patients; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

p-value comparing the Pearson's correlation between changes in WFIRS-P and change in ADHDRS-IV-Parent:Inv or ADHDRS-IV-Teacher:Inv to zero.

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Table 18. Correlation of Change in Total and Subscales of WFIRS-P at LOCF Endpoint with Change in ADHDRS-IV-Parent:Inv or ADHDRS-IV-Teacher:Inv (Enrolled ADHD Patients who Received At Least One Dose of Study Drug)

Visit	WFIRS-P	ADHDRS-IV-Parent				ADHDRS-IV-Teacher			
		n	r	95% CI	p-value (Pearson)	n	r	95% CI	p-value (Pearson)
LOCF	Overall	20	0.4534	0.0136 - 0.7462	0.045	19	0.2603	-0.2199 - 0.6390	0.282
	Family	19	0.1560	-0.3210 - 0.5698	0.524	18	-0.0521	-0.5067 - 0.4251	0.837
	Learning and School	20	0.6116	0.2318 - 0.8296	0.004	19	0.6177	0.2273 - 0.8371	0.005
	Life Skills	20	0.3297	-0.1321 - 0.6739	0.156	19	-0.1110	-0.5381 - 0.3614	0.651
	Child Self Concept	20	0.3668	-0.0904 - 0.6963	0.112	19	0.4002	-0.0660 - 0.7230	0.090
	Social Activities	20	0.1255	-0.3357 - 0.5381	0.598	19	0.0367	-0.4246 - 0.4828	0.882
	Risky Activities	20	0.2912	-0.1737 - 0.6500	0.213	19	0.2668	-0.2133 - 0.6431	0.270

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; ADHDRS-IV-Teacher:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Teacher Version: Investigator Administered and Scored; CI = confidence interval; LOCF = last observation carried forward; n = number of patients; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

p-value comparing the Pearson's correlation between changes in WFIRS-P and change in ADHDRS-IV-Parent:Inv or ADHDRS-IV-Teacher:Inv to zero.

Psychometric Properties of French Language Version of WFIRS-P

Internal consistency was measured using Cronbach's alpha (Table 19). Responsiveness was measured by change from baseline in WFIRS-P, change in ADHDRS-IV-Parent:Inv (Table 20), and change ADHDRS-IV-Teacher:Inv (Table 21).

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Table 19. Cronbach's Coefficient Alpha on WFIRS-P (Enrolled ADHD Patients who Received At Least One Dose of Study Drug)

WFIRS-P	Baseline		Visit 5		Visit 6		Visit 8		LOCF	
	n	Alpha	n	Alpha	n	Alpha	n	Alpha	n	Alpha
Overall	21	0.4375	19	0.3488	18	0.5519	16	0.3682	20	0.1356
Family	20	0.2224	18	0.1782	18	0.1088	16	0.2100	20	-.0246
Learning and School	21	-.0131	19	0.2673	18	0.5819	16	0.2397	20	0.2437
Life Skills	21	0.4099	19	0.1890	18	0.4166	16	0.3726	20	0.0938
Child Self Concept	21	0.4204	19	-.0374	18	0.2616	16	0.0665	20	0.0068
Social Activities	21	0.5098	19	0.4503	18	0.5811	16	0.3229	20	0.2459
Risky Activities	21	0.5085	19	0.5480	18	0.4231	16	0.4009	20	-.0079

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; LOCF = last observation carried forward; n = number of patients; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

Note: One patient had missing scores at Visit 5 and Visit 2 (Baseline) on WFIRS-P "Family."

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Table 20. Change from Baseline in WFIRS-P at Endpoint and Change of Total Score in ADHDRS-IV-Parent:Inv (Enrolled ADHD Patients who Received At Least One Dose of Study Drug)

		Change in ADHDRS-IV-Parent								
Visit	WFIRS	Change Group	n	Mean (SD)	Median	Min, Max		95% CI		p-value (a)
LOCF	Overall	Improved (1)	15	-0.32 (0.282)	-0.30	-1.10,	0.17	-0.48 -	-0.17	0.025 (1 vs 2)
		No Change (2)	5	0.04 (0.301)	0.10	-0.32,	0.36	-0.34 -	0.41	
		Worsened (3)	0							
	Family	Improved (1)	15	-0.29 (0.318)	-0.40	-0.90,	0.30	-0.47 -	-0.12	0.571 (1 vs 2)
		No Change (2)	4	-0.18 (0.399)	-0.15	-0.63,	0.20	-0.82 -	0.45	
		Worsened (3)	0							
	Learning and School	Improved (1)	15	-0.50 (0.446)	-0.50	-1.20,	0.40	-0.75 -	-0.25	0.050 (1 vs 2)
		No Change (2)	5	-0.00 (0.515)	0.00	-0.80,	0.50	-0.64 -	0.64	
		Worsened (3)	0							
	Life Skills	Improved (1)	15	-0.46 (0.473)	-0.40	-1.50,	0.20	-0.72 -	-0.20	0.069 (1 vs 2)
		No Change (2)	5	0.02 (0.507)	0.20	-0.80,	0.50	-0.61 -	0.65	
		Worsened (3)	0							
	Child Self Concept	Improved (1)	15	-0.29 (0.533)	-0.33	-1.00,	1.00	-0.58 -	0.01	0.089 (1 vs 2)
		No Change (2)	5	0.20 (0.506)	0.00	-0.33,	1.00	-0.43 -	0.83	
		Worsened (3)	0							
	Social Activities	Improved (1)	15	-0.23 (0.435)	-0.14	-1.14,	0.57	-0.47 -	0.01	0.355 (1 vs 2)
		No Change (2)	5	-0.00 (0.562)	0.00	-0.86,	0.71	-0.70 -	0.70	
		Worsened (3)	0							
	Risky Activities	Improved (1)	15	-0.13 (0.246)	-0.10	-0.80,	0.10	-0.26 -	0.01	0.011 (1 vs 2)
		No Change (2)	5	0.24 (0.261)	0.10	0.10,	0.70	-0.08 -	0.56	
		Worsened (3)	0							

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ADHDRS-IV-Parent:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored; CI = confidence interval; LOCF = last observation carried forward; Max = maximum; Min = minimum; n = number of patients; SD = standard deviation; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

a p-value between groups using ANOVA with contrasts on change group.

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Table 21. Change from Baseline in WFIRS-P at Endpoint and Change of Total Score in ADHDRS-IV-Teacher:Inv (Enrolled ADHD Patients who Received At Least One Dose of Study Drug)

		Change in ADHDRS-IV-Teacher								
Visit	WFIRS	Change Group	n	Mean (SD)	Median	Min, Max		95% CI		p-value (a)
LOCF	Overall	Improved (1)	12	-0.31 (0.295)	-0.22	-1.10,	0.10	-0.50 -	-0.12	0.064 (1 vs 2)
		No Change (2)	3	0.08 (0.340)	0.17	-0.30,	0.36	-0.77 -	0.92	0.354 (1 vs 3)
		Worsened (3)	4	-0.15 (0.302)	-0.23	-0.40,	0.28	-0.63 -	0.34	0.350 (2 vs 3)
	Family	Improved (1)	12	-0.25 (0.378)	-0.15	-0.90,	0.30	-0.49 -	-0.01	0.574 (1 vs 2)
		No Change (2)	3	-0.13 (0.303)	-0.18	-0.40,	0.20	-0.88 -	0.63	0.515 (1 vs 3)
		Worsened (3)	3	-0.40 (0.000)	-0.40	-0.40,	-0.40	-0.40 -	-0.40	0.342 (2 vs 3)
	Learning and School	Improved (1)	12	-0.62 (0.338)	-0.65	-1.20,	0.00	-0.83 -	-0.40	<.001 (1 vs 2)
		No Change (2)	3	0.40 (0.100)	0.40	0.30,	0.50	0.15 -	0.65	0.014 (1 vs 3)
		Worsened (3)	4	-0.10 (0.374)	-0.15	-0.50,	0.40	-0.70 -	0.50	0.062 (2 vs 3)
	Life Skills	Improved (1)	12	-0.33 (0.509)	-0.25	-1.50,	0.30	-0.66 -	-0.01	0.579 (1 vs 2)
		No Change (2)	3	-0.13 (0.850)	0.20	-1.10,	0.50	-2.25 -	1.98	0.605 (1 vs 3)
		Worsened (3)	4	-0.50 (0.408)	-0.50	-0.90,	-0.10	-1.15 -	0.15	0.393 (2 vs 3)
	Child Self Concept	Improved (1)	12	-0.36 (0.437)	-0.33	-1.00,	0.33	-0.64 -	-0.08	0.057 (1 vs 2)
		No Change (2)	3	0.33 (0.577)	0.00	0.00,	1.00	-1.10 -	1.77	0.162 (1 vs 3)
		Worsened (3)	4	0.08 (0.739)	0.00	-0.67,	1.00	-1.09 -	1.26	0.542 (2 vs 3)
	Social Activities	Improved (1)	12	-0.24 (0.387)	-0.14	-1.14,	0.14	-0.48 -	0.01	0.166 (1 vs 2)
		No Change (2)	3	0.19 (0.577)	0.29	-0.43,	0.71	-1.24 -	1.62	0.627 (1 vs 3)
		Worsened (3)	4	-0.11 (0.588)	-0.07	-0.86,	0.57	-1.04 -	0.83	0.407 (2 vs 3)
	Risky Activities	Improved (1)	12	-0.08 (0.255)	0.00	-0.80,	0.10	-0.25 -	0.08	0.638 (1 vs 2)
		No Change (2)	3	0.00 (0.100)	0.00	-0.10,	0.10	-0.25 -	0.25	0.087 (1 vs 3)
		Worsened (3)	4	0.20 (0.374)	0.15	-0.20,	0.70	-0.40 -	0.80	0.345 (2 vs 3)

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ADHDRS-IV-Teacher:Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Teacher Version: Investigator Administered and Scored; CI = confidence interval; LOCF = last observation carried forward; Max = maximum; Min = minimum; n = number of patients; SD = standard deviation; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent Report.

a p-value between groups using ANOVA with contrasts on change group.

Safety

Table 22 summarizes the treatment-emergent adverse events (TEAEs). None of the patients experienced any serious adverse events, and there were no deaths reported during the study period.

Table 23 summarizes the change from baseline to endpoint in vital signs, height and weight.

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Table 22. Treatment-Emergent Adverse Events in Decreasing Frequency (Enrolled ADHD Patients who Received At Least One Dose of Study Drug)

Preferred Term	Enrolled ADHD Patients (N = 21)	
	n (a)	%
Patient with no Treatment Emergent Adverse Event	1	4.8
Patient with >= 1 Treatment Emergent Adverse Events	20	95.2
Abdominal pain	8	38.1
Somnolence	8	38.1
Headache	7	33.3
Decreased appetite	5	23.8
Excitability	4	19.0
Fatigue	3	14.3
Initial insomnia	3	14.3
Nausea	3	14.3
Pyrexia	3	14.3
Tonsillitis	3	14.3
Vomiting	3	14.3
Asthenia	2	9.5
Dizziness	2	9.5
Irritability	2	9.5
Nasopharyngitis	2	9.5
Abdominal pain upper	1	4.8
Alopecia	1	4.8
Chest discomfort	1	4.8

(continued)

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Table 22. Treatment-Emergent Adverse Events in Decreasing Frequency (Enrolled ADHD Patients who Received At Least One Dose of Study Drug) (concluded)

Preferred Term	Enrolled ADHD Patients (N = 21)	
	n (a)	%
Constipation	1	4.8
Cough	1	4.8
Decreased interest	1	4.8
Depressed mood	1	4.8
Enuresis	1	4.8
Erythema	1	4.8
Herpes simplex	1	4.8
Incorrect dose administered	1	4.8
Influenza	1	4.8
Insomnia	1	4.8
Nasal congestion	1	4.8
Oliguria	1	4.8
Otitis externa	1	4.8
Pharyngitis	1	4.8
Pharyngolaryngeal pain	1	4.8
Pneumonia	1	4.8
Torticollis	1	4.8
Varicella	1	4.8

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; N = sample size; n = number of patients.

a Patients may be counted in more than one category.

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Table 23. Vital Signs, Height, and Weight: Mean Change from Baseline to Endpoint (Study Period II) (Enrolled ADHD Patients who Received At Least One Dose of Study Drug)

Vital Sign		n	Mean (SD)	Median	Min, Max	95% CI	p-value		
							(a)	(b)	(c)
Diastolic BP (mmHg)	Baseline	21	63.8 (7.35)	64.0	50, 80	60.5 - 67.2			
	Endpoint	21	66.7 (5.38)	68.0	58, 80	64.2 - 69.1			
	Change from Baseline	21	2.9 (7.71)	0.0	-10, 20	-0.7 - 6.4	0.431	0.105	0.138
Systolic BP (mmHg)	Baseline	21	104.3 (7.36)	104.0	90, 120	100.9 - 107.6			
	Endpoint	21	103.0 (8.82)	100.0	88, 118	98.9 - 107.0			
	Change from Baseline	21	-1.3 (8.63)	0.0	-18, 14	-5.3 - 2.6	0.631	0.487	0.645
Heart Rate (bpm)	Baseline	21	77.0 (10.35)	80.0	56, 88	72.2 - 81.7			
	Endpoint	21	87.0 (9.29)	88.0	68, 104	82.8 - 91.3			
	Change from Baseline	21	10.1 (10.63)	8.0	-4, 36	5.3 - 14.9	0.006	<.001	<.001
Height (cm)	Baseline	21	129.0 (7.86)	129.0	114.0, 148.0	125.4 - 132.6			
	Endpoint	21	131.1 (8.23)	130.5	117.0, 152.0	127.4 - 134.8			
	Change from Baseline	21	2.1 (1.28)	2.0	0.0, 4.0	1.5 - 2.7	0.231	<.001	<.001
Weight (kg)	Baseline	21	28.3 (5.76)	26.5	21.7, 41.3	25.7 - 31.0			
	Endpoint	21	28.8 (5.43)	26.4	21.7, 39.5	26.3 - 31.3			
	Change from Baseline	21	0.5 (1.22)	0.2	-1.9, 2.6	-0.1 - 1.0	0.669	0.085	0.112

Abbreviations: BP = blood pressure; CI = confidence interval; Max = maximum; Min = minimum; n = number of patients; SD = standard deviation.

a p-value using Shapiro-Wilk normality test.

b p-value using paired t-test comparing mean change to zero.

c p-value using Wilcoxon signed rank test.

References

- DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. 1998. ADHD Rating Scale-IV. Checklist, norms, and clinical interpretations. New York, NY: The Guilford Press.
- Faries DE, Yalcin D, Harder D, Heiligenstein JH. 2001. Validation of the ADHD Rating Scale as a clinician-administered and scored instrument. *J Atten Disord* 5(2):107-115.
- Gioia GA, Isquith PK, Guy SC, Kenworthy L. 2000. Behavior Rating Inventory of Executive Function™ (BRIEF™). Odessa, FL: Psychological Assessment Resources.
- Guy W. 1976. ECDEU assessment manual for psychopharmacology, revised. Bethesda, MD: US Department of Health, Education, and Welfare.
- Korkman M, Kirk U, Kemp S. 1998. NEPSY: A developmental neuropsychological assessment. San Antonio, TX: Psychological Corporation.
- Manly T, Anderson V, Nimmo-Smith I, Turner A, Watson P, Robertson IH. 2001. The differential assessment of children's attention: the Test of Everyday Attention for Children (TEA-Ch), normative sample and ADHD performance. *J Child Psychol Psychiatry* 42(8):1065-1081.
- [NIMH] National Institutes of Mental Health. 1985. *Psychopharmacol Bull* 21:839-943.

Summary ID# 9855

Clinical Study Summary: Study B4Z-US-LYDQ

A Double-Blind Placebo-Controlled Study of Atomoxetine Hydrochloride in the Treatment of Adults with ADHD and Comorbid Social Anxiety Disorder

Date summary approved by Lilly: 24 April 2008

Title of Study: A Double-Blind Placebo-Controlled Study of Atomoxetine Hydrochloride in the Treatment of Adults with ADHD and Comorbid Social Anxiety Disorder	
Investigator(s): This multicenter study included 30 principal investigators.	
Study Center(s): This study was conducted at 30 study centers in one country.	
Length of Study: 23.5 months Date first patient enrolled (first patient visit): 22 June 2005 Date last patient visit completed Study Period II: 13 April 2007 Date last patient visit completed for entire study: 10 May 2007	Phase of Development: 4
Objectives: Primary: The primary objective of this study was to test the hypothesis that atomoxetine given orally, twice-daily, at doses from 40 mg/day to 100 mg/day is superior to placebo in reducing signs and symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD) in adults diagnosed using the <i>Diagnostic and Statistical Manual of Mental Disorders, Text Revision</i> (DSM-IV-TR™; APA 2000) criteria as measured by the mean change in the Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV) Total ADHD Symptom score after up to 16 weeks of treatment. Secondary: If atomoxetine was assessed to be statistically significantly superior to placebo, based on the primary analyses of the CAARS-Inv:SV Total ADHD Symptom score, then key secondary objectives were tested using the Gatekeeper strategy. For these objectives, atomoxetine and placebo were compared in a stepwise fashion, in order as indicated below. Testing was stopped when a measure failed to show statistical significance favoring atomoxetine ($p \geq 0.05$). Secondary objectives in order of preference, as follows: - To test the hypothesis that atomoxetine is noninferior to placebo in treating the symptoms of social anxiety comorbid with ADHD as measured by the mean change in the total score of the Liebowitz Social Anxiety Scale (LSAS) after up to 16 weeks of treatment. - To test the hypothesis that atomoxetine is superior to placebo in treating symptoms of social anxiety comorbid with ADHD as measured by the mean change in the total score of the LSAS after up to 16 weeks of treatment. Other secondary objectives: - To test the hypothesis that atomoxetine improves comorbid symptoms of ADHD and social anxiety compared to placebo after up to 16 weeks of treatment as measured by the mean change in the Clinical Global Impression Overall-Severity (CGI-Overall-S [previously stated as CGI-O-S in protocol]) score. - To demonstrate that atomoxetine is superior to placebo in improving symptoms of social anxiety comorbid with adult ADHD as measured by patient self-report using the mean change in the Trait subscale score of State-Trait Anxiety Inventory (STAI) after up to 16 weeks of treatment. - To demonstrate that atomoxetine is superior to placebo in improving symptoms of anxiety comorbid with adult ADHD as measured by patient self-report using the mean change in the State subscale score of STAI after up to 16 weeks of treatment. - To test the hypothesis that atomoxetine improves a measure of cognition (vigilance) comorbid with adult ADHD and social anxiety compared to placebo as measured by change from baseline in mean response times, errors of commission, and errors of omission on the Conners' Continuous Performance Test II (Conners' CPT-II [previously stated as CPT-II in protocol]) after up to 16 weeks of treatment. - To test the hypothesis that atomoxetine improves symptoms of social adjustment in adult patients with ADHD and comorbid social anxiety compared to placebo as measured by the mean change in the total score of the Social Adjustment Scale Self-Report (SAS-SR) after up to 16 weeks of treatment. - To demonstrate that atomoxetine is superior to placebo in improving measures of quality of life in adult patients with ADHD and comorbid social anxiety as determined by the mean change in the total score of the Adult ADHD Quality of Life-29 (AAQoL-29) after up to 16 weeks of treatment. - To assess the effect of atomoxetine in treating symptoms of depression in adults with ADHD and comorbid social anxiety as measured by the mean change in the total score of the Montgomery-Asberg Depression Rating Scale (MADRS) after up to 16 weeks of treatment.	

- To test the hypothesis that atomoxetine is superior to placebo in improving quality of sleep in adults with ADHD and comorbid social anxiety as measured by the mean change in the total score of the Pittsburgh Sleep Quality Index (PSQI) after up to 16 weeks of treatment. - To compare the safety of atomoxetine with placebo in a population of adult patients who met DSM-IV-TR criteria for ADHD and social anxiety disorder (SAD) after up to 16 weeks of treatment.
Study Design: Study B4Z-US-LYDQ (LYDQ) was a Phase 4, multicenter, randomized, double-blind, parallel, placebo-controlled trial of atomoxetine hydrochloride in adult patients diagnosed with ADHD and comorbid anxiety. Study LYDQ consisted of 3 study periods: Study Period I: Screening period Study Period II: Double-blind 16-week phase where patients were randomized to atomoxetine at 40 to 100 mg/day or placebo. Study Period III: optional 8-week open-label extension period - patients completing Study Period II were dosed with atomoxetine at 36 to 100 mg/day. See Figure LYDQ.1 for study design diagram.
Number of Patients: Planned: 440 (220 atomoxetine and 220 placebo) Randomized: 224 atomoxetine, 218 placebo (Qualified; primary and secondary gated analyses: 176 active drug, 166 placebo) Completed Study Period II: 127 atomoxetine, 137 placebo Entered Study Period III. Open-Label Period: 256 (acute period randomization: 122 atomoxetine, 134 placebo) Completed Study Period III: 223
Diagnosis and Main Criteria for Inclusion: Male and female outpatients ages 18-65 who met DSM-IV-TR criteria for adult ADHD as assessed by the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) and for SAD as assessed by the Structured Clinical Interview for DSM-IV-TR™ Axis Disorders-Research Version (SCID-RV). Concomitant Axis I diagnoses that were also allowed (current or lifetime) were specific phobias, Generalized Anxiety Disorder (GAD), current dysthymia, and major depressive disorder (current diagnosis was allowed only if diagnosed greater than 6 months immediately prior to Visit 1). Patients were required to have a LSAS score of 50 or greater with no more than a 30% decrease in scores between Visit 1 and Visit 2 as well as a CGI-Overall-S Scale score of 4 or greater at Visit 1 and Visit 2. Patients who completed the acute therapy period were eligible to continue open-label treatment with atomoxetine.
Test Product, Dose, and Mode of Administration: Study Period II: Atomoxetine hydrochloride target dose of 80 mg/day (range of 40 mg/day to 100 mg/day), given twice daily (BID), given orally as 20 mg or 25 mg capsules. During Study Period III: Atomoxetine hydrochloride dosed BID or once daily (QD); market image bottles of Strattera were supplied at 18mg, 25mg and 40mg dose capsules.
Reference Therapy, Dose, and Mode of Administration: placebo given orally twice daily.
Duration of Treatment: 6 months : 16 weeks in Study Period II and 8 weeks in Study Period III
Variables: <u>Efficacy:</u> <u>Primary:</u> CAARS-Inv:SV Total ADHD Symptom score <u>Gated secondary:</u> LSAS Total score <u>Secondary:</u> CAARS-Inv:SV Hyperactivity/Impulsivity, Inattention and ADHD Index subscale scores; the LSAS subscale scores (Performance Fear, Performance Avoidance, Social Fear, Social Avoidance); CGI-Overall-S; STAI Trait and State subscale scores; Conners' CPT-II Total and subscores; SAS-SR Total and subscores (Work Role, Social and Leisure, Extended Family, Primary Relationship, Parental, and Family Unit).

Safety:

Treatment differences in percentages of treatment-emergent adverse events (TEAEs); changes from baseline to endpoint for laboratory data, vital signs (including height and weight), electrocardiogram (ECG) intervals, Pittsburgh Sleep Quality Index (PSQI), and the Montgomery-Asberg Depression Rating Scale (MADRS).

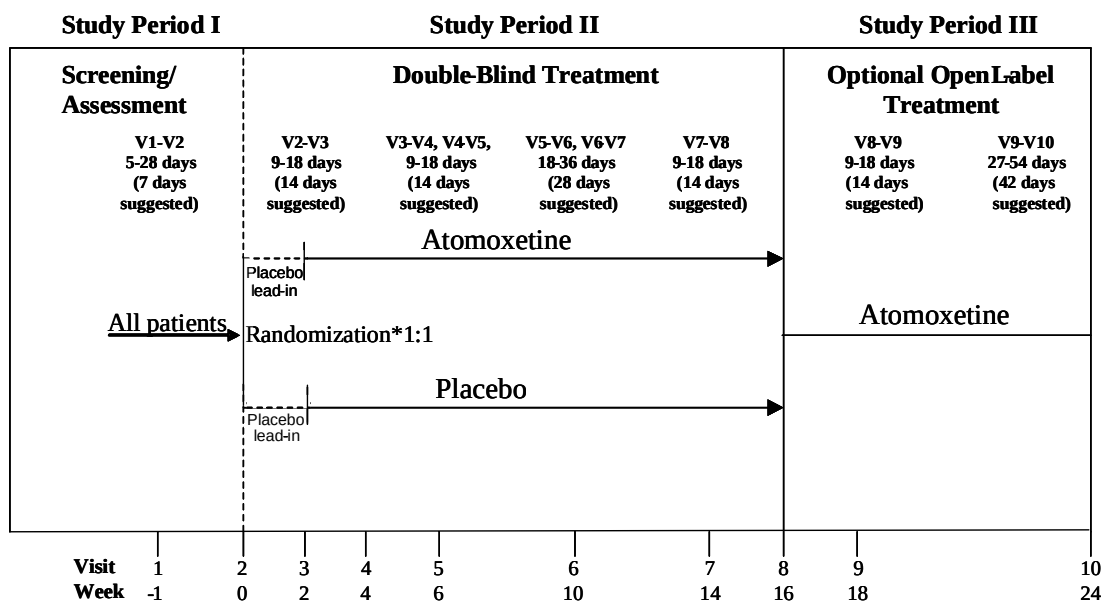
Health Outcomes:

AAQoL-29 Total score and Life Productivity, Psychological Health, Life Outlook, and Relationships subscale scores.

Evaluation Methods:

Statistical: The primary efficacy analysis for the CAARS-Inv:SV Total ADHD Symptom score was an analysis of covariance (ANCOVA) on the mean change from baseline to last-observation-carried-forward (LOCF) endpoint scores during Study Period II. The ANCOVA model contained terms for baseline value, treatment group, and investigational site. The primary analysis included only qualified patients. To assess the overall robustness of the primary analyses, the CAARS-Inv:SV Total ADHD Symptom score was analyzed based on the treatment group comparison of Visit 8 values based on a contrast from a repeated measures analysis for the post-baseline scores during Study Period II. Each analysis was based on the restricted maximum likelihood method. An unstructured covariance structure was used to model the within-subject variance. The independent effects in the model were investigational site, treatment group, visit, baseline value, and treatment-by-visit interaction. Secondary evidence of a drug effect was based on the treatment term from this repeated measures model. The gated LSAS measure was analyzed using a1-sided 97.5% confidence interval constructed on the change score of atomoxetine minus placebo using least-square means from the LOCF to assess non-inferiority. If non-inferiority is achieved then proceeded to the test of the main effect of treatment using LOCF ANCOVA. Other secondary measures were analyzed using mixed model repeated measures, LOCF ANCOVA, or Fisher's exact test.

Changes from baseline (Visits 8) to endpoint were summarized for efficacy and health outcomes variables collected during the open-label period. Within group changes from baseline were tested using Student's t-test. Between group differences on the mean change from baseline were tested using least squares means from an analysis of covariance (ANCOVA) model with terms for baseline value, treatment group, and investigational site. Safety analyses included calculation of the percentage of TEAEs; changes from baseline to final value for laboratory data, vital signs (including weight), and ECG intervals; and percentages of treatment-emergent out-of-range laboratory values as well as categorical changes in QTc intervals that exceeded clinically significant ranges. Mean changes were assessed using Student's t-test for vital signs and ECGs, and Wilcoxon Signed-Rank test for lab measurements.



R* = Randomization: Randomization occurred at Visit 2. For patients randomized to atomoxetine, the timing and duration of treatment with placebo (Visit 2 to Visit 3) was blinded to site personnel and to patients.

Figure LYDQ.1. Study design for Study B4Z-US-LYDQ.

Summary of Results:

Study Period II: Double-blind phase

Patient Demographics

Four hundred and forty two patients were randomized in this study; 342 patients were deemed as qualified patients of which 329 had a post-placebo lead-in phase measure (beyond Visit 3) and were included in the primary and gated secondary analyses. Qualified patients were classified as those patients who showed no more than a 25% reduction in anxiety symptoms as measured on the LSAS total score while on placebo during the double-blind placebo lead-in period (Visit 2 to Visit 3) prior to the commencement of active treatment. Overall, more patients randomized to the study were male and the majority of patients were Caucasian, of mixed or inattentive ADHD subtype, featured generalized SAD, and had no prior stimulant use (Table LYDQ.1). The age range of patients in this study was 18.18 to 64.69 years. Characteristics among the entered, randomized, and qualified patients between groups were similar. A greater body mass index (BMI) for patients randomized to the atomoxetine group was the only statistically significant difference among randomized patients.

Table LYDQ.1. Patient Demographic and Other Baseline Characteristics
Double-Blind Period
All Randomized Patients

Demographic and Other Baseline Characteristics Information		Atomoxetine N=224		Placebo N=218		p- Value
		n	Percent	n	Percent	
Gender	Female	102	45.54	103	47.25	.775
	Male	122	54.46	115	52.75	
Origin	African Descent	27	12.05	15	6.88	.138
	Western Asian	0	0.0	2	0.92	
	Caucasian	165	73.66	162	74.31	
	East/Southeast Asian	1	0.45	5	2.29	
	Hispanic	27	12.05	28	12.84	
	Other	4	1.79	6	2.75	
At Least One Dose of Study Drug	Yes	212	100	211	100	
Previous Stimulant Use	Yes	50	22.32	54	24.77	.787
	No	173	77.23	163	74.77	
	Unknown	1	0.45	1	0.46	
DSM-IV ADHD Subtype	Hyperactive/Impulsive	4	1.79	2	0.92	.239
	Inattentive	84	37.50	97	44.50	
	Mixed	134	59.82	119	54.59	
	Missing	2	0.89	0	0	
Social Anxiety Disorder Subtype	Generalized	200	89.29	184	84.40	.200
	Non-generalized	22	9.82	33	15.14	
	Not applicable	2	0.89	1	0.46	
Generalized Anxiety Disorder	Currently present	53	23.77	50	22.94	.562
CYP2D6 ADHD Subtype	Extn	207	94.52	206	94.93	1.00
	Slow	12	5.48	11	5.07	

(continued)

**Table LYDQ.1. Patient Demographic and Other Baseline Characteristics
Double-Blind Period
All Randomized Patients (concluded)**

Demographic and Other Baseline Characteristics Information		Mean	Median	Std	Max	Min	p-Value
Age	Atomoxetine	37.88	37.21	11.83	64.69	18.18	0.857
	Placebo	38.10	39.06	11.42	64.41	18.14	
Weight	Atomoxetine	85.06	81.35	23.04	197.90	38.30	0.052
	Placebo	81.26	79.00	17.58	133.60	41.90	
Height	Atomoxetine	170.90	170.50	10.01	198.00	150.00	0.818
	Placebo	171.11	170.50	10.51	192.00	132.00	
Body Mass Index	Atomoxetine	28.96	27.95	6.68	58.41	14.96	0.028
	Placebo	27.68	26.82	5.23	45.77	17.00	

Primary Efficacy

Table LYDQ.2 displays the mean change from baseline to LOCF endpoint of the CAARS-Inv:SV Total ADHD Symptom score for all qualified patients. Statistically significantly greater mean change decrease from baseline (29.61 ± 10.37) to LOCF endpoint in the CAARS-Inv:SV Total ADHD Symptom score (-8.73 ± 10.02) was demonstrated for qualified atomoxetine-treated patients compared with qualified placebo-treated patients (-5.60 ± 10.15 ; $p < .001$).

**Table LYDQ.2. CAARS-Inv:SV Total ADHD Symptom Score
Mean Change from Baseline to LOCF Endpoint
All Qualified Patients Who Entered Double-Blind Period**

Treatment Assignment	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	p-Value ^a
Atomoxetine	29.61 (10.37)	20.88 (11.25)	-8.73 (10.02)	<.001
Placebo	31.21 (9.43)	25.61 (10.56)	-5.60 (10.15)	

Abbreviations: CAARS-Inv:SV = Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version; LOCF = last observation carried forward; SD = standard deviation.

^a p-Value from baseline to LOCF endpoint scores using least squares means from an ANCOVA model with terms for investigator, treatment, and baseline as covariates.

Gated Secondary Efficacy:

This study employed a gatekeeper strategy to examine anxiety symptoms as assessed by the mean change in the LSAS Total score. The results for this study demonstrated that atomoxetine did not increase anxiety symptoms and, in fact, significantly reduced anxiety symptoms while reducing ADHD symptoms. Specifically, for the LSAS Total score, atomoxetine proved to be noninferior (first gated measure) to placebo and superior (second gated measure) to placebo on the LSAS Total score in qualified patients. The LSAS total score mean change from baseline to LOCF endpoint for qualified atomoxetine-treated patients was -22.93 ± 25.27 .

Secondary Efficacy:

Secondary analyses of the CAARS-Inv:SV Total ADHD Symptom score measures using repeated measures analyses revealed statistically significantly greater decrease in symptom scores at each postbaseline visit for atomoxetine-treated patients compared to placebo for both the qualified and randomized patients. Likewise, evaluation of the CAARS-Inv:SV subscale scores of Inattention and Hyperactivity-Impulsivity revealed statistically significantly greater mean change decrease in symptom scores from baseline to LOCF for qualified and randomized atomoxetine-treated patients compared to placebo-treated patients. Additionally, further results from a secondary analyses of the LSAS total using a repeated measures analyses for the change from baseline scores (Visit 4 through Visit 8) revealed statistically significantly greater decrease in symptom scores for atomoxetine-treated patients over placebo-treated patients at each postbaseline visit. Similar results for atomoxetine over placebo were noted when all randomized patients were analyzed.

Results of the CGI-Overall-S showed atomoxetine-treated patients having statistically greater decrease in signs and symptoms of both ADHD and anxiety compared with placebo-treated patients on the mean change to LOCF endpoint. In addition, the STAI T-Anxiety score reflecting how patients “generally” feel was statistically significantly lower in atomoxetine-patients compared to placebo-treated patients, though there was no statistical separation for the STAI S-Anxiety score. The SAS-SR measure did not statistically separate from placebo.

Table LYDQ.3. Secondary Efficacy Outcomes
Mean Change from Baseline to LOCF Endpoint
All Patients Who Entered Double-Blind Period

	Atomoxetine			Placebo			
Mean (SD)	Baseline	Endpoint	Change	Baseline	Endpoint	Change	p Value
CAARS:Inv:SV ADHD Index Subscale ^b	19.8 (6.8)	14.1 (7.7)	-5.7 (7.3)	20.5 (5.8)	17.3 (7.1)	-3.2 (6.7)	<.001
CAARS:Inv:SV Hyperactivity/Impulsivity Subscale ^b	12.7 (5.9)	8.7 (5.6)	-3.9 (5.3)	12.7 (5.6)	10.7 (5.7)	-2.0 (5.2)	<.001
CAARS:Inv:SV Inattention Subscale ^b	17.0 (6.0)	12.2 (6.9)	-4.8 (5.7)	18.5 (5.4)	14.9 (6.0)	-3.6 (6.2)	.001
LSAS Total Score ^b	85.3 (23.6)	62.4 (29.7)	-22.9 (25.3)	82.1 (21.3)	67.7 (26.9)	-14.4 (20.3)	<.001
LSAS Performance Fear Score ^b	22.4 (6.6)	17.0 (8.0)	-5.4 (6.7)	22.2 (5.9)	18.3(7.3)	-3.9 (5.9)	.01
LSAS Performance Avoidance Score ^b	22.0 (7.1)	15.7 (8.2)	-6.2 (7.7)	21.2 (6.6)	17.3 (7.7)	-4.0 (6.0)	.002
LSAS Social Fear Score ^b	20.5 (6.1)	15.4 (7.9)	-5.1 (6.1)	19.5 (5.4)	16.3 (6.9)	-3.2 (5.3)	.002
LSAS Social Avoidance Score ^b	20.5 (6.5)	14.2 (7.7)	-6.3 (6.8)	19.1 (6.3)	15.8 (7.4)	-3.4 (6.0)	<.001
CGI-O-S ^c	4.3 (0.8)	3.5 (1.1)	-.76 (1.1)	4.4 (0.9)	3.8 (1.0)	-.60 (1.0)	.02
STAI-State ^c	50.0 (11.9)	42.8 (13.2)	-7.2 (13.9)	48.2 (11.6)	43.2 (12.5)	-5.0 (12.0)	.27
STAI-Trait ^c	56.2 (10.4)	47.3 (13.1)	-8.9 (11.2)	54.7 (10.2)	48.7 (12.2)	-6.0 (9.0)	.008
SAS ^c	2.4 (0.4)	2.1 (0.5)	-0.3 (0.4)	2.4 (0.5)	2.1 (0.5)	-0.2 (0.4)	.05

a Abbreviations: LOCF, last observation carried forward; ANCOVA, analysis of covariance; SD, standard deviation; CAARS:Inv:SV, Conners' Adult ADHD Rating Scale: Investigator-rated: Screening Version; ADHD, attention-deficit/hyperactivity disorder; LSAS, Liebowitz Social Anxiety Scale; CGI-O-S, Clinical Global Impression-Overall-Severity; STAI, State-Trait Anxiety Inventory; SAS, Social Adjustment Scale-Self Report; AAQoL, Adult ADHD Quality of Life Scale-29.

b All qualified patients (those who had no more than a 25% decrease in LSAS Total score during placebo lead-in).

c All randomized patients.

Health Outcomes:

Results of mean change from baseline to LOCF endpoint analysis for the AAQoL-29 Total and subscale scores are presented below (Table LYDQ.4). Statistically significant increase in the atomoxetine group in quality of life scores were observed on the Total and Psychological Health Domain and Quality subscale scores. There were no statistically significant differences between atomoxetine and placebo on the overall Conners' CPT-II measures.

**Table LYDQ.4. AAQoL-29 Total Score and Subscale Scores
Mean Change from Baseline to LOCF Endpoint
All Patients Who Entered Double-Blind Period**

Mean (SD)	Atomoxetine			Placebo			p Value
	Baseline	Endpoint	Change	Baseline	Endpoint	Change	
AAQoL Total Score	44.1 (15.2)	59.1 (18.3)	14.9 (17.1)	45.3 (13.6)	56.4 (16.5)	11.1 (15.0)	.03
AAQoL Life Outlook Domain	46.1 (15.5)	57.6 (18.8)	11.5 (17.6)	46.1 (14.3)	54.9 (16.8)	8.8 (14.9)	.07
AAQoL Life Productivity Domain	41.7 (19.3)	58.9 (22.6)	17.2 (21.9)	42.9 (18.2)	55.8 (20.8)	12.9 (19.8)	.09
AAQoL Psychological Health Domain ^a	41.2 (20.0)	57.0 (22.7)	15.8 (21.9)	42.1 (18.5)	53.3 (20.8)	11.2 (19.3)	.03
AAQoL Quality of Relationships Domain	50.5 (18.9)	64.2 (18.4)	13.7 (20.5)	53.0 (19.0)	62.8 (18.6)	9.8 (19.1)	.10

^a All randomized patients.

Safety:

The average atomoxetine total daily dose was 80 mg/day (dose ranged from 40 mg/day to 100 mg/day). There were no deaths in this study. Twenty-three of 224 atomoxetine-treated patients and 18 of 218 placebo-treated patients discontinued because of an adverse event (AE). The most commonly reported TEAEs ($\geq 10\%$) for atomoxetine-treated patients were headache, insomnia, nausea, dry mouth, nasopharyngitis, and decreased appetite. There were no statistically significant differences between groups in the number of patients reporting at least one TEAE ($p=.054$). The following TEAEs occurred more often in atomoxetine-treated patients compared to placebo: insomnia ($p=.020$), nausea ($p=.010$), dry mouth ($p<.001$), and dizziness ($p=.023$) (Table LYDQ.5). Two serious AEs of gallstones and biliary dyskinesia occurred in the atomoxetine group. Both patients fully recovered from the events, though the patient with gallstones discontinued from the study and the patient reporting biliary dyskinesia completed Study Period II.

Table LYDQ.5. TEAEs for all randomized patients occurring in at least 5% of patients in either treatment group.

	Atomoxetine (N=212)	Placebo (N=211)	
	n (%)	n (%)	p Value
Patients with at least 1 TEAE ^a	183 (86.3)	167 (79.1)	.05
Headache	43 (20.3)	30 (14.2)	.12
Insomnia	36 (17.0)	19 (9.0)	.02
Nausea	34 (16.0)	16 (7.6)	.01
Dry Mouth	33 (15.6)	9 (4.3)	<.001
Nasopharyngitis	23 (10.8)	17 (8.1)	.41
Decreased Appetite	22 (10.4)	12 (5.7)	.11
Constipation	16 (7.5)	8 (3.8)	.14
Dizziness	16 (7.5)	5 (2.4)	.02
Fatigue	13 (6.1)	12 (5.7)	1.00
Initial Insomnia	12 (5.7)	6 (2.8)	.23
Irritability	11 (5.2)	15 (7.1)	.43
Somnolence	11 (5.2)	7 (3.3)	.47
Anxiety	10 (4.7)	13 (6.2)	.53
Pharyngolaryngeal Pain	9 (4.2)	12 (5.7)	.51
Erectile Dysfunction ^b	6 (5.2)	1 (0.9)	.12
Upper Respiratory Tract Infection	6 (2.8)	11 (5.2)	.23

a Abbreviation: TEAE, treatment-emergent adverse event.

b Percentage based on men only (atomoxetine n=115; placebo n=109).

Table LYDQ.6 presents a summary of all laboratory analytes that showed a statistically significant mean change from baseline to LOCF endpoint for all patients who took at least one dose of study drug during the double-blind period.

Table LYDQ.6. Laboratory Analytes with Statistically Significant Mean Change from Baseline to LOCF Endpoint Double-Blind Period

Analyte	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	p-Value^a
Alkaline phosphatase (U/L)					
Atomoxetine	168	72.80 (18.98)	74.23 (19.17)	1.43 (9.90)	0.001
Placebo	165	72.27 (18.04)	70.67 (17.04)	-1.60 (7.92)	
Platelet Count (GI/L)					
Atomoxetine	164	271.34 (65.25)	280.26 (68.68)	8.93 (46.62)	0.011
Placebo	157	260.21 (54.40)	259.52 (55.53)	-0.69 (33.85)	

Abbreviations: LOCF = last observation carried forward; SD = standard deviation.

a p-Values are from the comparisons among therapy groups using Type III sums of squares from an ANCOVA model; Change = Baseline Investigator Therapy.

Population: All patients who took at least one dose of study drug during the double-blind period.

Table LYDQ.7 presents statistically significant results in mean change from baseline to LOCF endpoint for vital signs and weight among all patients who took at least one dose of study drug during the double-blind period. Statistically significant increases in diastolic blood pressure and pulse were observed.

**Table LYDQ.7. Vital Signs and Weight
Mean Change from Baseline to LOCF Endpoint
Double-Blind Period**

Safety Outcome	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	p-Value ^a
Diastolic BP					
Atomoxetine	211	76.60 (8.66)	77.99 (8.69)	1.39 (9.15)	0.003
Placebo	210	75.83 (8.31)	75.39 (9.10)	-0.44 (8.11)	
Pulse					
Atomoxetine	211	72.72 (10.20)	76.33 (11.67)	3.58 (11.51)	<.001
Placebo	210	70.71 (9.18)	72.00 (9.34)	1.29 (9.57)	

Abbreviations: BMI = body mass index; BP = blood pressure; BPM = beats per minute; LOCF = last observation carried forward; SD = standard deviation.

a p-Values are from from baseline to endpoint (LOCF) scores using least squares means from an ANCOVA model with terms for investigator, treatment, and baseline as a covariate.

Population: All patients who took at least one dose of study drug during the double-blind period.

There were no statistically significant differences in mean change from baseline to LOCF endpoint for ECG QRS interval, data-corrected QT interval (QTcD), or Fridericia-corrected QT interval. Table LYDQ.8 shows the ECG measures that showed a statistically significant change from baseline to endpoint.

Table LYDQ.8. Electrocardiograms with Statistically Significant Mean Change from Baseline to LOCF Endpoint Double-Blind Period

ECG	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	p-Value ^a
Derived RR Interval ^b					
Atomoxetine	159	912.10 (140.64)	834.96 (132.08)	-77.14 (129.34)	<.001
Placebo	160	935.42 (142.37)	920.30 (145.21)	-15.12 (115.67)	
Heart rate (BPM)					
Atomoxetine	159	67.37 (10.67)	76.63 (11.44)	6.26 (10.62)	<.001
Placebo	160	65.63 (9.99)	66.76 (10.17)	1.13 (8.11)	
PR Interval (msec)					
Atomoxetine	159	155.00 (20.25)	150.52 (19.35)	-4.48 (11.93)	0.002
Placebo	160	155.36 (19.97)	155.01 (19.84)	-0.34 (11.52)	
QT interval (msec)					
Atomoxetine	159	392.07 (28.75)	382.16 (25.84)	-9.91 (23.35)	<.001
Placebo	160	394.59 (28.25)	393.30 (28.50)	-1.29 (21.30)	
QT Derived RR Interval ^c					
Atomoxetine	159	408.18 (21.76)	412.34 (20.60)	4.16 (14.92)	0.042
Placebo	160	406.70 (22.38)	407.96 (20.13)	1.26 (15.26)	
QTcB interval (msec)					
Atomoxetine	159	412.52 (24.16)	420.47 (23.66)	7.96 (17.82)	<.001
Placebo	160	409.99 (24.79)	411.98 (22.24)	1.99 (17.33)	

Abbreviations: BPM = beats per minute; LOCF = last observation carried forward; msec = milliseconds; QTcB = Bazett-corrected QT interval; SD = standard deviation.

^a p-Values are from from baseline to endpoint (LOCF) scores using least squares means from an ANCOVA model with terms for investigator, treatment, and baseline as a covariate..

^b Derived RR interval = 1000*60/heart rate.

^c Derived RR interval = 1000*0.40

Population: All patients who took at least one dose of study drug during the double-blind period.

Additional safety measures utilized for this study were the MADRS depression scale and the PSQI sleep quality scale. Baseline scores on the MADRS for patients randomized to either atomoxetine or placebo were subthreshold for depression and suicidal ideation (as measured by MADRS Item 10). By the end of study, patients in both groups continued to be subthreshold for depression and suicidal ideation. Baseline scores for patients randomized to either atomoxetine or placebo demonstrated some impairment in quality of sleep. Analyses of the PSQI revealed that atomoxetine mean change scores were not statistically significantly different from placebo.

Study Period III: Open-label Period

Patient Demographics

A total of 256 patients entered the open-label period (Study Period III, Visit 9 and Visit 10). Most patients (N=223, 87.11%) completed the open-label period. Reasons for discontinuation from Study LYDQ were: Adverse Event (N=12, 4.69%), Patient Decision (N=10, 3.91%), Unable to Contact Patient (N=9, 3.52%), Sponsor Decision (N=1, 0.39%), and Lack of Efficacy (N=1, 0.39%). The majority of patients were Caucasian (75%). The mean age of patients was 39.2 years (range, 18.54 – 64.69), and 50.8% were female. The majority of patients were of mixed (54.7%) or inattentive (42.6%) ADHD subtype, featured generalized SAD (85.6%), and had no prior stimulant use (76.2%).

Primary Efficacy

Table LYDQ.9 summarizes the mean change from baseline to LOCF endpoint in the CAARS-Inv:SV Total ADHD Symptom score during the open-label period for patients overall as well as stratified by treatment assignment during Study Period II (Double-blind Period). During the open-label period, patients as a group overall or stratified by atomoxetine and placebo acute treatment groups experienced statistically significant reductions in the CAARS-Inv:SV Total ADHD Symptom score for those with continued atomoxetine treatment and for those switched from placebo to atomoxetine.

**Table LYDQ.9. CAARS-Inv:SV Total ADHD Symptom Score
Mean Change from Baseline to LOCF Endpoint
All Patients Who Entered Open-Label Period**

Acute Treatment Assignment ^a	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	Within Group p-Value ^b	Between Group p-Value ^c
Atomoxetine	119	18.18 (10.46)	16.02 (9.46)	-2.16 (5.52)	<.001	.076
Placebo	133	23.87 (10.96)	18.57 (9.80)	-5.30 (9.34)	<.001	
Total	252	21.18 (11.08)	17.37 (9.71)	-3.81 (7.91)	<.001	

Abbreviations: CAARS-Inv:SV = Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version; LOCF = last observation carried forward; SD = standard deviation.

^a All patients received treatment with atomoxetine in the open-label period. Acute treatment assignment represents the treatment group during the acute period (Study Period II).

^b p-Value from Student's t-test.

^c p-Value from baseline to LOCF endpoint scores using least squares means from an ANCOVA model with terms for investigator, treatment, and baseline as covariates.

Secondary Efficacy:

Table LYDQ.10 summarizes the mean change from baseline to LOCF endpoint in the LSAS total score during the open-label period for patients overall as well as stratified by treatment assignment during the double-blind period (Study Period II). During the open-label period, patients as a group overall or stratified by atomoxetine and placebo acute treatment groups experienced statistically significant reductions in the LSAS total score for those with continued atomoxetine treatment and for those switched from placebo to atomoxetine.

Table LYDQ.10. LSAS Total Score
Mean Change from Baseline to LOCF Endpoint
All Patients Who Entered Open-Label Period

Acute Treatment Assignment ^a	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	Within Group p-Value ^b	Between Group p-Value ^c
Atomoxetine	119	51.98 (30.16)	45.80 (27.61)	-6.18 (14.97)	<.001	.698
Placebo	133	62.21 (28.90)	53.61 (28.15)	-8.60 (17.98)	<.001	
Total	252	57.38 (29.88)	49.92 (28.11)	-7.46 (16.64)	<.001	

Abbreviations: LOCF = last observation carried forward; LSAS = Liebowitz Social Anxiety Scale; SD = standard deviation.

^a All patients received treatment with atomoxetine in the open-label period. Acute treatment assignment represents the treatment group during the acute period (Study Period II).

^b p-Value from Student's t-test.

^c p-Value from baseline to LOCF endpoint scores using least squares means from an ANCOVA model with terms for investigator, treatment, and baseline as covariates.

Table LYDQ.11 presents the mean changes from baseline to LOCF endpoint of the secondary efficacy outcomes evaluated during the open-label period among all patients who entered the open-label period. Statistically significant reduction from baseline was observed on the CAARS-Inv:SV subscale scores. Statistically significant mean change decrease from baseline to endpoint was observed for anxiety as measured by LSAS subscale scores and STAI scales and for social adjustment as measured by the SAS-SR total score and subscales for work role, social and leisure, extended family, and family unit, but not for the SAS-SR primary relationship and parental subscales. Statistically significant mean change decrease from baseline to endpoint on the CGI-Overall-S was observed.

Table LYDQ.11. Secondary Efficacy Outcomes
Mean Change from Baseline to LOCF Endpoint
All Patients Who Entered Open-Label Period

Secondary Outcome	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	p-Value ^a
CAARS-Inv:SV Hyperactivity/Impulsivity Subscale Score	252	9.05 (5.82)	7.25 (4.76)	-1.81 (4.17)	<.001
CAARS-Inv:SV Inattention Subscale Score	252	12.13 (6.40)	10.12 (6.07)	-2.01 (4.69)	<.001
CAARS-Inv:SV ADHD Index Subscale Score	252	14.34 (7.47)	11.98 (6.77)	-2.35 (5.30)	<.001
LSAS Total Fear Score	252	29.84 (15.05)	25.88 (13.99)	-3.96 (8.48)	<.001
LSAS Total Avoidance Score	252	27.54 (15.35)	24.04 (14.51)	-3.50 (8.91)	<.001
LSAS Performance Fear Subscale Score	252	15.65 (8.05)	13.63 (7.42)	-2.02 (4.70)	<.001
LSAS Performance Avoidance Subscale Score	252	14.34 (8.35)	12.57 (7.84)	-1.77 (5.18)	<.001
LSAS Social Fear Subscale Score	252	14.19 (7.67)	12.25 (7.16)	-1.93 (4.28)	<.001
LSAS Social Avoidance Subscale Score	252	13.16 (7.78)	11.48 (7.33)	-1.68 (4.52)	<.001
CGI-Overall-S	252	3.51 (1.12)	3.10 (1.06)	-0.41 (0.91)	<.001
STAI Anxiety Trait Score	240	46.50 (12.04)	43.33 (12.36)	-3.17 (7.87)	<.001
STAI Anxiety State Score	238	40.84 (11.76)	39.18 (11.75)	-1.66 (9.56)	.008
SAS-SR Total Score	241	2.03 (0.39)	1.95 (0.39)	-0.08 (0.27)	<.001
SAS-SR Work Role Subscore	232	1.80 (0.60)	1.66 (0.47)	-0.14 (0.55)	<.001
SAS-SR Social and Leisure Subscore	241	2.37 (0.53)	2.31 (0.55)	-0.06 (0.45)	.029
SAS-SR Extended Family Subscore	241	1.79 (0.53)	1.71 (0.50)	-0.08 (0.45)	.006
SAS-SR Primary Relationship Subscore	135	2.08 (0.53)	2.02 (0.52)	-0.06 (0.40)	.092
SAS-SR Parental Subscore	95	1.64 (0.50)	1.63 (0.48)	-0.01 (0.35)	.734
SAS-SR Family Unit Subscore	239	1.93 (0.73)	1.82 (0.67)	-0.11 (0.57)	.004

Abbreviations: ADHD = attention-deficit hyperactivity disorder; CAARS-Inv:SV = Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version; CGI-Overall-S = Clinical Global Impression-Overall-Severity; LOCF = last observation carried forward; LSAS = Liebowitz Social Anxiety Scale; SAS-SR = Social Adjustment Scale-Self Rating; SD = standard deviation; STAI = State-Trait Anxiety Inventory.

^a p-Value from Student's t-test.

Health Outcomes:

Results of mean change from baseline to LOCF endpoint analysis for the AAQoL-29 Total and subscale scores are presented below (Table LYDQ.12). Statistically significant mean change increase in quality of life scores were observed on the Total and all subscale scores.

**Table LYDQ.12. AAQoL-29 Total Score and Subscale Scores
Mean Change from Baseline to LOCF Endpoint
All Patients Who Entered Open-Label Period**

AAQoL Score/Subscore	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	p-Value^a
Total Score	237	59.60 (16.40)	63.94 (15.52)	4.34 (12.70)	<.001
Life Productivity Subscale Score	237	59.22 (20.89)	64.51 (19.09)	5.29 (17.29)	<.001
Psychological Health Subscale Score	236	57.57 (19.74)	62.51 (18.71)	4.94 (17.38)	<.001
Life Outlook Subscale Score	236	57.89 (17.20)	60.88 (16.78)	2.98 (13.86)	.001
Relationships Subscale Score	237	65.06 (16.96)	68.34 (16.76)	3.28 (14.98)	<.001

Abbreviations: AAQoL-29 = Adult ADHD Quality of Life-29; LOCF = last observation carried forward; SD = standard deviation.

^a p-Value from Student's t-test.

Safety:

The mean final daily dose prescribed was 82.89 mg (1.06 mg/kg). There were no deaths in this study. During the open-label phase, 6 patients reported a serious adverse event: cerebrovascular accident, pyrexia, suicide attempt, accidental overdose, biliary dyskinesia, and accidental overdose. Of note: the patient who attempted suicide had a prior history of depressed mood and the investigator felt this event was not related to atomoxetine treatment. Twelve patients discontinued due to an AE: insomnia, dry mouth, ejaculation disorder, urinary retention, dry mouth, dry mouth, poor quality sleep, chest pain, constipation, irritability, erectile dysfunction, and hepatic enzyme increased. A total of 158 (61.7%) patients experienced at least 1 TEAE. The most common AEs ($\geq 5\%$) were dry mouth 29 (11.3%), headache 17 (6.6%), nausea 16 (6.3%), decreased appetite 14 (5.5%), and insomnia 14 (5.5%).

Baseline values on the Suicidal Thoughts item of the MADRS for patients entering the open-label phase were subthreshold and statistically unchanged by the end of the study. No statistically significant difference was observed for PSQI global score.

Table LYDQ.13 presents a summary of all laboratory analytes that showed a statistically significant mean change from baseline to LOCF endpoint for all patients who took at least one dose of study drug during the open-label period.

Table LYDQ.13. Laboratory Analytes with Statistically Significant Mean Change from Baseline to LOCF Endpoint Open-Label Period

Analyte	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	p-Value ^a
Alkaline phosphatase (U/L)	220	73.46 (18.63)	74.50 (18.40)	1.04 (7.44)	.039
Bicarbonate (mmol/L)	215	25.90 (2.30)	26.34 (2.36)	0.44 (2.26)	.007
Total bilirubin (umol/L)	216	8.82 (4.70)	8.40 (4.77)	-0.42 (3.74)	.029
Eosinophils (GI/L)	206	0.15 (0.11)	0.15 (0.11)	-0.01 (0.09)	.049
Uric acid (umol/L)	220	316.56 (94.44)	308.05 (91.58)	-8.51 (45.17)	.001

Abbreviations: LOCF = last observation carried forward; SD = standard deviation.

^a p-Values are from Wilcoxon signed-rank test.

Population: All patients who took at least one dose of study drug during the open-label period.

Table LYDQ.14 presents mean change from baseline to LOCF endpoint for vital signs and weight among all patients who entered the open-label period. Statistically significant increases in systolic blood pressure, diastolic blood pressure, and pulse as well as statistically significant decreases in weight and body mass index (BMI) were observed. However, none of these changes were considered clinically significant. Note that baseline BMIs were above the recommended cutoff value of 25 and in the overweight range.

Table LYDQ.14. Vital Signs and Weight Mean Change from Baseline to LOCF Endpoint Open-Label Period

Safety Outcome	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	p-Value ^a
Systolic BP	252	119.05 (12.38)	121.43 (12.30)	2.38 (10.81)	<.001
Diastolic BP	252	76.08 (9.14)	77.77 (8.78)	1.69 (8.12)	.001
Pulse	252	74.04 (11.08)	76.58 (11.03)	2.54 (10.46)	<.001
Weight (kg)	252	82.55 (21.15)	81.97 (20.99)	-0.58 (2.33)	<.001
BMI	252	28.47 (6.37)	28.27 (6.32)	-0.20 (0.78)	<.001

Abbreviations: BMI = body mass index; BP = blood pressure; BPM = beats per minute; LOCF = last observation carried forward; SD = standard deviation.

^a p-Values are from Student's t-test.

Population: All patients who took at least one dose of study drug during the open-label period.

There were no statistically significant differences in mean change from baseline to LOCF endpoint for ECG QRS interval, data-corrected QT interval (QTcD), or Fridericia-corrected QT interval. Table LYDQ.15 shows the ECG measures that showed a statistically significant change from baseline to endpoint.

Table LYDQ.15. Electrocardiograms with Statistically Significant Mean Change from Baseline to LOCF Endpoint Open-Label Period

ECG	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	p-Value ^a
Derived RR Interval ^b	205	877.46 (156.96)	828.82 (131.65)	-48.64 (114.84)	<.001
Heart rate (BPM)	205	70.49 (12.15)	74.16 (11.41)	3.67 (9.42)	<.001
PR Interval (msec)	205	153.08 (18.94)	151.12 (18.04)	-1.96 (11.49)	.015
QT interval (msec)	205	388.42 (30.02)	381.84 (28.92)	-6.58 (22.18)	<.001
QTcB interval (msec)	205	417.21 (23.36)	421.40 (22.65)	4.19 (18.37)	.001

Abbreviations: BPM = beats per minute; LOCF = last observation carried forward; msec = milliseconds; QTcB = Bazett-corrected QT interval; SD = standard deviation.

^a p-Values are from Student's t-test.

^b Derived RR interval = 1000*60/heart rate.

Population: All patients who took at least one dose of study drug during the open-label period.

Summary ID# 9916

Clinical Study Summary: Study B4Z-FW-LYDP

Title of Study: The Haemodynamic Effects of Inhaled Salbutamol in the Absence and Presence of Atomoxetine

Date summary approved by Lilly: 27 January 2006

Brief Summary of Results

The primary objective of this open-label, fixed sequence crossover study was to assess the heart rate response to a standard inhaled dose of salbutamol in the presence and absence of steady-state atomoxetine dosing.

- Placebo-corrected heart rate increased by a mean maximum of 3.6 (± 9.8) bpm in the first 30 minutes after inhalation of a standard dose of salbutamol (200 mcg) in the absence of atomoxetine and by 3.5 (± 9.1) bpm after inhalation of salbutamol in the presence of steady-state atomoxetine dosing. There was no statistically significant difference between these effects [95% confidence interval for difference in the maximal rise (-6.4, 6.1) bpm].
- Systolic blood pressure (during 0-30 minutes) did not change after salbutamol inhalation in the presence or absence of atomoxetine.
- Diastolic blood pressure decreased after inhaling a standard dose of salbutamol. The magnitude of this fall was decreased by atomoxetine.
- The absolute heart rates after multiple inhalations of salbutamol were similar in the presence or absence of atomoxetine. The magnitude of the rise in heart rate after multiple inhalations of salbutamol was decreased by atomoxetine.

Title of Study: The Haemodynamic Effects of Inhaled Salbutamol in the Absence and Presence of Atomoxetine.	
Investigator(s): This single-center study included 1 principal investigator.	
Study Center(s): This study was conducted at 1 study center in 1 country.	
Length of Study: Approximately 2 months Date of first subject enrolled: 9 December 2004 Date of last subject completed: 31 January 2005	Phase of Development: Marketed Product conducted as Phase 1 study
Objectives: <u>Primary Objective:</u> - To assess the heart rate response to a standard inhaled dose of salbutamol in the presence and absence of steady-state atomoxetine dosing. <u>Secondary Objectives:</u> - To explore the effect of steady-state atomoxetine dosing on diastolic/systolic blood pressure changes after inhaled doses of salbutamol. - To explore the effects of steady-state atomoxetine dosing on heart rate responses after multiple salbutamol inhalations.	
Study Design: This was an open-label, fixed sequence crossover study involving 21 healthy subjects. Each subject received 2 treatments in a randomized fashion on Days 1 and 2 where inhalations of either salbutamol or placebo occurred without atomoxetine. Inhalations were made via a spacer and each dose set consisted of 2 puffs (equivalent of 200 µg of salbutamol) from the metered-dose inhaler (MDI). A standard dose of 2 puffs (200 µg) salbutamol was administered at time 0, followed by 3 further sets of 2 puffs at 35, 45 and 55 min (a total of 4 dose sets (800 µg, 8 puffs) on each inhalation dosing day). Atomoxetine 80 mg was given once daily for 5 consecutive days (Days 3 to 7), during which subjects were dosed with salbutamol or placebo inhalations at atomoxetine steady state (Days 6 and 7) in a similar randomized fashion. Pharmacodynamic parameters of heart rate (HR) and blood pressure (BP) were taken predose and at specific time intervals for up to 115 minutes throughout the study. A follow-up visit occurred within 14 days of the last inhalation dose.	
Number of Subjects: <u>Planned:</u> 24 subjects to receive Atomoxetine, Salbutamol and Placebo. <u>Entered:</u> 23 subjects (16 males, 5 females) were enrolled into the study. <u>Completed:</u> - Atomoxetine: Male 16, Female 5, Total 21 - Salbutamol: Male 16, Female 5, Total 21 - Placebo: Male 16, Female 5, Total 21	
Diagnosis and Main Criteria for Inclusion: Overtly healthy males or females as determined by medical history and physical examination, aged between 21 and 40 years, inclusive, within the range of Body Mass Index (BMI) 18.5 – 30.0 kg/m ² , normal / acceptable clinical laboratory results with normal supine blood pressure and heart rate, who provided written informed consent.	
Study Drug, Dose, and Mode of Administration: - Atomoxetine (Strattera®) 80 mg/day, given orally once a day as two 40-mg capsules. - Salbutamol (Ventolin™Evohaler™) 200 µg/dose (equivalent of 2 puffs), given by inhalation using a spacer device. - Salbutamol Placebo (no active ingredient), given by inhalation using a spacer device.	
Comparator, Dose, and Mode of Administration: Not applicable.	
Duration of Treatment: Atomoxetine (Strattera®), dosed orally once a day for 5 consecutive days. Salbutamol (Ventolin™Evohaler™)/Placebo, 8 puffs once daily inhaled for 2 consecutive days (Days 1 and 2) without atomoxetine and another set of 8 puffs once daily inhaled for 2 consecutive days (Days 6 and 7)	

during atomoxetine dosing.

Variables:

Safety: Physical examination, safety laboratory tests, vital signs, adverse events, ECG measurements (screening) and as clinically indicated.

Bioanalytical: Blood samples were collected prior to commencement of salbutamol/placebo inhalations on day 6 of study to confirm subjects' exposure to atomoxetine.

Pharmacodynamic: The pharmacodynamic parameters examined were heart rate (HR) and systolic/diastolic blood pressure (BP). Additional parameters derived from HR were maximal HR increase from baseline for each treatment within 0 to 30 minutes and within 35 to 115 minutes, and maximal HR change between treatments for each subject, within 0 to 30 minutes ($HR_{\max(0-30)}$) and within 35 to 115 minutes ($HR_{\max(35-115)}$).

Evaluation Methods:

Statistical: A mixed-effects model, using the analysis of covariance technique was used for the analysis of heart rate (HR). Averaged baseline (predose) values of Days 1 and 2 were used as baseline values for all treatment periods and as a continuous covariate in the model. The fixed categorical effects included atomoxetine, salbutamol, time and all interactions. Subject and subject by atomoxetine by salbutamol were considered as random effects and the toeplitz covariance structure was used to model the residual matrix. Least square means were estimated for all treatments at each time point. Differences in means were formed with the 95% confidence intervals, and p-values. The parameter $HR_{\max(0-30)}$ was summarized using descriptive statistics. Systolic diastolic blood pressure measured from time 0 to 30 minutes postdose were analyzed using the same method as heart rate.

Safety: Descriptive adverse events listing.

Pharmacodynamic: Heart rate (HR), systolic and diastolic blood pressure (SBP and DBP) were the pharmacodynamic outcome parameters. Additional parameters of ($HR_{\max(0-30)}$) minus ($HR_{\max(35-115)}$) were also examined as mentioned above.

Results:

Subject Demographics

Table 1 shows a summary of subject demographics ; total of 23 healthy subjects were entered and enrolled in this study. Subject population made up predominantly male (78.3% of enrolled subjects), with a mean age of 24.1 years (range 21 to 31 years) and mean BMI of 22.3 across both genders.

Subject Disposition

Of the 23 subjects who entered the study, 23 were randomly assigned to treatment, 21 received at least one dose of study drug and completed the study. The 2 subjects that did not complete the study were enrolled into the study but were not dosed due to subjects's own decision to discontinue from study and physician's decision to discontinue from study respectively.

Safety

All safety analyses included 21 of the 23 subjects entered into the study. There were two discontinuations due to a subject decision and a physician decision. These discontinuations occurred prior to any study drug dosing, and the subjects were not included in safety analyses. There were no deaths or other serious adverse events in this study and no subject discontinued the study because of an adverse event.

The 21 subjects who received one or more doses of atomoxetine reported a total of 78 adverse events, 73 of which were reported by the investigator as possibly related to atomoxetine, while 9 out of 21 subjects who received salbutamol reported 10 adverse events, 7 of which were possibly related to salbutamol. Table 2 shows the number of subjects with adverse events possibly related to atomoxetine and salbutamol. The most common adverse events were dizziness, nausea, somnolence and dry throat. Most adverse events were of mild or moderate severity. Only one event related to drug treatment, disturbed sleep, was rated severe. This event started approximately 5 days after dosing with atomoxetine and lasted for about 2 weeks. All treatment-emergent adverse events had resolved at the time of discharge from the study.

There were no clinically significant alterations in laboratory values during the course of the study.

Pharmacokinetic/Pharmacodynamic Outcomes

No pharmacokinetic parameters were evaluated. Adequate atomoxetine exposure, was confirmed by concentrations within the expected range on Day 6.

All subjects who completed at least 1 study day (Days 1, 2, 6, or 7) were included in the analysis set for the pharmacodynamic (PD) analyses.

Table 3 presents average heart rate (HR) measured prior to salbutamol or placebo dosing in the absence (Days 1 and 2) and presence (Days 6 and 7) of atomoxetine. There was a significant increase in HR after 5 days of atomoxetine dosing.

Figure 1 presents mean HR response versus time profiles. Figure 2 illustrates the mean HR differences between treatments, from 2.5 minutes to 115 minutes.

After inhalation of a standard 200 µg dose of salbutamol (in the absence of atomoxetine), the HR showed a mean increase (IS–IP) of not more than 3.3 bpm at any time point during the first 30 minutes, with the upper 95% confidence limit not exceeding 7.9 bpm. The effect of the same dose of salbutamol on HR in the presence of atomoxetine (AIS–AIP), showed a mean increase of not more than 6.6 bpm during the first 30 minutes, with the upper 95% confidence limit not exceeding 11.2 bpm.

The effect of atomoxetine on the HR response to salbutamol ([AIS–AIP]–[IS–IP]) during the first 30 minutes was not statistically significant. The highest difference was at 22.5 minutes, where a mean of 5 bpm with a 95% confidence interval of (-1.5, 11.5) was observed.

After multiple doses of salbutamol (that is, at time points beyond 30 minutes), atomoxetine did not affect the HR response to salbutamol ([AIS–AIP]–[IS–IP]). The highest difference was at 45 minutes, where a mean difference of 1 bpm with a 95% confidence interval of (-7.0, 9.1) was observed.

Consistent with the time point analysis above, the maximal HR increased within 30 minutes after inhalation of 200 µg salbutamol also did not show an effect of atomoxetine on HR response to salbutamol. The mean maximal increase of 3.5 bpm in the presence of atomoxetine (AIS-AIP) was not significantly different from the 3.6 bpm in the absence of atomoxetine (IS-IP).

Table 4 presents maximum HR increase from averaged baseline (predose of Days 1 and 2) within 0 minute to 30 minutes. Table 5 presents the maximal pairwise HR differences after inhalation of salbutamol or placebo in the presence and absence of atomoxetine.

Figure 3 and Figure 5 present average systolic and diastolic blood pressure (SBP and DBP) versus time profiles. Table 5 shows the average SBP and DBP measured prior to salbutamol or placebo in the absence (Days 1 and 2) and presence (Days 6 and 7) of atomoxetine. Figure 4 and Figure 6 illustrate the least square mean differences between systolic and diastolic blood pressure between treatments.

There was an increase in SBP and DBP of approximately 3 to 5 mm Hg after 5 days of atomoxetine dosing (Table 6).

There was no effect of 200 µg salbutamol on SBP and DBP in the absence of atomoxetine (IS-IP) within 30 minutes of administration. The effect of salbutamol on SBP and DBP in the presence of atomoxetine (AIS-AIP) showed an overall mean increase of about 5 mm Hg, with the upper 95% confidence limit not exceeding 10 mm Hg. The effect of atomoxetine on SBP and DBP response to salbutamol ([AIS-AIP]–[IS-IP]) was not significant. The highest difference in SBP was at 22.5 minutes, where a mean difference of 5.5 mm Hg with a 95% confidence interval of (-0.9, 11.9) was observed. The highest differences in DBP were at 22.5 minutes and 30 minutes, where mean differences of 4.8 mmHg with 95% confidence intervals of (0.0, 9.7) and (-0.1, 9.6), respectively, were observed. At time points beyond 30 minutes, atomoxetine did not show an effect on salbutamol response in SBP and DBP.

Table 1. Subject Demographics

Variable	N = 23	Mean	SD	Min, Max
Age (yr)		24.1	2.3	21, 31
Height (cm)		170.7	8.5	151.4, 185.0
Weight (kg)		65.2	9.2	44.6, 80.5
BMI (kg/m ²)		22.3	2.7	19.2, 29.6

Gender	N = 23	Percentage
Male	18	78.3
Female	5	21.7

Table 2. Number of Subjects with Adverse Events Possibly/Probably Related to Atomoxetine or Salbutamol

Adverse Event - MedDRA Preferred Term	Total Subjects With Event	Total Occurrences	Total Occurrences possibly related to Atomoxetine	Total Occurrences possibly related to Salbutamol
ABDOMINAL DISTENSION	1	1	1	-
ABDOMINAL PAIN UPPER	1	1	1	-
ANOREXIA	5	5	5	-
APPLICATION SITE ERYTHEMA	1	1	-	-
ASTHENIA	1	1	1	-
DECREASED APPETITE	1	1	1	-
DIZZINESS	9	11	10	-
DRY THROAT	5	6	1	3
DYSPNOEA EXERTIONAL	1	1	-	-
FATIGUE	2	2	2	-
FEELING COLD	3	3	3	-
FEELING OF RELAXATION	2	2	2	-
FLATULENCE	1	1	-	-
HEADACHE	1	1	-	-
HOT FLUSH	1	1	1	-
INCREASED UPPER AIRWAY SECRETION	1	1	-	-
LETHARGY	1	2	-	1
LOOSE STOOLS	1	1	1	-
NASAL CONGESTION	1	1	-	-
NAUSEA	8	12	11	1
PALPITATIONS	3	4	4	-
PHARYNGOLARYNGEAL PAIN	1	1	-	-
PYREXIA	1	1	-	-
RESTLESSNESS	1	1	1	-
RHINORRHOEA	2	2	-	1
SLEEP DISORDER	4	4	3	1
SOMNOLENCE	8	18	17	-
STOMACH DISCOMFORT	2	3	3	-
THIRST	1	1	1	-
VENIPUNCTURE SITE BRUISE	5	5	-	-
VOMITING	3	4	4	-

Table 3. Comparison of Mean Heart Rate (bpm) Measured Prior to Salbutamol or Placebo Administration in the Absence (Day 1 and 2) and Presence (Day 6 and 7) of Atomoxetine

Treatment	LSM	LSM Difference (95% CI) [P-Value]	
		AIS-IS	AIS-IP
IS	67.5	9.3 (5.5, 13.1) [<.001]	6.1 (2.3, 9.9) [0.002]
IP	70.6		
AIS	76.8		
AIP	75.4		

Abbreviations: CI= confidence interval, LSM= least square means.

IS, IP occurred on days 1, 2 and AIS, AIP occurred on days 6, 7 respectively.

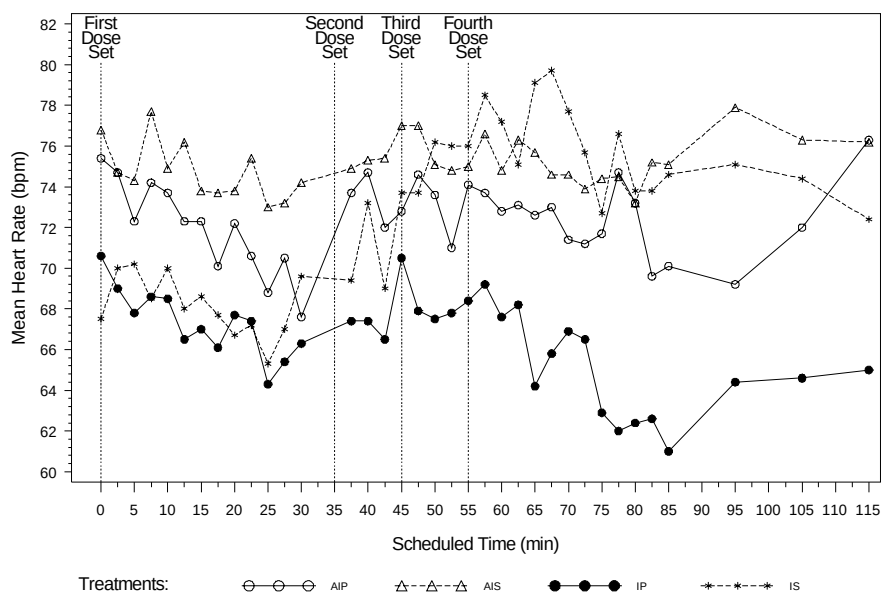


Figure 1. Mean heart rate (bpm) profiles for each treatment group.

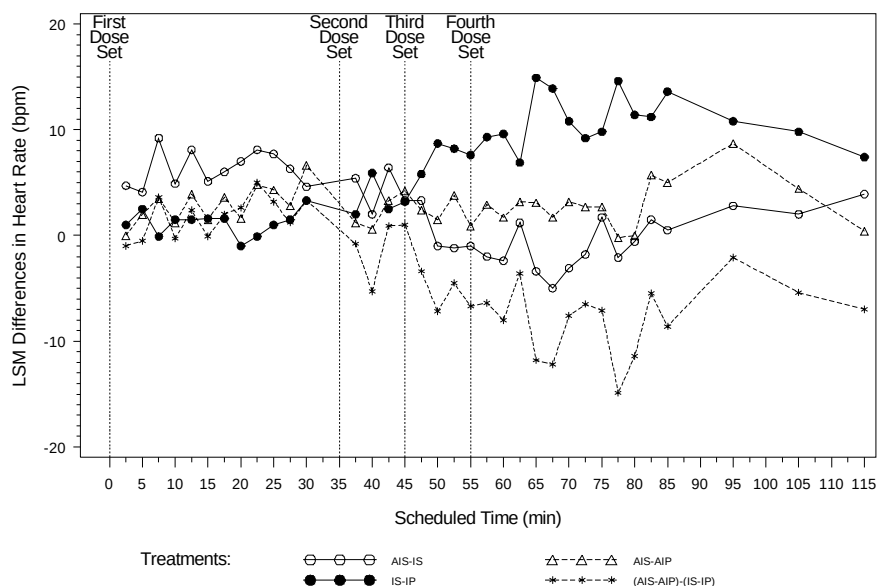


Figure 2. Least squares mean differences of heart rate (bpm) profiles between treatment groups.

Table 4. Comparison of Maximal Increase of Heart Rate from Averaged Baseline, Within 0 to 30 Minutes, After the Administration of Inhaled Salbutamol or Placebo in the Absence and Presence of Atomoxetine (ANCOVA Model with Averaged Baseline Values [Days 1 and 2] as a Covariate)

		LSM Difference (95% CI) [P-Value]				
Time Interval	Treatment	LSM	AIS-IS	AIS-AIP	IS-IP	(AIS-AIP)-(IS-IP)
0-30 mins	IS	13.0	3.5 (-0.9, 7.9) [0.119]	3.5 (-0.9, 7.9) [0.122]	3.6 (-0.8, 8.0) [0.105]	-0.2 -6.4, 6.1 [0.957]
	IP	9.4				
	AIS	16.5				
	AIP	13.1				

Abbreviations: CI= confidence interval, LSM= least square means, SD= standard deviation.

Table 5. Summary of Maximal Pairwise Heart Rates Differences (bpm), Within 0 to 30 Minutes, Between Heart Rates Measured After the Inhalation of Salbutamol or Placebo in the Absence and Presence of Atomoxetine

Parameter	Treatment	N	Minimum	Maximum	Median	Arithmetic Mean (SD) (95% CI)
HRmax(0-30)	AIS-IS	21	4	33	19	20.0 (8.1) (16.3, 23.6)
	AIS-AIP	21	0	34	14	16.1 (8.5) (12.3, 20.0)
	AIS-IP	21	3	34	18	19.8 (8.3) (16.0, 23.5)
	IS-IP	21	3	42	15	15.6 (9.4) (11.4, 19.9)
	(AIS-AIP)- (IS-IP)	21	0	40	19	19.9 (11.1) (14.8, 24.9)

Abbreviations: SD= standard deviation, CI= confidence interval.

Table 6. Comparison of Mean Systolic and Diastolic Blood Pressure (mm Hg) Measured Prior to Each Salbutamol or Placebo Administration in the Absence (Day 1 and 2) and Presence (Day 6 and 7) of Atomoxetine

Parameter	Treatment	LSM	LSM Difference (95% CI) [P-Value]	
			AIS-IS	AIS-IP
Diastolic BP	IS	66.6	4.4 (1.1, 7.7) [0.010]	3.8 (0.5, 7.1) [0.025]
	IP	67.1		
	AIS	71.0		
	AIP	68.8		
Systolic BP	IS	114.9	5.7 (1.4, 10.1) [0.011]	2.0 (-2.4, 6.3) [0.372]
	IP	118.6		
	AIS	120.6		
	AIP	119.7		

Abbreviations: CI= confidence interval, LSM= least square means.

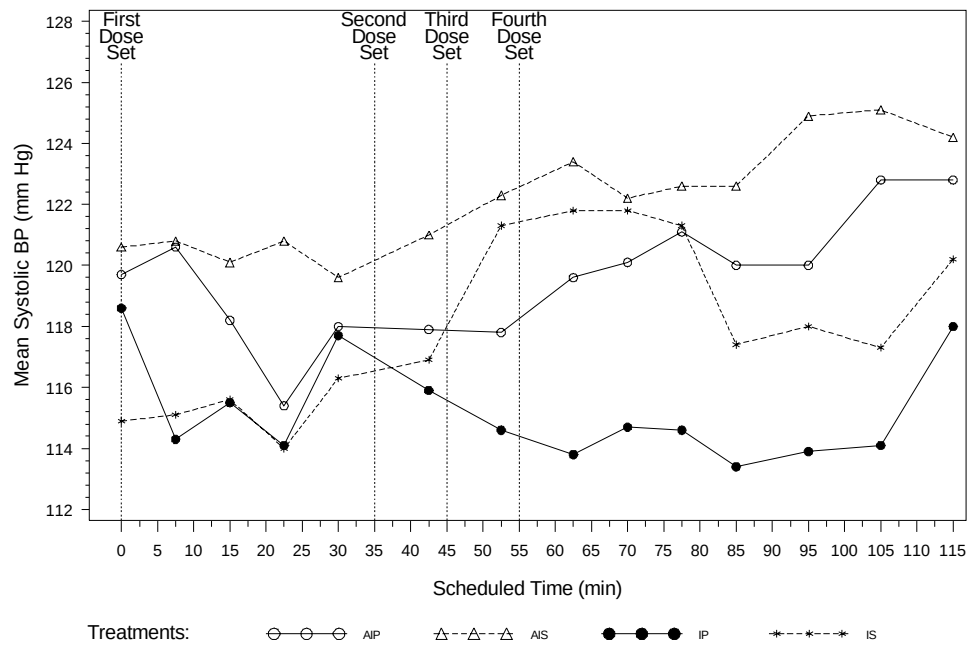


Figure 3. Mean systolic blood pressure (mm Hg) profiles for each treatment group.

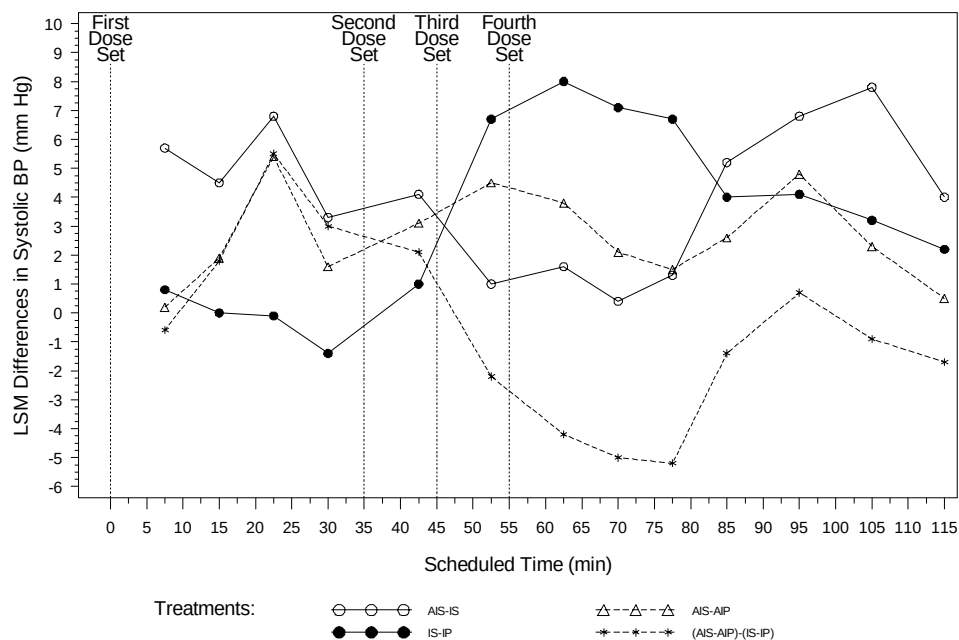


Figure 4. Least squares mean differences of systolic blood pressure (mm Hg) profiles between treatment groups.

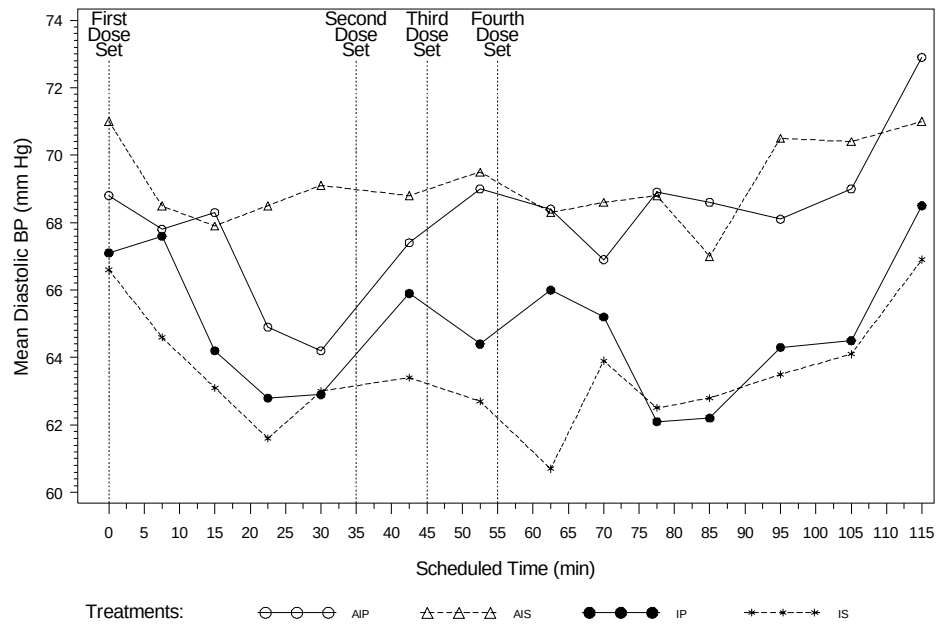


Figure 5. Mean diastolic blood pressure (mm Hg) profiles for each treatment group.

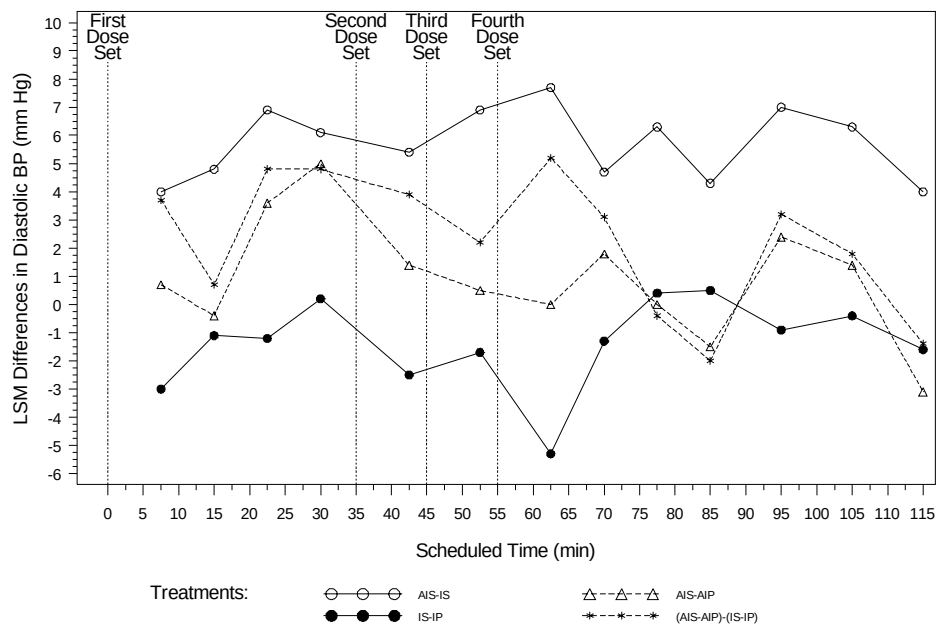


Figure 6. Least squares mean differences of diastolic blood pressure (mm Hg) profiles between treatment groups.