Summary ID#2556

Clinical Study Summary: Study B4Z-MC-LYAA

Title of Study: A Phase III Randomized, Double-Blind Comparison of Placebo and Tomoxetine 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 *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (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-desmethylatomoxetine 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

Table LYAA.2. CAARS-Inv:SV Total ADHD Symptom Score
Repeated Measures, Least Squares Mean
Study Period II
B4Z-MC-LYAA

	Atomoxetine			Placebo			Treatment Difference		
Visit	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)

Table LYAA.3. CAARS-Inv:SV Total ADHD Symptom Scores
Change from Baseline to Endpoint
Study Period II
B4Z-MC-LYAA

		Baseline		Endpoint		Change		p-Value(A)	p-value(B)
Treatment Group	n	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)

Table LYAA.4. CAARS-Inv:SV Inattentive, Hyperactive/Impulsive, and ADHD Index Subscales Change from Baseline to Endpoint Study Period II B4Z-MC-LYAA

		Baseline		Endpoint		Change		p-Value(A)	p-value(B)
Treatment Group	n	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)

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

		Baseline		Endpoint		Change		p-Value(A)	p-value(B)
Treatment Group	n	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)

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)

		Baseline		Endpoint		Change		p-Value(A)	p-value(B)
Treatment Group	n	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)

Table LYAA.6. CGI-ADHD-S
Change from Baseline to Endpoint
Study Period II
B4Z-MC-LYAA

		Baseline		Endpoint		Change		p-Value(A)	p-value(B)
Treatment Group	n	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)

Table LYAA.7. WRAADDS
Change from Baseline to Endpoint
Study Period II
B4Z-MC-LYAA

		Baseline		Endpoint		Change		p-Value(A)	p-value(B)
Treatment Group	n	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)

Table LYAA.8. HAMD-17 and HAMA
Change from Baseline to Endpoint
Study Period II
B4Z-MC-LYAA

Treatment Group	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	p-Value(A)	p-value(B)
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)

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 Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	p-Value(A)	p-value(B)
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)

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)

		Baseline		Endpoint		Change		p-Value(A)	p-value(B)
Treatment Group	n	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.B4ZO.LYAACTRM.FINAL(AE2C1002)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

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)