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**PROPRIETARY DRUG NAME/INN:** Atomoxetine; Bupirone

**THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:** See USPI

**NCT #:** NCT00174226

**PROTOCOL NO.:** A9001245

**PROTOCOL TITLE:** 8-Week, Double-Blind, 3-Arm Parallel, Placebo-Controlled, Randomized Efficacy and Safety Trial of Atomoxetine, Atomoxetine Plus Bupirone, and Placebo in Adults With Attention Deficit Hyperactivity Disorder

**Study Centers:** 8 centers in the United States

**Study Initiation and Completion Dates:** 02 November 2004 to 19 January 2006

**Phase of Development:** Phase 2

**Study Objectives:**

**Primary Objective** – To assess the efficacy of Atomoxetine-Bupirone (ATX-BSP) combination therapy versus placebo and Atomoxetine (ATX) monotherapy in adult subjects with attention deficit hyperactivity disorder (ADHD) as measured by the mean change across weeks in the Adult ADHD Investigator Symptom Rating Scale (AISRS) total score.

**Secondary Objectives** –

- To characterize the safety of ATX-BSP administration as compared to placebo and ATX monotherapy;
- To assess the efficacy of ATX-BSP compared to placebo and ATX monotherapy in improving the symptoms of ADHD as measured by:
  - Proportion of responders who achieved a minimum of 30% decrease in total score on the AISRS at the end of Week 7
  - Proportion of responders who achieved a “1” or “2” on the ADHD Clinical Global Impression-Severity scale (CGI-S)
- To assess the efficacy of ATX-BSP compared to placebo and ATX monotherapy in treating symptoms as measured by the Brown ADD Scale (Brown);

- To assess the efficacy of ATX-BSP compared to placebo and ATX monotherapy in treating co-morbid depressive symptoms as measured by the Montgomery Asberg Depression Rating Scale (MADRS);
- To assess the efficacy of ATX-BSP compared to placebo and ATX monotherapy in treating co-morbid anxiety symptoms as measured by the Hamilton Anxiety Scale (HAM-A);
- To assess the effect of ATX-BSP as compared to placebo and ATX monotherapy on mood states as measured by the Profile of Mood States (POMS);
- To assess the effect of ATX-BSP as compared with placebo and ATX monotherapy on cognition as measured by the Stroop Color/Word test (Stroop) and the Groton Maze Learning Test (GMLT);
- To assess the efficacy of ATX-BSP as compared with placebo and ATX monotherapy on disability as measured by the Sheehan Disability Scale (SDS);
- To assess the safety and tolerability of ATX-BSP compared to placebo and ATX monotherapy as measured by the Medical Outcome Study-Sleep Scale (MOS-SS), Subject Rated Drug Effect Questionnaire (SRDEQ), and the Sexual Dysfunction Questionnaire (SDQ).

## METHODS

**Study Design:** This was a randomized, double-blind (investigator and subject-blinded), parallel, placebo-controlled study in adult subjects with ADHD. The study consisted of a 1 to 3 week screening/washout phase, followed by an 8-week treatment phase. Week 8 of the treatment phase was used to taper the treatment medication and the final visit for safety occurred at the end of that week. The treatment groups were as follows:

1. Placebo
2. ATX 80 mg per day, with divided doses. Dose could be increased up to 100 mg per day, with divided doses.
3. ATX 80 mg per day, with divided doses, and 45 mg BSP per day, with divided doses. ATX could be increased up to 100 mg per day with divided doses.

There was a titration and stabilization period during the first 4 weeks. At the end of Week 4, the dose may have remained at the Week 4 level for the remainder of the treatment period, or could have been increased to ATX 100 mg, based on tolerability and efficacy (CGI-C score was to be >2).

**Number of Patients (planned and analyzed):** All treated subjects were included in safety analyses. The Full Analysis Set (used for all efficacy analyses) consisted of all treated subjects with at least a Baseline and 1 post-baseline efficacy measure. The number of subjects included in these analyses is provided in the results tables for each measure.

**Diagnosis and Main Criteria for Inclusion:** Subjects aged 18 to 55 years, inclusive, who met the diagnostic criteria for Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition ADHD, based on clinical assessment and confirmed by structured interview (Adult ADHD Clinician Diagnostic Scale version 1.2) were eligible to be enrolled in the study. Subjects were to have a score of  $\geq 4$  on the CGI-S Scale for ADHD and a score of  $\geq 24$  on the AISRS at Screening and randomization.

**Study Treatment:** Marketed Strattera<sup>®</sup> 40 mg, Strattera<sup>®</sup> 60 mg, Buspar<sup>®</sup> 15 mg, BSP (generic) 7.5 mg, and blinding capsules were utilized for this study. All supplies were stored according to manufacturers' guidelines. The marketed study medications were obtained from commercial sources. Blinded packaging was carried out by the sponsor.

### **Efficacy Evaluations:**

#### **Primary Efficacy Evaluation– AISRS Total Score**

This is a rating scale to assess symptoms of ADHD in adults. The range of the score (sum of the responses to each of the 18 individual questionnaire items) is 0 to 54. Higher scores indicate a higher level of ADHD. The AISRS was evaluated at Screening, Baseline, Weeks 1-4, Week 7, and at the end-of-study visit. The primary analysis set for efficacy was the full analysis set (FAS) including all randomized subjects who took at least 1 dose of study drug, and had any post-baseline assessment of any efficacy measure. The FAS was referred to as intent-to-treat population for MADRS, HAM-A, POMS, SDS, TSQM, Stroop, SDQ, MOS, and SRDEQ analyses.

#### **Secondary Efficacy Evaluations**

The secondary efficacy evaluations done in this study are summarized in [Table S1](#).

**Table S1. Secondary Efficacy Evaluations**

Assessment	Score Range	Score Description	Time Points Evaluated
<b>Adult ADHD Clinical Diagnostic Scale (AISRS)</b>			
Total score response	Decrease from Baseline to post-baseline score of $\geq 30\%$	Higher score = worse response	Screening, Baseline, Weeks 1-4, Week 7, and EOS
Sub-scale score	0-27		
<b>Clinical Global Impression of Severity (CGI-S)</b>			
CGI-S response	Post-baseline score of '1' (not at all ill) or '2' (borderline ill)	Higher score = more severe illness	Screening, Baseline, Weeks 1-4, Week 7, and EOS
CGI-S score	'1' (no at all ill) to '7' (among the most extremely ill subjects)		
<b>Clinical Global Impression of Change (CGIC)</b>			
CGI-C response	Post-baseline response of '1' (very much improved) or '2' (much improved)	Higher score = less improvement	Weeks 1-4, Week 7 and EOS
CGI-C score	'1' (very much improved) to '7' (very much worse)		
<b>Montgomery and Asberg Depression Rating Scale (MADRS)</b>			
	'0' (most favorable, least depressed) to '60' (least favorable, most depressed)	Higher score = worse response	Baseline and Week 7
<b>Hamilton Anxiety Scale (HAM-A)</b>			
Total score	'0' (most favorable, least anxious) to '56' (least favorable, most anxious)	Higher score = least favorable	Baseline and Week 7
Sub-scale score	0 to 28		
<b>Profile of Mood States (POMS)</b>			
Total mood disturbance	-32 to 200	Higher score = less favorable response	Baseline and Week 7
Individual scale scores			
<b>Sheehan Disability Scale (SDS)</b>			
Total score	0 to 30	Higher score = less favorable response	Baseline and Week 7
Individual sub-scale scores	0 to 10		
<b>Stroop Color and Word Test</b>			
Interference score	Mean value score = 0	Positive score = less interference	Baseline and Week 7
<b>Brown Attention-Deficit Disorder (ADD) Scale</b>			
Total score	0 to 120	Higher score indicating less favorable response	Baseline, Weeks 1-4, and Week 7
Cluster scores	0 to 27		

EOS = end of study

## Pharmacokinetic and Other Evaluations:

**Pharmacokinetic Evaluations:** Venous blood samples (3 mL) were collected for ATX and 7 mL for BSP during each of the 2 designated visits on Days 28 and 49. Samples were analyzed using a high-performance liquid chromatography tandem mass spectrometry method. Calibration standard responses were linear over the range of 5.20 to 1560 ng/mL for ATX and 0.050 to 10.0 ng/mL for BSP using a linear and  $1/x^2$  linear least squares regression. Assay precision, expressed as the between-day coefficients of variation of the estimated concentrations of ATX quality control samples, was <8.4% for low (15.0 ng/mL), medium (150 ng/mL), high (1130 ng/mL), and diluted (3120 ng/mL) concentrations. For BSP, assay precision was less than 6.1% for low (0.150 ng/mL), medium (1.50 ng/mL), high (7.50 ng/mL), and diluted (20.0 ng/mL) concentrations.

**Other Evaluations:** These included Clinical Trial Site Scale (CTSS), Belief About Medication Questionnaire (BMQ), Sensitive Soma Scale (SSS), and Treatment Satisfaction Questionnaire for Medication (TSQM).

**Pharmacogenomic Evaluations:** Subjects enrolled in this study could additionally consent to participate in a voluntary pharmacogenomics (PG) study, for which separate informed consent was to be obtained. As part of this additional voluntary PG study, blood samples were collected at Day 28 or Day 49 for anonymized genotyping. In addition, due to the CYP 2D6 metabolism with ATX and the screening out of poor metabolizers, only extensive metabolizers were included in the voluntary PG study. Non-anonymized blood samples for CYP 2D6 test were collected at the Screening.

**Safety Evaluations:** Safety evaluations included clinical adverse event (AE) monitoring, vital signs (pulse rate, blood pressure and temperature), 12-lead electrocardiograms (ECGs), physical examination, and safety laboratory tests.

The medical outcome study sleep scale (MOS-SS) was used to assess sleep quality and covered sleep-related activities. The sexual dysfunction questionnaire (SDQ) was used to assess changes in measures of sexual functioning with 6 questions. MOS-SS and SDQ were assessed at baseline and Week 7. The subject related drug effect questionnaire (SRDEQ) was used to obtain subjective information on the effect of study drug from a subject's point of view covering 4 areas: drug effect present, intensity, liking, and other characteristics. SRDEQ was assessed at baseline, Weeks 1 to 4 and Week 7. SRDEQ consists of 26 items, each with a score of 0 (none) to 6 (extreme).

**Statistical Methods:** For the purpose of sample size calculation, assumptions for mean AISRS scores were 23.0 for ATX, 20.0 for ATX-BSP, and 28.0 for placebo with a common standard deviation of 10.0. The randomization was planned to be 1:2:2 with 43 subjects in placebo and 86 subjects each in ATX and ATX-BSP groups. The power estimate for comparison between ATX-BSP and ATX monotherapy was 75% given a 3-point difference between the treatment groups. The primary analysis was based on the intent-to-treat population defined as all subjects who were randomized, took at least 1 dose of study drug, and had at least 1 follow-up evaluation.

The primary efficacy parameter was the mean across weeks of the AISRS total scores. The mean difference for each treatment group was compared using a repeated measures mixed linear model with the following fixed effect terms: treatment, center, Week, treatment-by-Week interaction, and baseline AISRS score. Additionally, from the repeated measures model, estimates were used to compare treatment groups at each Week. Primary efficacy outcomes were 2 pairwise comparisons: ATX-BSP versus ATX monotherapy and ATX-BSP versus placebo.

The Brown total and composite scores were analyzed using a repeated measure mixed effects model for the change from baseline data from Weeks 1 to 7. The AISRS, CGI-C and CGI-S binary response variables were analyzed using a repeated measure generalized estimating equation model for the change from baseline data from Weeks 1 to 7. The CGI-C and CGI-S scores at Week 7 were analyzed using the Cochran-Mantel-Haenszel analysis. The MADRS, HAM-A, POMS, SDS, Stroop, TSQM, SDQ (total only) and MOS-SS scores were analyzed using analysis of covariance. For all scores the response variable was change from baseline to Week 7 and the model terms in the analysis were baseline, center, and treatment group.

## RESULTS

**Subject Disposition and Demography:** A total of 241 subjects were randomized and treated in this study. The number of subjects who completed the study and reason for discontinuation are summarized in [Table S2](#).

**Table S2. Subject Disposition**

Number (%) of subjects	Placebo	ATX	ATX-BSP
Treated	47	97	97
Completed	27 (57.4)	70 (72.2)	63 (64.9)
Discontinued due to:			
Adverse Event	7 (14.9)	11 (11.3)	15 (15.5)
Lack of Compliance	1 (2.1)	0 (0)	1 (1.0)
Subject withdrew consent	3 (6.4)	3 (3.1)	0 (0)
Lost to Follow-Up	9 (19.1)	9 (9.3)	16 (16.5)
Other	0 (0)	4 (4.1)	2 (2.1)

ATX = atomoxetine, ATX-BSP = atomoxetine + buspirone

Demographics and baseline characteristics were similar across treatment groups. A summary of subject characteristics is presented in [Table S3](#).

**Table S3. Subject Demographics and Baseline Characteristics**

Number (%) of subjects	Placebo (N=47)	ATX (N=97)	ATX-BSP (N=97)
<b>Gender</b>			
Male	28 (59.6)	59 (60.8)	55 (56.7)
Female	19 (40.4)	38 (39.2)	42 (43.3)
Premenopausal	6 (31.6)	7 (18.4)	10 (23.8)
Postmenopausal	2 (10.5)	3 (7.9)	7 (16.7)
Surgically sterilized	3 (15.8)	9 (23.7)	1 (2.4)
Menarchal	8 (42.1)	19 (50.0)	24 (57.1)
<b>Race</b>			
White	38 (80.9)	72 (74.2)	82 (84.5)
Black	3 (6.4)	7 (7.2)	6 (6.2)
Hispanic	4 (8.5)	13 (13.4)	7 (7.2)
Asian or Pacific Islander	1 (2.1)	1 (1.0)	2 (2.1)
American Indian or Alaskan Native	1 (2.1)	1 (1.0)	0 (0)
Other	0 (0)	3 (3.1)	0 (0)
	<b>Placebo (N) Mean ± SD</b>	<b>ATX (N) Mean ± SD</b>	<b>ATX-BSP (N) Mean ± SD</b>
Age (years)	(47) 38.26 ± 11.2	(97) 37.21 ± 11.0	(97) 35.59 ± 10.7
Weight (kg)	(47) 83.43 ± 16.7	(96) 84.56 ± 21.3	(97) 86.05 ± 22.4
Height (cm)	(46) 171.28 ± 11.5	(97) 173.33 ± 10.2	(97) 171.57 ± 9.7

ATX = atomoxetine, ATX-BSP = atomoxetine-bupirone, SD = standard deviation

**Efficacy Results: Primary Efficacy Result– AISRS Total Score**

Change from Baseline in the AISRS Total Score – The mean of the AISRS total score decreased from baseline to Week 7 in all 3 treatment groups. The change in mean total score was similar for ATX and ATX-BSP. AISRS total score is summarized by treatment and Week in [Table S4](#).

**Table S4. Summary of AISRS Total Score by Treatment and Week**

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 7
<b>Placebo (N = 47)</b>						
n	47	46	43	35	32	30
Mean ± SD	37.4 ± 8.31	33.0 ± 10.48	30.0 ± 11.77	26.4 ± 11.09	24.3 ± 12.14	22.9 ± 14.19
<b>ATX (N = 97)</b>						
n	97	91	86	80	76	71
Mean ± SD	36.3 ± 7.75	28.1 ± 11.57	24.7 ± 11.79	22.5 ± 13.05	20.6 ± 12.21	19.0 ± 11.44
<b>ATX-BSP (N = 94)</b>						
n	94	88	80	73	68	64
Mean ± SD	36.6 ± 7.29	28.3 ± 9.88	24.9 ± 9.95	21.7 ± 10.75	20.0 ± 11.86	18.2 ± 11.19

SD = standard deviation, ATX = atomoxetine, ATX-BSP = atomoxetine-bupirone

The comparison of change from baseline in the AISRS total score for ATX-BSP versus placebo was statistically significant (p-value <0.10) for all Weeks, indicating that the reduction for ATX-BSP was greater than for placebo ([Table S5](#)).

**Table S5. Repeated Measure Analysis for AISRS Total Score Change from Baseline**

	Week 1	Week 2	Week 3	Week 4	Week 7	Weeks 1-7
<b>ATX+BSP versus ATX</b>						
Estimate (S.E)	-0.14 (1.11)	-0.23 (1.30)	-1.31 (1.44)	-2.04 (1.56)	-1.67 (1.72)	-1.08 (1.21)
80% CI	-1.57, 1.28	-1.89, 1.44	-3.16, 0.54	-4.05, -0.04	-3.89, 0.55	-2.64, 0.49
One-sided p-value	0.450	0.431	0.183	0.096	0.167	0.188
<b>ATX + BSP versus Placebo</b>						
Estimate (S.E)	-4.23 (1.35)	-4.55 (1.58)	-4.93 (1.78)	-5.15 (1.95)	-5.13 (2.17)	-4.80 (1.50)
80% CI	-5.97, -2.50	-6.58, -2.52	-7.23, -2.64	-7.65, -2.64	-7.91, -2.34	-6.72, -2.87
One-sided p-value	0.001	0.002	0.003	0.005	0.010	0.001
<b>ATX versus Placebo</b>						
Estimate (S.E)	-4.09 (1.35)	-4.32 (1.57)	-3.63 (1.77)	-3.10 (1.93)	-3.46 (2.14)	-3.72 (1.49)
80% CI	-5.82, -2.36	-6.34, -2.31	-5.90, -1.35	-5.58, -0.62	-6.21, -0.70	-5.63, -1.81
One-sided p-value	0.001	0.003	0.021	0.055	0.054	0.007

ATX = atomoxetine, ATX-BSP = atomoxetine-buspirone, S.E = standard error, CI = confidence interval

Summary statistics for AISRS total and sub-scale scores change from baseline by treatment and Week is provided in [Table S6](#).

**Table S6. Summary Statistics for AISRS Total Scores - Change from Baseline by Treatment and Week**

	W1-Baseline	W2-Baseline	W3-Baseline	W4-Baseline	W7-Baseline	W7 (LOCF) -Baseline
<b>Placebo (N = 47)</b>						
n	46	43	35	32	30	47
Mean ± SD	-4.3 ± 5.97	-7.2 ± 9.29	-9.4 ± 8.30	-11.6 ± 10.66	-12.5 ± 13.00	-11.4 ± 11.85
<b>ATX (N = 97)</b>						
n	91	86	80	76	71	97
Mean ± SD	-7.9 ± 8.45	-11.0 ± 9.76	-13.3 ± 11.20	-15.3 ± 10.39	-17.0 ± 10.93	-14.3 ± 11.49
<b>ATX-BSP (N = 94)</b>						
n	88	80	73	68	64	94
Mean ± SD	-8.5 ± 8.01	-11.7 ± 8.30	-15.0 ± 8.91	-16.8 ± 9.90	-18.3 ± 10.49	-15.9 ± 10.99

W = week, LOCF = last observation carried forward, SD = standard deviation, ATX = atomoxetine, ATX-BSP = atomoxetine-buspirone

### Secondary Efficacy Result–

**AISRS Response–** The AISRS response increased from Week 1 to Week 7. AISRS response and the repeated measure analysis are summarized in [Table S7](#).

**Table S7. Summary of AISRS Response and Repeated Measure Analysis**

	Week 1	Week 2	Week 3	Week 4	Week 7	Weeks 1-7
<b>Response percentage</b>						
Placebo	15%	26%	40%	44%	47%	32%
ATX	30%	48%	58%	68%	69%	53%
ATX-BSP	34%	54%	70%	75%	78%	60%
<b>ATX+BSP versus ATX</b>						
Odds ratio	1.06	1.12	1.60	1.35	1.54	1.32
80% Confidence interval	0.69, 1.64	0.75, 1.67	1.03, 2.48	0.82, 2.23	0.90, 2.65	0.93, 1.86
One-sided p-value	0.426	0.361	0.084	0.219	0.151	0.153
<b>ATX+BSP versus Placebo</b>						
Odds ratio	2.76	3.33	3.66	4.37	4.51	3.67
80% Confidence interval	1.53, 4.99	1.94, 5.71	2.10, 6.38	2.36, 8.10	2.38, 8.56	2.33, 5.78
One-sided p-value	0.014	0.002	0.001	0.001	0.001	<0.001

AISRS = Adult ADHD investigator symptom rating scale, ATX = atomoxetine, ATX-BSP = atomoxetine-buspirone

### AISRS Sub-Scale Score

Attention Sub-Scale Score - The mean attention sub-scale score decreased from baseline to Week 7. The attention sub-scale score by treatment and Week is summarized in [Table S8](#).

**Table S8. Summary of AISRS Attention Sub-Scale Score by Treatment and Week**

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 7
<b>Placebo (N = 47)</b>						
N	47	46	43	35	32	30
Mean ± SD	14.0 ± 6.26	14.2 ± 5.97	12.6 ± 6.84	11.5 ± 7.22	10.3 ± 6.89	9.3 ± 7.15
<b>ATX (N = 97)</b>						
N	97	91	86	80	76	71
Mean ± SD	14.6 ± 6.62	13.2 ± 7.52	11.2 ± 7.31	10.7 ± 8.00	10.8 ± 8.65	9.4 ± 8.09
<b>ATX-BSP (N = 94)</b>						
N	94	88	80	73	68	64
Mean ± SD	14.0 ± 5.33	13.6 ± 5.52	12.0 ± 6.38	10.6 ± 6.93	8.8 ± 6.85	7.0 ± 5.69

AISRS = Adult ADHD investigator symptom rating scale, ATX = atomoxetine, ATX-BSP = atomoxetine-buspirone, SD = standard deviation

AISRS attention sub-scale differences in change from baseline indicate a greater improvement for ATX-BSP compared to placebo that increases over time (−0.53 at Week 1 to −2.96 at Week 7) ([Table S9](#)).

**Table S9. Repeated Measure Analysis of AISRS Attention Sub-Scale Score - Change from Baseline**

	Week 1	Week 2	Week 3	Week 4	Week 7	Weeks 1-7
<b>ATX+BSP versus ATX</b>						
Estimate (SE)	0.70 (0.9)	0.92 (1.0)	0.22 (1.1)	-1.91 (1.1)	-2.41 (1.1)	-0.50 (0.8)
80% CI	-0.48, 1.88	-0.34, 2.17	-1.15, 1.60	-3.35, -0.46	-3.85, -0.96	-1.49, 0.51
One-sided p-value	0.777	0.825	0.582	0.046	0.017	0.263
<b>ATX+BSP versus placebo</b>						
Estimate (SE)	-0.53 (1.1)	-0.78 (1.2)	-1.30 (1.3)	-2.42 (1.4)	-2.96 (1.4)	-1.60 (1.0)
80% CI	-1.96, 0.91	-2.31, 0.75	-3.02, 0.42	-4.26, -0.59	-4.80, -1.11	-2.84, -0.36
One-sided p-value	0.318	0.256	0.166	0.045	0.020	0.049
<b>ATX versus placebo</b>						
Estimate (SE)	-1.23 (1.1)	-1.70 (1.2)	-1.52 (1.3)	-0.52 (1.4)	-0.55 (1.4)	-1.10 (1.0)
80% CI	-2.66, 0.20	-3.21, -0.18	-3.22, 0.17	-2.33, 1.29	-2.37, 1.27	-2.33, 0.12
One-sided p-value	0.135	0.076	0.125	0.356	0.348	0.124

AISRS = Adult ADHD investigator symptom rating scale, ATX = atomoxetine, ATX-BSP = atomoxetine-buspiron, SE = standard error, CI = confidence interval

Impulse/Hyperactivity Score – The mean Impulse/Hyperactivity sub-scale score decreased from baseline to Week 7. The Impulse/Hyperactivity score by treatment and Week is summarized in [Table S10](#).

**Table S10. Summary of AISRS Impulse/Hyperactivity Score by Treatment and Week**

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 7
<b>Placebo (N = 47)</b>						
N	47	46	43	35	32	30
Mean ± SD	23.4 ± 12.22	18.8 ± 12.17	17.3 ± 10.87	14.9 ± 9.56	14.0 ± 9.56	13.6 ± 10.18
<b>ATX (N = 97)</b>						
N	97	91	86	80	76	71
Mean ± SD	21.6 ± 11.46	14.9 ± 9.23	13.5 ± 9.52	11.8 ± 9.14	9.8 ± 7.62	9.6 ± 6.14
<b>ATX-BSP (N = 94)</b>						
N	94	88	80	73	68	64
Mean ± SD	22.7 ± 9.76	14.7 ± 9.04	12.9 ± 8.20	11.1 ± 8.04	11.2 ± 9.62	11.2 ± 7.79

AISRS = Adult ADHD investigator symptom rating scale, ATX = atomoxetine, ATX-BSP = atomoxetine-buspiron, SD = standard deviation

The changes from baseline for ATX-BSP were similar to those of ATX for Weeks 1 to 7 ([Table S11](#)).

**Table S11. Repeated Measure Analysis of AISRS Impulse/Hyperactivity Score-Change from Baseline**

	Week 1	Week 2	Week 3	Week 4	Week 7	Weeks 1-7
<b>ATX+BSP versus ATX</b>						
Estimate (S.E)	-0.62 (1.13)	-0.90 (1.19)	-1.26 (1.18)	0.24 (1.31)	1.06 (1.21)	-0.30 (0.99)
80% CI	-2.06, 0.83	-2.43, 0.63	-2.77, 0.26	-1.45, 1.92	-0.50, 2.61	-1.57, 0.98
One-sided p-value	0.293	0.224	0.144	0.571	0.808	0.383
<b>ATX+BSP versus placebo</b>						
Estimate (S.E)	-3.80 (1.37)	-3.86 (1.45)	-3.70 (1.46)	-2.89 (1.65)	-1.97 (1.53)	-3.24 (1.22)
80% CI	-5.56, -2.04	-5.72, -2.00	-5.57, -1.82	-5.02, -0.77	-3.94, -0.00	-4.81, -1.67
One-sided p-value	0.003	0.004	0.006	0.041	0.100	0.004
<b>ATX versus placebo</b>						
Estimate (S.E)	-3.18 (1.37)	-2.96 (1.44)	-2.44 (1.45)	-3.13 (1.63)	-3.03 (1.51)	-2.95 (1.21)
80% CI	-4.94, -1.43	-4.80, -1.11	-4.30, -0.58	-5.23, -1.03	-4.97, -1.08	-4.51, -1.39
One-sided p-value	0.010	0.020	0.046	0.029	0.023	0.008

AISRS = Adult ADHD investigator symptom rating scale, ATX = atomoxetine, ATX-BSP = atomoxetine-buspirone, S.E = standard error, CI = confidence interval

### Clinical Global Impression of Severity

CGI-S Response - The CGI-S response and repeated measure analysis are summarized in [Table S12](#).

**Table S12. Summary of CGI-S Response and Repeated Measure Analysis**

	Week 1	Week 2	Week 3	Week 4	Week 7	Weeks 1-7
<b>Response percentage</b>						
Placebo	2%	5%	3%	9%	17%	6%
ATX	5%	9%	16%	20%	25%	15%
ATX-BSP	3%	6%	17%	19%	25%	13%
<b>ATX+BSP versus ATX</b>						
Odds ratio	0.50	0.64	1.19	1.15	1.15	0.87
80% Confidence interval	0.18, 1.42	0.30, 1.36	0.67, 2.11	0.67, 1.98	0.65, 2.05	0.53, 1.43
One-sided p-value	0.801	0.775	0.347	0.370	0.379	0.637
<b>ATX+BSP versus Placebo</b>						
Odds ratio	1.57	1.69	9.18	3.17	2.30	2.82
80% Confidence interval	0.31, 7.96	0.53, 5.45	2.66, 31.62	1.32, 7.61	1.03, 5.13	1.17, 6.79
One-sided p-value	0.361	0.282	0.011	0.046	0.093	0.066

CGI-S = clinical global impression of severity, ATX = atomoxetine, ATX-BSP = atomoxetine-buspirone

CGI-S Score – The mean CGI-S score decreased from baseline to Week 7 for all treatment groups ([Table S13](#)).

**Table S13. Summary of CGI-S Score by Treatment and Week**

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 7
<b>Placebo (N = 47)</b>						
N	47	46	44	35	32	30
Mean ± SD	4.7 ± 0.59	4.5 ± 0.69	4.3 ± 0.95	4.0 ± 0.77	3.8 ± 0.92	3.7 ± 1.12
<b>ATX (N = 97)</b>						
N	97	91	86	81	76	71
Mean ± SD	4.6 ± 0.58	4.1 ± 0.86	3.8 ± 0.95	3.5 ± 1.04	3.4 ± 1.01	3.1 ± 1.19
<b>ATX-BSP (N = 97)</b>						
N	97	90	82	76	69	65
Mean ± SD	4.7 ± 0.64	4.2 ± 0.93	3.9 ± 0.80	3.5 ± 0.99	3.3 ± 1.02	3.1 ± 1.04

CGI-S = clinical global impression of severity, ATX = atomoxetine, ATX-BSP = atomoxetine-buspirone, SD = standard deviation

### Clinical Global Impression of Change

CGI-C Response – The CGI-C response for ATX-BSP was greater than placebo for Weeks 1 to 7 (Table S14).

**Table S14. Summary of CGI-C Response and Repeated Measure Analysis**

	Week 1	Week 2	Week 3	Week 4	Week 7	Weeks 1-7
<b>Response percentage</b>						
Placebo	4%	14%	34%	31%	43%	23%
ATX	22%	31%	46%	46%	56%	39%
ATX-BSP	24%	39%	55%	59%	62%	46%
<b>ATX+BSP versus ATX</b>						
Odds ratio	1.16	1.38	1.43	1.85	1.30	1.41
80% confidence interval	0.74, 1.83	0.92, 2.08	0.95, 2.18	1.19, 2.86	0.82, 2.06	1.02, 1.94
One-sided p-value	0.336	0.157	0.134	0.036	0.236	0.088
<b>ATX+BSP versus Placebo</b>						
Odds ratio	6.73	3.86	2.69	3.75	2.45	3.65
80% confidence interval	2.64, 17.14	2.03, 7.37	1.55, 4.67	2.03, 6.95	1.36, 4.41	2.28, 5.83
One-sided p-value	0.005	0.004	0.011	0.003	0.026	0.0002

CGI-C = clinical global impression of change, ATX = atomoxetine, ATX-BSP = atomoxetine-buspirone

### CGI-C Score –

The mean CGI-C score decreased from baseline to Week 7 for all treatment groups (Table S15).

**Table S15. Summary of CGI-C Score by Treatment and Week**

	Week 1	Week 2	Week 3	Week 4	Week 7	Week 1-7
<b>Placebo (N = 46)</b>						
N	46	44	35	32	30	46
Mean ± SD	3.7 ± 0.67	3.5 ± 0.90	3.0 ± 0.89	3.1 ± 1.05	3.0 ± 1.03	3.2 ± 0.99
<b>ATX (N = 96)</b>						
N	91	86	81	76	71	91
Mean ± SD	3.2 ± 0.96	3.0 ± 0.99	2.7 ± 1.04	2.7 ± 1.04	2.5 ± 1.14	2.7 ± 1.16
<b>ATX-BSP (N = 93)</b>						
N	90	82	76	70	65	91
Mean ± SD	3.1 ± 0.88	2.9 ± 0.96	2.5 ± 0.97	2.4 ± 1.01	2.3 ± 0.99	2.5 ± 1.10

CGI-C = clinical global impression of change, ATX = atomoxetine, ATX-BSP = atomoxetine-buspirone, SD = standard deviation

### Montgomery and Asberg Depression Rating Scale

The change from baseline was greater in the ATX group in comparison to the ATX-BSP and placebo groups ([Table S16](#)).

**Table S16. MADRS Total score for Baseline, Week 7 and Change from Baseline**

	Placebo (N) Mean ± SD	ATX (N) Mean ± SD	ATX-BSP (N) Mean ± SD
Baseline	(47) 7.5 ± 4.86	(97) 7.9 ± 4.58	(97) 8.6 ± 4.78
Week 7	(30) 6.6 ± 5.74	(72) 5.7 ± 4.14	(65) 6.4 ± 4.66
Change from Baseline	(30) -0.6 ± 3.74	(72) -2.2 ± 5.87	(65) -1.9 ± 5.54

MADRS = Montgomery Asberg depression rating scale, ATX = atomoxetine, ATX-BSP = atomoxetine-buspirone, SD = standard deviation

### Hamilton Anxiety Rating Scale

The HAM-A scores for baseline, Week 7 and change from baseline are summarized in [Table S17](#).

**Table S17. HAM-A Scores for Baseline, Week 7 and Change from Baseline**

	Placebo (N) Mean ± SD	ATX (N) Mean ± SD	ATX-BSP (N) Mean ± SD
<b>HAM-A Total Score</b>			
Baseline	(46) 6.4 ± 4.22	(96) 7.0 ± 4.07	(95) 7.1 ± 3.71
Week 7	(31) 6.4 ± 5.45	(72) 5.6 ± 3.79	(64) 7.0 ± 4.09
Change from Baseline	(30) -0.3 ± 3.19	(72) -1.6 ± 4.58	(63) 0.0 ± 4.79
<b>HAM-A Psychic Sub-Scale Score</b>			
Baseline	(47) 4.9 ± 3.35	(96) 5.6 ± 3.13	(97) 5.9 ± 3.16
Week 7	(31) 4.7 ± 4.28	(72) 4.0 ± 2.99	(65) 4.6 ± 3.08
Change from Baseline	(31) -0.1 ± 2.88	(72) -1.7 ± 3.64	(65) -1.1 ± 3.33
<b>HAM Somatic Sub-Scale Score</b>			
Baseline	(46) 1.7 ± 1.69	(97) 1.5 ± 1.96	(95) 1.3 ± 1.50
Week 7	(31) 1.7 ± 2.18	(72) 1.6 ± 1.82	(64) 2.5 ± 2.37
Change from Baseline	(30) -0.0 ± 1.77	(72) 0.1 ± 2.33	(63) 1.2 ± 2.59

HAM-A = Hamilton anxiety scale, ATX = atomoxetine, ATX-BSP = atomoxetine-buspirone, SD = standard deviation

## Profile of Mood States

The POMS mean total and individual scores decreased from baseline to Week 7 indicating favorable response (Table S18).

**Table S18. Summary of POMS Total and Individual Scale Scores**

	Placebo (N) Mean ± SD	ATX (N) Mean ± SD	ATX-BSP (N) Mean ± SD
<b>Total Mood Disturbance</b>			
Baseline	(46) 20.6 ± 20.01	(94) 17.9 ± 17.82	(97) 20.0 ± 17.14
Week 7	(31) 14.3 ± 22.87	(72) 10.9 ± 16.23	(63) 10.4 ± 13.36
Change from Baseline	(30) -5.6 ± 14.85	(69) -9.5 ± 17.58	(63) -9.8 ± 15.51
<b>Tension-Anxiety</b>			
Baseline	(46) 5.1 ± 4.01	(94) 4.8 ± 3.98	(97) 5.2 ± 4.03
Week 7	(31) 3.6 ± 4.11	(72) 3.0 ± 3.21	(63) 2.8 ± 2.97
Change from Baseline	(30) -1.7 ± 3.55	(69) -2.2 ± 4.06	(63) -2.3 ± 3.61
<b>Depression-Dejection</b>			
Baseline	(46) 4.6 ± 4.61	(94) 3.8 ± 4.03	(97) 4.3 ± 4.03
Week 7	(31) 3.4 ± 4.74	(72) 2.6 ± 3.69	(63) 1.8 ± 2.64
Change from Baseline	(30) -1.2 ± 3.51	(69) -1.8 ± 4.41	(63) -2.7 ± 3.59
<b>Anger-Hostility</b>			
Baseline	(46) 4.3 ± 3.58	(94) 4.6 ± 4.50	(97) 5.1 ± 3.86
Week 7	(31) 2.9 ± 3.60	(72) 2.8 ± 3.60	(63) 2.5 ± 2.71
Change from Baseline	(30) -1.6 ± 3.73	(69) -2.2 ± 4.34	(63) -2.6 ± 3.82
<b>Vigor-Activity</b>			
Baseline	(46) 7.6 ± 4.74	(94) 8.6 ± 4.16	(97) 8.2 ± 4.71
Week 7	(31) 6.3 ± 4.38	(72) 6.6 ± 3.98	(63) 6.4 ± 4.16
Change from Baseline	(30) -2.2 ± 4.86	(69) -1.5 ± 4.73	(63) -1.8 ± 5.18
<b>Fatigue-Inertia</b>			
Baseline	(46) 7.1 ± 5.43	(94) 6.4 ± 5.21	(97) 6.1 ± 4.34
Week 7	(31) 5.1 ± 5.61	(72) 4.5 ± 4.59	(63) 5.0 ± 4.40
Change from Baseline	(30) -1.8 ± 3.67	(69) -2.3 ± 5.39	(63) -1.2 ± 4.57
<b>Confusion-Bewilderment</b>			
Baseline	(46) 7.3 ± 4.07	(94) 7.0 ± 3.30	(97) 7.5 ± 3.38
Week 7	(31) 5.6 ± 3.96	(72) 4.6 ± 2.88	(63) 4.7 ± 3.07
Change from Baseline	(30) -1.4 ± 3.00	(69) -2.6 ± 3.65	(63) -2.9 ± 3.28

POMS = profile of mood states, ATX = atomoxetine, ATX-BSP = atomoxetine-bupirone, SD = standard deviation

## Sheehan Disability Scale Score

Mean SDS total and individual scores decreased from Baseline to Week 7. There was a greater reduction in the mean scores in the ATX-BSP treatment group than in the ATX and placebo treatment groups, respectively (Table S19).

**Table S19. Summary of SDS Total and Individual Score**

	<b>Placebo (N) Mean ± SD</b>	<b>ATX (N) Mean ± SD</b>	<b>ATX-BSP (N) Mean ± SD</b>
<b>SDS Total Score</b>			
Baseline	(43) 18.0 ± 6.79	(93) 16.7 ± 7.41	(93) 17.4 ± 6.56
Week 7	(31) 10.8 ± 8.62	(71) 9.0 ± 7.37	(63) 8.3 ± 6.50
Change from Baseline	(29) -6.3 ± 8.26	(68) -7.7 ± 7.72	(62) -9.3 ± 7.84
<b>Work/School Disruption</b>			
Baseline	(43) 6.5 ± 2.55	(93) 6.1 ± 2.75	(93) 6.3 ± 2.61
Week 7	(31) 3.9 ± 2.96	(71) 3.1 ± 2.95	(63) 3.1 ± 2.39
Change from Baseline	(29) -2.4 ± 3.00	(68) -2.8 ± 2.98	(62) -3.4 ± 3.09
<b>Social Life Disruption</b>			
Baseline	(46) 5.2 ± 2.79	(97) 5.0 ± 2.80	(97) 5.0 ± 2.55
Week 7	(31) 3.3 ± 3.09	(72) 2.9 ± 2.49	(65) 2.2 ± 2.27
Change from Baseline	(30) -1.6 ± 2.99	(72) -2.3 ± 2.93	(65) -2.7 ± 3.11
<b>Family/Home Disruption</b>			
Baseline	(46) 6.1 ± 2.65	(97) 5.6 ± 2.83	(97) 6.2 ± 2.56
Week 7	(31) 3.6 ± 3.21	(72) 3.1 ± 2.88	(65) 2.8 ± 2.44
Change from Baseline	(30) -2.2 ± 3.21	(72) -2.7 ± 3.21	(65) -3.5 ± 2.76

SDS = Sheehan disability scale, ATX = atomoxetine, ATX-BSP = atomoxetine-buspirone, SD = standard deviation

### Stroop Color and Word Test

The mean Stroop interference score increased from Baseline to Week 7 for placebo and ATX-BSP and reduced for ATX ([Table S20](#)).

**Table S20. Summary of Stroop Interference Scores by Treatment**

	<b>Placebo (N) Mean ± SD</b>	<b>ATX (N) Mean ± SD</b>	<b>ATX-BSP (N) Mean ± SD</b>
Baseline	(47) 2.9 ± 8.68	(97) 3.1 ± 9.68	(97) 2.3 ± 8.59
Week 7	(30) 4.3 ± 7.44	(72) 2.7 ± 8.44	(65) 5.3 ± 9.43
Change from Baseline	(30) 1.4 ± 6.93	(72) -0.3 ± 9.41	(65) 2.8 ± 9.29

Stroop = Stroop color and word test, ATX = atomoxetine, ATX-BSP = atomoxetine-buspirone, SD = standard deviation

### Brown ADD Scale

The mean Brown ADD total score was higher at Baseline for all treatment groups. The Brown ADD total score indicated a large difference (ranging from -8.71 to -14.06) in the change from baseline between ATX-BSP and placebo over Weeks 1 to 7 ([Table S21](#)).

**Table S21. Repeated Measure Analysis of Brown ADD Total Score – Change from Baseline**

	Week 1	Week 2	Week 3	Week 4	Week 7	Weeks 1-7
<b>ATX+BSP versus ATX</b>						
Estimate ( SE)	-0.12 (3.40)	-1.68 (3.67)	-4.59 (3.92)	-5.02 (4.25)	-3.54 (4.44)	-2.99 (3.45)
80% CI	-4.50, 4.25	-6.40, 3.04	-9.64, 0.45	-10.49, 0.45	-9.26, 2.17	-7.43, 1.44
One-sided	0.485	0.324	0.121	0.120	0.213	0.193
p-value						
<b>ATX+BSP versus Placebo</b>						
Estimate (SE)	-8.71 (4.05)	-10.27 (4.38)	-11.93 (4.77)	-11.17 (5.17)	-14.06 (5.43)	-11.23 (4.16)
80% CI	-13.92, -3.50	-15.90, -4.63	-18.06, -5.81	-17.82, -4.52	-21.05, -7.07	-16.57, -5.88
One-sided	0.016	0.010	0.007	0.016	0.005	0.004
p-value						

Brown ADD = Brown attention deficit disorder scale, ATX = atomoxetine, ATX-BSP = atomoxetine-buspiron, SE = standard error, CI = confidence interval

Brown cluster scores by treatment and Week are summarized in [Table S22](#).

**Table S22. Summary of Brown ADD Cluster Scores**

	Placebo (N) Mean ± SD	ATX (N) Mean ± SD	ATX-BSP (N) Mean ± SD
<b>Organizing and Activating to Work</b>			
Baseline	(42) 18.1 ± 5.56	(84) 18.4 ± 4.99	(88) 18.6 ± 4.88
Week 7	(30) 13.4 ± 7.82	(69) 11.9 ± 7.09	(64) 10.8 ± 7.04
<b>Sustaining Attention and Concentration</b>			
Baseline	(42) 19.9 ± 4.74	(83) 20.4 ± 5.44	(88) 20.1 ± 4.68
Week 7	(30) 13.4 ± 8.36	(69) 12.4 ± 8.22	(64) 10.5 ± 7.42
<b>Sustaining Energy and Effort</b>			
Baseline	(42) 15.2 ± 6.67	(84) 15.6 ± 6.40	(88) 15.7 ± 5.46
Week 7	(30) 10.4 ± 7.79	(68) 8.8 ± 6.71	(64) 9.4 ± 6.67
<b>Managing Affective Interference</b>			
Baseline	(42) 9.7 ± 5.12	(84) 9.7 ± 5.23	(87) 9.7 ± 4.92
Week 7	(30) 6.7 ± 5.55	(69) 6.1 ± 5.40	(64) 5.3 ± 4.66
<b>Utilizing Working Memory and Accessing Recall</b>			
Baseline	(42) 11.3 ± 4.61	(83) 12.0 ± 3.93	(88) 12.3 ± 3.56
Week 7	(30) 8.0 ± 5.94	(69) 7.7 ± 5.26	(64) 7.2 ± 4.91

Brown ADD = Brown attention deficit disorder scale, ATX = atomoxetine, ATX-BSP = atomoxetine-buspiron, SD = standard deviation

**Safety Results:** There were no deaths in the study. Two SAEs were reported; neither was considered by the investigator to be treatment related. [Table S23](#) provides a summary of the number of AEs and discontinuations due to AEs.

**Table S23. Overview of Adverse Events**

	Placebo N=47	ATX N=97	ATX-BSP N=97
<b>Number (%) of Subjects with AEs</b>			
All AEs	38 (80.9)	90 (92.8)	90 (92.8)
Associated AEs	33 (70.2)	87 (89.7)	89 (91.8)
<b>Number (%) of Subjects Withdrawn due to AEs</b>			
All AEs	7 (14.9)	12 (12.4)	16 (16.5)
Associated AEs	7 (14.9)	12 (12.4)	15 (15.5)
<b>Number (%) of Subjects with AEs by Maximum Intensity</b>			
All AEs			
Mild	13 (27.7)	25 (25.8)	26 (26.8)
Moderate	17 (36.2)	46 (47.4)	44 (45.4)
Severe	8 (17.0)	19 (19.6)	20 (20.6)
Associated AEs			
Mild	12 (25.5)	28 (28.9)	31 (32.0)
Moderate	13 (27.7)	44 (45.4)	40 (41.2)
Severe	8 (17.0)	15 (15.5)	18 (18.6)
<b>Number (%) of Subjects with non-fatal Serious AEs</b>			
All AEs	0	1 (1.0)	1 (1.0)
Associated AEs	0	0	0
<b>Number (%) of Subjects withdrawn due to Serious AEs</b>			
All AEs	0	0	1 (1.0)
Associated AEs	0	0	0

AE=Adverse events; All AEs = treatment emergent AEs, regardless of causality; Associated AEs = AEs considered by the investigator to be treatment related, ATX = atomoxetine, ATX-BSP = atomoxetine-buspirone

Insomnia was the most frequently reported AE in both the ATX group (43.3%) and the ATX-BSP group (42.3%). The most frequent AEs ( $\geq 20\%$ ) in subjects receiving ATX therapy were asthenia, headache, dry mouth, and nausea. Somnolence, dizziness, nausea, dry mouth, headache and asthenia were the most frequent AEs in the ATX-BSP group.

Treatment-emergent AEs occurring in  $\geq 10$  subjects in any treatment group are summarized in [Table S24](#).

**Table S24. Treatment Emergent AEs Occurring in  $\geq 10$  Subjects in Any Treatment Group**

Number (%) of Subjects AE (Preferred Term)	Placebo N = 47	ATX N = 97	ATX-BSP N = 97
Asthenia	8 (17.0)	25 (25.8)	22 (22.7)
Headache	6 (12.8)	28 (28.9)	26 (26.8)
Vasodilatation	0 (0.0)	5 (5.2)	10 (10.3)
Anorexia	3 (6.4)	19 (19.6)	16 (16.5)
Constipation	3 (6.4)	8 (8.2)	14 (14.4)
Dry mouth	6 (12.8)	29 (29.9)	36 (37.1)
Nausea	4 (8.5)	25 (25.8)	30 (30.9)
Dizziness	5 (10.6)	13 (13.4)	31 (32.0)
Insomnia	10 (21.3)	42 (43.3)	41 (42.3)
Libido decreased	2 (4.3)	12 (12.4)	4 (4.1)
Nervousness	4 (8.5)	17 (17.5)	14 (14.4)
Paresthesia	1 (2.1)	4 (4.1)	10 (10.3)
Somnolence	8 (17.0)	16 (16.5)	22 (22.7)
Sweating	1 (2.1)	10 (10.3)	7 (7.2)

AE = adverse event, ATX = atomoxetine, ATX-BSP = atomoxetine-buspirone  
 AE terms coded using MedDRA (version 9.0)

The ATX-BSP group had the highest number of discontinuations due to AEs (16 subjects), followed by the ATX group (12 subjects) and the placebo group (7 subjects). One subject in the ATX-BSP group was withdrawn due to a lymphoma-like reaction not considered by the investigator to be related to study drug.

Seven subjects were temporarily discontinued from treatment due to AEs (Table S25). Of these, 3 subjects in the ATX-BSP group and 1 subject in the placebo group temporarily discontinued treatment due to treatment related AEs.

**Table S25. Temporary Discontinuations**

Treatment	Adverse Event	Severity	Causality	Outcome
ATX-BSP	Vomiting	Severe	Possibly	Recovered
ATX-BSP	Back pain	Moderate	Unlikely	Recovered
	Pain	Moderate	Possibly	Recovered
ATX-BSP	Asthenia	Severe	Probably	Unknown
	Nervousness	Moderate	Probably	Unknown
	Confusion	Severe	Probably	Unknown
ATX-BSP	Infection	Mild	Definitely not	Recovered
ATX	Dyspnea	Moderate	Unlikely	Recovered
ATX	Constipation	Severe	Definitely not	Recovered
	Urination impaired	Severe	Definitely not	Recovered
Placebo	Nausea	Mild	Possibly	Recovered

ATX = atomoxetine, ATX-BSP = atomoxetine-bupirone

The ATX-BSP group had the highest number of subjects with treatment related laboratory abnormalities. Three subjects (all in the ATX-BSP group) had significant increases in white blood cell count (related to study drug). Four subjects were reported with ECG abnormalities. Most of the subjects (3 of 4) had ECG abnormalities at Screening and none of these were considered by the investigator to be clinically significant.

**SDQ Analysis**– The difference in SDQ total score between baseline and Week 7 showed a change in SDQ total score favoring ATX monotherapy. Subjects on the ATX-BSP combination therapy did not show a change from baseline at Week 7.

**MOS-SS Analysis**– Subjects in the ATX group showed lower mean change from baseline in total score compared to the ATX-BSP group at Week 7. Compared to the ATX and ATX-BSP groups, subjects on placebo treatment had fewer sleep-related problems at Week 7.

**CONCLUSIONS:**

- Comparison between ATX-BSP versus placebo indicated a reduction in the AISRS total score for ATX-BSP for all 7 weeks, with statistical significance favoring the combination therapy; in the comparison of ATX-BSP with ATX monotherapy, statistical significance was seen only at Week 4 and reduced scores were seen only at Weeks 3, 4 and 7.
- AISRS response rates were larger for ATX-BSP versus ATX, but these differences were not significant. Response rates for ATX-BSP and ATX were similar as measured by the

CGI-S. CGI-C response rates were larger for ATX-BSP versus ATX, but these were not significant, except at Week 4.

- The number of treatment-emergent AEs observed in the ATX and ATX-BSP groups were similar. The placebo group had a lower number of treatment-emergent AEs as compared to ATX monotherapy and ATX-BSP combination therapy.
- On the AISRS attention subscale, ATX-BSP produced significantly larger effects than ATX at Week 4 and 7, but no significantly smaller effects than ATX at Weeks 1, 2, and 3. ATX-BSP and ATX produced similar effects on the AISRS impulsivity/hyperactivity subscale.
- The difference in Brown total score from Baseline to Week 7 indicated greater improvement in ADD symptoms in ATX-BSP than ATX, but these differences were not significantly significant.
- The data from this study do not provide clear evidence of overall benefit of ATX-BSP over ATX, but is suggestive of some potentially significant benefit to adult subjects early in treatment.