2. 7399 Synopsis

Clinical Study Report Synopsis: Study B4Z-IT-LYCY

Title of Study: An Italian Randomized, Double-blind Placebo Controlled Study of the Efficacy of Atomoxetine Hydrochloride in the Treatment of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder and Comorbid Oppositional Defiant Disorder	
Number of Investigator(s): This multi-center study included 13 Principal Investigators.	
Study Center(s): This study was conducted at 13 study centers in Italy.	
Publication(s) Based on the Study: None at this time.	
Length of Study: 44 months Date of first patient enrolled: 13/10/2004 Date of last patient completed: 16/05/2008	**Phase of Development:** IIIb

Objectives:

The primary objective of this study was to test the hypothesis that atomoxetine was superior to placebo in improving ADHD symptomatology after 8 weeks of double-blind treatment on fixed dosage of atomoxetine (1.2 mg/kg/day, once daily) in pediatric outpatients with ADHD and ODD.

The secondary objectives of the study were to assess whether:

- **Atomoxetine was superior to placebo in improving symptoms of ADHD as measured by mean change in Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S);**
- **Parent support induced a different response on ADHD symptoms in respect to ODD symptoms evaluated by the mean change in the ADHD subscale and in the Oppositional subscale of the SNAP-IV respectively;**
- **Atomoxetine was superior to placebo in reducing symptoms of Oppositional Defiant Disorders as measured by mean change in ODD symptoms on the investigator-rated Oppositional subscale of the SNAP-IV;**
- **Atomoxetine was superior to placebo in improving mood of children and adolescents with ADHD as measured by the anxiety/depression scales [Screen for Child Anxiety Related Emotional Disorders (SCARED), and Children's Depression Rating Scale-Revised (CDRS-R)];**
- **Atomoxetine was superior to placebo in improving problem behaviors related to ADHD (even in the school setting) as measured by Conners' Parent and Teacher Rating scale- Revised: Short Form (CPRS-R:S and CTRS-R:S);**
- **Atomoxetine had a superior effect in comparison to placebo on the emotional and social well being of the child and the family evaluated by the total score on the Child Health and Illness Profile – Child Edition (CHIP-CE).**

Other secondary objectives were: to assess whether the changes observed over 8 weeks were maintained over the open-label long-term phase of the study; to evaluate the long-term tolerability and safety of atomoxetine as assessed by adverse events (AEs) elicited during open-ended questioning.

Study Design: This was a phase IIIb multicenter, randomized, placebo controlled, trial in pediatric patients, aged 6 years to 15 years with ADHD and ODD.

The entire study included four study periods:

a) Study period I (screening phase): this was a screening and assessment/evaluation period, ranging from 3 to 28 days, to ensure eligibility for the study, and was started after parent's consent was obtained.

b) Study period II (open-label, parent support phase): during this 6-week phase, the investigators provided a standardized management for the parental support. Parents received weekly series of advice on the management of the behavioral problems of their children from qualified psychologists or child psychiatrists, based on standardized procedures. Response criteria were defined as an improvement in CGI-S score of 2 or more from baseline and at least a 30% decrease from baseline in the 18 items of the ADHD subscale score of investigator-rated SNAP-IV. Only patients who did not respond to the parent support phase were randomized to the study period III.

c) Study period III (randomized, double blind, placebo-controlled phase). This was an 8-week period of double blind treatment in which patients were randomly assigned to treatment with atomoxetine or placebo in a ratio of 3:1.

d) Study period IV (long-term, open-label extension phase). This was an optional, open-label, long-term extension phase for patients who had completed study period III, in which all patients had the choice to receive open label atomoxetine treatment for a long-term period until the drug became commercially available.

The study periods I-III included 14 visits: visits 1 was the screening visit, weekly visits during the study period II (parent support phase, visits 2-8) and during the initial 4 weeks of the phase III (randomized double blind phase, visits 8-12); the remaining visits (13 and 14) took place every two weeks. Data of study period IV were collected in further 10 visits (conducted approximately every two months from the end of study period III up to 24 months of treatment).

Number of Patients: Planned: 130 randomized Entered: 156 entered the parent support phase, 17 discontinued (2 of them responded to parental support) Randomized: 139 (atomoxetine: 107; placebo: 32). Completed (study period III): 134 in total (atomoxetine: 102; placebo: 32)
Diagnosis and Main Criteria for Inclusion: Child or adolescent male or female outpatients, aged 6 to 15 years. Meeting DSM-IV diagnostic criteria for ADHD (any subtype) and ODD and score at least 1.5 standard deviations above the age norm for their diagnostic ADHD-RS subtype at both Visit 1 and 2. A SNAP-IV ODD subscale score of at least 15 at both Visit 1 and Visit 2. Laboratory results, including serum chemistry, hematology, and urinalysis, with no clinically significant abnormalities Normal intelligence in the judgment of the investigator □i.e. a score of > 70 on an Intelligence Quotient (IQ) test□. Patients and parents reliable to keep appointments for clinic visits and all tests, including venipuncture, and examinations required by the protocol. Patients and parents able to communicate effectively with the investigator and study coordinator as well as able to complete the self reported scales used in the study. Patients able to swallow capsules.
Test Product, Dose, and Mode of Administration: At the start of Study period III (randomized, double blind, placebo-controlled phase), patients who did not respond to the 6-weeks period of parent support were randomly assigned to treatment with atomoxetine or placebo capsules in a ratio of 3:1. Patients randomized to atomoxetine were titrated, in 7 days, from 0.5 mg/kg/day (allowed range from 0.5 to 0.8 mg/kg/day) to the target dose of 1.2 mg/kg/day (allowed range from 1.0 to 1.4 mg/kg/day), to be administered for the first 8 weeks of the study once daily in the morning. In case of onset of fatigue or somnolence during the day the investigator could decide to administer the dose in the evening. Atomoxetine was made available in the following dose strengths: 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, and 40 mg. At the end of the 8-weeks double blind period, patients had the choice to receive open label atomoxetine treatment for a long-term period.
Reference Therapy, Dose, and Mode of Administration: Matched placebo capsules, once daily in the morning.
Duration of Treatment: 8 weeks in total in Study period III (randomized, double blind, placebo-controlled phase), up to 24 months in Study period IV (long-term, open-label extension phase)

Variables:

Efficacy:

Primary: ADHD subscale score of the SNAP-IV (i.e. based on the 18 Inattention, and Hyperactivity/Impulsivity items)

Secondary:

- ODD subscale score of the SNAP-IV;
- Other ADHD subscales (inattention and hyperactivitiy/impulsivity) of the SNAP-IV
- CGI-S;
- Children's Depression Rating Scale-Revised (CDRS-R) and the Screen for Child Anxiety Related Emotional Disorders (SCARED) - Parent Version;
- Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) and the Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R:S);
- Child Health and Illness Profile -Child Edition (CHIP-CE) total score, domains, and subscores.

Safety:

Adverse events, body weight, height, vital signs (blood pressure and heart rate, body temperature).

Evaluation Methods:

Statistical:

The sample size calculation was based on the primary outcome variable, i.e. the 18 items of the ADHD subscale score of the investigator-rated SNAP-IV. Using an estimate of the common standard deviation of 13 points, a sample of 130 patients (in a 3:1 ratio amoxetine:placebo) would give about 80% power to detect a difference of 8 points on the SNAP-IV between groups, which can be considered as clinically relevant. The sample size was determined using a two-sided test with alpha = 0.05, and assumed that up to 10% of patients discontinued the study without providing post-baseline efficacy data in the randomized phase.

The analysis of the primary and secondary efficacy endpoints, and of vital signs, was carried out using an analysis of covariance (ANCOVA) model on the last observation carried forward (LOCF) change from baseline to endpoint, in the double blind randomized phase of the study. The baseline score and the site were included in the model as covariates.

Adverse events were coded using the MedDRA dictionary. Events were considered treatment emergent adverse events (TEAE) if they started or worsened after the first intake of study medication compared to the pre-baseline period. Rates of patients with TEAE in the double blind phase of the study were compared between groups using the Fisher's exact test.

The available data collected in the Study period IV (long-term, open-label extension phase) were presented only descriptively, and were reported at each time point in visits 14-24, as well as in terms of changes from Visit 14 (end of the randomized placebo-controlled phase) to Visit 24/Last Visit (i.e. before 24).

Summary:
Patient Population:

A total of 156 patients (mean age: 9.9 years, 92.9% males) were screened and entered the parent support phase. Seventeen patients discontinued the study during the parent support phase before randomization (mainly due to patient/caregiver's or Investigator's decision). Two patients (1.3% of screened) responded to the parent psychological intervention and were not randomized.
All 139 remaining patients were randomized and analyzed for safety, and 137 for efficacy (2 did not have post-baseline data) in the randomized treatment phase (Study period III). In the atomoxetine group, 5 patients discontinued the study during the double blind randomized phase (reasons are reported in the adverse events section).
A total of 132 patients (atomoxetine: 100; placebo: 32) entered the Study period IV (long-term, open-label extension phase with atomoxetine). The results of the mean decreases from Visit 24/Last (before 24) to Visit 14 were available in 119 patients in total for SNAP-IV, in 121 for CGI-ADHD-S, in 108 for CHIP-CE total and achievement domain (in 118 for the other CHIP-CE domains), in 119 for CDRS-R total score, in 118 for SCARED total score and for CPRS-R:S, and in 65 for CTRS-R:S.
Patient Demographics:
The two study groups were homogeneous for demographic data, DSM-IV ADHD diagnosis and anxiety/affective disorders at baseline (Table 1).
Previous psychotherapy (of any type) was documented in 18 patients (17.1%) in the atomoxetine group and 6 (18.8%) in the placebo group, while 21 (20.0%) and 4 (12.5%) patients, respectively, received previous drug therapy. The mean starting dose of atomoxetine was 0.61 ± 0.08 mg/kg/day (range 0.44-0.80) and was titrated to 1.10 ± 0.13 mg/kg/day (range 0.85-1.33) at the end of the randomized phase of the study.

Table 1. Demographic data, DSM-IV ADHD and anxiety/affective diagnoses at entry

	Atomoxetine (n = 105)	**Placebo (n = 32)**
Demographic data:		
Age, years, *mean ± SD (range)* Gender, M/F, *number (%)*	9.7 ± 2.2 (6.1-14.6) M: 98 (93.3); F: 7 (6.7)	10.0 ± 2.4 (6.2-15.4)M: 29 (90.6); F: 3 (9.4)41.4 ±
Weight, kg, *mean ± SD (range)*	39.3 ± 15.8 (20-90)	14.1 (22-78)
Height, cm, mean ± SD (range)	140.1 ± 15.2 (110-174)	141.6 ± 15.3 (116-177)
BMI, kg/m^2, *mean ± SD (range)*	19.3 ± 4.2 (13.8-32.8)	20.1 ± 3.5 (14.7-28.5)
DSM-IV ADHD subtype from present disorders:		
Inattentive, *number (%)* Hyperactive, *number (%)*	7 (6.7) 4 (3.8)	1 (3.1) 3 (9.4)
Combined, *number (%)*	94 (89.5)	28 (87.5)
Age at onset of ADHD symptoms, years, *mean ± SD (range)*	4.2 ± 1.8 (1-12)	3.7 ± 1.4 (2-7)
Anxiety diagnoses from K-SADS:		
Generalized anxiety disorders, *number (%)*	10 (9.5)	5 (15.6%)
Obsessive compulsive disorders, *number (%)*	2 (1.9)	1 (3.1)
Panic, *number (%)*	2 (1.9)	1 (3.1)
Separation anxiety disorders, *number (%)*	5 (4.8)	0 (0.0)
Specific phobias, *number (%)*	8 (7.6)	2 (6.3)
Affective diagnoses from K-SADS:		
Adjustment disorder, *number (%)*	1 (1.0)	0 (0.0)
Dysthymia, *number (%)*	9 (8.6)	0 (0.0)
Major depressive disorders, *number (%)*	2 (1.9)	0 (0.0)
Seasonal pattern disorders, *number (%)*	1 (1.0)	1 (3.1)
Any other depressive disorders, *number (%)*	0 (0.0)	1 (3.1)

Primary Efficacy Endpoint:
A non-clinically significant decrease in all SNAP-IV subscales scores was observed during the parent support phase. The mean score (± standard deviation) for the ADHD subscale (i.e. the sum of the 18 items for inattention and hyperactivity/impulsivity) was 43.3 ± 6.6 at the start and 42.1 ± 6.9 at the end of this phase, 21.9 ± 3.3 and 21.3 ± 3.6 for the inattention subscore, 21.4 ± 4.2 and 20.8 ± 4.3 for the hyperactivity/impulsivity subscore, and 18.1 ± 2.5 and 17.2 ± 3.3 for the ODD subscore.
During the randomized phase of the study, the mean changes (± standard deviation) from visit 8 to the last visit in this phase (i.e. visit 14 LOCF) in the ADHD subscale were -8.1 ± 9.2 and -2.0 ± 4.7, respectively in the atomoxetine and in the placebo group ($p<0.001$ between groups). A significantly stronger decrease of mean scores for all SNAP-IV subscales from visit 8 to the last visit was observed in the atomoxetine group, compared to placebo ($p<0.01$) (Table 2).

Table 2. Results of the SNAP-IV subscales scores during the randomized double blind phase (values are means ± standard deviation)

	Atomoxetine (n = 105)			**Placebo (n = 32)**		
	Visit 8	Last Visit	Change from Visit 8	Visit 8	Last Visit	Change from Visit 8
ADHD subscale	42.7 ± 6.2	34.6 ± 10.2	-8.1 ± 9.2**	41.5 ± 6.9	39.5 ± 8.7	-2.0 ± 4.7
Inattention	21.6 ± 3.2	17.5 ± 5.2	-4.2 ± 4.9**	21.2 ± 4.3	20.4 ± 4.8	-0.8 ± 3.0
Hyperactivity/impulsivity	21.1 ± 4.2	17.1 ± 6.0	-3.9 ± 5.0*	20.3 ± 3.6	19.0 ± 5.2	-1.3 ± 2.8
ODD	17.2 ± 3.0	14.5 ± 4.8	-2.7 ± 4.1*	17.5 ± 3.8	17.2 ± 3.9	-2.2 ± 3.9

*$p<0.01$, **$p<0.001$ between groups based on least square means from the ANCOVA model

In the open-label extension phase, patients previously on atomoxetine experienced a further decrease in the ADHD subscale. The mean change from Visit 14 to Visit 24/Last visit (i.e. visit 24 or earlier in the discontinued patients) in patients previously on atomoxetine was -9.0 (95% CI: -11.4 to -6.6), while a similar decrease was also observed in those previously on placebo (mean change: -8.9; 95% CI: -13.7 to -4.2). A similar pattern was also observed in the inattention, hyperactivity/impulsivity, and ODD subscores.
Secondary Efficacy Endpoints:
CGI-S:
The mean CGI-ADHD-S score did not change from the start (mean score: 5.2) to the end (mean score: 5.1) of the parent support phase. A CGI-ADHD-S decrease in the atomoxetine group was observed during the randomized double-blind phase (mean change at endpoint: -0.6), compared to the placebo group ($p<0.001$ between groups).
A further decrease from the end of the randomized double-blind phase was observed in the open-label extension phase in patients previously treated with atomoxetine (mean change from Visit 14 to Visit 24/Last visit: -1.0; 95% CI: -1.2 to -0.7), and in patients previously treated with placebo (mean change: -1.3; 95% CI: -1.8 to -0.7).
CDRS-R and SCARED:
The mean total scores of CDRS-R and SCARED changed in the parent support phase: the mean changes from baseline to the end of the parent support phase were -0.6 ± 4.1 and -0.3 ± 7.5, respectively.
The mean changes of CDRS-R total score from visit 8 to the last visit in the randomized treatment period were -0.5 ± 4.4 in the atomoxetine group and -0.1 ± 5.0 in the placebo group ($p = 0.870$ between groups). The corresponding changes of SCARED were -2.1 ± 7.6 and -1.7 ± 6.5, respectively in the two groups ($p = 0.836$ between groups).
In the open-label extension phase, the CDRS-R total score changed by -3.2 (95% CI: -4.9 to -1.5) in patients previously treated with atomoxetine and changed by 0.5 (95% CI: -3.7 to 4.7) in those previously on placebo. The corresponding changes of SCARED were -3.6 (95% CI: -5.5 to -1.8) and -4.9 (95% CI: -8.9 to -1.0), respectively in the two treatment groups.

CPRS-R:S and CTRS-R:S:
The mean changes in the ADHD index in the parent support phase were -1.5 ± 4.3 in the CPRS-R:S and -1.1 ± 3.6 in the CTRS-R:S.
The results of the CPRS-R:S and the CTRS-R:S in the randomized phase are summarized in Table 3. Statistically significant differences vs. placebo were found in all subscales of the CPRS-R:S and in the oppositional subscale of the CTRS-R:S. For further subscales of the CTRS-R:S the following p-values were calculated: cognitive problems, p = 0.113; hyperactivity, p = 0.051; ADHD index, p = 0.061.

Table 3. Results of the CPRS-R:S and the CTRS-R:S in the randomized double blind phase (values are means ± standard deviation)

Subscales	Atomoxetine		Placebo	
	Visit 8	Last visit	Visit 8	Last visit
CPRS-R:S				
Oppositional	11.7 ± 3.8	10.5 ± 4.4**	12.2 ± 3.0	13.0 ± 4.2
Cognitive problems	14.3 ± 3.1	12.0 ± 4.2***	14.2 ± 3.2	14.4 ± 3.5
Hyperactivity	12.0 ± 3.8	9.8 ± 4.4*	12.0 ± 4.0	11.3 ± 4.6
ADHD index	28.2 ± 4.9	23.1 ± 7.1***	28.4 ± 5.2	28.3 ± 5.6
CTRS-R:S				
Oppositional	7.6 ± 4.3	6.5 ± 4.1**	10.8 ± 3.8	10.9 ± 3.1
Cognitive problems	8.2 ± 4.3	12.0 ± 4.2	8.5 ± 3.7	8.5 ± 3.3
Hyperactivity	12.8 ± 5.5	10.7 ± 5.6	16.3 ± 3.4	15.2 ± 4.6
ADHD index	25.3 ± 8.4	21.8 ± 8.9	29.9 ± 6.0	28.4 ± 6.1

*p<0.01, **p<0.01, ***p<0.001 between groups based on least square means from the ANCOVA model

In the open-label extension phase, the mean decreases from Visit 24/Last to Visit 14 in the CPRS-R:S oppositional subscale were -1.6 (95% CI: -2.5 to -0.8) and -1.9 (95% CI: -3.6 to -0.3), respectively in patients previously treated with atomoxetine and those previously on placebo, -1.3 (95% CI: -2.2 to -0.5) and -3.1 (95% CI: -4.6 to -1.6) in the cognitive subscale, -2.5 (95% CI: -3.5 to -1.6) and -2.6 (95% CI: -4.5 to -0.6) in the hyperactivity subscale, and -3.5 (95% CI: -5.0 to -1.9) and -7.1 (95% CI: -9.9 to -4.3) in the ADHD index, in the respective treatment cohorts.
The corresponding decreases of the CTRS-R:S in the open-label extension phase were -0.7 (95% CI: -1.4 to 0.1) and -3.5 (95% CI: -5.4 to -1.7) in the oppositional subscale, -0.7 (95% CI: -1.6 to 0.1) and -0.6 (95% CI: -2.6 to 1.4) in the cognitive subscale, -2.0 (95% CI: -3.3 to -0.7) and -3.9 (95% CI: -6.8 to -0.9) in the hyperactivity subscale, and -3.3 (95% CI: -5.1 to -1.5) and -6.5 (95% CI: -10.8 to -2.2) in the ADHD index, respectively, in the atomoxetine and placebo cohort.

CHIP-CE Questionnaire:
Mean changes in CHIP-CE total, and domain scores during the parent support phase were ≤ 1.5 points.
Table 4 shows the CHIP-CE total, domains and subscores during the randomized double blind phase. The mean changes of CHIP-CE total score from visit 8 to the last visit were 3.6 with atomoxetine and 1.2 with placebo (p = 0.071 between groups). The comparisons between groups showed statistically significant differences, in favor of atomoxetine, for the risk avoidance domain (p = 0.013), and for the emotional comfort (p = 0.007) and the individual risk avoidance (p = 0.007) subscores.

Table 4. CHIP-CE total, domains and subscores scores during the randomized double blind phase (values are means ± standard deviation)

	Atomoxetine (n = 105)		Placebo (n = 32)	
	Visit 8	Last Visit	Visit 8	Last Visit
Total score	27.1 ± 10.4	30.7 ± 11.7	26.9 ± 11.2	28.2 ± 10.8

Satisfaction	30.9 ± 13.2	33.3 ± 15.6	30.7 ± 12.4	48.6 ± 9.0
Satisfaction with health	39.9 ± 12.5	40.2 ± 14.1	38.3 ± 14.0	41.2 ± 16.0
Satisfaction with self	25.8 ± 13.3	30.0 ± 15.8	27.3 ± 12.7	28.8 ± 12.7
Comfort	47.3 ± 8.9	49.4 ± 10.1	49.5 ± 9.8	48.6 ± 9.0
Physical comfort	52.3 ± 8.5	53.6 ± 8.7	55.1 ± 9.1	55.8 ± 7.2
Emotional comfort	43.7 ± 10.2	45.8 ± 12.0**	44.3 ± 11.4	41.2 ± 12.1
Restricted activity	48.9 ± 10.2	50.4 ± 9.7	50.8 ± 9.9	53.2 ± 7.0
Risk avoidance	30.5 ± 11.9	33.9 ± 11.5*	29.4 ± 12.8	29.5 ± 11.0
Individual risk avoidance	35.5 ± 13.0	38.2 ± 11.9**	36.8 ± 13.9	35.0 ± 13.6
Threats to achievements	31.4 ± 12.1	34.6 ± 11.4	29.3 ± 11.9	30.5 ± 11.0
Resilience	31.3 ± 12.7	33.7 ± 11.9	32.0 ± 11.4	33.8 ± 12.5
Family involvement	36.7 ± 12.7	38.4 ± 12.1	37.8 ± 12.0	36.8 ± 12.5
Social problems solving	33.6 ± 16.2	35.1 ± 11.8	35.0 ± 11.2	36.6 ± 11.8
Physical activity	41.6 ± 10.9	43.4 ± 12.0	40.2 ± 12.5	43.7 ± 13.4
Achievement	28.5 ± 10.2	30.8 ± 11.0	26.7 ± 10.2	27.9 ± 10.2
Academic performance	30.7 ± 10.2	28.6 ± 9.9	32.3 ± 10.7	29.0 ± 9.8
Peer relations	34.2 ± 11.9	36.4 ± 11.8	34.4 ± 13.0	35.8 ± 13.3

*p<0.05, **p<0.01 between groups based on least square means from the ANCOVA model

In the open-label extension phase, the following changes were observed both in patients previously on atomoxetine and in those previously treated with placebo with regard to CHIP-CE total (mean changes from Visit 14 to Visit 24/Last visit: +2.9 ± 9.9 and +3.3 ± 12.5, respectively), comfort (+2.3 ± 9.6 and +2.7 ± 9.3), risk avoidance (+4.6 ± 10.4 and +4.4 ± 10.2) and achievement (+2.5 ± 9.7 and +2.5 ± 11.8) domains, and in emotional comfort (+3.0 ± 10.4 and +3.9 ± 10.6), individual risk avoidance (+4.8 ± 10.9 and +4.0 ± 10.9), threats to achievement (+3.7 ± 10.5 and +3.7 ± 10.8), social problem solving (+2.6 ± 12.6 and +3.9 ± 16.5) and peer relation (+4.9 ± 10.2 and +4.1 ± 13.5) subscores. Satisfaction with health subscore improved only in patients previously on placebo (-1.0 ± 14.2 and +3.5 ± 17.0), while physical comfort subscore improved only in patients previously on atomoxetine (+2.3 ± 8.3 and +0.2 ± 8.5). The mean score of satisfaction and resilience domains, and of satisfaction with self, family involvement and academic performance subscores did not change in both subgroups during the open-label extension phase. The mean change of the score of the physical activity subscore was -2.4 ± 12.2 and -5.3 ± 14.7, respectively in patients previously treated with atomoxetine or placebo, while restricted activity subscore changed by -2.4 ± 12.2 in patients who previously received atomoxetine.

Safety:

Adverse events:

Table 5 shows the TEAEs reported in at least 5% of patients in any group during the randomized double blind phase of the study. The most common individual adverse events with a significantly higher incidence in atomoxetine treated patients were anorexia (atomoxetine: 33.6 %; placebo: 9.4%), somnolence (29.9% vs. 6.3%) and nausea (20.6% vs. 0.0%). All adverse events except 5 cases were of mild or moderate severity and 3 patients treated with atomoxetine discontinued the study due to adverse events. No death and no serious adverse events were reported until visit 14.

Table 5. Treatment-emergent adverse events reported in at least 5% of patients in any group during the randomized double blind phase of the study

Adverse event	Atomoxetine (n = 107)		Placebo (n = 32)		p-value
	n	%	n	%	
Anorexia	36	33.6	3	9.4	0.006
Somnolence	32	29.9	2	6.3	0.004

Adverse event	Atomoxetine (n = 107)		Placebo (n = 32)		p-value
	n	%	n	%	
Headache	23	21.5	4	12.5	0.316
Nausea	22	20.6	0	0.0	0.002
Abdominal pain	16	15.0	2	6.3	0.245
Vomiting	15	14.0	1	3.1	0.118
Abdominal pain upper	11	10.3	4	12.5	0.748
Decreased appetite	10	9.3	0	0.0	0.116
Influenza	9	8.4	0	0.0	0.117
Nervousness	7	6.5	2	6.3	>0.999
Weight decreased	6	5.6	1	3.1	>0.999
Insomnia	5	4.7	2	6.3	0.661
Diarrhea	4	3.7	2	6.3	0.621

n = number of patients; p values refer to comparisons between groups

Approximately half of patients reported adverse events in the long-term, open-label extension phase of the study. Headache (in 17.0% and 9.4% of patients previously treated with atomoxetine and placebo, respectively), anorexia (7.0% and 16.8%), nausea (11.0% and 3.1%) and vomiting (10.0% and 6.3%) were the most common events reported in Study period IV while receiving atomoxetine.

Five patients previously on atomoxetine and one previously treated with placebo discontinued during the long-term, open-label extension phase. Reasons of discontinuations in the previous atomoxetine subgroup were: weight decrease and asthenia (1 patient); headache (1 patient); anorexia and nausea (1 patient); anorexia, affective disorder and insomnia (1 patient); rash (1 patient). Reason of discontinuations in one patient who previously received placebo was Wolff Parkinson White syndrome.

Body weight and height:

No changes of mean body weight and height were observed during the parent support phase, while the results in the randomized phase showed an increase of 0.5 kg body weight with placebo and a decrease of 1.2 kg with atomoxetine ($p<0.001$), as well as a mean height increase of 1.5 cm in the placebo group and of 1 cm in the atomoxetine group ($p=0.021$). In the long-term, open-label extension phase, a statistically significant body weight gain was observed in patients previously on atomoxetine (mean change: 4.4 kg; 95% CI: 3.3 to 5.5) but not in those previously receiving placebo (mean change: 2.2 kg; 95% CI: -0.3 to 4.8).

Vital signs:

The mean changes in vital signs from visit 8 to the end of randomized phase in the atomoxetine group and in the placebo group were 1.0 and 5.1 mmHg in systolic blood pressure ($p = 0.482$), -0.2 and 2.3 mmHg in diastolic blood pressure ($p = 0.557$), and in 3.7 and 1.5 bpm in heart rate ($p = 0.312$), respectively. No difference between groups was observed in body temperature. No clinically significant changes in blood pressure and heart rate were reported in the long-term, open-label extension phase.