Clinical trial results:
A Randomized, Double-blind Comparison of Atomoxetine Hydrochloride and Placebo for Symptoms of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents With Autism Spectrum Disorder

Summary

EudraCT number	2006-000304-16
Trial protocol	Outside EU/EEA
Global end of trial date	01 October 2008

Results information

Result version number	v1 (current)
This version publication date	22 December 2021
First version publication date	22 December 2021

Trial information

Trial identification

Sponsor protocol code	B4Z-UT-S017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00380692
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 10483

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 October 2006
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 October 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine whether atomoxetine is effective in reducing ADHD (Attention Deficit/Hyperactivity Disorder) symptoms in children and adolescents with ASD (Autism Spectrum Disorder).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 97
Worldwide total number of subjects	97
EEA total number of subjects	97

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	97
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Not Applicable

Period 1

Period 1 title	Study Period II - Double Blind
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Atomoxetine

Arm description:

atomoxetine: 0.5 mg/kg/day daily (QD), by mouth (PO) for 1 week, atomoxetine 0.8mg/kg/day QD, PO for 1 week, 1.2mg/kg/day QD, PO for 6 weeks then atomoxetine 0.5-1.2 mg/kg/day QD, PO for up to 20 weeks.

Arm type	Experimental
Investigational medicinal product name	Atomoxetine
Investigational medicinal product code	
Other name	LY139603; Strattera
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

0.5 mg/kg/day daily (QD), by mouth (PO) for 1 week, atomoxetine 0.8mg/kg/day QD, PO for 1 week, 1.2mg/kg/day QD, PO for 6 weeks then atomoxetine 0.5-1.2 mg/kg/day QD, PO for up to 20 weeks.

Arm title	Placebo

Arm description:

placebo: daily (QD), by mouth (PO) for 8 weeks. Then patients can take atomoxetine 0.5-1.2 mg/kg/day QD, PO up to 20 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

placebo: daily (QD), by mouth (PO) for 8 weeks.

Number of subjects in period 1	Atomoxetine	Placebo
Started	48	49
Completed	43	46
Not completed	5	3
Parent/Caregiver Decision	1	-
Physician decision	-	1
Adverse event, non-fatal	1	-
Protocol deviation	2	2
Lack of efficacy	1	-

Period 2

Period 2 title	Study Period III - Open Label
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Atomoxetine

Arm description:

atomoxetine: 0.5 mg/kg/day daily (QD), by mouth (PO) for 1 week, atomoxetine 0.8mg/kg/day QD, PO for 1 week, 1.2mg/kg/day QD, PO for 6 weeks then atomoxetine 0.5-1.2 mg/kg/day QD, PO for up to 20 weeks.

Arm type	Experimental
Investigational medicinal product name	Atomoxetine
Investigational medicinal product code	
Other name	LY139603; Strattera
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

0.5 mg/kg/day daily (QD), by mouth (PO) for 1 week, atomoxetine 0.8mg/kg/day QD, PO for 1 week, 1.2mg/kg/day QD, PO for 6 weeks then atomoxetine 0.5-1.2 mg/kg/day QD, PO for up to 20 weeks.

Arm title	Placebo

Arm description:

placebo: daily (QD), by mouth (PO) for 8 weeks. Then patients can take atomoxetine 0.5-1.2 mg/kg/day QD, PO up to 20 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

placebo: daily (QD), by mouth (PO) for 8 weeks.

Number of subjects in period 2[1]	Atomoxetine	Placebo
Started	42	46
Completed	36	34
Not completed	6	12
Parent/Caregiver Decision	1	1
Consent withdrawn by subject	-	1
Physician decision	-	3
Adverse event, non-fatal	5	3
Lack of efficacy	-	4

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: One patient who completed Study Period II did not enter Study Period III.

Baseline characteristics

Reporting groups	
Reporting group title	Atomoxetine
Reporting group description:	
atomoxetine: 0.5 mg/kg/day daily (QD), by mouth (PO) for 1 week, atomoxetine 0.8mg/kg/day QD, PO for 1 week, 1.2mg/kg/day QD, PO for 6 weeks then atomoxetine 0.5-1.2 mg/kg/day QD, PO for up to 20 weeks.	
Reporting group title	Placebo
Reporting group description:	
placebo: daily (QD), by mouth (PO) for 8 weeks. Then patients can take atomoxetine 0.5-1.2 mg/kg/day QD, PO up to 20 weeks.	

Reporting group values	Atomoxetine	Placebo	Total
Number of subjects	48	49	97
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	9.9	10.0	
standard deviation	± 2.72	± 2.90	-
Gender categorical			
Units: Subjects			
Female	6	8	14
Male	42	41	83
Race/Ethnicity			
Units: Subjects			
Caucasian	48	47	95
African	0	1	1
Hispanic	0	1	1
Region of Enrollment			
Units: Subjects			
Netherlands	48	49	97

End points

End points reporting groups

Reporting group title	Atomoxetine
Reporting group description:	
atomoxetine: 0.5 mg/kg/day daily (QD), by mouth (PO) for 1 week, atomoxetine 0.8mg/kg/day QD, PO for 1 week, 1.2mg/kg/day QD, PO for 6 weeks then atomoxetine 0.5-1.2 mg/kg/day QD, PO for up to 20 weeks.	
Reporting group title	Placebo
Reporting group description:	
placebo: daily (QD), by mouth (PO) for 8 weeks. Then patients can take atomoxetine 0.5-1.2 mg/kg/day QD, PO up to 20 weeks.	
Reporting group title	Atomoxetine
Reporting group description:	
atomoxetine: 0.5 mg/kg/day daily (QD), by mouth (PO) for 1 week, atomoxetine 0.8mg/kg/day QD, PO for 1 week, 1.2mg/kg/day QD, PO for 6 weeks then atomoxetine 0.5-1.2 mg/kg/day QD, PO for up to 20 weeks.	
Reporting group title	Placebo
Reporting group description:	
placebo: daily (QD), by mouth (PO) for 8 weeks. Then patients can take atomoxetine 0.5-1.2 mg/kg/day QD, PO up to 20 weeks.	

Primary: ADHD Rating Scale-IV-Parent Version: Investigator Scored - Total Score

End point title	ADHD Rating Scale-IV-Parent Version: Investigator Scored - Total Score
End point description:	
Measures the 18 symptoms contained in the Diagnostic and Statistical Manual of Mental Disorders, Version IV (DSM-IV) diagnosis of Attention-Deficit/Hyperactivity Disorder. Individual item scores range from 0 (none/never or rarely) to 3 (severe/very often). Total scores range from 0 to 54.	
End point type	Primary
End point timeframe:	
Baseline and 8 weeks	

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48[1]	49[2]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline Total Score	40.7 (± 7.47)	38.6 (± 8.43)		
8 Week Endpoint Total Score	32.3 (± 10.97)	37.3 (± 9.57)		

Notes:

[1] - Baseline Total Score= 48 participants
8 Week Endpoint Total Score= 43 participants
[2] - Baseline Total Score = 49 Participants
8 Week Endpoint Total Score = 47 Participants

Statistical analyses

Statistical analysis title	ADHD Rating Scale-IV-Parent Version
Comparison groups	Placebo v Atomoxetine
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10
upper limit	-3.4
Variability estimate	Standard error of the mean
Dispersion value	1.7

Notes:

[3] - P-value for treatment group differences over time.

Secondary: Clinical Global Impressions-ADHD-Improvement (CGI-ADHD - I)

End point title	Clinical Global Impressions-ADHD-Improvement (CGI-ADHD - I)

End point description:

Measures total improvement (or worsening) of a patient's ADHD symptoms from the beginning of treatment (1=very much improved, 7=very much worsened).

End point type	Secondary

End point timeframe:

8 weeks, 28 weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	46		
Units: units on a scale				
geometric mean (standard deviation)				
8 Week Improvement Score	3.5 (± 1.08)	3.9 (± 0.96)		
28 Week Improvement Score	2.5 (± 1.14)	2.7 (± 1.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Conners' Teacher Rating Scale - Revised: Short Form (CTRS-R:S)

End point title	Conners' Teacher Rating Scale - Revised: Short Form (CTRS-R:S)

End point description:

A 28-item rating scale (0 [not at all/never] to 3 [very much true/very often]) completed by the teacher to assess problem behaviors related to ADHD. Subscale total scores range from 0 to 15 for Oppositional and Cognitive Problems, 0 to 21 for Hyperactivity, and 0 to 36 for ADHD Index.

End point type	Secondary

End point timeframe:

Baseline, 8 weeks, 28 weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	44		
Units: units on a scale				
geometric mean (standard deviation)				
Oppositional: Baseline (n=42, n=44)	4.1 (± 3.54)	3.6 (± 3.53)		
Oppositional: 8 Week (n=36, n=36)	3.8 (± 4.43)	3.4 (± 3.35)		
Oppositional: 28 Week (n=26, n= 25)	2.3 (± 3.33)	1.4 (± 1.98)		
Hyperactivity: Baseline (n=42, n=44)	8.8 (± 5.50)	8.2 (± 5.06)		
Hyperactivity: 8 Week (n=36, n=36)	7.6 (± 5.54)	8.3 (± 5.63)		
Hyperactivity: 28 Week (n=26, n=25)	6.0 (± 4.90)	5.2 (± 4.13)		
Cognitive/Attention: Baseline (n=40, n=44)	6.8 (± 4.45)	4.8 (± 3.68)		
Cognitive/Attention: 8 Week (n=34, n=36)	6.1 (± 4.56)	4.6 (± 3.53)		
Cognitive/Attention: 28 Week (n=26, n=25)	4.7 (± 3.58)	4.6 (± 3.85)		
ADHD: Baseline (n=42, n=44)	18.5 (± 9.27)	18.1 (± 7.49)		
ADHD: 8 Week (n=36, n=36)	15.8 (± 9.85)	17.2 (± 8.69)		
ADHD: 28 Week (n=26, n=25)	13.5 (± 8.61)	12.5 (± 5.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: ADHD Rating Scale-IV-Parent Version: Investigator Scored Total Score

End point title	ADHD Rating Scale-IV-Parent Version: Investigator Scored Total Score

End point description:

Measures the 18 symptoms contained in the DSM-IV diagnosis of Attention-Deficit/Hyperactivity Disorder. Individual item scores range from 0 (none/never or rarely) to 3 (severe/very often). Total scores range from 0 to 54.

End point type	Secondary

End point timeframe:

28 weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35		
Units: Units on a Scale				
geometric mean (standard deviation)	23.6 (± 11.81)	25.9 (± 10.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Sleep Measure Scale

End point title	Sleep Measure Scale

End point description:

10-item parent-based scale assessing sleep problems (6 point Likert scale). Scores: Difficulty falling asleep (1-6); Quality of sleep (3-18); Functional outcome (6-36). Lower scores indicate higher problems with item. Open-ended items: Time to fall asleep (1 [0-15 minutes] to 5 [>1 hour]); Total hours (numbers associated with hours of sleep).

End point type	Secondary

End point timeframe:

Baseline, 8 weeks, 28 weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: Units on a Scale				
geometric mean (standard deviation)				
Time to Fall Asleep: Baseline (n=48, n=49)	2.9 (± 1.49)	2.8 (± 1.41)		
Time to Fall Asleep: 8 Week (n=43, n=46)	2.6 (± 1.43)	3.0 (± 1.34)		
Time to Fall Asleep: 28 Week (n=35, n=35)	3.1 (± 1.49)	2.6 (± 1.14)		
Difficulty Falling Asleep: Baseline (n=48, n=49)	3.4 (± 1.91)	3.3 (± 1.58)		
Difficulty Falling Asleep: 8 Week (n=43, n=46)	3.6 (± 1.80)	3.3 (± 1.64)		
Difficulty Falling Asleep: 28 Week (n=38, n=36)	3.2 (± 1.76)	3.7 (± 1.69)		
Total Hours of Sleep: Baseline (n=48, n=49)	9.1 (± 1.38)	9.3 (± 1.46)		
Total Hours of Sleep: 8 Weeks (n=42, n=46)	8.9 (± 1.49)	9.1 (± 1.51)		
Total Hours of Sleep: 28 Week (n=36, n=34)	8.9 (± 1.61)	9.2 (± 1.12)		
Quality of Sleep: Baseline (n=48, n=49)	14.1 (± 2.85)	14.4 (± 2.84)		

Quality of Sleep: 8 Week (n=43, n=46)	14.2 (± 3.08)	14.9 (± 2.86)		
Quality of Sleep: 28 Week (n=38, n=36)	14.6 (± 2.88)	15.0 (± 2.35)		
Functional Outcome During Day:Baseline (n=48,n=49)	29.6 (± 4.69)	30.0 (± 4.07)		
Functional Outcome During Day:8 Week (n=43,n=46)	29.1 (± 5.09)	30.0 (± 4.80)		
Functional Outcome During Day:28Week (n=38,n=36)	27.8 (± 6.38)	29.6 (± 4.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Aberrant Behavior Checklist (ABC)

End point title	Aberrant Behavior Checklist (ABC)

End point description:

The ABC is a 58-item informant-based scale comprised of five subscales (Irritability [15 items], Lethargy [16], Stereotypic Behaviors [7], Hyperactivity [16], Inappropriate Speech [4]). Individual item scores range from 0 (no problem) to 3 (severe problem). Subscale scores are total of individual item scores in subscale: Irritability (0-45); Lethargy (0-48); Stereotypic (0-21); Hyperactivity (0-48); Inappropriate Speech (0-12).

End point type	Secondary

End point timeframe:

Baseline, 8 weeks, 28 weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: units on a scale				
geometric mean (standard deviation)				
Irritiability: Baseline (n=47, n=49)	2.9 (± 1.49)	2.8 (± 1.41)		
Irritiability: 8 Week (n=43, n=46)	2.6 (± 1.43)	3.0 (± 1.34)		
Irritiability: 28 Week (n=38, n=36)	3.1 (± 1.49)	2.6 (± 1.14)		
Lethargy: Baseline (n=47, n=49)	3.4 (± 1.91)	3.3 (± 1.58)		
Lethargy: 8 Week (n=43, n=46)	3.6 (± 1.80)	3.3 (± 1.64)		
Lethargy: 28 Week (n=38 , n=36)	3.2 (± 1.76)	3.7 (± 1.69)		
Stereotypic: Baseline (n=47, n=49)	9.1 (± 1.38)	9.3 (± 1.46)		
Stereotypic: 8 Week (n=43, n=46)	8.9 (± 1.49)	9.1 (± 1.51)		
Stereotypic: 28 Week (n=38, n=36)	8.9 (± 1.61)	9.2 (± 1.12)		
Hyperactivity: Baseline (n=47, n=49)	14.1 (± 2.85)	14.4 (± 2.84)		
Hyperactivity: 8 Week (n=43, n=45)	14.2 (± 3.08)	14.9 (± 2.86)		
Hyperactivity: 28 Week (n=38, n=36)	14.6 (± 2.88)	15.0 (± 2.35)		
Inappropriate Speech: Baseline (n=47, n=49)	29.6 (± 4.69)	30.0 (± 4.07)		
Inappropriate Speech: 8 Week (n=43, n=46)	29.1 (± 5.09)	30.0 (± 4.80)		

Inappropriate Speech: 28 Week (n=38, n=36)	27.8 (± 6.38)	29.6 (± 4.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Children's Social Behavior Questionnaire (CSBQ) Total Score

End point title	Children's Social Behavior Questionnaire (CSBQ) Total Score

End point description:

CSBQ is filled out by parents and consists of 49 items. Items are rated in an ordinal rather than a discrete fashion in order to establish the extent to which problems are present. The CSBQ consists of six subscales. Individual item scores range from 0=does not apply to 2=applies clearly. Total score ranges from 0 to 98.

End point type	Secondary

End point timeframe:

Baseline, 8 weeks, 28 weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: units on a scale				
geometric mean (standard deviation)				
Baseline (n=48, n=49)	53.6 (± 14.81)	52.4 (± 15.97)		
8 Week (n=43, n=46)	46.1 (± 15.88)	50.2 (± 14.62)		
28 Week (n=38, n=35)	40.4 (± 19.55)	43.6 (± 17.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: General Health Questionnaire (GHQ) Total Score

End point title	General Health Questionnaire (GHQ) Total Score

End point description:

Parental distress is measured with the GHQ. The raw total score (based on 0-0-1-1 scoring system) can be used as an overall index of psychological distress, ranging from 0 to 12 with higher scores indicating more distress.
APD: Randomized participants with value at timepoint.

End point type	Secondary

End point timeframe:

Baseline, 8 weeks, 28 weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=48, n=49)	2.9 (± 3.45)	4.0 (± 3.79)		
8 Week (n=43, n=46)	2.3 (± 3.35)	3.1 (± 3.31)		
28 Week (n=38, n=36)	1.7 (± 2.61)	2.3 (± 2.70)		

Statistical analyses

No statistical analyses for this end point

Secondary: Nijmeegse Ouderlijke Stress Index (NOSI) Total Score

End point title	Nijmeegse Ouderlijke Stress Index (NOSI) Total Score

End point description:

The NOSI contains 123 items to be completed by the primary caregiver. Individual item scores range from 1 (completely agree) to 6 (completely disagree). Total scores range from 123 to 738.

End point type	Secondary

End point timeframe:

Baseline, 8 weeks, 28 weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: units on a scale				
geometric mean (standard deviation)				
Baseline (n=42, n=44)	368.6 (± 79.22)	379.5 (± 78.74)		
8 Week (n=38, n=39)	350.0 (± 75.07)	368.8 (± 81.83)		
28 Week (n=35, n=34)	325.2 (± 85.76)	328.4 (± 89.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amsterdam Neuropsychological Tasks (ANT): Focused Attention Task -

Error Rates

End point title	Amsterdam Neuropsychological Tasks (ANT): Focused Attention Task - Error Rates

End point description:

Focused attention assessed distractibility. Child needs to identify a specific target (eg, Cherry); non-target is any other fruit. Child presses "yes" when target occurs in relevant position (eg, one of vertical positions on diamond). Child presses "no" when target is absent, or when target appears on horizontal position (irrelevant target). Error rates are percentage of missing relevant targets and percentage of false alarms in response to (irr)relevant (non)targets based on number of errors/total number of trials X 100.
APD: Number of participants with baseline and a non-missing postbaseline value at visit.

End point type	Secondary

End point timeframe:

Baseline, 8 Weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: error rate (percentage)				
arithmetic mean (standard deviation)				
Irrelevant Targets Baseline (n=35, n=44)	12.3 (± 13.95)	11.8 (± 16.06)		
Irrelevant Targets 8 Week (n=35, n=44)	10.0 (± 16.09)	13.3 (± 14.36)		
Relevant Nontargets Baseline (n=35, n=44)	5.7 (± 8.15)	2.9 (± 5.97)		
Relevant Nontargets 8 Week (n=35, n=44)	5.1 (± 9.48)	3.3 (± 7.04)		
Relevant Targets Baseline (n=35, n=44)	4.8 (± 5.49)	6.9 (± 9.04)		
Relevant Targets 8 Week (n=35, n=44)	7.3 (± 9.42)	7.2 (± 14.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amsterdam Neuropsychological Tasks (ANT): Focused Attention Task - Reaction Times for Hits and Correct Rejections

End point title	Amsterdam Neuropsychological Tasks (ANT): Focused Attention Task - Reaction Times for Hits and Correct Rejections

End point description:

Task is the same as described in Outcome Measure #10. Reaction times (RT) for hits are mean RTs of correct responses to relevant targets. RTs for correct rejections are mean RTs for correct rejections are mean RTs for correct no responses to irrelevant targets and relevant nontargets.
APD: Number of participants with baseline and a non-missing postbaseline value at visit.

End point type	Secondary

End point timeframe:

Baseline, 8 Weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: milliseconds				
arithmetic mean (standard deviation)				
Irrelevant Target Baseline (n=34, n=42)	1260.1 (± 413.09)	1217.3 (± 533.92)		
Irrelevant Target 8 Week (n=32, n=43)	1167.8 (± 493.57)	1206.0 (± 547.64)		
Relevant Nontarget Baseline (n=34, n=43)	1208.4 (± 509.62)	1220.9 (± 550.25)		
Relevant Nontarget 8 Week (n=33, n=43)	1165.4 (± 570.35)	1168.9 (± 569.16)		
Mean Reaction Time Hits Baseline (n=34, n=42)	1045.6 (± 411.14)	1084.4 (± 518.50)		
Mean Reaction Time Hits 8 Week (n=33, n=43)	1013.0 (± 505.52)	1017.7 (± 475.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amsterdam Neuropsychological Tasks (ANT): Focused Attention Task - Standard Deviation of Reaction Times for Hits and Correct Rejections

End point title	Amsterdam Neuropsychological Tasks (ANT): Focused Attention Task - Standard Deviation of Reaction Times for Hits and Correct Rejections

End point description:

Task is the same as described in Outcome Measure #10. Standard deviations of reaction times (RT) assess intraindividual variability in RT and refer to the same conditions as those for mean reaction times described in Outcome Measure #11.

End point type	Secondary

End point timeframe:

Baseline, 8 Weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: milliseconds				
arithmetic mean (standard deviation)				
Irrelevant Target Baseline (n=33, n=39)	421.0 (± 263.84)	429.4 (± 382.61)		
Irrelevant Target 8 Week (n=29, n=41)	341.0 (± 259.84)	431.7 (± 363.62)		

Relevant Nontarget Baseline (n=33, n=40)	442.2 (± 374.99)	565.6 (± 455.54)		
Relevant Nontarget 8 Week (n=30, n=41)	442.6 (± 413.74)	455.6 (± 376.87)		
Standard Deviation Hits Baseline (n=33, n=39)	434.3 (± 302.61)	497.9 (± 365.48)		
Standard Deviation Hits 8 Week (n=30, n=41)	381.5 (± 286.96)	393.9 (± 299.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amsterdam Neuropsychological Tasks (ANT): Memory Search Task - Error Rates

End point title	Amsterdam Neuropsychological Tasks (ANT): Memory Search Task - Error Rates

End point description:

The memory search task aims at measuring serial search processes to be carried out in working memory. There are 2 blocks (loads) with 40 trials each. Load 1 has 1 target to identify (e.g., an animal). A "yes" is required whenever the target is part of the displayed set of four stimuli (all animals). Load 2 has 2 targets. Whenever 1 of the targets appears in the successively displayed sets of four animals, a "yes" is required. Targets are present in 50% of trials. Error rates are the percentages of errors made in each task condition, based on the number of errors/total number of trials X 100.
APD: Number of participants with baseline and a non-missing postbaseline value at visit.

End point type	Secondary

End point timeframe:

Baseline, 8 Weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: error rate (percentage)				
arithmetic mean (standard deviation)				
Absent Targets Load 2 Baseline (n=33, n=35)	2.0 (± 3.52)	4.4 (± 9.61)		
Absent Targets Load 2 8 Week (n=34, n=35)	4.0 (± 6.83)	4.3 (± 6.20)		
Absent Targets Load 1 Baseline (n=34, n=35)	5.9 (± 14.06)	5.1 (± 5.49)		
Absent Targets Load 1 8 Week (n=34, n=35)	5.3 (± 6.96)	7.6 (± 13.25)		
Present Targets Load 1 Baseline (n=34, n=35)	6.5 (± 9.66)	6.6 (± 6.84)		
Present Targets Load 1 8 Week (34, n=35)	7.6 (± 9.07)	7.9 (± 10.93)		
Present Targets Load 2 Baseline (n=33, n=35)	9.5 (± 9.38)	9.7 (± 10.07)		
Present Targets Load 2 8 Week (n=34, n=35)	8.7 (± 10.10)	10.1 (± 9.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amsterdam Neuropsychological Tasks (ANT): Memory Search Task - Reaction Times for Hits and Correct Rejections

End point title	Amsterdam Neuropsychological Tasks (ANT): Memory Search Task - Reaction Times for Hits and Correct Rejections

End point description:

Memory search task aims at measuring serial search processes to be carried out in working memory. There are 2 blocks (loads) with 40 trials each. Load 1 has 1 target to remember (one animal). A "yes" is required whenever the target is part of displayed set of 4 animals. Load 2 has 2 animals. A "yes" is required whenever one of the animals appears in successively displayed sets of 4 animals. Targets are present in 50% of the trials. Reaction time (RT) for hits is mean RT of correct "yes" responses to targets. RT correct rejections are mean RTs of correct "no" responses when target was missing.
APD: Number of participants with baseline and a non-missing postbaseline value at visit.

End point type	Secondary

End point timeframe:

Baseline, 8 Weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: milliseconds				
arithmetic mean (standard deviation)				
Load 1 Baseline (n=33, n=35)	1051.9 (± 338.41)	1010.4 (± 382.92)		
Load 1 8 Week (n=34, n=34)	1014.8 (± 394.58)	928.7 (± 301.04)		
Load 2 Baseline (n=32, n=34)	1411.0 (± 357.50)	1387.2 (± 595.37)		
Load 2 8 Week (n=34, n=34)	1130.4 (± 460.66)	1294.2 (± 552.25)		
Reaction Time Hits Load 1 Baseline (n=33, n=35)	932.7 (± 295.14)	881.7 (± 304.42)		
Reaction Time Hits Load 1 8 Week (n=34, n=34)	882.4 (± 327.30)	786.8 (± 257.19)		
Reaction Time Hits Load 2 Baseline (n=32, n=34)	1131.5 (± 293.84)	1111.8 (± 442.97)		
Reaction Time Hits Load 2 8 Week (n=34, n=34)	1060.0 (± 343.53)	1110.8 (± 445.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amsterdam Neuropsychological Tasks (ANT): Pursuit Motor Control Task - Accuracy

End point title	Amsterdam Neuropsychological Tasks (ANT): Pursuit Motor Control Task - Accuracy

End point description:

A complex visuo-motor flexibility task that aims at measuring eye-hand co-ordination and fine motor control. By moving mouse cursor, the child is required to follow as closely as possible a target that randomly moves across the PC-screen. Accuracy is the mean distance between the mouse cursor and the moving target.
APD: Number of participants with baseline and non-missing postbaseline value at visit.

End point type	Secondary

End point timeframe:

Baseline, 8 weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: millimeters				
arithmetic mean (standard deviation)				
Baseline (n=30,n=33)	7.8 (± 5.62)	8.1 (± 5.49)		
8 Week (n=31,n=33)	8.2 (± 6.88)	10.1 (± 11.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amsterdam Neuropsychological Tasks (ANT): Pursuit Motor Control Task - Stability of Movement

End point title	Amsterdam Neuropsychological Tasks (ANT): Pursuit Motor Control Task - Stability of Movement

End point description:

A complex visuo-motor flexibility task that measures eye-hand co-ordination and fine motor control. By moving mouse cursor, the child is required to follow as closely as possible a target that randomly moves across the PC-screen. Stability is within subject variability of mean distance between cursor and target.
APD: Number of participants with baseline and non-missing postbaseline value at visit.

End point type	Secondary

End point timeframe:

Baseline, 8 weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	33		
Units: millimeters				
arithmetic mean (standard deviation)				
Baseline (n=30,n=33)	7.6 (± 8.24)	8.2 (± 7.90)		
8 Week (n=31,n=33)	8.2 (± 8.61)	9.4 (± 9.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amsterdam Neuropsychological Tasks (ANT): Go/No-Go Response Inhibition Task - Error Rates

End point title	Amsterdam Neuropsychological Tasks (ANT): Go/No-Go Response Inhibition Task - Error Rates

End point description:

Measures inhibition of pre-potent responses. 24 Go signals (open squares) are presented, randomly mixed with 24 No-Go signals (closed squares). Subjects are required to press a key if a Go signal (target) appears on the screen but to withhold a response if they see a No-Go signal. Error rate is the percentage of key presses to No-Go signals/total number of trials X 100.
APD: Number of participants with baseline and a non-missing postbaseline value at visit.

End point type	Secondary

End point timeframe:

Baseline, 8 weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	45		
Units: error rate (percentage)				
arithmetic mean (standard deviation)				
Absent Target Baseline	8.0 (± 16.30)	6.8 (± 8.49)		
Absent Target 8 Week	4.5 (± 4.75)	9.0 (± 15.07)		
Present Target Baseline	2.0 (± 5.25)	2.9 (± 6.14)		
Present Target 8 Week	3.7 (± 10.01)	1.9 (± 5.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amsterdam Neuropsychological Tasks (ANT): Flanker Interference Task - Error Rates

End point title	Amsterdam Neuropsychological Tasks (ANT): Flanker Interference Task - Error Rates

End point description:

Measures ability to neglect stimuli interfering with predefined stimulus-response coupling. Child presented with displays of 9 colored squares. Child responds to color of central square by pressing left mouse key when blue, and right mouse key when yellow. Part 1 (40 trials), surrounding squares may be same color (compatible) or different (neutral). Part 2 (80 trials), in 50% of trials, surrounding squares have color corresponding to predefined key press for other hand (incompatible). Error rates are percentages of errors in response to compatible and incompatible signals, respectively.
APD: Number of participants with baseline and one non-missing postbaseline value at visit.

End point type	Secondary

End point timeframe:

Baseline, 8 weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	35		
Units: error rate (percentages)				
arithmetic mean (standard deviation)				
Compatible Signals Baseline (n=32, n=35)	7.7 (± 9.80)	8.5 (± 10.06)		
Compatible Signals 8 Week (n=33, n=35)	-2.1 (± 8.92)	-1.8 (± 11.43)		
Incompatible Signals Baseline (n=32, n=35)	8.4 (± 10.33)	9.1 (± 6.62)		
Incompatible Signals 8 Week (n=32, n=35)	-0.4 (± 11.11)	0.1 (± 8.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amsterdam Neuropsychological Tasks (ANT): Flanker Interference Task - Reaction Times

End point title	Amsterdam Neuropsychological Tasks (ANT): Flanker Interference Task - Reaction Times

End point description:

Task is the same as described in Outcome Measure #19. Mean reaction times (RTs) are computed for correct responses to compatible and incompatible flankers, respectively.
APD: Number of participants with baseline and non-missing postbaseline value at visit.

End point type	Secondary

End point timeframe:

Baseline, 8 weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	35		
Units: milliseconds				
arithmetic mean (standard deviation)				
Compatible Flankers Part 2 Baseline (n=31,n=34)	863.1 (± 234.70)	925.4 (± 384.55)		
Compatible Flankers Part 2 8 Week (n=33,n=35)	901.1 (± 350.27)	897.7 (± 376.63)		
Incompatible Flankers Part 2 Baseline (n=31,n=35)	959.4 (± 295.32)	976.5 (± 412.76)		
Incompatible Flankers Part 2 8 Week (n=33,n=35)	931.9 (± 347.99)	946.2 (± 419.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cytochrome P450 2D6 Genotype

End point title	Cytochrome P450 2D6 Genotype

End point description:

Genotype characterization was used to determine participants' metabolic status.
APD: All randomized participants.

End point type	Secondary

End point timeframe:

baseline

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: participants				
number (not applicable)				
Extensive Metabolizer	28	28		
Intermediate Metabolizer	13	15		
Poor Metabolizer	6	6		
Missing	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Core Study	
Adverse event reporting additional description:	
B4Z-UT-S017(b)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Atomoxetine
Reporting group description: -	

Serious adverse events	Placebo	Atomoxetine	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Atomoxetine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 49 (65.31%)	39 / 48 (81.25%)	
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	1 / 49 (2.04%)	3 / 48 (6.25%)	
occurrences (all)	1	3	
headache			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	9 / 49 (18.37%)	12 / 48 (25.00%)	
occurrences (all)	13	17	
psychomotor hyperactivity			

alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	4 / 49 (8.16%)	1 / 48 (2.08%)	
occurrences (all)	4	1	
General disorders and administration site conditions			
fatigue			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	4 / 49 (8.16%)	11 / 48 (22.92%)	
occurrences (all)	4	12	
pyrexia			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	3 / 49 (6.12%)	0 / 48 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	3 / 49 (6.12%)	4 / 48 (8.33%)	
occurrences (all)	4	5	
abdominal pain upper			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	3 / 49 (6.12%)	9 / 48 (18.75%)	
occurrences (all)	3	9	
diarrhoea			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	3 / 49 (6.12%)	1 / 48 (2.08%)	
occurrences (all)	3	1	
nausea			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	4 / 49 (8.16%)	14 / 48 (29.17%)	
occurrences (all)	5	15	
vomiting			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	5 / 49 (10.20%)	7 / 48 (14.58%)	
occurrences (all)	6	10	
Psychiatric disorders			

aggression			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	3 / 49 (6.12%)	2 / 48 (4.17%)	
occurrences (all)	3	2	
early morning awakening			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	0 / 49 (0.00%)	5 / 48 (10.42%)	
occurrences (all)	0	5	
initial insomnia			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	5 / 49 (10.20%)	3 / 48 (6.25%)	
occurrences (all)	5	3	
Musculoskeletal and connective tissue disorders			
myalgia			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	0 / 49 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	3	
Infections and infestations			
influenza			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	0 / 49 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	3 / 49 (6.12%)	13 / 48 (27.08%)	
occurrences (all)	3	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported