Clinical trial results:
A Randomized, Double Blind Comparison of the Effects of Atomoxetine versus Placebo on Neuropsychological Outcomes across the Day in Children with Attention-Deficit/Hyperactivity Disorder (ADHD) by Use of a Computer Based Continuous Performance Test (cb CPT).

Summary

EudraCT number	2006-001470-25
Trial protocol	DE
Global end of trial date	26 May 2009

Results information

Result version number	v1 (current)
This version publication date	15 November 2020
First version publication date	15 November 2020

Trial information

Trial identification

Sponsor protocol code	11148

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00546910
WHO universal trial number (UTN)	-

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, 1 877 CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877 2854559,

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	26 May 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 May 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a two-arm, parallel, randomized, double-blind, placebo-controlled Phase 4 multicenter trial to compare the whole day efficacy of atomoxetine versus placebo in children aged 6 through 12 years with Attention-Deficit/Hyperactivity Disorder (ADHD) treated in an inpatient, day-patient and outpatient setting in Germany. Core symptoms will be measured during once or bi-weekly visits, three times per visit-day, by a computer based Continuous Performance Test. Following an initial 3-28-day screening and washout phase, patients will be assigned to double-blind treatment with atomoxetine or placebo. In the verum arm, a one-week atomoxetine treatment period with the 0.5 mg/kg per day lead-in dose will be succeeded by a 7 week period at the target dose of 1.2 mg/kg per day.

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 2007
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	Germany: 125
Worldwide total number of subjects	125
EEA total number of subjects	125

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)	117
Adolescents (12-17 years)	8

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:

NA

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Atomoxetine

Arm description:

0.5 milligram per kilogram (mg/kg) per day lead-in dose for 1 week followed by 7 weeks at 1.2 mg/kg per day dose.

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

Dosage and administration details:

0.5 milligram per kilogram (mg/kg) per day lead-in dose for 1 week followed by 7 weeks at 1.2 mg/kg per day dose.

Arm title	Placebo

Arm description:

Placebo matched to 1 week lead-in and 7 week standard target dose of atomoxetine.

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

Dosage and administration details:

Placebo matched to 1 week lead-in and 7 week standard target dose of atomoxetine.

Number of subjects in period 1	Atomoxetine	Placebo
Started	63	62
Completed	54	51
Not completed	9	11
Consent withdrawn by subject	2	-
Physician decision	-	1
Adverse event, non-fatal	2	3
Lack of efficacy	5	7

Baseline characteristics

Reporting groups	
Reporting group title	Atomoxetine
Reporting group description:	
0.5 milligram per kilogram (mg/kg) per day lead-in dose for 1 week followed by 7 weeks at 1.2 mg/kg per day dose.	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to 1 week lead-in and 7 week standard target dose of atomoxetine.	

Reporting group values	Atomoxetine	Placebo	Total
Number of subjects	63	62	125
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	9.1	8.9	
standard deviation	± 1.93	± 1.64	-
Gender categorical			
Units: Subjects			
Female	16	12	28
Male	47	50	97
Race/Ethnicity			
Units: Subjects			
Caucasian	62	62	124
African	1	0	1
Diagnosis			
Breakdown of Attention Deficit/Hyperactivity Disorder (ADHD) diagnosis according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).			
Units: Subjects			
ADHD-Combined Type	40	48	88
ADHD-Predominantly Inattentive Type	17	11	28
ADHD- Predominantly Hyperactive-Impulsive	6	3	9
Number of Participants with Family History of ADHD			
Number of participants with at least one biological relative (mother, father, sibling [brother, sister] or grandparent) with ADHD.			

Units: Subjects			
At least one known relative with ADHD	36	35	71
None or missing	27	27	54
Number of Participants with Prior Therapy For Attention-Deficit/Hyperactive Disorder (ADHD)			
Summarizes number of participants who received previous medication and non-medication attention-deficit/hyperactive disorder (ADHD) therapy.			
Units: Subjects			
Previous treatment for ADHD	26	27	53
None or missing	37	35	72
Number of Participants with Psychiatric Comorbidities			
Summarizes the psychologic comorbidities of participants. Because some participants may have one or more comorbidities while others may not, the breakdown of psychiatric comorbidities by treatment group does not equal the overall baseline number of participants in each treatment group.			
Units: Subjects			
At least one psychiatric comorbidity	25	25	50
None or missing	38	37	75
Summary Of Participants' Living Arrangements			
Summarizes the participants' living arrangements according to where they live most of the time.			
Units: Subjects			
Nuclear Family (Biological Mother and Father)	38	36	74
Single Mother	15	17	32
Step Parent (One Biologic and one step parent)	10	9	19
Region of Enrollment			
Units: Subjects			
Germany	63	62	125
ADHD Rating Scale-IV Parent Version: Investigator Administered & Scored, Total Score			
ADHD Rating Scale-IV Parent Version: Investigator Administered & Scored (ADHD-RS-IV-PV:IR) measures the 18 symptoms contained in the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision (DSM-IV-TR) 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.			
Units: units on a scale			
arithmetic mean	37.30	36.68	
standard deviation	± 10.62	± 12.53	-
Clinical Global Impressions - Severity Of Attention Deficit Hyperactive Disorder Score			
Clinical Global Impressions- Severity Of Attention Deficit Hyperactive Disorder (CGI-S-ADHD) measures severity of the patient's overall severity of ADHD symptoms (1=normal, not at all ill; 7=among the most extremely ill patients).			
Units: units on a scale			
arithmetic mean	5.11	5.05	
standard deviation	± 1.02	± 1.11	-
Time Since Initial Diagnosis Of ADHD			
Units: Years			
arithmetic mean	1.8	1.6	
standard deviation	± 2.23	± 1.89	-
Time Since Onset Of ADHD Symptoms			

Units: Years			
arithmetic mean	4.9	5.2	
standard deviation	± 2.12	± 1.95	-
Weekly Rating Of Evening & Morning Behavior-Revised-Investigator Rated (Total)			
Weekly Rating Of Evening & Morning Behavior-Revised-Investigator Rated (WREMB-R-Inv) measures the level of difficulty of 11 common morning or evening behaviors (e.g. getting out of bed, doing homework, sitting through dinner). Possible scores for each item range from 0 (no difficulty) to 3 (a lot of difficulty) with a Total score (maximum score=33), Morning subscore (maximum score=9), Evening subscore (maximum score=24), and Item 11 score which pertains to degree of difficulty falling asleep (maximum score=3).			
Units: Units on a scale			
arithmetic mean	21.70	21.58	
standard deviation	± 7.64	± 7.91	-

End points

End points reporting groups

Reporting group title	Atomoxetine
Reporting group description:	
0.5 milligram per kilogram (mg/kg) per day lead-in dose for 1 week followed by 7 weeks at 1.2 mg/kg per day dose.	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to 1 week lead-in and 7 week standard target dose of atomoxetine.	

Primary: Change From Baseline Computer-based Continuous Performance Test (cb-CPT; Qbtech AB, Sweden), Variable: Hyperactivity (Includes Time Active [TA], Distance [DIS], Area [AR], Microevents [ME], Motion Simplicity [MS]) Q-scores At Week 8

End point title	Change From Baseline Computer-based Continuous Performance Test (cb- CPT; Qbtech AB, Sweden), Variable: Hyperactivity (Includes Time Active [TA], Distance [DIS], Area [AR], Microevents [ME], Motion Simplicity [MS]) Q-scores At Week 8

End point description:

Infra-red camera tracks movement of head reflector on patient performing computer test. Hyperactivity test variables: TA=percent time patient moved>1 centimeter (cm)/second; DIS=path of movement (m); AR=total area (cm2) of movements; ME=number of position changes>1 mm; MS=degree (percent) of directional changes. Results are converted to Q-scores (age and sex-adjusted normalized scores with a mean=0 and standard deviation (SD)=1 in general population, expressing the probability determined by the Gamma function in terms of SD of Gaussian density). Higher scores reflect more severe symptoms.

Analysis population description (APD): Full analysis population (N=125) including all randomized participants taking at least one dose of study medication.

End point type	Primary

End point timeframe:

Baseline, 8 weeks (W8)

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	62		
Units: Q-scores				
arithmetic mean (standard deviation)				
Baseline: TA-Morning	0.62 (± 1.27)	0.84 (± 0.84)		
Baseline: TA- Noon	0.65 (± 1.13)	0.76 (± 0.79)		
Baseline: TA- Evening	0.66 (± 1.26)	0.85 (± 0.83)		
W8 Change: TA- Morning	-0.32 (± 1.00)	0.06 (± 0.84)		
W8 Change: TA- Noon	-0.60 (± 1.13)	0.15 (± 0.74)		
W8 Change: TA- Evening	-0.55 (± 1.08)	0.03 (± 0.76)		
Baseline: DIS- Morning	1.41 (± 1.69)	1.62 (± 1.68)		
Baseline: DIS- Noon	1.55 (± 1.86)	1.62 (± 1.74)		
Baseline: DIS- Evening	1.47 (± 1.86)	1.75 (± 1.73)		
W8 Change: DIS- Morning	-0.51 (± 1.80)	0.38 (± 1.75)		

W8 Change: DIS- Noon	-1.06 (± 1.94)	0.49 (± 1.52)		
W8 Change: DIS- Evening	-0.87 (± 1.71)	0.07 (± 1.54)		
Baseline: AR- Morning	1.14 (± 1.65)	1.40 (± 1.56)		
Baseline: AR- Noon	1.25 (± 1.66)	1.45 (± 1.59)		
Baseline: AR- Evening	1.19 (± 1.81)	1.58 (± 1.67)		
W8 Change: AR- Morning	-0.38 (± 1.58)	0.39 (± 1.60)		
W8 Change: AR- Noon	-0.87 (± 1.70)	0.40 (± 1.18)		
W8 Change: AR- Evening	-0.71 (± 1.53)	-0.00 (± 1.45)		
Baseline: ME- Morning	0.97 (± 1.32)	1.15 (± 1.11)		
Baseline: ME- Noon	0.98 (± 1.29)	1.09 (± 1.19)		
Baseline: ME- Evening	0.94 (± 1.45)	1.18 (± 1.18)		
W8 Change: ME- Morning	-0.47 (± 1.42)	0.20 (± 1.19)		
W8 Change: ME- Noon	-0.82 (± 1.48)	0.28 (± 1.01)		
W8 Change: ME- Evening	-0.72 (± 1.41)	0.06 (± 1.06)		
Baseline: MS- Morning	0.21 (± 1.08)	0.38 (± 1.01)		
Baseline: MS- Noon	0.25 (± 1.12)	0.32 (± 0.95)		
Baseline: MS- Evening	0.22 (± 1.21)	0.35 (± 1.05)		
W8 Change: MS- Morning	-0.22 (± 1.29)	-0.04 (± 1.07)		
W8 Change: MS- Noon	-0.39 (± 1.37)	-0.12 (± 0.94)		
W8 Change: MS- Evening	-0.38 (± 1.31)	-0.19 (± 1.09)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.001 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.87

Notes:

[1] - Superiority or Other (legacy)

[2] - P-value is for Time Active overall for morning, noon and evening. Primary tests were performed hierarchically to adjust for multiplicity. Time Active was tested at rank 8. Positive values for the mean difference are in favor of the atomoxetine arm.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Atomoxetine v Placebo

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.001 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.57

Notes:

[3] - Superiority or legacy

[4] - P-value is for Distance overall for morning, noon and evening. Primary tests were performed hierarchically to adjust for multiplicity. Distance was tested at rank 5.
Positive values for the mean difference are in favor of the atomoxetine arm.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.001 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.35

Notes:

[5] - Superiority or legacy

[6] - P-value is for Area overall for morning, noon and evening. Primary tests were performed hierarchically to adjust for multiplicity. Area was tested at rank 6.
Positive values for the mean difference are in favor of the atomoxetine arm.

Statistical analysis title	Statistical Analysis 4
Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	< 0.001 [8]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.22

Notes:

[7] - Superiority or legacy

[8] - P-value is for Microevents overall for morning, noon and evening. Primary tests were performed hierarchically to adjust for multiplicity. Microevents was tested at rank 3.
Positive values for the mean difference are in favor of the atomoxetine arm.

Statistical analysis title	Statistical Analysis 5
Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	< 0.001 [10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.58

Notes:

[9] - Superiority or legacy

[10] - P-value is for Motion Simplicity overall for morning, noon and evening. Primary tests were performed hierarchically to adjust for multiplicity.Motion Simplicity was tested at rank 9.
+ve values for the mean difference are in favor of the atomoxetine

Primary: Change From Baseline cb CPT Variable: Inattention (Includes Reaction Time Variation[RTV], Omission Error [OR], Mean Reaction Time [mRT], Normalized Variation Of Reaction Time [nVRT]) Q-scores At Week 8

End point title	Change From Baseline cb CPT Variable: Inattention (Includes Reaction Time Variation[RTV], Omission Error [OR], Mean Reaction Time [mRT], Normalized Variation Of Reaction Time [nVRT]) Q-scores At Week 8

End point description:

Computer test. Patient is to press button if target appears, but not at non-target. Inattention test variables: mRT=average time (ms) from target presentation to response; RTV=standard deviation of mRT; nVRT=RTV expressed in terms of RT (variation as a percent of mean value); OE= percent of omitted targets. Results are converted to Q-scores (age and sex-adjusted normalized scores with a mean=0 and SD=1 in the general population, expressing the probability determined by the Gamma function in terms of SD of Gaussian density). Higher scores reflect more severe symptoms.

APD: Full analysis population (N=125) including all randomized participants taking at least one dose of study medication.

End point type	Primary

End point timeframe:

Baseline, 8 weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	62		
Units: Q-scores				
arithmetic mean (standard deviation)				
Baseline: RTV-Morning	2.93 (± 2.41)	2.49 (± 1.62)		
Baseline: RTV-Noon	2.95 (± 2.11)	2.48 (± 1.92)		

Baseline: RTV-Evening	2.63 (± 2.49)	2.19 (± 2.00)		
W8: RTV-Morning	-0.89 (± 2.29)	-0.09 (± 1.78)		
W8: RTV-Noon	-1.07 (± 1.92)	0.00 (± 1.70)		
W8: RTV-Evening	-0.90 (± 1.98)	-0.00 (± 1.88)		
Baseline: OR- Morning	1.12 (± 1.24)	1.13 (± 1.19)		
Baseline: OR- Noon	1.31 (± 1.32)	1.30 (± 1.32)		
Baseline: OR- Evening	1.22 (± 1.43)	1.28 (± 1.34)		
W8: OR- Morning	0.01 (± 1.83)	0.54 (± 1.14)		
W8: OR- Noon	0.03 (± 1.45)	0.53 (± 1.17)		
W8: OR- Evening	-0.04 (± 1.50)	0.52 (± 1.20)		
Baseline: mRT- Morning	2.42 (± 2.03)	1.92 (± 1.53)		
Baseline: mRT- Noon	2.40 (± 1.78)	2.02 (± 1.49)		
Baseline: mRT- Evening	2.23 (± 1.77)	1.86 (± 1.49)		
W8: mRT- Morning	-0.18 (± 1.84)	0.35 (± 1.28)		
W8: mRT- Noon	-0.35 (± 1.53)	0.12 (± 1.42)		
W8: mRT- Evening	-0.13 (± 1.40)	0.48 (± 1.37)		
Baseline: nVRT-Morning	1.00 (± 1.60)	0.93 (± 1.28)		
Baseline: nVRT-Noon	1.06 (± 1.48)	0.82 (± 1.26)		
Baseline: nVRT-Evening	0.92 (± 1.81)	0.68 (± 1.31)		
W8: nVRT-Morning	-0.59 (± 1.58)	-0.36 (± 1.15)		
W8: nVRT-Noon	-0.65 (± 1.48)	-0.09 (± 0.97)		
W8: nVRT-Evening	-0.65 (± 1.75)	-0.33 (± 1.19)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	< 0.001 [12]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.35

Notes:

[11] - Superiority or legacy

[12] - P-value is for Reaction Time Variation overall for morning, noon & evening.Primary tests were performed hierarchically to adjust for multiplicity.Reaction time variation was tested at rank 1
+ve values for mean difference are in favor of atomoxetine

Statistical analysis title	Statistical Analysis 2
Comparison groups	Atomoxetine v Placebo

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	< 0.001 [14]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.93

Notes:

[13] - Superiority or legacy

[14] - P-value is for Omission Error overall for morning, noon and evening. Primary tests were performed hierarchically to adjust for multiplicity. Omission error was tested at rank 7.
Positive values for the mean difference are in favor of the atomoxetine

Statistical analysis title	Statistical Analysis 3
Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	< 0.001 [16]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.65

Notes:

[15] - Superiority or legacy

[16] - P-value is for Mean Reaction Time overall for morning, noon and evening. Primary tests were performed hierarchically to adjust for multiplicity. Mean reaction time was tested at rank 2.
+ve values for mean difference are in favor of the atomoxetine

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Superiority or legacy	
Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	< 0.001 [18]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	0.73

Notes:

[17] - Superiority or legacy

[18] - P-value is for Normalized Variation of Reaction Time overall for morning, noon & evening. Primary tests were performed hierarchically to adjust for multiplicity. Normalized Variation of Reaction Time was tested at rank 10.

Primary: Change From Baseline cb CPT Variable: Impulsivity (Includes Commission Error [CE], Anticipatory Response [AR]) Q-scores At Week 8

End point title	Change From Baseline cb CPT Variable: Impulsivity (Includes Commission Error [CE], Anticipatory Response [AR]) Q-scores At Week 8

End point description:

Computer test. Patient is to press button if target appears, but not at non-target. Impulsivity variables during test: CE=percent of response to non-target; ANT=percent of responses prior to target presentation. Results are converted to Q-scores (age and sex-adjusted normalized scores with a mean=0 and standard deviation=1 in the general population, expressing the probability determined by the Gamma function in terms of standard deviation of Gaussian density). Higher scores reflect more severe symptoms.

End point type	Primary

End point timeframe:

Baseline, 8 weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	62		
Units: Q-scores				
arithmetic mean (standard deviation)				
Baseline: CE- Morning	-0.68 (± 1.34)	-0.89 (± 1.03)		
Baseline: CE- Noon	-0.65 (± 1.29)	-0.85 (± 0.94)		
Baseline: CE- Evening	-0.80 (± 1.23)	-0.87 (± 1.06)		
W8: CE- Morning	-0.88 (± 1.33)	-0.32 (± 0.90)		
W8: CE- Noon	-0.94 (± 1.33)	-0.44 (± 0.82)		
W8: CE- Evening	-0.76 (± 1.31)	-0.49 (± 0.92)		
Baseline: AR- Morning	0.41 (± 1.15)	0.15 (± 0.88)		
Baseline: AR- Noon	0.28 (± 1.06)	0.12 (± 0.85)		
Baseline: AR- Evening	0.32 (± 1.16)	0.08 (± 0.85)		
W8: AR- Morning	-0.50 (± 0.98)	-0.34 (± 0.84)		
W8: AR-Noon	-0.54 (± 0.87)	-0.31 (± 0.84)		
W8: AR- Evening	-0.52 (± 0.83)	-0.28 (± 0.78)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	< 0.001 [20]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.68

Notes:

[19] - Superiority or legacy

[20] - P-value is for Commission Error overall for morning, noon and evening. Primary tests were performed hierarchically to adjust for multiplicity. Commission Error was tested at rank 4.
Positive values for mean difference are in favor of the atomoxetine

Statistical analysis title	Statistical Analysis 2
Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.022 [22]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.31

Notes:

[21] - Superiority or legacy

[22] - P-value is for Anticipatory Response overall for morning, noon and evening. Anticipatory Response was not tested in the primary analysis but is a secondary endpoint.
Positive values for the mean difference are in favor of the atomoxetine arm.

Primary: Change From Baseline cb CPT Variable: Other (Includes Error Rate [ER] and Multi Response [MR]) Q-scores At Week 8

End point title	Change From Baseline cb CPT Variable: Other (Includes Error Rate [ER] and Multi Response [MR]) Q-scores At Week 8

End point description:

Computer test. Patient is to press button if target appears, but not at non-target. Other variables during test: ER=percent of overall incorrect responses (CE and OE); MR=percent of multiple responses per presentation of target (patient responds more than once to target). Results are converted to Q-scores (age and sex-adjusted normalized scores with a mean=0 and standard deviation=1 in the general population, expressing the probability determined by the Gamma function in terms of standard deviation of Gaussian density). Higher scores reflect more severe symptoms.

APD: Full analysis population (N=125) including all randomized participants taking at least one dose of study medication.

End point type	Primary

End point timeframe:

Baseline, 8 weeks

End point values	Atomoxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	62		
Units: Q-scores				
arithmetic mean (standard deviation)				
Baseline: ER- Morning	0.37 (± 1.56)	0.30 (± 1.15)		
Baseline: ER- Noon	0.52 (± 1.46)	0.41 (± 1.24)		
Baseline: ER- Evening	0.37 (± 1.58)	0.41 (± 1.24)		
W8: ER- Morning	-0.41 (± 2.06)	0.35 (± 1.10)		
W8: ER- Noon	-0.44 (± 1.70)	0.32 (± 1.06)		
W8: ER- Evening	-0.43 (± 1.80)	0.28 (± 1.10)		
Baseline: MR- Morning	-0.04 (± 1.25)	-0.26 (± 0.84)		
Baseline: MR- Noon	0.01 (± 1.15)	-0.30 (± 0.95)		
Baseline: MR- Evening	0.03 (± 1.25)	-0.34 (± 0.89)		
W8: MR- Morning	-0.23 (± 1.15)	-0.24 (± 0.78)		
W8: MR- Noon	-0.45 (± 0.97)	-0.16 (± 0.83)		
W8: MR- Evening	-0.35 (± 1.30)	-0.16 (± 0.77)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	< 0.001 [24]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.18

Notes:

[23] - Superiority or legacy

[24] - P-value is for Error Rate overall for morning, noon and evening. Error Rate was not tested in the primary analysis but is a secondary endpoint.
Positive values for the mean difference are in favor of the atomoxetine arm.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Superiority or legacy

Comparison groups	Atomoxetine v Placebo

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0.178 [26]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.28

Notes:

[25] - Superiority or legacy

[26] - P-value is for Multi Response overall for morning, noon and evening. Multi Response was not tested in the primary analysis but is a secondary endpoint.
Positive values for the mean difference are in favor of the atomoxetine arm.

Secondary: Change From Baseline Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered And Scored (ADHDRS-IV-Parent:Inv) Total Score At Week 8

End point title	Change From Baseline Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered And Scored (ADHDRS-IV-Parent:Inv) Total Score At Week 8

End point description:

Measures the 18 symptoms contained in the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision (DSM-IV-TR) 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.

APD: Full analysis population (N=125) including all randomized participants taking at least one dose of study medication.

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	63	62		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline to Visit 7 (Week 8)	-17.19 (± 15.63)	-4.76 (± 11.51)		
Baseline to LOCF	-15.78 (± 15.19)	-4.21 (± 10.89)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:	
Comparison of atomoxetine vs. placebo at Visit 7 (Week 8).	
Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	< 0.001 [28]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	11.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.2
upper limit	14.99

Notes:

[27] - Superiority or legacy

[28] - P-value for ADHD-RS Total Score.
Positive values for the mean difference are in favor of the atomoxetine arm.

Secondary: Change From Baseline Clinical Global Impressions-Severity of ADHD (CGI-S-ADHD) Score at Week 8

End point title	Change From Baseline Clinical Global Impressions-Severity of ADHD (CGI-S-ADHD) Score at Week 8

End point description:

CGI-S-ADHD measures severity of the patient's overall severity of ADHD symptoms (1=normal, not at all ill; 7=among the most extremely ill patients).

APD: Full analysis population (N=125) including all randomized participants taking at least one dose of study medication.

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	63	62		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline to Visit 7 (Week 8)	-1.78 (± 1.61)	-0.63 (± 1.11)		
Baseline to LOCF	-1.52 (± 1.63)	-0.40 (± 1.17)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Comparison of atomoxetine vs. placebo at Visit 7 (Week 8).

Comparison groups	Atomoxetine v Placebo

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	< 0.001 [30]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.46

Notes:

[29] - Superiority or legacy

[30] - P-value for CGI-S ADHD score.
Positive values for the mean difference are in favor of the atomoxetine arm.

Secondary: Change From Baseline Weekly Rating Of Evening and Morning Behavior-Revised-Investigator Rated, Total and Subscores at Week 8

End point title	Change From Baseline Weekly Rating Of Evening and Morning Behavior-Revised-Investigator Rated, Total and Subscores at Week 8

End point description:

Weekly Rating Of Evening & Morning Behavior-Revised-Investigator Rated (WREMB-R-Inv) measures the level of difficulty of 11 common morning or evening behaviors (e.g. getting out of bed, doing homework, sitting through dinner). Possible scores for each item range from 0 (no difficulty) to 3 (a lot of difficulty) with a Total score (maximum score=33), Morning subscore (maximum score=9), Evening subscore (maximum score=24), and Item 11 score which pertains to degree of difficulty falling asleep (maximum score=3).

APD: Full analysis population (N=125) including all randomized participants taking at least one dose of study medication.

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	63	62		
Units: units on a scale				
arithmetic mean (standard deviation)				
Total Score: Baseline to Visit 7 (Week 8)	-10.72 (± 10.21)	-5.10 (± 6.83)		
Total Score: Baseline to LOCF	-9.59 (± 9.98)	-3.90 (± 7.83)		
Evening Subscore: Baseline to Visit 7 (Week 8)	-6.91 (± 6.38)	-3.57 (± 4.36)		
Evening Subscore: Baseline to LOCF	-6.30 (± 6.21)	-3.03 (± 5.18)		
Morning Subscore: Baseline to Visit 7 (Week 8)	-2.81 (± 3.04)	-1.16 (± 2.74)		
Morning Subscore: Baseline to LOCF	-2.46 (± 3.00)	-0.65 (± 2.94)		
Item 11 Subscore: Baseline to Visit 7 (Week 8)	-1.00 (± 1.60)	-0.37 (± 1.00)		
Item 11 Subscore: Baseline to LOCF	-0.83 (± 1.60)	-0.23 (± 1.05)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	< 0.001 [32]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	5.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.55
upper limit	7.92

Notes:

[31] - Superiority or legacy

[32] - P-value for Total Score.
Positive values for the mean difference are in favor of the atomoxetine arm.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Atomoxetine
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	= 0.001 [34]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.49
upper limit	5.44

Notes:

[33] - Superiority or legacy

[34] - P-value for Evening subscore.
Positive values for the mean difference are in favor of the atomoxetine arm.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Atomoxetine v Placebo

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	< 0.002 [36]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.93

Notes:

[35] - Superiority or legacy

[36] - P-value for Morning subscore.
Positive values for the mean difference are in favor of the atomoxetine arm.

Statistical analysis title	Statistical Analysis 4
Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	< 0.001 [38]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.93

Notes:

[37] - Superiority or legacy

[38] - P-value for Item 11 (difficulty falling asleep).
Positive values for the mean difference are in favor of the atomoxetine arm.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Entire Study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.0

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

Serious adverse events	Atomoxetine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (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: 4 %

Non-serious adverse events	Atomoxetine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 63 (50.79%)	27 / 62 (43.55%)	
Nervous system disorders			
Headache			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	3 / 63 (4.76%)	5 / 62 (8.06%)	
occurrences (all)	3	5	
General disorders and administration site conditions			
Fatigue			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	4 / 63 (6.35%)	1 / 62 (1.61%)	
occurrences (all)	4	2	
Pyrexia			

alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	3 / 63 (4.76%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Abdominal pain			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	7 / 63 (11.11%)	2 / 62 (3.23%)	
occurrences (all)	8	2	
Abdominal pain upper			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	2 / 63 (3.17%)	3 / 62 (4.84%)	
occurrences (all)	2	3	
Nausea			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	6 / 63 (9.52%)	2 / 62 (3.23%)	
occurrences (all)	7	2	
Vomiting			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	3 / 63 (4.76%)	2 / 62 (3.23%)	
occurrences (all)	3	2	
Respiratory, thoracic and mediastinal disorders			
Pharyngolaryngeal pain			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	4 / 63 (6.35%)	0 / 62 (0.00%)	
occurrences (all)	4	0	
Psychiatric disorders			
Aggression			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	0 / 63 (0.00%)	4 / 62 (6.45%)	
occurrences (all)	0	5	
Infections and infestations			
Influenza			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	0 / 63 (0.00%)	3 / 62 (4.84%)	
occurrences (all)	0	4	

Nasopharyngitis			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	3 / 63 (4.76%)	2 / 62 (3.23%)	
occurrences (all)	3	2	
Respiratory tract infection			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	1 / 63 (1.59%)	3 / 62 (4.84%)	
occurrences (all)	1	3	
Upper respiratory tract infection			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	4 / 63 (6.35%)	0 / 62 (0.00%)	
occurrences (all)	4	0	
Metabolism and nutrition disorders			
Anorexia			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	3 / 63 (4.76%)	0 / 62 (0.00%)	
occurrences (all)	3	0	

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