



Clinical trial results:

A Randomized, Double-Blind, Crossover Comparison of Atomoxetine and Placebo in Child Outpatients With Attention-Deficit/Hyperactivity Disorder, Reading Disorder, or Comorbid Attention-Deficit/Hyperactivity Disorder and Reading Disorder.

Summary

EudraCT number	2006-001866-18
Trial protocol	Outside EU/EEA
Global end of trial date	01 December 2007

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-MC-LYCK
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00191906
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 7955

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 April 2005
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 December 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test the hypothesis that a 4 week treatment with atomoxetine is more effective than placebo in patients with combined type Attention Deficit/Hyperactivity Disorder (ADHD), patients with only Reading Disorder, and patients with combined type ADHD and Reading 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 April 2005
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	Belgium: 49
Country: Number of subjects enrolled	Netherlands: 72
Worldwide total number of subjects	121
EEA total number of subjects	121

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)	121
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:

Period I: screening/washout (89 patients screened, 13 screen-failures;45 controls screened). Period II (Visits 2-5): patients received treatment for 4 weeks and then underwent 2-week washout period after which they crossed over to receive the alternate treatment for 4 additional weeks. Period III (Visits 6-12): optional open-label (1 country only).

Period 1

Period 1 title	Study Period II
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 First, Then Placebo

Arm description:

Atomoxetine 1.2 mg/kg/day, by mouth for 4 weeks, 2 week washout period and then cross-over to placebo, every day, by mouth for 4 weeks.

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

Dosage and administration details:

Atomoxetine, 1.2 mg/kg/day, by mouth (PO).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo, every day (QD), by mouth (PO).

Arm title	Placebo First, Then Atomoxetine
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Arm description:

Placebo every day, by mouth for 4 weeks, 2 week washout period and then cross-over to atomoxetine 1.2 mg/kg/day, by mouth for 4 weeks.

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

Dosage and administration details:

Placebo, every day (QD), by mouth (PO).

Investigational medicinal product name	Atomoxetine Hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Atomoxetine, 1.2 mg/kg/day, by mouth (PO).	
Arm title	Normal Control

Arm description:

Untreated normal controls were children selected from the general population. The normal control was matched (have same proportion) by sex (male/female) and by age (have same age range) as the study population.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Reading Disordered Control

Arm description:

Untreated reading disordered control group was comprised of children with reading disorder who received standard remedial teaching therapy.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Atomoxetine First, Then Placebo	Placebo First, Then Atomoxetine	Normal Control
Started	39	37	27
Completed	39	32	26
Not completed	0	5	1
Parent/Caregiver Decision	-	1	-
Consent withdrawn by subject	-	3	-
Adverse event, non-fatal	-	1	-
Entry Criteria Exclusion	-	-	1

Number of subjects in period 1	Reading Disordered Control
Started	18
Completed	18
Not completed	0
Parent/Caregiver Decision	-
Consent withdrawn by subject	-
Adverse event, non-fatal	-
Entry Criteria Exclusion	-

Period 2

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Atomoxetine First, Then Placebo
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Arm description:

Atomoxetine 1.2 mg/kg/day, by mouth for 4 weeks, 2 week washout period and then cross-over to placebo, every day, by mouth for 4 weeks.

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

Dosage and administration details:

Placebo, every day (QD), by mouth (PO).

Investigational medicinal product name	Atomoxetine Hydrochloride
Investigational medicinal product code	LY139603
Other name	Strattera
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Atomoxetine, 1.2 mg/kg/day, by mouth (PO).

Arm title	Placebo First, Then Atomoxetine
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Arm description:

Placebo every day, by mouth for 4 weeks, 2 week washout period and then cross-over to atomoxetine 1.2 mg/kg/day, by mouth for 4 weeks.

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

Dosage and administration details:

Atomoxetine, 1.2 mg/kg/day, by mouth (PO).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo, every day (QD), by mouth (PO).

Number of subjects in period 2^[1]	Atomoxetine First, Then Placebo	Placebo First, Then Atomoxetine
Started	14	11
Completed	9	7
Not completed	5	4
Parent/Caregiver Decision	1	-
Adverse event, non-fatal	1	-
Lost to follow-up	-	1
Lack of efficacy	3	3

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: These are patients who continued in optional open-label period (1 country). All received atomoxetine.

Baseline characteristics

Reporting groups

Reporting group title	Atomoxetine First, Then Placebo
Reporting group description: Atomoxetine 1.2 mg/kg/day, by mouth for 4 weeks, 2 week washout period and then cross-over to placebo, every day, by mouth for 4 weeks.	
Reporting group title	Placebo First, Then Atomoxetine
Reporting group description: Placebo every day, by mouth for 4 weeks, 2 week washout period and then cross-over to atomoxetine 1.2 mg/kg/day, by mouth for 4 weeks.	
Reporting group title	Normal Control
Reporting group description: Untreated normal controls were children selected from the general population. The normal control was matched (have same proportion) by sex (male/female) and by age (have same age range) as the study population.	
Reporting group title	Reading Disordered Control
Reporting group description: Untreated reading disordered control group was comprised of children with reading disorder who received standard remedial teaching therapy.	

Reporting group values	Atomoxetine First, Then Placebo	Placebo First, Then Atomoxetine	Normal Control
Number of subjects	39	37	27
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	10.0 ± 1.34	9.9 ± 1.25	9.9 ± 1.01
Gender categorical Units: Subjects			
Female	13	10	10
Male	26	27	17
Region of Enrollment Units: Subjects			
Belgium	18	15	0
Netherlands	21	22	27

Reporting group values	Reading Disordered Control	Total	
Number of subjects	18	121	
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	10.6 ± 0.99	-	
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Gender categorical Units: Subjects			
Female	5	38	
Male	13	83	
Region of Enrollment Units: Subjects			
Belgium	16	49	
Netherlands	2	72	

End points

End points reporting groups

Reporting group title	Atomoxetine First, Then Placebo
Reporting group description: Atomoxetine 1.2 mg/kg/day, by mouth for 4 weeks, 2 week washout period and then cross-over to placebo, every day, by mouth for 4 weeks.	
Reporting group title	Placebo First, Then Atomoxetine
Reporting group description: Placebo every day, by mouth for 4 weeks, 2 week washout period and then cross-over to atomoxetine 1.2 mg/kg/day, by mouth for 4 weeks.	
Reporting group title	Normal Control
Reporting group description: Untreated normal controls were children selected from the general population. The normal control was matched (have same proportion) by sex (male/female) and by age (have same age range) as the study population.	
Reporting group title	Reading Disordered Control
Reporting group description: Untreated reading disordered control group was comprised of children with reading disorder who received standard remedial teaching therapy.	
Reporting group title	Atomoxetine First, Then Placebo
Reporting group description: Atomoxetine 1.2 mg/kg/day, by mouth for 4 weeks, 2 week washout period and then cross-over to placebo, every day, by mouth for 4 weeks.	
Reporting group title	Placebo First, Then Atomoxetine
Reporting group description: Placebo every day, by mouth for 4 weeks, 2 week washout period and then cross-over to atomoxetine 1.2 mg/kg/day, by mouth for 4 weeks.	
Subject analysis set title	Atomoxetine
Subject analysis set type	Safety analysis
Subject analysis set description: Atomoxetine, 1.2 mg/kg/day, by mouth for 4 weeks.	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description: Placebo, daily, by mouth for 4 weeks.	
Subject analysis set title	ADHD-Combined Type (ADHD-C)
Subject analysis set type	Safety analysis
Subject analysis set description: atomoxetine-treated Attention-Deficit/Hyperactivity Disorder-Combined Type	
Subject analysis set title	Reading Disorder
Subject analysis set type	Safety analysis
Subject analysis set description: atomoxetine-treated Reading Disorder.	
Subject analysis set title	Reading Disordered Control
Subject analysis set type	Safety analysis
Subject analysis set description: Untreated reading disordered control group was comprised of children with reading disorder who received standard remedial teaching therapy.	
Subject analysis set title	ADHD-C+RD
Subject analysis set type	Safety analysis
Subject analysis set description: atomoxetine-treated Comorbid Attention-Deficit/Hyperactivity Disorder-Combined Type + Reading	

Primary: Stop Signal Reaction Time (SSRT) as Derived From the Stop Signal Reaction Time Paradigm

End point title	Stop Signal Reaction Time (SSRT) as Derived From the Stop Signal Reaction Time Paradigm
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End point description:

SSRT measures response execution (go trials) and response inhibition (stop trials). Go trials consist of stimulus (airplane). Child to press response button corresponding to direction airplane is pointing. Stop trials consist of go trial and audible stop signal. Initial delay between go trial and stop signal = 250 msec. If child succeeded in inhibiting response, delay on next stop trial increased by 50 msec, otherwise, delay decreased by 50 msec. SSRT = subtract mean delay from mean go signal reaction time. Lower scores mean better ability to suppress response when presented with stop signal. Analysis population description (APD): All efficacy information is summarized and/or presented in data listings based on the Safety sample: Includes all patients who were randomized to double-blind treatment and received at least one dose of study drug.

End point type	Primary
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End point timeframe:

Baseline and Week 4 of initial therapy and Week 4 of crossover therapy

End point values	Atomoxetine	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71	76		
Units: milliseconds (msec)				
least squares mean (standard error)				
ADHD-Combined Type	299.90 (± 13.29)	308.82 (± 14.53)		
Reading Disorder	265.61 (± 14.24)	260.51 (± 16.02)		
ADHD-C + Reading Disorder	277.38 (± 13.80)	292.53 (± 15.46)		
Overall	280.97 (± 7.96)	287.29 (± 8.84)		

Statistical analyses

Statistical analysis title	SSRT
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Statistical analysis description:

Least Squares Mean (LSMean) values were calculated from the measurements taken at baseline and at the end of each 4 week therapy period. Repeated measures model including terms for baseline, study arm, treatment sequence, visit, treatment, and treatment-by-study-arm interaction.

Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.504 ^[1]
Method	Repeated Measures

Notes:

[1] - P-value for Overall. No adjustments for multiple comparisons - not applicable. All statistical tests were performed using a 0.05 significance level.

Secondary: Change From Baseline in Mean Stop Signal Reaction Time Comparison of ADHD-C to Normal Control Group in ≥ 10 Year Old Subset

End point title	Change From Baseline in Mean Stop Signal Reaction Time Comparison of ADHD-C to Normal Control Group in ≥ 10 Year Old Subset ^[2]
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End point description:

SSRT measures response execution (go trials) and response inhibition (stop trials). Go trials consist of stimulus (airplane). Child to press response button corresponding to direction airplane is pointing. Stop trials consist of go trial and audible stop signal. Initial delay between go trial and stop signal = 250 msec. If child succeeded in inhibiting response, delay on next stop trial increased by 50 msec, otherwise, delay decreased by 50 msec. SSRT = subtract mean delay from mean go signal reaction time. Lower scores mean better ability to suppress response when presented with stop signal. APD: All efficacy information is summarized and/or presented in data listings based on the Safety sample: Includes all patients who were randomized to double-blind treatment and received at least one dose of study drug.

End point type	Secondary
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End point timeframe:

Baseline and 4 weeks of therapy

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No inferential statistics were planned or conducted for all baseline period arms.

End point values	Normal Control	ADHD-Combined Type (ADHD-C)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8	5		
Units: milliseconds				
arithmetic mean (standard deviation)	11.22 ($\pm$ 62.77)	7.95 ($\pm$ 48.21)		

Statistical analyses

Statistical analysis title	Mean Stop Signal Reaction Time
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Statistical analysis description:

ANCOVA model with baseline value, study arm as covariates for ADHD-C versus Normal controls.

Comparison groups	Normal Control v ADHD-Combined Type (ADHD-C)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97 ^[3]
Method	ANCOVA

Notes:

[3] - There were no adjustments for multiple comparisons - not applicable. All statistical tests were performed using a 0.05 significance level.

Secondary: Change From Baseline in Mean Stop Signal Reaction Time Comparison of ADHD-C+RD and RD to Reading Disordered Control Group in ≥ 10 Year Old Subset

End point title	Change From Baseline in Mean Stop Signal Reaction Time Comparison of ADHD-C+RD and RD to Reading Disordered
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End point description:

SSRT measures response execution (go trials) and response inhibition (stop trials). Go trials consist of stimulus (airplane). Child to press response button corresponding to direction airplane is pointing. Stop trials consist of go trial and audible stop signal. Initial delay between go trial and stop signal = 250 msec. If child succeeded in inhibiting response, delay on next stop trial increased by 50 msec, otherwise, delay decreased by 50 msec. SSRT = subtract mean delay from mean go signal reaction time. Lower scores mean better ability to suppress response when presented with stop signal. APD: All efficacy information is summarized and/or presented in data listings based on the Safety sample: Includes all patients who were randomized to double-blind treatment and received at least one dose of study drug.

End point type	Secondary
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End point timeframe:

Baseline and 4 weeks of therapy

End point values	Reading Disorder	Reading Disordered Control	ADHD-C+RD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	14	16	
Units: milliseconds				
arithmetic mean (standard deviation)	-34.0 ($\pm$ 33.91)	0.05 ($\pm$ 24.08)	-0.25 ($\pm$ 53.41)	

Statistical analyses

Statistical analysis title	Mean Stop Signal Reaction Time Comparison 1
Comparison groups	ADHD-C+RD v Reading Disordered Control
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	= 0.579 ^[5]
Method	ANCOVA

Notes:

[4] - ANCOVA model with baseline value, study arm as covariates for ADHD-C+RD versus RD controls.

[5] - There were no adjustments for multiple comparisons - not applicable. All statistical tests were performed using a 0.05 significance level.

Statistical analysis title	Mean Stop Signal Reaction Time Comparison 2
Comparison groups	Reading Disordered Control v Reading Disorder
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.144 ^[7]
Method	ANCOVA

Notes:

[6] - ANCOVA model with baseline value, study arm as covariates for RD versus RD controls.

[7] - There were no adjustments for multiple comparisons - not applicable. All statistical tests are performed using a 0.05 significance level.

Secondary: Lexical Decision Task Mean Reaction Time: Correct Words

End point title	Lexical Decision Task Mean Reaction Time: Correct Words
End point description:	
Measure of reaction time to identify whether a word displayed on a computer is a real or correct word versus a pseudo word. During the performance of the lexical decision task that was presented on a computer, the reaction times and accuracy of responses were measured. Data presented are the mean reaction times over the 4 weeks of each therapy for identifying correct words correctly. APD: All efficacy information is summarized and/or presented in data listings based on the Safety sample: Includes all patients who were randomized to double-blind treatment and received at least one dose of study drug.	
End point type	Secondary
End point timeframe:	
Baseline and Week 4 of initial therapy and Week 4 of crossover therapy	

End point values	Atomoxetine	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	73		
Units: milliseconds				
least squares mean (standard error)				
ADHD-Combined Type	1182.9 (± 50.23)	1291.9 (± 38.13)		
Reading Disorder	1172.4 (± 51.75)	1198.6 (± 40.24)		
ADHD-C + Reading Disorder	1201.9 (± 51.22)	1305.9 (± 39.43)		
Overall	1185.7 (± 29.49)	1265.5 (± 22.61)		

Statistical analyses

Statistical analysis title	Lexical Decision Task Mean Reaction Time
Statistical analysis description:	
Repeated measures model including terms for baseline, study arm, treatment sequence, visit, treatment, and treatment by study-arm-interaction.	
Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.005 ^[9]
Method	Repeated Measures

Notes:

[8] - Least Squares Mean (LSMean) values were calculated from the measurements taken at baseline and at the end of each 4 week therapy period.

[9] - P-value for Overall. There were no adjustments for multiple comparisons - not applicable. All statistical tests were performed using a 0.05 significance level.

Secondary: Lexical Decision Task Mean Reaction Time: Pseudo Words

End point title	Lexical Decision Task Mean Reaction Time: Pseudo Words
End point description:	
Measure of reaction time to identify whether a word displayed on a computer is a pseudo word versus a real or correct word. During the performance of the lexical decision task that was presented on a computer, the reaction times and accuracy of responses were measured. Data presented are the mean reaction times over the 4 weeks of each therapy for identifying pseudo words correctly. APD: All efficacy	

information is summarized and/or presented in data listings based on the Safety sample: Includes all patients who were randomized to double-blind treatment and received at least one dose of study drug.

End point type	Secondary
End point timeframe:	
Baseline and Week 4 of initial therapy and Week 4 of crossover therapy	

End point values	Atomoxetine	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	73		
Units: milliseconds				
least squares mean (standard error)				
ADHD-Combined Type	1403.0 (± 63.72)	1475.4 (± 50.08)		
Reading Disorder	1365.0 (± 65.62)	1412.2 (± 52.90)		
ADHD-C + Reading Disorder	1426.1 (± 64.83)	1487.0 (± 51.73)		
Overall	1398.0 (± 37.33)	1458.2 (± 29.63)		

Statistical analyses

Statistical analysis title	Lexical Decision Task Mean Reaction Time
Statistical analysis description:	
Least Squares Mean (LSMean) values were calculated from the measurements taken at baseline and at the end of each 4 week therapy period. Repeated measures model including terms for baseline, study arm, treatment sequence, visit, treatment, and treatment-by-study-arm interaction.	
Comparison groups	Placebo v Atomoxetine
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.097 ^[10]
Method	Repeated Measures

Notes:

[10] - P-value for Overall. There were no adjustments for multiple comparisons - not applicable. All statistical tests were performed using a 0.05 significance level.

Secondary: Working Memory by Corsi Block Tapping Test (CBTT)

End point title	Working Memory by Corsi Block Tapping Test (CBTT)
End point description:	
Measures the visuo-spatial working memory span, and corresponds to the longest sequence of blocks that has been reproduced correctly at least once. Scores can range from 3 to 8, with the higher score indicating better function. APD: All efficacy information is summarized and/or presented in data listings based on the Safety sample: Includes all patients who were randomized to double-blind treatment and received at least one dose of study drug.	
End point type	Secondary
End point timeframe:	
Baseline and Week 4 of initial therapy and Week 4 of crossover therapy	

End point values	Atomoxetine	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	69	73		
Units: blocks correctly sequenced				
least squares mean (standard error)				
ADHD-Combined Type	5.29 (± 0.22)	4.98 (± 0.21)		
Reading Disorder	5.50 (± 0.23)	5.14 (± 0.23)		
ADHD-C + Reading Disorder	5.92 (± 0.23)	5.29 (± 0.23)		
Overall	5.57 (± 0.13)	5.14 (± 0.13)		

Statistical analyses

Statistical analysis title	CBTT
Statistical analysis description:	
Repeated measures model including terms for study arm, treatment sequence, treatment, and treatment-by-study-arm interaction.	
Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	other ^[11]
P-value	= 0.003 ^[12]
Method	Repeated Measures

Notes:

[11] - Least Squares Mean (LSMean) values were calculated from the measurements taken at baseline and at the end of each 4 week therapy period.

[12] - P-value for Overall. There were no adjustments for multiple comparisons - not applicable. All statistical tests were performed using a 0.05 significance level.

Secondary: Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored - Total Score

End point title	Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored - Total Score
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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 score is the sum of the scores on the 18 items and range from 0 to 54. APD: All efficacy information is summarized and/or presented in data listings based on the Safety sample: Includes all patients who were randomized to double-blind treatment and received at least one dose of study drug.

End point type	Secondary
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End point timeframe:

Baseline and Week 4 of initial therapy and Week 4 of crossover therapy

End point values	Atomoxetine	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	47		
Units: units on a scale				
least squares mean (standard error)				
ADHD-Combined Type	30.86 (± 2.14)	35.20 (± 1.78)		
ADHD-Combined Type + Reading Disorder	22.44 (± 2.38)	35.17 (± 2.07)		
Overall	26.65 (± 1.60)	35.18 (± 1.34)		

Statistical analyses

Statistical analysis title	Attention-Deficit/Hyperactivity Disorder
Comparison groups	Placebo v Atomoxetine
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	< 0.001 ^[14]
Method	Repeated Measures

Notes:

[13] - Least Squares Mean (LSMean) values were calculated from the measurements taken at baseline and at the end of each 4 week therapy period. Repeated measures model including terms for baseline, study arm, treatment sequence, visit, treatment, and treatment-by-study-arm interaction.

[14] - P-value for Overall. There were no adjustments for multiple comparisons - not applicable. All statistical tests were performed using a 0.05 significance level.

Secondary: Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored - Inattention Subscale

End point title	Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored - Inattention Subscale
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End point description:

Measures the degree of inattention symptoms based on answers to 9 items. Individual item scores range from 0 (none/never or rarely) to 3 (severe/very often), for a total Inattention Subscale score range of 0 to 27. APD: All efficacy information is summarized and/or presented in data listings based on the Safety sample: Includes all patients who were randomized to double-blind treatment and received at least one dose of study drug.

End point type	Secondary
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End point timeframe:

Baseline and Week 4 of initial therapy and Week 4 of crossover therapy

End point values	Atomoxetine	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	47		
Units: units on a scale				
least squares mean (standard error)				
ADHD-Combined Type	15.27 (± 1.09)	17.82 (± 0.93)		
ADHD-Combined Type + Reading Disorder	12.25 (± 1.22)	18.28 (± 1.09)		
Overall	13.76 (± 0.82)	18.05 (± 0.70)		

Statistical analyses

Statistical analysis title	Attention-Deficit/Hyperactivity Disorder
Statistical analysis description:	
Least Squares Mean (LSMean) values were calculated from the measurements taken at baseline and at the end of each 4 week therapy period. Repeated measures model including terms for baseline, study arm, treatment sequence, visit, treatment, and treatment-by-study-arm interaction.	
Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[15]
Method	Repeated Measures

Notes:

[15] - P-value for Overall. There were no adjustments for multiple comparisons - not applicable. All statistical tests were performed using a 0.05 significance level.

Secondary: Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored - Hyperactivity-Impulsivity Subscale

End point title	Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored - Hyperactivity-Impulsivity Subscale
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End point description:

Measures the degree of hyperactivity-impulsivity symptoms, based on answers to 9 items. Individual item scores range from 0 (none/never or rarely) to 3 (severe/very often) for a total Hyperactivity-Impulsivity Subscale score of 0 to 27. APD: All efficacy information is summarized and/or presented in data listings based on the Safety sample: Includes all patients who were randomized to double-blind treatment and received at least one dose of study drug.

End point type	Secondary
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End point timeframe:

Baseline and Week 4 of initial therapy and Week 4 of crossover therapy

End point values	Atomoxetine	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	47		
Units: units on a scale				
least squares mean (standard error)				
ADHD-Combined Type	15.51 (± 1.14)	17.24 (± 0.96)		
ADHD-Combined Type + Reading Disorder	10.32 (± 1.27)	17.03 (± 1.12)		
Overall	12.91 (± 0.85)	17.13 (± 0.73)		

Statistical analyses

Statistical analysis title	Attention-Deficit/Hyperactivity Disorder
Statistical analysis description: Least Squares Mean (LSMean) values were calculated from the measurements taken at baseline and at the end of each 4 week therapy period. Repeated measures model including terms for baseline, study arm, treatment sequence, visit, treatment, and treatment-by-study-arm interaction.	
Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[16]
Method	Repeated Measures

Notes:

[16] - P-value for Overall. There were no adjustments for multiple comparisons - not applicable. All statistical tests were performed using a 0.05 significance level.

Secondary: Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored - Total T-Score

End point title	Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored - Total T-Score
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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 score is computed as the sum of the scores on each of the 18 items. Total score is the sum of the scores on the 18 items and range from 0 to 54. Total T-score = (Total Score - 50)/10. Total T-score ranges from -5 (low severity) to 0.4 (high severity). APD: All efficacy information is summarized and/or presented in data listings based on the Safety sample: Includes all patients who were randomized to double-blind treatment and received at least one dose of study drug.

End point type	Secondary
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End point timeframe:

Baseline and Week 4 of initial therapy and Week 4 of crossover therapy

End point values	Atomoxetine	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	47		
Units: T-Score of units on a scale				
least squares mean (standard error)				
ADHD-Combined Type	-1.91 (± 0.21)	-1.48 (± 0.18)		
ADHD-Combined Type + Reading Disorder	-2.76 (± 0.24)	-1.48 (± 0.21)		
Overall	-2.34 (± 0.16)	-1.48 (± 0.13)		

Statistical analyses

Statistical analysis title	Attention-Deficit/Hyperactivity Disorder
Statistical analysis description: Least Squares Mean (LSMean) values were calculated from the measurements taken at baseline and at the end of each 4 week therapy period. Repeated measures model including terms for baseline, study arm, treatment sequence, visit, treatment, and treatment-by-study-arm interaction	
Comparison groups	Atomoxetine v Placebo

Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[17]
Method	Repeated Measures

Notes:

[17] - P-value for Overall. There were no adjustments for multiple comparisons - not applicable. All statistical tests were performed using a 0.05 significance level.

Secondary: Clinical Global Impression-Attention Deficit Hyperactivity Disorder-Improvement Scale

End point title	Clinical Global Impression-Attention Deficit Hyperactivity Disorder-Improvement Scale
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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). APD: All efficacy information is summarized and/or presented in data listings based on the Safety sample: Includes all patients who were randomized to double-blind treatment and received at least one dose of study drug.

End point type	Secondary
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End point timeframe:

4 week therapy endpoint

End point values	Atomoxetine	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	52		
Units: units on a scale				
least squares mean (standard error)				
ADHD-Combined Type	3.69 (± 0.24)	3.70 (± 0.23)		
ADHD-Combined Type + Reading Disorder	2.98 (± 0.24)	3.76 (± 0.24)		
Overall	3.34 (± 0.17)	3.73 (± 0.16)		

Statistical analyses

Statistical analysis title	Clinical Global Impression-Attention
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Statistical analysis description:

Repeated measures model including terms for study arm, treatment sequence, visit, treatment, and treatment-by-study-arm interaction.

Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094 ^[18]
Method	Repeated Measures

Notes:

[18] - P-value for Overall. There were no adjustments for multiple comparisons - not applicable. All statistical tests were performed using a 0.05 significance level.

Secondary: Clinical Global Impression-Attention Deficit Hyperactivity Disorder-

Severity Scale

End point title	Clinical Global Impression-Attention Deficit Hyperactivity Disorder-Severity Scale
End point description: 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: All efficacy information is summarized and/or presented in data listings based on the Safety sample: Includes all patients who were randomized to double-blind treatment and received at least one dose of study drug.	
End point type	Secondary
End point timeframe: 4 week therapy endpoint	

End point values	Atomoxetine	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	52		
Units: units on a scale				
least squares mean (standard error)				
ADHD-Combined Type	4.05 (± 0.21)	3.73 (± 0.19)		
ADHD-Combined Type + Reading Disorder	3.65 (± 0.21)	4.34 (± 0.20)		
Overall	3.85 (± 0.14)	4.04 (± 0.13)		

Statistical analyses

Statistical analysis title	Clinical Global Impression-Attention Deficit
Statistical analysis description: Repeated measures model including terms for baseline, study arm, treatment sequence, visit, treatment, and treatment-by-study-arm interaction.	
Comparison groups	Atomoxetine v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.312 ^[19]
Method	Repeated Measures

Notes:

[19] - P-value for Overall. There were no adjustments for multiple comparisons - not applicable. All statistical tests were performed using a 0.05 significance level.

Secondary: Change From Baseline in Phonological Task Mean Reaction Time Comparison of ADHD-C to Normal Control Group in >=10 Year Old Subset: Pseudohomophones

End point title	Change From Baseline in Phonological Task Mean Reaction Time Comparison of ADHD-C to Normal Control Group in >=10 Year Old Subset: Pseudohomophones ^[20]
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End point description:

Measure of reaction time in determining whether the stimulus sounds like a real word ('yes' response) or not ('no' response) using pseudohomophones and pseudo words. Data presented here are for reaction time to identifying pseudohomophones correctly. APD: All efficacy information is summarized and/or presented in data listings based on the Safety sample: Includes all patients who were randomized to double-blind treatment and received at least one dose of study drug.

End point type	Secondary
End point timeframe:	
Baseline and 4 weeks of therapy	
Notes:	
[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.	
Justification: No inferential statistics were planned or conducted for all baseline period arms.	

End point values	Normal Control	ADHD-Combined Type (ADHD-C)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	6	5		
Units: milliseconds				
arithmetic mean (standard deviation)	-339.17 (± 176.32)	-230.40 (± 239.43)		

Statistical analyses

Statistical analysis title	Phonological Task Mean Reaction Time
Statistical analysis description:	
ANCOVA model with baseline value, study arm as covariates for ADHD-C versus normal controls.	
Comparison groups	Normal Control v ADHD-Combined Type (ADHD-C)
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.508 ^[21]
Method	ANCOVA

Notes:

[21] - There were no adjustments for multiple comparisons - not applicable. All statistical tests were performed using a 0.05 significance level.

Secondary: Change From Baseline in Phonological Task Mean Reaction Time Comparison of ADHD-C to Normal Control Group in ≥10 Year Old Subset: Pseudo Words

End point title	Change From Baseline in Phonological Task Mean Reaction Time Comparison of ADHD-C to Normal Control Group in ≥10 Year Old Subset: Pseudo Words ^[22]
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End point description:

Measure of reaction time in determining whether the stimulus sounds like a real word ('yes' response) or not ('no' response) using pseudo homophones and pseudo words. Data presented here are for reaction time to identifying pseudo words correctly. APD: All efficacy information is summarized and/or presented in data listings based on the Safety sample: Includes all patients who were randomized to double-blind treatment and received at least one dose of study drug.

End point type	Secondary
End point timeframe:	
Baseline and 4 weeks of therapy	
Notes:	
[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.	
Justification: No inferential statistics were planned or conducted for all baseline period arms.	

End point values	Normal Control	ADHD-Combined Type (ADHD-C)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	6	5		
Units: milliseconds				
arithmetic mean (standard deviation)	-536.00 (± 303.27)	-523.20 (± 524.36)		

Statistical analyses

Statistical analysis title	Phonological Task Mean Reaction Time
Statistical analysis description: ANCOVA model with baseline value, study arm as covariate for ADHD-C versus normal controls.	
Comparison groups	Normal Control v ADHD-Combined Type (ADHD-C)
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.769 ^[23]
Method	ANCOVA

Notes:

[23] - There were no adjustments for multiple comparisons - not applicable. All statistical tests were performed using a 0.05 significance level.

Secondary: Change From Baseline in Phonological Task Mean Reaction Time Comparison of ADHD-C+RD and RD to Reading Disordered Control Group in >=10 Year Old Subset: Pseudohomophones

End point title	Change From Baseline in Phonological Task Mean Reaction Time Comparison of ADHD-C+RD and RD to Reading Disordered Control Group in >=10 Year Old Subset: Pseudohomophones
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End point description:

Measure of reaction time in determining whether the stimulus sounds like a real word ('yes' response) or not ('no' response) using pseudo homophones and pseudo words. Data presented here are for reaction time to identifying pseudohomophones correctly. APD: All efficacy information is summarized and/or presented in data listings based on the Safety sample: Includes all patients who were randomized to double-blind treatment and received at least one dose of study drug.

End point type	Secondary
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End point timeframe:

Baseline and 4 weeks of therapy

End point values	Reading Disorder	Reading Disordered Control	ADHD-C+RD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	14	16	
Units: milliseconds				
arithmetic mean (standard deviation)	-241.00 (± 317.47)	-254.86 (± 266.46)	-170.81 (± 243.33)	

Statistical analyses

Statistical analysis title	Phonological Task Mean Reaction Time Comparison 2
Statistical analysis description: ANCOVA model with baseline value, study arm as covariate for RD versus RD controls.	
Comparison groups	Reading Disorder v Reading Disordered Control
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.663 ^[24]
Method	ANCOVA

Notes:

[24] - There were no adjustments for multiple comparisons - not applicable. All statistical tests were performed using a 0.05 significance level.

Statistical analysis title	Phonological Task Mean Reaction Time Comparison 1
Statistical analysis description: ANCOVA model with baseline value, study arm as covariates for ADHD-C+RD versus RD controls.	
Comparison groups	Reading Disordered Control v ADHD-C+RD
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.302 ^[25]
Method	ANCOVA

Notes:

[25] - There were no adjustments for multiple comparisons - not applicable. All statistical tests were performed using a 0.05 significance level.

Secondary: Change From Baseline in Phonological Task Mean Reaction Time Comparison of ADHD-C+RD and RD to Reading Disordered Control Group in ≥ 10 Year Old Subset: Pseudo Words

End point title	Change From Baseline in Phonological Task Mean Reaction Time Comparison of ADHD-C+RD and RD to Reading Disordered Control Group in ≥ 10 Year Old Subset: Pseudo Words
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End point description:

Measure of reaction time in determining whether the stimulus sounds like a real word ('yes' response) or not ('no' response) using pseudo homophones and pseudo words. Data presented here are for reaction time to indentifying pseudo words correctly. APD: All efficacy information is summarized and/or presented in data listings based on the Safety sample: Includes all patients who were randomized to double-blind treatment and received at least one dose of study drug.

End point type	Secondary
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End point timeframe:

Baseline and 4 weeks of therapy

End point values	Reading Disorder	Reading Disordered Control	ADHD-C+RD	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	14	16	
Units: milliseconds				
arithmetic mean (standard deviation)	-213.00 ($\pm$ 512.33)	-368.14 ($\pm$ 422.42)	-113.06 ($\pm$ 432.68)	

Statistical analyses

Statistical analysis title	Phonological Task Mean Reaction Time Comparison 2
Comparison groups	Reading Disorder v Reading Disordered Control
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority ^[26]
P-value	= 0.179 ^[27]
Method	ANCOVA

Notes:

[26] - ANCOVA model with baseline value, study arm as covariate for RD versus RD controls.

[27] - There were no adjustments for multiple comparisons - not applicable. All statistical tests were performed using a 0.05 significance level.

Statistical analysis title	Phonological Task Mean Reaction Time Comparison 1
Statistical analysis description: ANCOVA model with baseline value, study arm as covariate for ADHD-C+RD versus RD controls.	
Comparison groups	Reading Disordered Control v ADHD-C+RD
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07 ^[28]
Method	ANCOVA

Notes:

[28] - There were no adjustments for multiple comparisons - not applicable. All statistical tests were performed using a 0.05 significance level.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire Study

Adverse event reporting additional description:

All patients who were randomized to double-blind treatment and received at least one dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo, daily, by mouth for 4 weeks.

Reporting group title	Atomoxetine
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Reporting group description:

Atomoxetine, 1.2 mg/kg/day, by mouth for 4 weeks.

Serious adverse events	Placebo	Atomoxetine	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 76 (0.00%)	0 / 74 (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: 0 %

Non-serious adverse events	Placebo	Atomoxetine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 76 (35.53%)	35 / 74 (47.30%)	
Vascular disorders			
pallor			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	2 / 76 (2.63%)	2 / 74 (2.70%)	
occurrences (all)	2	2	
raynaud's phenomenon			
alternative dictionary used: MedDRA 10.0			

subjects affected / exposed occurrences (all)	0 / 76 (0.00%) 0	1 / 74 (1.35%) 1	
Surgical and medical procedures tooth extraction alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all)	1 / 76 (1.32%) 1	0 / 74 (0.00%) 0	
General disorders and administration site conditions fatigue alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all)	1 / 76 (1.32%) 1	9 / 74 (12.16%) 9	
feeling abnormal alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all)	0 / 76 (0.00%) 0	2 / 74 (2.70%) 2	
irritability alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all)	1 / 76 (1.32%) 1	3 / 74 (4.05%) 3	
malaise alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all)	0 / 76 (0.00%) 0	2 / 74 (2.70%) 2	
peripheral coldness alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all)	0 / 76 (0.00%) 0	1 / 74 (1.35%) 1	
pyrexia alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all)	2 / 76 (2.63%) 2	1 / 74 (1.35%) 1	
Social circumstances			

job dissatisfaction alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all)	1 / 76 (1.32%) 1	1 / 74 (1.35%) 1	
Respiratory, thoracic and mediastinal disorders cough alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) dyspnoea alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) epistaxis alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) pharyngolaryngeal pain alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) rhinalgia alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) rhinorrhoea alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all)	2 / 76 (2.63%) 2 1 / 76 (1.32%) 1 1 / 76 (1.32%) 1 2 / 76 (2.63%) 2 1 / 76 (1.32%) 1 0 / 76 (0.00%) 0	3 / 74 (4.05%) 3 0 / 74 (0.00%) 0 0 / 74 (0.00%) 0 2 / 74 (2.70%) 2 0 / 74 (0.00%) 0 1 / 74 (1.35%) 1	
Psychiatric disorders apathy alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) eating disorder	0 / 76 (0.00%) 0	2 / 74 (2.70%) 2	

alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
emotional disorder			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
fear			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 76 (1.32%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
initial insomnia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 76 (1.32%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
insomnia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	2 / 76 (2.63%)	2 / 74 (2.70%)	
occurrences (all)	2	2	
middle insomnia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
negativism			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
nightmare			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 76 (1.32%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
sleep disorder			
alternative dictionary used: MedDRA 10.0			

subjects affected / exposed occurrences (all)	0 / 76 (0.00%) 0	2 / 74 (2.70%) 2	
Investigations weight increased alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all)	2 / 76 (2.63%) 2	1 / 74 (1.35%) 1	
Injury, poisoning and procedural complications joint sprain alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) upper limb fracture alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) wound alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all)	1 / 76 (1.32%) 1 1 / 76 (1.32%) 1 1 / 76 (1.32%) 1	0 / 74 (0.00%) 0 1 / 74 (1.35%) 1 1 / 74 (1.35%) 1	
Nervous system disorders disturbance in attention alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) dizziness alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) headache alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) poor quality sleep alternative dictionary used: MedDRA 10.0	0 / 76 (0.00%) 0 1 / 76 (1.32%) 1 10 / 76 (13.16%) 10	1 / 74 (1.35%) 1 1 / 74 (1.35%) 1 11 / 74 (14.86%) 11	

subjects affected / exposed occurrences (all) somnolence alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) syncope alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all)	1 / 76 (1.32%) 1 1 / 76 (1.32%) 1 1 / 76 (1.32%) 1	1 / 74 (1.35%) 1 2 / 74 (2.70%) 2 1 / 74 (1.35%) 1	
Ear and labyrinth disorders ear pain alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all)	2 / 76 (2.63%) 2	1 / 74 (1.35%) 1	
Eye disorders eyelid oedema alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) mydriasis alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) visual disturbance alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all)	0 / 76 (0.00%) 0 0 / 76 (0.00%) 0 0 / 76 (0.00%) 0	1 / 74 (1.35%) 1 1 / 74 (1.35%) 1 1 / 74 (1.35%) 1	
Gastrointestinal disorders abdominal pain alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) abdominal pain upper alternative dictionary used: MedDRA 10.0	2 / 76 (2.63%) 2	6 / 74 (8.11%) 6	

subjects affected / exposed	2 / 76 (2.63%)	5 / 74 (6.76%)	
occurrences (all)	2	5	
diarrhoea			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 76 (1.32%)	4 / 74 (5.41%)	
occurrences (all)	1	4	
dysphagia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 76 (1.32%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
nausea			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 76 (1.32%)	8 / 74 (10.81%)	
occurrences (all)	1	8	
tooth disorder			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 76 (1.32%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
vomiting			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 76 (0.00%)	5 / 74 (6.76%)	
occurrences (all)	0	5	
Skin and subcutaneous tissue disorders			
erythema			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
rash erythematous			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 76 (1.32%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
rash pruritic			
alternative dictionary used: MedDRA 10.0			

subjects affected / exposed occurrences (all) 1 / 76 (1.32%) 1	1 / 74 (1.35%) 1	
skin discolouration alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) 0 / 76 (0.00%) 0	1 / 74 (1.35%) 1	
swelling face alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) 1 / 76 (1.32%) 1	0 / 74 (0.00%) 0	
Renal and urinary disorders enuresis alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) 1 / 76 (1.32%) 1	1 / 74 (1.35%) 1	
Musculoskeletal and connective tissue disorders muscle spasms alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) 1 / 76 (1.32%) 1 pain in extremity alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) 1 / 76 (1.32%) 1	0 / 74 (0.00%) 0 0 / 74 (0.00%) 0	
Infections and infestations bronchitis alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) 0 / 76 (0.00%) 0 gastroenteritis alternative dictionary used: MedDRA 10.0 subjects affected / exposed occurrences (all) 0 / 76 (0.00%) 0 gastroenteritis viral alternative dictionary used: MedDRA 10.0	1 / 74 (1.35%) 1 3 / 74 (4.05%) 3	

subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
influenza			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	1 / 76 (1.32%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
nasopharyngitis			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	2 / 76 (2.63%)	2 / 74 (2.70%)	
occurrences (all)	2	2	
pharyngitis			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
tonsillitis			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
urinary tract infection			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
anorexia			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
decreased appetite			
alternative dictionary used: MedDRA 10.0			
subjects affected / exposed	2 / 76 (2.63%)	6 / 74 (8.11%)	
occurrences (all)	2	6	
oral intake reduced			
alternative dictionary used: MedDRA 10.0			

subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2004	- The open-label extension (Study Period III) has been removed; - Secondary objectives were modified; - Inclusion and exclusion criteria's were revised; - The 2.5 mg and 25 mg capsules were removed from the list of study materials as the capsules will not be available in blister packs during the double-blind crossover phase; - The final visit was changed throughout the protocol from Visit 10 to Visit 5, due to the deletion of Study Period III; - The Study Schedule has been modified to remove the open-label extension, revise the end-of-study procedures.
07 March 2005	- The word "clinical" has been replaced with the word "subclinical" to more accurately describe the norms for the Disruptive Behaviour Disorder Rating Scale (DBD); - Slight clarifications were made to inclusion and exclusion criteria; - Study schedule was revised to reflect the change in visit intervals, the deletion of the thyroid stimulating hormone (TSH) test; - Clarifications made on Disease Diagnostic Criteria
09 February 2006	- Screening procedure, Inclusion and Exclusion criteria was revised; - criteria for diagnosing Reading Disorder was clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported