



## Clinical trial results:

### Long-Term Extension, Open-Label Study of Atomoxetine Hydrochloride in Child Outpatients With Attention-Deficit/Hyperactivity Disorder

#### Summary

EudraCT number	2017-000686-68
Trial protocol	Outside EU/EEA
Global end of trial date	01 August 2009

#### 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-JE-LYDA
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00191386
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 9315

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 August 2009
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 August 2009
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate long-term safety and efficacy of Atomoxetine in Japanese pediatric patients with Attention-Deficit/Hyperactivity Disorder (AD/HD).

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 May 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	Japan: 228
Worldwide total number of subjects	228
EEA total number of subjects	0

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)	0
Adolescents (12-17 years)	228
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This study was as a follow-up investigation of ADHD pediatric patients who completed Study LYBC (NCT00191295).

### Pre-assignment

Screening details:

Not Applicable

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Arm title	Atomoxetine
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Arm description:

0.5 milligrams per kilogram (mg/kg) twice daily (BID), orally (PO) titrated to 1.2 mg/kg BID, PO over 2 weeks then 1.2 to 1.8 mg/kg BID, PO for 6 months and up to 4 years

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

Dosage and administration details:

0.5 milligrams per kilogram (mg/kg) twice daily (BID), orally (PO) titrated to 1.2 mg/kg BID, PO over 2 weeks then 1.2 to 1.8 mg/kg BID, PO for 6 months and up to 4 years.

Number of subjects in period 1	Atomoxetine
Started	228
6 Months	183
12 Months	149
2 Years	105
3 Years	65 <sup>[1]</sup>
Completed	68
Not completed	160
Consent withdrawn by subject	96
Physician decision	11
Adverse event, non-fatal	16
Entry Criteria Exclusion	3
Lost to follow-up	1

Protocol deviation	18
Lack of efficacy	15

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Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

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

## Baseline characteristics

### Reporting groups

Reporting group title	Atomoxetine
Reporting group description:	
0.5 milligrams per kilogram (mg/kg) twice daily (BID), orally (PO) titrated to 1.2 mg/kg BID, PO over 2 weeks then 1.2 to 1.8 mg/kg BID, PO for 6 months and up to 4 years	

Reporting group values	Atomoxetine	Total	
Number of subjects	228	228	
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	10.69		
standard deviation	± 2.48	-	
Gender categorical			
Units: Subjects			
Female	33	33	
Male	195	195	
Race/Ethnicity, Customized			
Units: Subjects			
East Asian	228	228	
Region of Enrollment			
Units: Subjects			
Japan	228	228	
ADHD Rating Scale-IV-Translated in Japanese Parent Version: Investigator Administered/Scored			
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 (ADHD). 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	22.23		
standard deviation	± 10.42	-	

## End points

### End points reporting groups

Reporting group title	Atomoxetine
Reporting group description: 0.5 milligrams per kilogram (mg/kg) twice daily (BID), orally (PO) titrated to 1.2 mg/kg BID, PO over 2 weeks then 1.2 to 1.8 mg/kg BID, PO for 6 months and up to 4 years	

### Primary: Number of Participants With Adverse Events for Long Term Safety and Tolerability

End point title	Number of Participants With Adverse Events for Long Term Safety and Tolerability <sup>[1]</sup>
End point description: Details on the actual adverse events are presented in the Reported Adverse Events Section.	
End point type	Primary
End point timeframe: Baseline through 4 years	

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis planned for this outcome.

End point values	Atomoxetine			
Subject group type	Reporting group			
Number of subjects analysed	228			
Units: Participants number (not applicable)				
Serious Adverse Events	6			
All Other Nonserious Adverse Events	222			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline at Various Timepoints in Attention Deficit Hyperactivity Disorder Rating Scale-IV-Translated in Japanese Parent Version: Investigator Administered and Scored (ADHDRS-IV-J:I) Total Score

End point title	Change From Baseline at Various Timepoints in Attention Deficit Hyperactivity Disorder Rating Scale-IV-Translated in Japanese Parent Version: Investigator Administered and Scored (ADHDRS-IV-J:I) Total Score
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.	
End point type	Secondary

End point timeframe:

Baseline, 6 Months, 12 Months, 2 Years, 3 Years, 4 Years

<b>End point values</b>	Atomoxetine			
Subject group type	Reporting group			
Number of subjects analysed	228			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Total Score 6 Months (n=228)	-14.1 (± 9.3)			
Total Score 12 Months (n=178)	-16.0 (± 9.2)			
Total Score 2 Years (n=143)	-17.7 (± 9.4)			
Total Score 3 Years (n=105)	-20.0 (± 9.2)			
Total Score 4 Years (n=62)	-20.1 (± 10.5)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline at Various Timepoints in the Clinical Global Impressions-Attention Deficit Hyperactivity Disorder-Severity (CGI-ADHD-S)

End point title	Change From Baseline at Various Timepoints in the Clinical Global Impressions-Attention Deficit Hyperactivity Disorder-Severity (CGI-ADHD-S)
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End point description:

Measures severity of the participant's overall severity of ADHD symptoms (1=normal, not at all ill; 7=among the most extremely ill patients).

End point type	Secondary
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End point timeframe:

Baseline, 6 Months, 12 Months, 2 Years, 3 Years, 4 Years

<b>End point values</b>	Atomoxetine			
Subject group type	Reporting group			
Number of subjects analysed	228			
Units: Units on a scale				
arithmetic mean (standard deviation)				
6 Months	-1.1 (± 1.1)			
12 Months	-1.3 (± 1.1)			
2 Years	-1.4 (± 1.0)			
3 Years	-1.6 (± 1.0)			
4 Years	-1.8 (± 1.1)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Cytochrome P450 2D6 (CYP2D6) Phenotype Status

End point title	Cytochrome P450 2D6 (CYP2D6) Phenotype Status
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End point description:

Participants were categorized as either extensive metabolizers (EM) or poor metabolizers (PM). CYP2D6 is the primary atomoxetine metabolizing enzyme. The CYP2D6 genotype were analysed by testing the \*2, \*3, \*4, \*5, \*6, \*7, \*8, and \*10 alleles. Metabolizer status was determined by focusing on the normal(wild type, \*2), decreased(\*10), and defective allele(\*3, \*4, \*5, \*6, \*7, or \*8). PM were assigned to the patients had two defective alleles in any combination of \*3, \*4, \*5, \*6, \*7, or \*8 alleles. EM was all except for PM.

End point type	Secondary
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End point timeframe:

Over 1 year

End point values	Atomoxetine			
Subject group type	Reporting group			
Number of subjects analysed	228			
Units: Participants				
number (not applicable)				
Extensive Metabolizer	225			
Poor Metabolizer	3			

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Entire Study

Adverse event reporting additional description:

B4Z-JE-LYDA

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.0
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### Reporting groups

Reporting group title	atomoxetine
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Reporting group description: -

<b>Serious adverse events</b>	atomoxetine		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 228 (2.63%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
eye injury			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 228 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
asthma			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 228 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
hepatic function abnormal			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	1 / 228 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
schizophrenia			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 228 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
thyroiditis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 228 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
pneumonia mycoplasmal			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 228 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	atomoxetine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	222 / 228 (97.37%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
skin papilloma			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	13 / 228 (5.70%)		
occurrences (all)	17		
Injury, poisoning and procedural complications			

arthropod sting alternative dictionary used: MedDRA 12.0 subjects affected / exposed occurrences (all)	18 / 228 (7.89%) 41		
contusion alternative dictionary used: MedDRA 12.0 subjects affected / exposed occurrences (all)	30 / 228 (13.16%) 51		
excoriation alternative dictionary used: MedDRA 12.0 subjects affected / exposed occurrences (all)	17 / 228 (7.46%) 30		
fall alternative dictionary used: MedDRA 12.0 subjects affected / exposed occurrences (all)	18 / 228 (7.89%) 26		
joint sprain alternative dictionary used: MedDRA 12.0 subjects affected / exposed occurrences (all)	22 / 228 (9.65%) 30		
Surgical and medical procedures tooth extraction alternative dictionary used: MedDRA 12.0 subjects affected / exposed occurrences (all)	14 / 228 (6.14%) 22		
Nervous system disorders headache alternative dictionary used: MedDRA 12.0 subjects affected / exposed occurrences (all)  somnolence alternative dictionary used: MedDRA 12.0 subjects affected / exposed occurrences (all)	67 / 228 (29.39%) 173  34 / 228 (14.91%) 37		
General disorders and administration site conditions			

<p>malaise</p> <p>alternative dictionary used: MedDRA 12.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>14 / 228 (6.14%)</p> <p>20</p>		
<p>pyrexia</p> <p>alternative dictionary used: MedDRA 12.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>34 / 228 (14.91%)</p> <p>43</p>		
<p>Eye disorders</p> <p>conjunctivitis allergic</p> <p>alternative dictionary used: MedDRA 12.0</p> <p>subjects affected / exposed occurrences (all)</p> <p>myopia</p> <p>alternative dictionary used: MedDRA 12.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>13 / 228 (5.70%)</p> <p>17</p> <p>12 / 228 (5.26%)</p> <p>13</p>		
<p>Gastrointestinal disorders</p> <p>abdominal pain</p> <p>alternative dictionary used: MedDRA 12.0</p> <p>subjects affected / exposed occurrences (all)</p> <p>constipation</p> <p>alternative dictionary used: MedDRA 12.0</p> <p>subjects affected / exposed occurrences (all)</p> <p>dental caries</p> <p>alternative dictionary used: MedDRA 12.0</p> <p>subjects affected / exposed occurrences (all)</p> <p>diarrhoea</p> <p>alternative dictionary used: MedDRA 12.0</p> <p>subjects affected / exposed occurrences (all)</p> <p>nausea</p>	<p>53 / 228 (23.25%)</p> <p>106</p> <p>17 / 228 (7.46%)</p> <p>25</p> <p>23 / 228 (10.09%)</p> <p>24</p> <p>42 / 228 (18.42%)</p> <p>58</p>		

<p>alternative dictionary used: MedDRA 12.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>28 / 228 (12.28%) 47</p>		
<p>stomatitis</p> <p>alternative dictionary used: MedDRA 12.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>20 / 228 (8.77%) 27</p>		
<p>toothache</p> <p>alternative dictionary used: MedDRA 12.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>12 / 228 (5.26%) 12</p>		
<p>vomiting</p> <p>alternative dictionary used: MedDRA 12.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>29 / 228 (12.72%) 45</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>cough</p> <p>alternative dictionary used: MedDRA 12.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>22 / 228 (9.65%) 27</p>		
<p>epistaxis</p> <p>alternative dictionary used: MedDRA 12.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>22 / 228 (9.65%) 55</p>		
<p>oropharyngeal pain</p> <p>alternative dictionary used: MedDRA 12.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>12 / 228 (5.26%) 14</p>		
<p>rhinitis allergic</p> <p>alternative dictionary used: MedDRA 12.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>22 / 228 (9.65%) 30</p>		
<p>upper respiratory tract inflammation</p> <p>alternative dictionary used: MedDRA 12.0</p>			

subjects affected / exposed	49 / 228 (21.49%)		
occurrences (all)	139		
<b>Skin and subcutaneous tissue disorders</b>			
eczema			
alternative dictionary used:			
MedDRA 12.0			
subjects affected / exposed	21 / 228 (9.21%)		
occurrences (all)	29		
urticaria			
alternative dictionary used:			
MedDRA 12.0			
subjects affected / exposed	12 / 228 (5.26%)		
occurrences (all)	24		
<b>Infections and infestations</b>			
bronchitis			
alternative dictionary used:			
MedDRA 12.0			
subjects affected / exposed	23 / 228 (10.09%)		
occurrences (all)	39		
gastroenteritis			
alternative dictionary used:			
MedDRA 12.0			
subjects affected / exposed	36 / 228 (15.79%)		
occurrences (all)	53		
gastroenteritis viral			
alternative dictionary used:			
MedDRA 12.0			
subjects affected / exposed	18 / 228 (7.89%)		
occurrences (all)	25		
impetigo			
alternative dictionary used:			
MedDRA 12.0			
subjects affected / exposed	15 / 228 (6.58%)		
occurrences (all)	17		
influenza			
alternative dictionary used:			
MedDRA 12.0			
subjects affected / exposed	55 / 228 (24.12%)		
occurrences (all)	62		
nasopharyngitis			
alternative dictionary used:			
MedDRA 12.0			

<p>subjects affected / exposed occurrences (all)</p> <p>otitis media alternative dictionary used: MedDRA 12.0 subjects affected / exposed occurrences (all)</p> <p>pharyngitis alternative dictionary used: MedDRA 12.0 subjects affected / exposed occurrences (all)</p> <p>rhinitis alternative dictionary used: MedDRA 12.0 subjects affected / exposed occurrences (all)</p>	<p>127 / 228 (55.70%) 420</p> <p>12 / 228 (5.26%) 14</p> <p>26 / 228 (11.40%) 46</p> <p>17 / 228 (7.46%) 31</p>		
<p>Metabolism and nutrition disorders decreased appetite alternative dictionary used: MedDRA 12.0 subjects affected / exposed occurrences (all)</p>	<p>30 / 228 (13.16%) 36</p>		

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported