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

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

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 [1]
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

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[1]

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

End point values	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)

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

End point timeframe:

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

End point values	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

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

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

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups	
Reporting group title	atomoxetine

Reporting group description: -

Serious adverse events	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 %

Non-serious adverse events	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)	67 / 228 (29.39%) 173		
somnolence alternative dictionary used: MedDRA 12.0 subjects affected / exposed occurrences (all)	34 / 228 (14.91%) 37		
General disorders and administration site conditions			

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

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

subjects affected / exposed	49 / 228 (21.49%)		
occurrences (all)	139		
Skin and subcutaneous tissue disorders			
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		
Infections and infestations			
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			

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

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