Clinical trial results:
A Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of Fixed-dose Once-daily Oral Aripiprazole in Children and Adolescents with Tourette's Disorder

Summary

EudraCT number	2012-003488-23
Trial protocol	HU FI BE SE ES GB IT DE NL BG
Global end of trial date	03 September 2013

Results information

Result version number	v1 (current)
This version publication date	02 March 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	31-12-293

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01727700
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, Maryland, United States, 20850
Public contact	Eva Kohegyi, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 6095246790, Eva.Kohegyi@otsuka-us.com
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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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 December 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 September 2013
Global end of trial reached?	Yes
Global end of trial date	03 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of aripiprazole with placebo in the suppression of tics in children and adolescents (7-17 years) with a diagnosis of Tourette's Disorder (TD) and to evaluate the safety and tolerability of aripiprazole once-daily treatment with oral tablets in children and adolescents with a diagnosis of TD.

Protection of trial subjects:

This study was designed and monitored in compliance with the protocol and in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline, and the applicable local laws and regulatory requirements of the countries in which the trial was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2012
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	Canada: 27
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	United States: 92
Worldwide total number of subjects	133
EEA total number of subjects	14

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)	66
Adolescents (12-17 years)	67

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial in children and adolescents (aged 7-17 years) with TD. 171 participants were screened, of which 133 were randomized to treatment.

Pre-assignment

Screening details:

The trial consisted of a pretreatment phase and a treatment phase. Pretreatment phase consisted of a screening and washout (when applicable) period. This was followed by an 8-week treatment phase starting with the baseline visit (Day 0). Participants were randomized 1:1:1 to aripiprazole high dose, aripiprazole low dose or placebo.

Period 1

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

Blinding implementation details:

During the trial, the treatment assignment code list was available only to an independent biostatistician. Except in cases of emergency unblinding, subjects, investigational site personnel, OPDC employees, and all other trial personnel remained blinded to the identity of the treatment assignments until every subject had completed trial treatment and the database had been locked.

Arms

Are arms mutually exclusive?	Yes
Arm title	Aripiprazole low dose

Arm description:

For participants who weighed < 50 kg at baseline, low dose was 5 mg/day. For participants who weighed ≥ 50 kg at baseline, low dose was 10 mg/day. All participants randomized to aripiprazole began treatment at 2 mg/day, with the dose titrated to 5 mg/day after 2 days. The dose was titrated to achieve the randomized dose. All participants were to have reached their randomized dose by Week 3 (Day 21) and were to remain on that dose.

Arm type	Experimental
Investigational medicinal product name	Aripiprazole
Investigational medicinal product code	
Other name	Abilify, OPC-14597
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For participants who weighed < 50 kg at baseline, low dose was one 5 mg/day plus 1 placebo tablet. For participants who weighed ≥ 50 kg at baseline, low dose was one 10 mg/day and 1 placebo tablet.

Arm title	Aripiprazole high dose

Arm description:

For participants who weighed < 50 kg at baseline, high dose was 10 mg/day. For participants who weighed ≥ 50 kg at baseline, high dose was 20 mg/day. All participants randomized to aripiprazole began treatment at 2 mg/day, with the dose titrated to 5 mg/day after 2 days. The dose was then titrated weekly until the randomized dose was achieved. All participants were to have reached their randomized dose by Week 3 (Day 21) and were to remain on that dose.

Arm type	Experimental

Investigational medicinal product name	Aripiprazole
Investigational medicinal product code	
Other name	Abilify, OPC-14597
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For participants who weighed < 50 kg at baseline, high dose was 10 mg/day plus 1 placebo tablet. For participants who weighed ≥ 50 kg at baseline, high dose was two 10 mg/day plus no placebo tablet.

Arm title	Placebo

Arm description:

Participants received matching placebo tablets in the same way as aripiprazole.

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:

Matching placebo tablets in the same way as aripiprazole.

Number of subjects in period 1	Aripiprazole low dose	Aripiprazole high dose	Placebo
Started	44	45	44
Completed	42	35	42
Not completed	2	10	2
Consent withdrawn by subject	-	3	1
Adverse Event	-	7	1
Protocol Violation	2	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Aripiprazole low dose
Reporting group description:	
For participants who weighed < 50 kg at baseline, low dose was 5 mg/day. For participants who weighed ≥ 50 kg at baseline, low dose was 10 mg/day. All participants randomized to aripiprazole began treatment at 2 mg/day, with the dose titrated to 5 mg/day after 2 days. The dose was titrated to achieve the randomized dose. All participants were to have reached their randomized dose by Week 3 (Day 21) and were to remain on that dose.	
Reporting group title	Aripiprazole high dose
Reporting group description:	
For participants who weighed < 50 kg at baseline, high dose was 10 mg/day. For participants who weighed ≥ 50 kg at baseline, high dose was 20 mg/day. All participants randomized to aripiprazole began treatment at 2 mg/day, with the dose titrated to 5 mg/day after 2 days. The dose was then titrated weekly until the randomized dose was achieved. All participants were to have reached their randomized dose by Week 3 (Day 21) and were to remain on that dose.	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo tablets in the same way as aripiprazole.	

Reporting group values	Aripiprazole low dose	Aripiprazole high dose	Placebo
Number of subjects	44	45	44
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	11.1	11.8	11.6
standard deviation	± 3.1	± 2.8	± 2.8
Gender categorical			
Units: Subjects			
Female	8	10	11
Male	36	35	33

Reporting group values	Total		
Number of subjects	133		
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			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	29		
Male	104		

End points

End points reporting groups

Reporting group title	Aripiprazole low dose

Reporting group description:

For participants who weighed < 50 kg at baseline, low dose was 5 mg/day. For participants who weighed ≥ 50 kg at baseline, low dose was 10 mg/day. All participants randomized to aripiprazole began treatment at 2 mg/day, with the dose titrated to 5 mg/day after 2 days. The dose was titrated to achieve the randomized dose. All participants were to have reached their randomized dose by Week 3 (Day 21) and were to remain on that dose.

Reporting group title	Aripiprazole high dose

Reporting group description:

For participants who weighed < 50 kg at baseline, high dose was 10 mg/day. For participants who weighed ≥ 50 kg at baseline, high dose was 20 mg/day. All participants randomized to aripiprazole began treatment at 2 mg/day, with the dose titrated to 5 mg/day after 2 days. The dose was then titrated weekly until the randomized dose was achieved. All participants were to have reached their randomized dose by Week 3 (Day 21) and were to remain on that dose.

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo tablets in the same way as aripiprazole.

Primary: Change from Baseline to Week 8 in Yale Global Tic Severity Scale (YGTSS) Total Tic Score (TTS)

End point title	Change from Baseline to Week 8 in Yale Global Tic Severity Scale (YGTSS) Total Tic Score (TTS)

End point description:

The YGTSS is a semi-structured clinical interview designed to measure current (time frame of the past 1 week) tic severity. This scale consists of a tic inventory, with 5 separate rating scales to rate the severity of symptoms, and an impairment ranking. Ratings are made along 5 different dimensions on a scale of 0 to 5 for motor and vocal tics each, including number, frequency, intensity, complexity, and interference. Summation of these 10 scores (ie, 0-50) provides a TTS that was the primary outcome measure in this trial. The YGTSS ranking of impairment score rated on a 50-point scale anchored from 0 (no impairment) to 50 (severe impairment) to assess impairment experienced in areas of self-esteem, family life, social acceptance, and school scores. Intent-to-Treat (ITT) Population: All participants randomly assigned to the double-blind treatment. Ns are number of participants with Baseline and a Week-8 assessment of the given variable.

End point type	Primary

End point timeframe:

Baseline to Week 8

End point values	Aripiprazole low dose	Aripiprazole high dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	35	42	
Units: Units on a scale				
least squares mean (standard error)	-13.35 (± 1.59)	-16.94 (± 1.61)	-7.09 (± 1.55)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 8

Statistical analysis description:

Assuming 5% of participants may drop out of the trial without a post-baseline efficacy evaluation, a total of 126 participants were required to provide at least 80% power to detect a treatment difference of -5 (common standard deviation [SD] of 8.5) between at least 1 of 2 aripiprazole dose levels and placebo in the primary outcome.

Comparison groups	Aripiprazole low dose v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [1]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-6.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.18
upper limit	-2.34

Notes:

[1] - The Hochberg procedure was used to adjust for multiplicity.

Statistical analysis title	Statistical analysis 2 at Week 8

Statistical analysis description:

Assuming 5% of participants may drop out of the trial without a post-baseline efficacy evaluation, a total of 126 participants were required to provide at least 80% power to detect a treatment difference of -5 (common standard SD of 8.5) between at least 1 of 2 aripiprazole dose levels and placebo in the primary outcome.

Comparison groups	Placebo v Aripiprazole high dose
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-9.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.84
upper limit	-5.86

Notes:

[2] - The Hochberg procedure was used to adjust for multiplicity.

Secondary: Change in Clinical Global Impressions Scale-Tourette's Syndrome (CGI-TS) Score at Week 8

End point title	Change in Clinical Global Impressions Scale-Tourette's Syndrome (CGI-TS) Score at Week 8

End point description:

To assess CGI-TS severity, the rater or physician answered the following question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" The

change score was obtained from CGI-TS improvement scale assessment: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. ITT Population: All participants randomly assigned to the double-blind treatment. At Week 8, data were available for 42 participants in the low dose, 35 in the high dose and 42 in the placebo group.

End point type	Secondary

End point timeframe:

Week 8

End point values	Aripiprazole low dose	Aripiprazole high dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	35	42	
Units: Units on a scale				
least squares mean (standard error)	2.12 (± 0.21)	2.13 (± 0.21)	3.15 (± 0.2)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 8
Comparison groups	Aripiprazole low dose v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [3]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.54
upper limit	-0.52

Notes:

[3] - The Hochberg procedure was used to adjust for multiplicity.

Statistical analysis title	Statistical analysis 2 at Week 8
Comparison groups	Aripiprazole high dose v Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [4]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.54
upper limit	-0.49

Notes:

[4] - The Hochberg procedure was used to adjust for multiplicity.

Secondary: Mean change from Baseline to Endpoint (Week 8) in Total YGTSS Score

End point title	Mean change from Baseline to Endpoint (Week 8) in Total YGTSS Score

End point description:

The YGTSS consists of a tic inventory, with 5 separate rating scales to rate the severity of symptoms (on a scale of 0 to 5 for 5 different dimensions, including number, frequency, intensity, complexity, and interference) of motor and vocal tics, and an impairment ranking. The Total YGTSS score is the summation of the severity scores of motor and vocal tics and also the ranking of impairment (range of 0 to 100). A missing value of a YGTSS item scale could result in a missing Total YGTSS score. A reduction in Total YGTSS score from baseline represents an improvement in symptoms. ITT Population: All participants randomly assigned to the double-blind treatment. At Week 8, data were available for 42 participants in the low dose, 35 in the high dose and 42 in the placebo group.

End point type	Secondary

End point timeframe:

Baseline to Week 8

End point values	Aripiprazole low dose	Aripiprazole high dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	35	42	
Units: Units on a scale				
least squares mean (standard error)	-26.69 (± 3.34)	-32.8 (± 3.39)	-13.43 (± 3.27)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 8
Comparison groups	Aripiprazole low dose v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0017 [5]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-13.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.43
upper limit	-5.08

Notes:

[5] - Treatment, week, treatment by week interaction, region, and weight group were fixed categorical effects; baseline value as a fixed covariate.

Statistical analysis title	Statistical analysis 2 at Week 8
Comparison groups	Aripiprazole high dose v Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-19.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.7
upper limit	-11.04

Notes:

[6] - Treatment, week, treatment by week interaction, region, and weight group were fixed categorical effects; baseline value as a fixed covariate.

Secondary: Mean change from Baseline to Endpoint (Week 8) in CGI-TS Severity Score

End point title	Mean change from Baseline to Endpoint (Week 8) in CGI-TS Severity Score

End point description:

The CGI-TS Severity scale (range 0-7) is a single-item rating score, with higher scores representing greater severity or less improvement. A response of 0 (not assessed) is considered and handled as missing data. ITT Population: All participants randomly assigned to the double-blind treatment. At Week 8, data were available for 42 participants in the low dose, 35 in the high dose and 42 in the placebo group.

End point type	Secondary

End point timeframe:

Baseline to Week 8

End point values	Aripiprazole low dose	Aripiprazole high dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	35	42	
Units: Units on a scale				
least squares mean (standard error)	-1.35 (± 0.19)	-1.47 (± 0.19)	-0.55 (± 0.19)	

Statistical analyses

Statistical analysis title	Statistiscal analysis 1 at Week 8
Comparison groups	Aripiprazole low dose v Placebo

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [7]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.27
upper limit	-0.33

Notes:

[7] - Treatment, week, treatment by week interaction, region, and weight group were fixed categorical effects; baseline value as a fixed covariate.

Statistical analysis title	Statistical analysis 2 at Week 8
Comparison groups	Aripiprazole high dose v Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [8]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.41
upper limit	-0.44

Notes:

[8] - Treatment, week, treatment by week interaction, region, and weight group were fixed categorical effects; baseline value as a fixed covariate.

Secondary: Response Rate

End point title	Response Rate

End point description:

Clinical response is defined as > 25% improvement from baseline to Week 8 in YGTSS TTS or a CGI-TS Change score of 1 [very much improved] or 2 [much improved] at Week 8. Response will be considered as missing only if both YGTSS TTS and CGI-TS change score are missing. As long as one of them is non-missing, response outcome will be determined based on the non-missing score. ITT Population: All participants randomly assigned to the double-blind treatment. At Week 8, data were available for 42 participants in the low dose, 35 in the high dose and 42 in the placebo group.

End point type	Secondary

End point timeframe:

Week 8

End point values	Aripiprazole low dose	Aripiprazole high dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	35	42	
Units: Percentage of participants				
number (not applicable)	73.8	88.6	54.8	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 8
Comparison groups	Aripiprazole low dose v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0835 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response ratio
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.88

Notes:

[9] - P-value derived from Cochran-Mantel-Haenszel (CMH) General Association Test adjusting for region and weight group. The response ratio >1 favours aripiprazole.

Statistical analysis title	Statistical analysis 2 at Week 8
Comparison groups	Aripiprazole high dose v Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response ratio
Point estimate	1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	2.16

Notes:

[10] - P-value derived from CMH General Association Test adjusting for region and weight group. The response ratio >1 favours aripiprazole.

Secondary: Treatment discontinuation rate

End point title	Treatment discontinuation rate

End point description:

Treatment discontinuation rate will be calculated as the number of discontinued participants (ie, those who were withdrawn from the trial without completing the Week 8 visit) over the number of all randomized participants. ITT Population: All participants randomly assigned to the double-blind

treatment.

End point type	Secondary

End point timeframe:

Week 8

End point values	Aripiprazole low dose	Aripiprazole high dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	45	44	
Units: Percentage of participants				
number (not applicable)	4.5	22.5	4.5	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 8
Comparison groups	Placebo v Aripiprazole low dose
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9187 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Discontinuation ratio
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	7.05

Notes:

[11] - Discontinuation ratio < 1 favors aripiprazole. P-value derived from CMH General Association Test adjusting for region and weight group.

Statistical analysis title	Statistical analysis 2 at Week 8
Comparison groups	Placebo v Aripiprazole low dose
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9576 [12]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	7.05

Notes:

[12] - Hazard ratio < 1 favors aripiprazole. P-value derived from Cox proportional hazard regression adjusting for region and weight group.

Statistical analysis title	Statistical analysis 3 at Week 8
Comparison groups	Aripiprazole high dose v Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0132 [13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Discontinuation ratio
Point estimate	4.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	14.95

Notes:

[13] - Discontinuation ratio < 1 favors aripiprazole. P-value derived from CMH General Association Test adjusting for region and weight group.

Statistical analysis title	Statistical analysis 4 at Week 8
Comparison groups	Placebo v Aripiprazole high dose
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0278 [14]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	5.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	14.95

Notes:

[14] - Hazard ratio < 1 favors aripiprazole. P-value derived from Cox proportional hazard regression adjusting for region and weight group.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were recorded from the time of signing the informed consent up to 30 days after the last trial visit.

Adverse event reporting additional description:

An AE is defined as any untoward medical occurrence with the use of study drug. AE was considered serious if fatal, life threatening, disabling or incapacitating, required in participant hospitalization or prolonged hospitalization, congenital anomaly/birth defect or other medically significant event.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Aripiprazole low dose

Reporting group description:

For participants who weighed < 50 kg at baseline, low dose was 5 mg/day. For participants who weighed ≥ 50 kg at baseline, low dose was 10 mg/day. All participants randomized to aripiprazole began treatment at 2 mg/day, with the dose titrated to 5 mg/day after 2 days. The dose was titrated to achieve the randomized dose. All participants were to have reached their randomized dose by Week 3 (Day 21) and were to remain on that dose.

Reporting group title	Aripiprazole high dose

Reporting group description:

For participants who weighed < 50 kg at baseline, high dose was 10 mg/day. For participants who weighed ≥ 50 kg at baseline, high dose was 20 mg/day. All participants randomized to aripiprazole began treatment at 2 mg/day, with the dose titrated to 5 mg/day after 2 days. The dose was then titrated weekly until the randomized dose was achieved. All participants were to have reached their randomized dose by Week 3 (Day 21) and were to remain on that dose.

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo tablets in the same way as aripiprazole.

Serious adverse events	Aripiprazole low dose	Aripiprazole high dose	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 44 (0.00%)	0 / 45 (0.00%)	0 / 44 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Aripiprazole low dose	Aripiprazole high dose	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 44 (47.73%)	29 / 45 (64.44%)	8 / 44 (18.18%)

Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 44 (0.00%)	3 / 45 (6.67%)	0 / 44 (0.00%)
occurrences (all)	0	3	0
Headache			
subjects affected / exposed	3 / 44 (6.82%)	4 / 45 (8.89%)	1 / 44 (2.27%)
occurrences (all)	3	4	1
Lethargy			
subjects affected / exposed	0 / 44 (0.00%)	5 / 45 (11.11%)	0 / 44 (0.00%)
occurrences (all)	0	5	0
Sedation			
subjects affected / exposed	8 / 44 (18.18%)	4 / 45 (8.89%)	1 / 44 (2.27%)
occurrences (all)	8	5	1
Somnolence			
subjects affected / exposed	5 / 44 (11.36%)	7 / 45 (15.56%)	1 / 44 (2.27%)
occurrences (all)	5	7	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 44 (6.82%)	7 / 45 (15.56%)	0 / 44 (0.00%)
occurrences (all)	3	7	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 44 (6.82%)	4 / 45 (8.89%)	1 / 44 (2.27%)
occurrences (all)	3	4	1
Vomiting			
subjects affected / exposed	2 / 44 (4.55%)	3 / 45 (6.67%)	2 / 44 (4.55%)
occurrences (all)	2	4	2
Psychiatric disorders			
Restlessness			
subjects affected / exposed	0 / 44 (0.00%)	3 / 45 (6.67%)	1 / 44 (2.27%)
occurrences (all)	0	3	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 44 (6.82%)	4 / 45 (8.89%)	0 / 44 (0.00%)
occurrences (all)	3	4	0
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1	1 / 45 (2.22%) 1	3 / 44 (6.82%) 4
Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 4	3 / 45 (6.67%) 3	1 / 44 (2.27%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 October 2012	Protocol amendment 1 clarified the concomitant use of benzodiazepines, changed the titration scheme, specified the entire Swanson, Nolan and Pelham-IV (SNAP-IV) rating scale, rather than the attention-deficit/hyperactivity disorder (ADHD) subscales; removed the Gilles de la Tourette Syndrome-Quality of Life scale assessments; added weight-based dosing stratification.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported