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

Summary

EudraCT number	2011-000467-27
Trial protocol	HU
Global end of trial date	06 November 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	31-10-272

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01418339
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development &Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, Maryland 20850
Public contact	Eva Kohegyi, MD, Otsuka Pharmaceutical Development &Commercialization, Inc., 1 609 524-6790,
Scientific contact	Eva Kohegyi, MD, Otsuka Pharmaceutical Development &Commercialization, Inc., 1 609 524-6790,

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	28 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 November 2013
Global end of trial reached?	Yes
Global end of trial date	06 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary: 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). The primary efficacy measure is change from Baseline to endpoint (Week 8) on the Total Tic score (TTS) of the Yale Global Tic Severity Scale (YGTSS). The secondary objective was to evaluate the safety and tolerability of aripiprazole treatment with oral tablets in children and adolescents with a diagnosis of TD. Secondary efficacy measures include Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS) and Gilles de la Tourette Syndrome - Quality of Life Scale (GTS-QOL).

Protection of trial subjects:

The trial was conducted in accordance with the protocol, legal and regulatory requirements, as well as the general principles set forth in Guidelines for Good Clinical Practice (GCP) (International Conference on Harmonization [ICH] 1996). In addition, the study was conducted in accordance with applicable local regulatory requirements and laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 July 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Korea, Republic of: 17
Country: Number of subjects enrolled	Mexico: 17
Country: Number of subjects enrolled	Taiwan: 22
Country: Number of subjects enrolled	United States: 42
Worldwide total number of subjects	135
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)	61
Adolescents (12-17 years)	74
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 152 participants were screened and 135 were randomised to treatment. The randomized participants were recruited from 45 study sites in the following 6 countries: United States (US), Hungary, Canada, Taiwan, South Korea, and Mexico. 124 participants were included in the modified intention-to-treat (mITT) population.

Pre-assignment

Screening details:

The trial consisted of a pretreatment and treatment phase. The pretreatment phase consisted of a Screening period, a washout period (when applicable), and a Baseline visit. This was followed by an 8-week treatment phase. There was also a follow-up period (30 ± 3 days) for those participants who did not roll over into the open-label study.

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 participant had completed trial treatment and the database had been locked.

Arms

Are arms mutually exclusive?	Yes
Arm title	Aripiprazole

Arm description:

Aripiprazole was administered orally once a week (QW) for 8 weeks. Participants randomised to aripiprazole began on a 52.5 milligrams (mg) QW dose on Day 0. At the Week 1 visit, according to the investigator's discretion based on efficacy and tolerability, the dose of aripiprazole could remain at 52.5 mg QW or could be increased to 77.5 mg QW. The dose could be increased to 110 mg QW for efficacy as early as Week 2. For the remainder of the trial, the dose was to be adjusted up and down among these 3 dose levels, as determined by investigator discretion. 82 participants were included in the mITT which was all participants randomly assigned to the double-blind treatment, with the exclusion of participants randomized at sites 002 and 005. These two centres were terminated from conducting this trial due to their failure to abide by GCPs and the protocol requirements.

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

Dosage and administration details:

52.5 mg to 110 mg QW for 8 weeks.

Arm title	Placebo

Arm description:

Participants received matching placebo tablets in the same way as aripiprazole. 42 participants were included in the mITT which was all participants randomly assigned to the double-blind treatment, with the exclusion of participants randomized at sites 002 and 005. These two centres were terminated from conducting this trial due to their failure to abide by GCPs and the protocol requirements.

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:

Participants received matching placebo tablets in the same way as aripiprazole

Number of subjects in period 1	Aripiprazole	Placebo
Started	90	45
Completed	78	35
Not completed	12	10
Consent withdrawn by subject	1	2
Adverse event	5	2
Lack of efficacy	6	6

Baseline characteristics

Reporting groups

Reporting group title	Aripiprazole

Reporting group description:

Aripiprazole was administered orally once a week (QW) for 8 weeks. Participants randomised to aripiprazole began on a 52.5 milligrams (mg) QW dose on Day 0. At the Week 1 visit, according to the investigator's discretion based on efficacy and tolerability, the dose of aripiprazole could remain at 52.5 mg QW or could be increased to 77.5 mg QW. The dose could be increased to 110 mg QW for efficacy as early as Week 2. For the remainder of the trial, the dose was to be adjusted up and down among these 3 dose levels, as determined by investigator discretion. 82 participants were included in the mITT which was all participants randomly assigned to the double-blind treatment, with the exclusion of participants randomized at sites 002 and 005. These two centres were terminated from conducting this trial due to their failure to abide by GCPs and the protocol requirements.

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo tablets in the same way as aripiprazole. 42 participants were included in the mITT which was all participants randomly assigned to the double-blind treatment, with the exclusion of participants randomized at sites 002 and 005. These two centres were terminated from conducting this trial due to their failure to abide by GCPs and the protocol requirements.

Reporting group values	Aripiprazole	Placebo	Total
Number of subjects	90	45	135
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
Adults (18-64 years)			0
From 65-84 years			0
Children (7-12 years)			0
Adolescents (13-17 years)			0
Age continuous			
Data are presented for the modified intention-to-treat (mITT) population. All subjects participants assigned to the double-blind treatment, with the exclusion of participants randomized at sites 002 and 005. These two centres were terminated from conducting this trial due to their failure to abide by GCPs and the protocol requirements. The mITT sample was used in place of the ITT sample, the primary dataset for all efficacy endpoints, and was analysed according to the treatment group to which subjects were randomized.			
Units: years			
arithmetic mean	12	11.5	
standard deviation	± 2.9	± 2.6	-
Gender categorical Units: Subjects			
Female	17	14	31
Male	73	31	104

End points

End points reporting groups

Reporting group title	Aripiprazole

Reporting group description:

Aripiprazole was administered orally once a week (QW) for 8 weeks. Participants randomised to aripiprazole began on a 52.5 milligrams (mg) QW dose on Day 0. At the Week 1 visit, according to the investigator's discretion based on efficacy and tolerability, the dose of aripiprazole could remain at 52.5 mg QW or could be increased to 77.5 mg QW. The dose could be increased to 110 mg QW for efficacy as early as Week 2. For the remainder of the trial, the dose was to be adjusted up and down among these 3 dose levels, as determined by investigator discretion. 82 participants were included in the mITT which was all participants randomly assigned to the double-blind treatment, with the exclusion of participants randomized at sites 002 and 005. These two centres were terminated from conducting this trial due to their failure to abide by GCPs and the protocol requirements.

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo tablets in the same way as aripiprazole. 42 participants were included in the mITT which was all participants randomly assigned to the double-blind treatment, with the exclusion of participants randomized at sites 002 and 005. These two centres were terminated from conducting this trial due to their failure to abide by GCPs and the protocol requirements.

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

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

End point description:

YGTSS is a semi-structured clinical interview designed to measure current (time frame of the past 1 week) tic severity. The scale consists of a tic inventory, with 5 separate rating scales to rate 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. Total tic score ranges from 0 to 50 with a higher score for more severe symptoms. The scale assesses areas of self-esteem, family life, social acceptance, and school scores. This is a fully validated scale in adults and has become a standard instrument for the evaluation of the severity of TD in children. Data are presented for the modified intention-to-treat population (mITT).

End point type	Primary

End point timeframe:

Baseline to Week 8

End point values	Aripiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[1]	34[2]		
Units: Units on a scale				
least squares mean (standard error)	-12.34 (± 0.88)	-7.72 (± 1.23)		

Notes:

[1] - Number of participants in the mITT with Baseline and Week 8 measurement of YGTSS-TTS.

[2] - Number of participants in the mITT with Baseline and Week 8 measurement of YGTSS-TTS.

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 8

Statistical analysis description:

The objective of the primary analysis was to compare the efficacy of QW oral aripiprazole with that of placebo through the change from baseline in YGTSS TTS. The statistical comparison was performed using a mixed model repeated measures (MMRM) linear model with treatment and visit week as factors, baseline YGTSS TTS as a covariate, and treatment-by-week interactions in the model at a significance level of 0.05 (2-sided).

Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.028 [3]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-4.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.62
upper limit	-1.63

Notes:

[3] - Derived from a repeated measures linear model with treatment, week, and treatment by week interaction as fixed categorical effects, the baseline value as a fixed covariate, and week as the time variable for repeated measures.

Secondary: Change in CGI-TS Score at Week 8

End point title	Change in CGI-TS Score at Week 8

End point description:

To CGI-TS 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. Data are presented for the mITT population.

End point type	Secondary

End point timeframe:

Baseline to Week 8

End point values	Aripiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70[4]	33[5]		
Units: Units on a scale				
least squares mean (standard error)	2.29 (± 0.12)	2.81 (± 0.17)		

Notes:

[4] - Number of participants in mITT with baseline CGI-TS severity and Week 8 CGI-TS change score.

[5] - Number of participants in mITT with baseline CGI-TS severity and Week 8 CGI-TS change score.

Statistical analyses

Statistical analysis title	Statisitcal analysis at Week8
Comparison groups	Aripiprazole v Placebo

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0124 [6]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	-0.12

Notes:

[6] - Derived from a repeated measures linear model with treatment, week, and treatment by week interaction as fixed categorical effects, the baseline CGI-TS severity score as a fixed covariate, and week as the time variable for repeated measures.

Secondary: Change from Baseline to Week 8 in GTS-QOL

End point title	Change from Baseline to Week 8 in GTS-QOL

End point description:

The GTS-QOL is a disease-specific patient-reported scale for the measurement of health-related quality of life in patients with TD, taking into account the complexity of the clinical picture of the disease.he questionnaire consists of a 27-item, TD-specific scale with 4 subscales (psychological, physical, obsessional, and cognitive).

End point type	Secondary

End point timeframe:

Baseline to Week 8

End point values	Aripiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[7]	34[8]		
Units: Units on a scale				
least squares mean (standard error)	10.04 (± 1.83)	12.04 (± 2.6)		

Notes:

[7] - Number of participants in the mITT with baseline and Week 8 GTS-QOL Overall Score.

[8] - Number of participants in the mITT with baseline and Week 8 GTS-QOL Overall Score.

Statistical analyses

Statistical analysis title	Statistical analysis at Week 8
Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.5317 [9]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.31
upper limit	4.32

Notes:

[9] - Derived from a repeated measures linear model with treatment, week, and treatment by week interaction as fixed categorical effects, the baseline value as a fixed covariate, and week as the time variable for repeated measures.

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

End point title	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.

End point type	Secondary

End point timeframe:

Baseline to Week 8

End point values	Aripiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[10]	34[11]		
Units: Units on a scale				
least squares mean (standard error)	-25.05 (± 1.9)	-15.61 (± 2.65)		

Notes:

[10] - Number of participants in the mITT with baseline and Week 8 Total YGTSS Score.

[11] - Number of participants in the mITT with baseline and Week 8 Total YGTSS Score.

Statistical analyses

Statistical analysis title	Statistical analysis at Week 8
Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0046 [12]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-9.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.92
upper limit	-2.97

Notes:

[12] - Derived from a repeated measures linear model with treatment, week, and treatment by week interaction as fixed categorical effects, the baseline value as a fixed covariate, and week as the time variable for repeated measures.

Secondary: Change from Baseline to Endpoint (Week 8) in CGI-TS Severity

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

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.

End point type	Secondary

End point timeframe:

Baseline to Week 8

End point values	Aripiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[13]	34[14]		
Units: Units on a scale				
least squares mean (standard error)	-1.62 (± 0.12)	-1.01 (± 0.17)		

Notes:

[13] - Number of participants in the mITT with baseline and Week 8 measurement of the given variable.

[14] - Number of participants in the mITT with baseline and Week 8 measurement of the given variable.

Statistical analyses

Statistical analysis title	Statistical analysis at Week 8
Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0043 [15]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.02
upper limit	-0.19

Notes:

[15] - Derived from a repeated measures linear model with treatment, week, and treatment by week interaction as fixed categorical effects, the baseline value as a fixed covariate, and week as the time variable for repeated measures.

Secondary: Clinical Response

End point title	Clinical Response

End point description:

Clinical response was defined as > 25% improvement from baseline to endpoint (Week 8) in YGTSS TTS or a CGI-TS change score of 1 (very much improved) or 2 (much improved) at endpoint (Week 8).

End point type	Secondary

End point timeframe:

Week 8

End point values	Aripiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[16]	34[17]		
Units: Percentage of participants				
number (not applicable)	81.7	61.8		

Notes:

[16] - Number of subjects with YGTSS or CGI change score at week 8.

[17] - Number of subjects with YGTSS or CGI change score at week 8.

Statistical analyses

Statistical analysis title	Statitical Analysis at Week 8
Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0269 [18]
Method	Chi-squared
Parameter estimate	Response ratio
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.76

Notes:

[18] - Response Ratio > 1 favours aripiprazole. P-value derived from Chi-square test.

Secondary: Treatment discontinuation rate

End point title	Treatment discontinuation rate

End point description:

Treatment discontinuation rate was 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.

End point type	Secondary

End point timeframe:

Week 8

End point values	Aripiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	42		
Units: Percentage of participants				
number (not applicable)	14.6	23.8		

Statistical analyses

Statistical analysis title	Statitical analysis 1 at Week 8
Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2056 [19]
Method	Chi-squared
Parameter estimate	Response ratio
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.3

Notes:

[19] - Discontinuation ratio < 1 favours aripiprazole. P-value derived from Chi-square test.

Statistical analysis title	Statistical analysis 2 at Week 8
Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2376 [20]
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.3

Notes:

[20] - Hazard ratio < 1 favours aripiprazole. P-value derived from Cox proportional hazard regression.

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 events reported for safety population (N=135).

Adverse event reporting additional description:

AE is defined as any untoward medical occurrence with the use of study drug. AE was considered serious if fatal, life threatening, disabling/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

Reporting group description:

Aripiprazole was administered orally once a week (QW) for 8 weeks. Participantsd to aripiprazole began on a 52.5 milligrams (mg) QW dose on Day 0. At the Week 1 visit, according to the investigator's discretion based on efficacy and tolerability, the dose of aripiprazole could remain at 52.5 mg QW or could be increased to 77.5 mg QW. The dose could be increased to 110 mg QW for efficacy as early as Week 2. For the remainder of the trial, the dose was to be adjusted up and down among these 3 dose levels, as determined by investigator discretion. 82 participants were included in the mITT which was all participants randomly assigned to the double-blind treatment, with the exclusion of participants randomized at sites 002 and 005. These two centres were terminated from conducting this trial due to their failure to abide by GCPs and the protocol requirements.

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo tablets in the same way as aripiprazole. 42 participants were included in the mITT which was all participants randomly assigned to the double-blind treatment, with the exclusion of participants randomized at sites 002 and 005. These two centres were terminated from conducting this trial due to their failure to abide by GCPs and the protocol requirements.

Serious adverse events	Aripiprazole	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 90 (3.33%)	0 / 45 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 90 (1.11%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 90 (1.11%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 90 (1.11%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 90 (1.11%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dystonia			
subjects affected / exposed	2 / 90 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
General disorders and administration site conditions			
Hyperthermia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Aripiprazole	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 90 (42.22%)	8 / 45 (17.78%)	
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 90 (13.33%)	2 / 45 (4.44%)	
occurrences (all)	17	3	
Somnolence			
subjects affected / exposed	15 / 90 (16.67%)	3 / 45 (6.67%)	
occurrences (all)	24	4	

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 90 (8.89%)	0 / 45 (0.00%)	
occurrences (all)	8	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	12 / 90 (13.33%)	4 / 45 (8.89%)	
occurrences (all)	15	4	
Vomiting			
subjects affected / exposed	9 / 90 (10.00%)	1 / 45 (2.22%)	
occurrences (all)	9	1	
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	6 / 90 (6.67%)	1 / 45 (2.22%)	
occurrences (all)	6	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2013	In the amendment, the protocol was modified to remove the option to allow participants who discontinued due to lack of efficacy at Week 5 to enter the open-label extension trial. To clarify the protocol, new text was added describing exclusion of participants for QTc values > 450 milliseconds and the process for breaking the blind for an individual participant. The duration of the conduct of the trial was increased, based on the then current enrolment rates, and the statistical methods were updated. Vyvanse [lisdexamphetamine] was added throughout the protocol to the list of psychostimulant medications prescribed for the treatment of symptoms of Attention-Deficit Disorder/Attention-Deficit Hyperactivity Disorder, which were permitted during the trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported