Clinical trial results:
Safety and Efficacy of Aripiprazole in the Long-Term Maintenance Treatment of Pediatric Subjects with Irritability Associated with Autistic Disorder

Summary

EudraCT number	2017-000174-11
Trial protocol	Outside EU/EEA
Global end of trial date	20 June 2012

Results information

Result version number	v1 (current)
This version publication date	25 February 2018
First version publication date	25 February 2018

Trial information

Trial identification

Sponsor protocol code	CN138603

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01227668
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc
Sponsor organisation address	2440 Research Boulevard, , Rockville,, United States, MD 20850
Public contact	Angela Smith, Otsuka Pharmaceutical Development & Commercialization, Inc, +1 8609202209, angela.smith@otsuka-us.com
Scientific contact	Angela Smith, Otsuka Pharmaceutical Development & Commercialization, Inc, +1 8609202209, angela.smith@otsuka-us.com

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 January 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 June 2012
Global end of trial reached?	Yes
Global end of trial date	20 June 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of aripiprazole compared with placebo to prevent relapses in pediatric subjects who maintained a response for 12 weeks of aripiprazole treatment for their symptoms of irritability associated with autistic disorder as measured by the time from randomization to relapse.

Protection of trial subjects:

In accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline, in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) and the applicable local laws and regulatory requirements of the countries in which the trial was conducted, copies of the protocol, amendments, and informed consent form (ICF) were reviewed and approved by the governing institutional review board (IRB) or independent ethics committee (IEC) for each investigational site or country, as appropriate, prior to trial start or prior to implementation of the amendment at that site or country.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 March 2011
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	United States: 157
Worldwide total number of subjects	157
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)	114
Adolescents (12-17 years)	43

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

Subject disposition

Recruitment

Recruitment details:

A total of 215 subjects were enrolled in the study, and 157 (73%) completed the screening phase and entered Phase 1. Eighty-five subjects (54%) completed Phase 1 and were randomized in Phase 2 (41 and 44 in the aripiprazole and placebo groups, respectively).

Pre-assignment

Screening details:

The study included 2 phases: Phase 1 (stabilization phase) - 13 - 26 weeks of single-blind aripiprazole treatment and Phase 2 (randomization phase) - 16 weeks of double-blind treatment with aripiprazole or placebo.

Period 1

Period 1 title	Phase 1 (Stabilization phase)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Arm title	Aripiprazole

Arm description:

Phase 1 (stabilization phase) - Participants received 13 - 26 weeks of single-blind aripiprazole treatment

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

Dosage and administration details:

aripiprazole 2, 5, 10, and 15 mg tablets, once daily at the same time each day

Number of subjects in period 1	Aripiprazole
Started	157
Completed	85
Not completed	72
Consent withdrawn by subject	7
Administrative reason by Sponsor	11
Poor/Non compliance	2
Adverse event, non-fatal	12
Lost to follow-up	8
Subject no longer meets study criteria	7
Lack of efficacy	25

Period 2

Period 2 title	Phase 2 (Randomization phase)
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Phase 2: Randomization phase - Participants received 16 weeks of double-blind treatment with placebo

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 once daily at the same time each day

Arm title	Aripiprazole

Arm description:

Phase 2: Randomization phase - Participants received 16 weeks of double-blind treatment with aripiprazole

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

Dosage and administration details:

aripiprazole 2, 5, 10, and 15 mg tablets, once daily at the same time each day

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline characteristics were presented based on Phase 2 as Baseline period.

Number of subjects in period 2[2]	Placebo	Aripiprazole
Started	44	41
Completed	19	22
Not completed	25	19
Consent withdrawn by subject	-	5
Poor/Non compliance	1	-
Adverse event, non-fatal	1	-
Lost to follow-up	-	1

Lack of efficacy	23	13

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 215 subjects were enrolled in the study, and 157 (73%) completed the screening phase and entered Phase 1. Eighty-five subjects (54%) completed Phase 1 and were randomized in Phase 2 (41 and 44 in the aripiprazole and placebo groups, respectively).

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Phase 2: Randomization phase - Participants received 16 weeks of double-blind treatment with placebo	
Reporting group title	Aripiprazole
Reporting group description:	
Phase 2: Randomization phase - Participants received 16 weeks of double-blind treatment with aripiprazole	

Reporting group values	Placebo	Aripiprazole	Total
Number of subjects	44	41	85
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	10.8	10.1	
standard deviation	± 2.77	± 2.8	-
Gender categorical			
Units: Subjects			
Female	6	11	17
Male	38	30	68

End points

End points reporting groups

Reporting group title	Aripiprazole
Reporting group description:	
Phase 1 (stabilization phase) - Participants received 13 - 26 weeks of single-blind aripiprazole treatment	
Reporting group title	Placebo
Reporting group description:	
Phase 2: Randomization phase - Participants received 16 weeks of double-blind treatment with placebo	
Reporting group title	Aripiprazole
Reporting group description:	
Phase 2: Randomization phase - Participants received 16 weeks of double-blind treatment with aripiprazole	
Subject analysis set title	The Phase 1 Safety Sample
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Phase 1 Safety Sample comprised all subjects who took at least 1 dose of single-blind aripiprazole in Phase 1 (Stabilization Phase)	
Subject analysis set title	Phase 1 Efficacy
Subject analysis set type	Full analysis
Subject analysis set description:	
The Phase 1 Efficacy Sample comprised all subjects who were in the Phase 1 Safety Sample and had at least 1 efficacy evaluation after the start of Phase 1 study drug.	
Subject analysis set title	Randomized Sample
Subject analysis set type	Full analysis
Subject analysis set description:	
The Randomized Sample comprises all patients who are randomized in Phase 2 (Randomization Phase).	
Subject analysis set title	Phase 2 Safety Sample
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Phase 2 Safety Sample comprised all subjects in the Randomized Sample who took at least 1 dose of double-blind medication in Phase 2,	
Subject analysis set title	Phase 2 Efficacy Sample
Subject analysis set type	Full analysis
Subject analysis set description:	
The Phase 2 Efficacy Sample comprised all subjects who were in the Phase 2 Safety Sample and had at least 1 efficacy evaluation after the start of Phase 2 study drug.	

Primary: Percentage of Patients Relapsing by Week 16

End point title	Percentage of Patients Relapsing by Week 16
End point description:	
Time of relapse=date when patient meets relapse criteria. There are 4 definitions for relapse: 1. Patient meets the following criteria for 2 consecutive visits: (a) Aberrant Behavior Checklist Irritability score ≥25% than score at end of Phase 1 AND (b) Clinical Global Impression Improvement scale rating of 'Much Worse' or 'Very Much Worse' relative to rating at end of Phase 1. If relapse criteria met at 1 visit, 2nd visit should occur in about 1 week to reevaluate whether relapse criteria are still met. 2. Patient discontinues for "Lost to Follow-up" after a visit in which he or she met Definition 1 criteria (a&b). 3. Patient begins a prohibited drug (whether a study investigator or outside source prescribed) to treat worsening symptoms of irritability of autistic disorder after a visit where patient met Definition 1 criteria (a&b). 4. Patient discontinues due to hospitalization for worsening symptoms of irritability or due to lack of efficacy based on investigator's assessment.	
End point type	Primary
End point timeframe:	
From end of Phase 1 (Date of randomization) to Week 16 of Phase 2 (end of treatment)	

End point values	Placebo	Aripiprazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	41		
Units: Number of events				
Number of Events	22	13		

Statistical analyses

Statistical analysis title	Summary of Time from Randomization to Relapse
Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.097
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	1.12

Secondary: Adjusted Mean Change From Baseline to Week 16 on the Aberrant Behavior Checklist Irritability (ABC-I) Subscale Score (Last Observation Carried Forward [LOCF])

End point title	Adjusted Mean Change From Baseline to Week 16 on the Aberrant Behavior Checklist Irritability (ABC-I) Subscale Score (Last Observation Carried Forward [LOCF])

End point description:

ABC is an informant-based checklist used to assess and classify problem behaviors of children and adolescents with mental retardation. The 58 items are rated on a 4-point scale (0=not at all a problem to 3=the problem is severe in degree), and resolve into 5 subscales: 1) irritability, agitation; 2) lethargy, social withdrawal; 3) stereotypic behavior; 4) hyperactivity, noncompliance; and 5) inappropriate speech. The ABC can be completed by parents, special educators, psychologists, direct caregivers, nurses, and others knowing the participant. Psychometric assessment of the ABC indicates that its subscales have high internal consistency, adequate reliability, and established validity. The ABC-I Subscale Score ranges from 0 to 45, with a negative change in score signifying improvement. LOCF data set includes data recorded at a given visit or, if no observation was recorded at that visit, data carried forward from the prior visit. (chg=change; BL=baseline; APR=aripiprazole; vs=versus).

End point type	Secondary

End point timeframe:

From Baseline (end of Phase 1) to Week 16 of Phase 2 (end of treatment)

End point values	Placebo	Aripiprazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	39		
Units: Number of Partcipants				
arithmetic mean (standard error)				
ABC Irritability (ABC-I) Subscale Scores	9.6 (± 1.56)	5.2 (± 1.61)		

Statistical analyses

Statistical analysis title	ABC Irritability (ABC-I) Subscale Scores
Comparison groups	Placebo v Aripiprazole
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.051
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.8
upper limit	0

Secondary: Change From Baseline in Mean Clinical Global Impression Improvement (CGI-I) Scale Score at Week 16 (Last Observation Carried Forward [LOCF])

End point title	Change From Baseline in Mean Clinical Global Impression Improvement (CGI-I) Scale Score at Week 16 (Last Observation Carried Forward [LOCF])

End point description:

CG-I rating scale permits global evaluation of patient's improvement over time. At baseline (BL), CGI Severity of Illness assessment is performed, in which the clinician rates severity of patient's condition on a 7-point scale ranging from 1=no symptoms to 7=very severe symptoms. Higher total score=worse symptoms. At subsequent visits, clinician assesses patient's improvement relative to symptoms at baseline on CGI-I 7-point scale ranging from 1=very much improved to 7=very much worse. Since the drug targets irritability symptoms, the CGI focuses on severity of irritability secondary to autistic disorder. Lower score=more improved symptoms. LOCF data set includes data recorded at a given visit or, if nothing recorded, data areccarried forward from the prior visit. For secondary endpoints (endpt), hierarchical testing was used to keep overall experiment-wise type I error rate to <=0.05. (diff=difference; IS=irritability scale; PA=primary analysis; signif=significance/significantly).

End point type	Secondary

End point timeframe:

From Baseline (end of Phase 1) to Week 16 of Phase 2 (end of treatment)

End point values	Placebo	Aripiprazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	39		
Units: Number of Participants				
arithmetic mean (standard error)				
Mean change in CGI-I Score	4.8 (± 0.26)	4.2 (± 0.26)		

Statistical analyses

Statistical analysis title	Mean change in CGI-I Score
Comparison groups	Placebo v Aripiprazole
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.1

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were recorded from screening (7 - 42 days) up to the end of study treatment or early termination (ET)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15

Reporting groups	
Reporting group title	Phase 1 Aripiprazole
Reporting group description:	
Phase 1 (stabilization phase) - 13 - 26 weeks of single-blind aripiprazole treatment	
Reporting group title	Phase 2 Aripiprazole
Reporting group description:	
Phase 2: Randomization phase (16 weeks of double-blind treatment with aripiprazole)	
Reporting group title	Phase 2 Placebo
Reporting group description:	
Phase 2: Randomization phase (16 weeks of double-blind treatment with placebo)	

Serious adverse events	Phase 1 Aripiprazole	Phase 2 Aripiprazole	Phase 2 Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 155 (0.65%)	0 / 39 (0.00%)	0 / 43 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 155 (0.65%)	0 / 39 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Phase 1 Aripiprazole	Phase 2 Aripiprazole	Phase 2 Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	124 / 155 (80.00%)	22 / 39 (56.41%)	14 / 43 (32.56%)
Investigations			
Weight increased			

subjects affected / exposed	39 / 155 (25.16%)	0 / 39 (0.00%)	0 / 43 (0.00%)
occurrences (all)	47	0	0
Nervous system disorders			
Movement disorder			
subjects affected / exposed	0 / 155 (0.00%)	2 / 39 (5.13%)	0 / 43 (0.00%)
occurrences (all)	0	2	0
Headache			
subjects affected / exposed	8 / 155 (5.16%)	0 / 39 (0.00%)	0 / 43 (0.00%)
occurrences (all)	14	0	0
Lethargy			
subjects affected / exposed	8 / 155 (5.16%)	0 / 39 (0.00%)	0 / 43 (0.00%)
occurrences (all)	8	0	0
Somnolence			
subjects affected / exposed	23 / 155 (14.84%)	0 / 39 (0.00%)	0 / 43 (0.00%)
occurrences (all)	27	0	0
Tremor			
subjects affected / exposed	9 / 155 (5.81%)	0 / 39 (0.00%)	0 / 43 (0.00%)
occurrences (all)	11	0	0
Insomnia			
subjects affected / exposed	13 / 155 (8.39%)	0 / 39 (0.00%)	0 / 43 (0.00%)
occurrences (all)	14	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	13 / 155 (8.39%)	0 / 39 (0.00%)	0 / 43 (0.00%)
occurrences (all)	20	0	0
Pyrexia			
subjects affected / exposed	8 / 155 (5.16%)	0 / 39 (0.00%)	0 / 43 (0.00%)
occurrences (all)	8	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 155 (0.00%)	2 / 39 (5.13%)	0 / 43 (0.00%)
occurrences (all)	0	2	0
Vomiting			
subjects affected / exposed	22 / 155 (14.19%)	2 / 39 (5.13%)	2 / 43 (4.65%)
occurrences (all)	30	2	3
Diarrhoea			

subjects affected / exposed	11 / 155 (7.10%)	0 / 39 (0.00%)	0 / 43 (0.00%)
occurrences (all)	12	0	0
Psychiatric disorders			
Aggression			
subjects affected / exposed	9 / 155 (5.81%)	0 / 39 (0.00%)	0 / 43 (0.00%)
occurrences (all)	9	0	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	16 / 155 (10.32%)	4 / 39 (10.26%)	1 / 43 (2.33%)
occurrences (all)	18	5	1
Nasopharyngitis			
subjects affected / exposed	9 / 155 (5.81%)	0 / 39 (0.00%)	0 / 43 (0.00%)
occurrences (all)	9	0	0
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	20 / 155 (12.90%)	0 / 39 (0.00%)	0 / 43 (0.00%)
occurrences (all)	25	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 July 2011	This amendment was written to remove the interim analysis from the study. This was done on the advice of the United States Food and Drug Administration. • Clarification was made to allow for the Autism Diagnostic Interview- Revised (ADI-R) to be completed via telephone. • Included modifications made by Administrative Letter 01 dated 20 Dec 2010. Deleted references to aftercare from the protocol and correct typographical errors. • Correct Typographical errors and formatting errors. • This revision applies to all study sites and subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported