Clinical trial results:
A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Flexible-Dosed Parallel-Group Study of Aripiprazole Flexibly Dosed in the Treatment of Children and Adolescents with Autistic Disorder.

Summary

EudraCT number	2016-005111-40
Trial protocol	Outside EU/EEA
Global end of trial date	28 April 2008

Results information

Result version number	v1 (current)
This version publication date	21 April 2018
First version publication date	21 April 2018

Trial information

Trial identification

Sponsor protocol code	CN138178

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00365859
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 71,501

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Wallingford, Connecticut, United States, 06492
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	21 October 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 April 2008
Global end of trial reached?	Yes
Global end of trial date	28 April 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of flexibly dosed aripiprazole with that of placebo in reducing serious behavioral problems specifically irritability, agitation, and self-injurious behavior in children and adolescents with a diagnosis of AD, as measured by change from baseline to endpoint on the Irritability Subscale of the Aberrant Behavior Checklist (ABC).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles in the Declaration of Helsinki. The rights, safety, and well-being of the study subjects were the most important consideration and prevailed over the interests of science and society. This study was conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization and 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).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 June 2006
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	United States: 98
Worldwide total number of subjects	98
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)	77
Adolescents (12-17 years)	21

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

Subject disposition

Recruitment

Recruitment details:

A total of 164 patients were enrolled at 19 study centers in the United States.
The test product was aripiprazole, 2 to 15 mg/day, flexibly dosed. The reference product was placebo.

Pre-assignment

Screening details:

Screening phase (up to 42 days (consisting of a screening visit (Visit 1), a washout period and interim screening visit (Visit 1a) , and a baseline visit (Visit 2)). During screening eligibility assessments, safety assessments, efficacy assessments and clinical drug supplies were performed.

Period 1

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

Blinding implementation details:

Aripiprazole tablets and placebo tablets were indistinguishable in appearance and shape. Study medication for the 2 treatment groups looked identical. Bottles of study medication were labeled with a 3-panel, double-blind label. The labels contained information such as the batch number, container number, number of tablets per bottle, and storage conditions.

Arms

Are arms mutually exclusive?	Yes
Arm title	Aripiprazole

Arm description:

Aripiprazole (oral tablet) flexibly dosed (2 mg to 15 mg/day) taken once daily at the same time each day without regard to meals for 8 weeks. Approximately 100 patients (50 per treatment group) will be randomized to obtain 90 evaluable patients (45 per treatment arm).

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:

All randomized patients received test product aripiprazole at flexible dosing regimen (2 to 15 mg/day) for 8 weeks on the basis of treatment response and medication tolerability. Aripiprazole was given orally at a starting dose of 2 mg. The target daily dose was 5 mg, 10 mg, or 15 mg. The need of increase in dose was done based on the clinical response and tolerability.

Arm title	Placebo

Arm description:

Randomized patients were treated orally once daily with the matching placebo tablets.

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

Dosage and administration details:

All randomized patients received matching placebo (oral tablet) at flexible dosing regimen once daily at

the same time each day for 8 weeks.

Number of subjects in period 1	Aripiprazole	Placebo
Started	47	51
Completed	39	36
Not completed	8	15
Consent withdrawn by subject	1	2
Adverse event, non-fatal	5	3
Lost to follow-up	1	4
Lack of efficacy	1	6

Baseline characteristics

Reporting groups	
Reporting group title	Aripiprazole
Reporting group description:	
Aripiprazole (oral tablet) flexibly dosed (2 mg to 15 mg/day) taken once daily at the same time each day without regard to meals for 8 weeks. Approximately 100 patients (50 per treatment group) will be randomized to obtain 90 evaluable patients (45 per treatment arm).	
Reporting group title	Placebo
Reporting group description:	
Randomized patients were treated orally once daily with the matching placebo tablets.	

Reporting group values	Aripiprazole	Placebo	Total
Number of subjects	47	51	98
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	33	44	77
Adolescents (12-17 years)	14	7	21
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	5	7	12
Male	42	44	86

End points

End points reporting groups

Reporting group title	Aripiprazole
Reporting group description:	
Aripiprazole (oral tablet) flexibly dosed (2 mg to 15 mg/day) taken once daily at the same time each day without regard to meals for 8 weeks. Approximately 100 patients (50 per treatment group) will be randomized to obtain 90 evaluable patients (45 per treatment arm).	
Reporting group title	Placebo
Reporting group description:	
Randomized patients were treated orally once daily with the matching placebo tablets.	

Primary: Aberrant Behavior Checklist (ABC) irritability subscale score

End point title	Aberrant Behavior Checklist (ABC) irritability subscale score
End point description:	
To assess the efficacy of flexibly dosed aripiprazole with that of placebo, measured by mean change from baseline to endpoint (Week 8) in the ABC Irritability Subscale score. The ABC is an informant based symptom checklist for assessing the classifying 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 resolved into 5 subscales: (1) irritability, agitation; (2) lethargy, social withdrawal; (3) stereotypic behavior; (4) hyperactivity, noncompliance; and (5) inappropriate speech.	
End point type	Primary
End point timeframe:	
From screening phase (visit 1 and baseline visit 2 [up to 42 days]) to treatment phase (Week 1 to week 8).	

End point values	Aripiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	49		
Units: number				
arithmetic mean (standard error)				
Mean baseline (SE)	29.6 (± 1.01)	30.8 (± 1)		
Mean change week 8 (SE)	-12.9 (± 1.44)	-5 (± 1.43)		

Statistical analyses

Statistical analysis title	Treatment difference from Placebo
Comparison groups	Aripiprazole v Placebo

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	Median difference (final values)
Point estimate	-7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.7
upper limit	-4.1

Secondary: Aberrant Behavior Checklist (ABC) other subscale score

End point title	Aberrant Behavior Checklist (ABC) other subscale score

End point description:

To assess the efficacy of flexibly dosed aripiprazole with that of placebo, measured by mean change from baseline to endpoint (Week 8) in the ABC Irritability Subscale score. The ABC is an informant-based symptom checklist for assessing the classifying 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 resolved into 5 subscales: (1) irritability, agitation; (2) lethargy, social withdrawal; (3) stereotypic behavior; (4) hyperactivity, noncompliance; and (5) inappropriate speech.

End point type	Secondary

End point timeframe:

From screening phase (visit 1 and baseline visit 2 [up to 42 days]) to treatment phase (Week 1 to week 8).

End point values	Aripiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	49		
Units: Number				
arithmetic mean (standard error)				
ABC Hyperactivity Subscale Score is from 0 to 48.	-12.7 (± 1.52)	-2.8 (± 1.5)		
ABC Stereotypy Subscale Score is from 0 to 21.	-4.8 (± 0.63)	-2 (± 0.62)		
ABCInappropriateSpeechSubscaleScore is from0 to 12	-2.5 (± 0.39)	-0.4 (± 0.39)		
ABCSocialWithdrawal Subscale Score is from 0 to 48	-7.9 (± 1.15)	-6.2 (± 1.13)		

Statistical analyses

Statistical analysis title	Treatment difference from Placebo
Comparison groups	Aripiprazole v Placebo

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.001 [2]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.7
upper limit	-4.1

Notes:

[1] - The primary presentation of results will be the model-based estimates and standard errors (SE) and the 95% confidence intervals (CI) for the treatment differences (aripiprazole-placebo), which will be derived from the estimation (ESTIMATE) of the treatment contrast.

[2] - P-values were two-tailed tests of significance rounded to three decimal places, based on ANOVA/ANCOVA model.

Secondary: Clinical Global Impression of Severity (CGI-S)

End point title	Clinical Global Impression of Severity (CGI-S)

End point description:

To assess the efficacy of aripiprazole with placebo as measured by the clinician-rated Clinical Global Impression of Improvement (CGI-I) and Clinical Global Impression of Severity (CGI-S). At baseline, a CGI Severity of Illness (CGI-S) assessment is performed, in which the clinician rates the severity of a patient's condition on a 7-point scale ranging from 1 (no symptoms) to 7 (very severe symptoms). At subsequent visits, the clinician assesses the patient's improvement relative to the symptoms at baseline on a CGI-Improvement (CGI-I) item, a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

End point type	Secondary

End point timeframe:

Treatment phase (Visit 3 to visit 9 or early discontinuation).

End point values	Aripiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	49		
Units: Number				
arithmetic mean (standard error)				
CGI-S score (participant number=40,40)	-1.2 (± 0.14)	-0.4 (± 0.15)		
CGI-I score (participant number=46,49)	2.2 (± 0.18)	3.6 (± 0.18)		

Statistical analyses

Statistical analysis title	Treatment difference from Placebo (CGI-S)
Comparison groups	Aripiprazole v Placebo

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.001 [4]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	-0.4

Notes:

[3] - The primary presentation of results will be the model-based estimates and standard errors (SE) and the 95% confidence intervals (CI) for the treatment differences (aripiprazole-placebo), which will be derived from the estimation (ESTIMATE) of the treatment contrast.

[4] - P-values were two-tailed tests of significance rounded to three decimal places, based on ANOVA/ANCOVA model.

Statistical analysis title	Treatment difference from Placebo (CGI-I)
Comparison groups	Placebo v Aripiprazole
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANOVA
Parameter estimate	Median difference (final values)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	-1

Secondary: Response rate at week 8

End point title	Response rate at week 8

End point description:

Response rate, defined as a reduction of ≥ 25% in ABC Irritability Subscale score compared to baseline and a score of 1 or 2 in the CGI-I scale, was determined at Weeks 1 through week 8 of the study.

End point type	Secondary

End point timeframe:

From week 1 through week 8.

End point values	Aripiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	49		
Units: percentage				
number (not applicable)				
Number Responding (%)	24	7		

Statistical analyses

Statistical analysis title	Response rate vs Placebo
Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	3.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	7.7

Secondary: Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS)

End point title	Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS)

End point description:

The CY-BOCS is a 10-item, clinician-rated scale based on a semi-structured interview that was designed to measure the severity of obsessive-compulsive symptoms in patients below the age of 18. The CY-BOCS contains 5 items pertaining to obsessions (which will not be used in this trial) and 5 items pertaining to compulsions, which rate each symptom domain in terms of time spent, interference with functioning, distress, resistance, and control. Each item is rated on a 5-point scale, from 0 (no symptoms or minimum severity) to 4 (extreme symptoms or maximum severity).

End point type	Secondary

End point timeframe:

At week 8.

End point values	Aripiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: Mean				
arithmetic mean (standard error)				
Mean Baseline (SE)	12.8 (± 0.46)	13.7 (± 0.48)		
Mean Change Week 8 (SE)	-3.8 (± 0.5)	-0.8 (± 0.52)		

Statistical analyses

Statistical analysis title	Difference from Placebo
Comparison groups	Aripiprazole v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.001 [6]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	-1.6

Notes:

[5] - The primary presentation of results will be the model-based estimates and standard errors (SE) and the 95% confidence intervals (CI) for the treatment differences (aripiprazole-placebo), which will be derived from the estimation (ESTIMATE) of the treatment contrast.

[6] - P-values were two-tailed tests of significance rounded to three decimal places, based on ANOVA/ANCOVA model.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment period and or early discontinuation.

Adverse event reporting additional description:

An AE was defined as any new untoward medical occurrence or worsening of a preexisting medical condition regardless of causal relationship with treatment. An AE could be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11

Reporting groups

Reporting group title	Aripiprazole

Reporting group description:

Aripiprazole 2-mg, 5-mg, 10-mg, or 15-mg tablets, orally, once a day, with a starting dose of 2 mg and a target dose of 5 mg, 10 mg, or 15 mg.

Reporting group title	Placebo

Reporting group description:

At the baseline visit, eligible patients were randomized to receive either aripiprazole or placebo according to a computer-generated randomization schedule prepared by BMS using a permuted block design. Treatment assignments were governed by a randomization schedule designed to allocate patients between the 2 treatment arms in a 1:1 ratio.

Serious adverse events	Aripiprazole	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 47 (0.00%)	0 / 50 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	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	43 / 47 (91.49%)	36 / 50 (72.00%)	
Nervous system disorders			
Drooling			
subjects affected / exposed	4 / 47 (8.51%)	0 / 50 (0.00%)	
occurrences (all)	5	0	
Headache			

subjects affected / exposed	3 / 47 (6.38%)	8 / 50 (16.00%)	
occurrences (all)	3	11	
Sedation			
subjects affected / exposed	5 / 47 (10.64%)	1 / 50 (2.00%)	
occurrences (all)	9	1	
Somnolence			
subjects affected / exposed	8 / 47 (17.02%)	2 / 50 (4.00%)	
occurrences (all)	14	3	
Tremor			
subjects affected / exposed	4 / 47 (8.51%)	0 / 50 (0.00%)	
occurrences (all)	5	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 47 (21.28%)	2 / 50 (4.00%)	
occurrences (all)	15	3	
Pyrexia			
subjects affected / exposed	4 / 47 (8.51%)	1 / 50 (2.00%)	
occurrences (all)	5	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 47 (8.51%)	5 / 50 (10.00%)	
occurrences (all)	6	9	
Vomiting			
subjects affected / exposed	7 / 47 (14.89%)	2 / 50 (4.00%)	
occurrences (all)	9	2	
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	3 / 47 (6.38%)	1 / 50 (2.00%)	
occurrences (all)	5	1	
Psychiatric disorders			
Aggression			
subjects affected / exposed	3 / 47 (6.38%)	4 / 50 (8.00%)	
occurrences (all)	4	5	
Enuresis			
subjects affected / exposed	3 / 47 (6.38%)	4 / 50 (8.00%)	
occurrences (all)	3	4	

Insomnia subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 6	4 / 50 (8.00%) 7	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 2 / 47 (4.26%) 2 1 / 47 (2.13%) 2	 3 / 50 (6.00%) 4 5 / 50 (10.00%) 8	
Metabolism and nutrition disorders increased appetitie subjects affected / exposed occurrences (all)	 7 / 47 (14.89%) 11	 5 / 50 (10.00%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2006	• Decreased the screening washout period for patients from 2 weeks to 4 days. • Removed the requirement that sites have separate raters for safety and efficacy assessments. • Added the Pediatric Quality of Life Inventory with age-appropriate versions and the Caregiver Strain Questionnaire outcome measure scales to the protocol. • Clarified the requirements for mental age.
14 June 2007	• Decreased the number of days, after the last dose of study drug, that an efficacy evaluation will be included for analysis. • Specified that there must be documentation that confirms the mental age. • Added the use of a historical ADI-R as long as it was completed by a documented research reliable ADI-R rater. • Added height to the Baseline Visit. • Added the laboratory collection and evaluation of insulin. • Extended the enrollment period of the study from approximately 18 months to approximately 26 months. • Clarified that efficacy data will be reviewed by the Data Monitoring Committee but that these data will not be used to stop the trial. • Deleted the administration of the CY-BOCS from the list of Screening Visit requirements. • Added mental age assessment as a procedure that must be completed at the Baseline Visit if it was not done at a Screening Visit. • Corrected the amount of time, after the end of the study, a woman of childbearing potential must use an adequate method of contraception, to make the time periods consistent within this protocol and the other double-blind protocol. • Updated the medical monitor’s contact information. • Revised the wording of Reference 17 to be consistent with the reference in the other double-blind protocol. • Added a new reference for establishing an research reliable ADI-R rater. • Corrected typographical errors. • Updated SAE facsimile number

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported