Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole (BMS-337039/OPC-14597)

Clinical Summary for Protocol CN138603
NCT No. 01227668

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

Indication:	Irritability Associated with Autistic Disorder
Clinical Development Phase:	4
Sponsor:	Bristol-Myers Squibb Company 777 Scudders Mill Road Plainsboro, NJ Otsuka Pharmaceuticals Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland US
Trial Initiation Date:	07 Mar 2011
Trial Completion Date:	20 Jun 2012
Summary Issued:	23 Dec 2014

This summary is for public dissemination of information in accordance with local regulatory requirements.
These results are supplied for informational purposes only. Prescribing decisions should be made based on the approved package insert.
This trial was conducted in compliance with Good Clinical Practice guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research subjects, no trial procedures were performed on trial candidates until written consent or assent had been obtained from them and/or their legally acceptable representative. The informed consent form, protocol, and amendments for this trial were submitted to and approved by the institutional review board or ethics committee at each respective trial center.

Name of Investigational Medicinal Product: Aripiprazole (BMS-337039/OPC-14597)

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

Trial Center(s) by Region: 42 centers were initiated in the US, and 34 of those sites enrolled subjects.

Clinical Phase/Trial Type: 4/Multi-center, double-blind, therapeutic use trial

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale:

Based on the results of studies[1,2,3,4,5] of children and adolescents with other psychiatric disorders (ie, schizophrenia, manic or mixed episodes associated with bipolar I disorder, conduct disorder, as well as irritability associated with autistic disorder [AD]), it was anticipated that flexible dosing of aripiprazole starting at very low doses (2 mg, regardless of body weight) would be well tolerated in children and adolescents with AD. Further, the proposed dosing schema with a dose range of 2 - 15 mg/day was planned to allow subjects to reach therapeutic dose levels while maintaining good tolerability. Safety data from the current trial, together with data from two antecedent 8-week double-blind, placebo controlled studies (one fixed dose trial and one flexible dose trial) and the 52-week open label safety and tolerability trial would support the use of aripiprazole as a well-tolerated and effective treatment for irritability associated with AD. Moreover, the efficacy data from the current trial would provide data regarding maintenance treatment. The current trial, along with the two antecedent 8-week trials, and the 52-week open label safety and tolerability trial would address an important unmet medical need.

Publications: None to date.

Objectives: The primary objective was 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.

Secondary objectives of the trial were:

- To evaluate the long-term effect of aripiprazole on the mean change from end of Phase 1 to endpoint on the Irritability subscale of the Aberrant Behavior Checklist-Irritability Subscale Score (ABC-I)
- To evaluate the long-term effect of aripiprazole on the mean Clinical Global Impressions-Improvement Scale (CGI-I) Score at endpoint.

Methodology: This was a multicenter, double-blind, randomized, placebo-controlled trial with 2 parallel treatment groups designed to assess the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric subjects with irritability associated with AD. The trial 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.

Number of Subjects (Planned and Analyzed): A total of 215 subjects were enrolled in the trial, 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).

Diagnosis and Main Criteria for Inclusion/Exclusion: Male or female subjects 6 to 17 years of age at the time of the baseline visit meeting Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition, Text Revision (DSM-IV-TR) diagnostic criteria for autistic disorder and demonstrating behaviors such as tantrums, aggression, self-injurious behavior, or a combination of these problems were included in the trial. The diagnosis of AD was to be confirmed by the Autism Diagnostic Interview-Revised. Subjects were to have Clinical Global Impressions-Severity Scale (CGI-S) scores ≥ 4 AND an ABC-I Subscale score ≥ 18 at the screening and baseline visits and to have a mental age of at least 24 months, as assessed by the investigators.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration: Phase 1: Single-blind aripiprazole 2, 5, 10, and 15 mg tablets were provided in bottles of 20 tablets and were flexibly dosed (2 - 15 mg/day) taken once daily for a maximum of 26 weeks. All subjects were to have aripiprazole titrated from an initial dose of 2 mg/day and adjusted to optimize clinical benefit to the subject. Phase 2: Aripiprazole was continued at the dose prescribed at the end of Phase 1 once daily. The dose (within the range of 2 - 15 mg/day) could have been adjusted based on efficacy and tolerability.

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration: In Phase 2, subjects received a matching placebo and followed the same dosing schedule as the aripiprazole subjects in order to maintain the double-blind design of this trial.

Duration of Treatment: 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.

Trial Assessments:

Efficacy: CGI-I, ABC-I, ABC subscales and CGI-S.

Safety: adverse events (AEs), serious adverse events (SAEs), extrapyramidal symptom (EPS) measures, vital signs, routine laboratory tests, electrocardiograms (ECGs), and weight and body mass index (BMI).

Outcome assessments: Pediatric Quality of Life Inventory (PedsQL) and Caregiver Strain Questionnaire (CGSQ) evaluations.

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the time from randomization to relapse. CGI-I and ABC-I were assessed every 2 weeks. Additional assessments included other ABC subscales and CGI-S. Outcome assessments included PedsQL and CGSQ evaluations.

Safety: Safety was assessed by the frequency and severity of AEs and SAEs, EPS measures, changes in vital signs, routine laboratory tests, ECGs, and the mean change from baseline in weight and BMI.

Statistical Methods: The primary efficacy outcome measure was the time from randomization to relapse. A total of 30 relapses would have provided 80% power to detect a significant difference in time to relapse between the 2 treatment groups using the log-rank test. This assumed a relapse rate of 25% in the aripiprazole group, a relapse rate of 55% in the placebo group, and a 2-sided alpha level of 0.05. The hazard ratio for these assumed relapse rates was 0.36.

The primary efficacy outcome measure above was evaluated by a survival analysis using the Randomized Sample. The survivorship function and estimated survivorship curves were obtained from Kaplan-Meier estimates. Survival distributions of the 2 treatment groups were compared using the log-rank test, stratified by baseline body weight (2 categories: $\geq$ 40 kg and < 40 kg). The estimated hazard ratio and 95% confidence interval (CI) was obtained from the Cox regression model, with baseline body weight (2 categories: $\geq$ 40 kg and < 40 kg) as a stratification factor and with treatment group as a covariate.

The secondary outcome measures were mean change from baseline (end of Phase 1) to Week 16 endpoint (last observation carried forward [LOCF]) in the ABC-I, and mean CGI-I score at Week 16 endpoint using (LOCF). The mean change from baseline in the Irritability Subscale score was evaluated using analysis of covariance (ANCOVA) model that included the end of Phase 1 Irritability score as covariate, and treatment and baseline body weight (2 categories: $\geq$ 40 kg and < 40 kg) as main effects. The mean CGI-I score was evaluated using an ANCOVA model, with CGI-S end of Phase 1 score as covariate and treatment and baseline body weight (2 categories: $\geq$ 40 kg and < 40 kg) as main effects.

Analysis of the secondary efficacy measures was performed on the Phase 2 Efficacy Sample, and was repeated utilizing the observed cases (OC) data set.

For the analysis of the secondary outcome measures, a hierarchical testing procedure was used in order for the overall experiment-wise type I error rate to be kept at < 0.05.

Summary of Results:

Baseline Data, Disposition, and Demographics: A total of 215 subjects were enrolled in the trial, and 73% completed the screening phase and entered Phase 1 (Table 1). Fifty-four percent of subjects completed Phase 1 and were randomized in Phase 2. Overall, 54% and 43% of aripiprazole and placebo subjects, respectively, completed Phase 2, and the most common reason for discontinuation was lack of efficacy in both treatment groups.

Demographic characteristics for the randomized sample were comparable across treatment groups (Table 2). The majority of subjects were male and White, and the median age was 10 years. At baseline, overall mean ABC Irritability, Hyperactivity, Stereotypy, Social Withdrawal, and Inappropriate Speech Scores were slightly higher in the aripiprazole group than in the placebo group. Mean CGI-Severity Scores were similar in both groups.

Table-1 Disposition of Subjects

Subject Status	Placebo	Aripiprazole	Total
Enrolled	-	-	215
Screen failure or discontinued during screening Phase[a]	-	-	58 (27.0)
Adverse event	-	-	1 (0.5)
Subject withdrew consent	-	-	12 (5.6)
Lost to follow-up	-	-	8 (3.7)
Subject no longer meets trial criteria	-	-	36 (16.7)
Other	-	-	1 (0.5)
Completed screening phase and entered phase 1[a]	-	-	157 (73.0)
Discontinued during phase 1[b]	-	72 (45.9)	72 (45.9)
Adverse event	-	12 (7.6)	12 (7.6)
Subject withdrew consent	-	7 (4.5)	7 (4.5)
Lost to follow-up	-	8 (5.1)	8 (5.1)
Administrative reason by sponsor	-	11 (7.0)	11 (7.0)
Subject no longer meets trial criteria	-	7 (4.5)	7 (4.5)
Lack of efficacy	-	25 (15.9)	25 (15.9)
Poor/non-compliance	-	2 (1.3)	2 (1.3)
Completed phase 1[b]	-	85 (54.1)	85 (54.1)
Randomized	44	41	85
Discontinued during phase 2[c]	25 (56.8)	19 (46.3)	44 (51.8)
Adverse event	1 (2.3)	0	1 (1.2)
Subject withdrew consent	0	5 (12.2)	5 (5.9)

Table-1 Disposition of Subjects

Subject Status	Placebo	Aripiprazole	Total
Lost to follow-up	0	1 (2.4)	1 (1.2)
Lack of efficacy	23 (52.3)	13 (31.7)	36 (42.4)
Poor/non-compliance	1 (2.3)	0	1 (1.2)
Completed phase 2[c]	19 (43.2)	22 (53.7)	41 (48.2)

[a]Percentages are based on the number of subjects enrolled.

[b]Percentages are based on the number of subjects who completed the Screening Phase and entered Phase 1 (stabilization phase).

[c]Percentages are based on the number of subjects randomized using the randomized treatment.

Table-2 Demographic Characteristics, Randomized Sample

	Placebo N = 44	Aripiprazole N = 41	Total N = 85
Age (years)[a]			
N	44	41	85
Mean	10.8	10.1	10.4
Median	11.0	10.0	10.0
Min-max	6-17	6-16	6-17
SD	2.77	2.80	2.79
Gender, n (%)			
Male	38 (86.4)	30 (73.2)	68 (80.0)
Female	6 (13.6)	11 (26.8)	17 (20.0)
Race, n (%)			
White	28 (63.6)	31 (75.6)	59 (69.4)
Black/African American	11 (25.0)	8 (19.5)	19 (22.4)
Asian	3 (6.8)	0	3 (3.5)
American Indian/Alaska Native	1 (2.3)	0	1 (1.2)
Other	1 (2.3)	2 (4.9)	3 (3.5)
Weight (kg)[b]			
N	44	41	85
Mean	50.6	51.7	51.1
Median	44.2	43.6	43.6
Min-max	19-110	21-117	19-117
S.D.	21.91	24.38	23.00
Height (cm)[b]			
N	44	41	85
Mean	148.6	143.6	146.2
Median	146.4	142.5	145.0
Min-max	115-186	112-172	112-186
S.D.	18.24	14.24	16.53
BMI (kg/m^2)[b]			

Table-2 Demographic Characteristics, Randomized Sample			
	Placebo N = 44	**Aripiprazole N = 41**	**Total N = 85**
n	44	41	85
Mean	21.9	24.0	22.9
Median	20.7	22.6	22.9
Min-max	14-38	15-43	14-43
SD	5.19	7.37	6.38

[a]Age assessed at date of first dose of single-blind trial medication.

[b]Weight, Height, and BMI assessed at last measurement on or before first day of double-blind dosing in Phase 2.

Note: SD = standard deviation, BMI = body mass index.

Efficacy Results: There was no statistically significant difference (p = 0.097) between aripiprazole and placebo for the primary endpoint (time from randomization to relapse) (randomized sample). The Kaplan-Meier relapse rates at Week 16 were 32% for aripiprazole and 50% for placebo (hazard ratio of 0.57; 95% CI: 0.28, 1.12).

The mean change from baseline in ABC-I Subscale Score at Week 16 (LOCF data set, Phase 2 Efficacy Sample) was 5.2 and 9.6 in the aripiprazole and placebo groups, respectively (treatment difference of -4.4; 95% CI: -8.8, 0.0). The mean change from baseline in ABC-I Subscale Score at Week 16 (OC data set, Phase 2 Efficacy Sample) was improved in the aripiprazole group (-1.0) compared with the placebo group (3.6) (treatment difference of -4.55; 95% CI: -8.62, -0.48).

The mean change from baseline in CGI-I Score at Week 16 (LOCF data set, Phase 2 Efficacy Sample) was 4.2 and 4.8 in the aripiprazole and placebo groups, respectively (treatment difference of -0.6; 95% CI: -1.3, 0.1).

There was a treatment-by-race interaction (White versus non-White) for aripiprazole versus placebo for the time from randomization to relapse analysis, but the significance of this finding is limited by the sample size of the trial and the lack of overall significance in the primary analysis. The relapse rates at Week 16 for White subjects were 25.8% and 60.7% for aripiprazole and placebo, respectively (hazard ratio of 0.33; 95% CI: 0.14, 0.78), and the relapse rates at Week 16 for non-White subjects were 50.0% and 31.3% for aripiprazole and placebo, respectively (hazard ratio of 1.68; 95% CI: 0.49, 5.83).

The adjusted mean change from baseline in PedsQL at Week 16 (Phase 2 Efficacy Sample; LOCF data set) for all age groups combined was improved in both treatment groups for the combined scales and Emotional, Social, and Cognitive Functioning Subscales; however, the improvement was better in the aripiprazole group than in the placebo group. The adjusted mean change from baseline in CGSQ at Week 16 (Phase 2 Efficacy Sample; LOCF data set) was improved in both treatment groups for the global score and the Objective Strain, Subjective Externalized Strain, and Subjective Internalized Strain Subscores; however, the improvement was better in the aripiprazole group than in the placebo group.

Safety Results:

Phase 2 Safety Sample: No subjects died or had SAEs. One subject had an AE that started in Phase 1 and was randomized in error in Phase 2; this subject did not receive treatment in Phase 2. No treated subjects discontinued due to AEs.

The overall incidence of treatment-emergent AEs was higher in the aripiprazole group (56.4%) than in the placebo group (32.6%). Three subjects (7.7%) in the aripiprazole group had treatment-emergent EPS-related AEs (movement disorder in 2 subjects and akathisia, extrapyramidal disorder, and tremor in 1 subject each). In the placebo group, 3 subjects (7.0%) had treatment-emergent EPS-related AEs (akathisia, muscle twitching, and tremor in 1 subject each).

The median changes from baseline in laboratory values to endpoint were generally similar between the aripiprazole and placebo groups; however, numerical differences were observed for relative eosinophils, creatine kinase, prolactin, and uric acid. Few clinically relevant laboratory abnormalities were observed, except for non-fasting triglycerides and combined triglycerides. The adjusted mean change from baseline in serum prolactin (OC data set and Week 16 LOCF) was -0.2 and 4.6 ng/mL in the aripiprazole and placebo groups, respectively.

The median changes from baseline in vital signs to endpoint were similar in both treatment groups. Few potentially clinically relevant vital sign abnormalities were observed, except for a decrease in supine diastolic blood pressure (DBP) and a decrease in standing DBP. The adjusted mean change from baseline to Week 16 (LOCF) in weight z-score was significantly greater in the aripiprazole group (0.1 kg) than in the placebo group (-0.0 kg) (treatment difference of 0.15; 95% CI: 0.06, 0.24).

The rate of Tanner stage advancement was similar in the aripiprazole and placebo groups.

Phase 1 Safety Sample: No subjects died. One subject had an SAE (aggression) that was not considered related to aripiprazole by the investigator. Thirteen subjects (8.4%) had AEs that led to discontinuation; the only AEs that led to discontinuation reported in > 1 subject were aggression and weight increased (1.3% each). Eighty percent of subjects had treatment-emergent AEs, and the most common events were weight increased, somnolence, and vomiting. Twenty-seven subjects (17.4%) had treatment-emergent EPS-related AEs, and the only treatment-emergent EPS-related AE reported in ≥ 5% of subjects was tremor (6.5%).

Few clinically relevant laboratory abnormalities were observed, except for non-fasting triglycerides and combined triglycerides. The unadjusted mean change from baseline in serum prolactin at endpoint was -4.7 ng/mL.

Potentially clinically relevant vital sign abnormalities observed in ≥10% of subjects were a decrease in sitting DBP, sitting systolic blood pressure (SBP), standing SBP and DBP, and supine SBP and DBP and an increase in sitting DBP. Mean and median changes from baseline to Week 26 in weight generally increased over time. Eleven subjects had potentially clinically relevant ECG abnormalities (sinus tachycardia in 3 subjects, ventricle premature beat in 1 subject, and other abnormalities in 7 subjects).

Conclusions:

- Aripiprazole did not achieve statistical significance versus placebo on the primary outcome measure, the time to relapse. The effect size observed was smaller than what was used to power the trial. Similar findings were observed on the 2 secondary outcome measures: mean change from baseline (end of Phase 1) to Week 16 endpoint (LOCF) in ABC-I, and mean CGI-I score at Week 16 endpoint (LOCF).
- No SAEs or discontinuations of treatment due to AEs occurred during the randomized phase. AEs were as expected with aripiprazole in pediatric subjects. The Week 16 LOCF mean change in weight z-score during Phase 2 was -0.0 in the placebo group and 0.1 in the aripiprazole group. During Phase 2, median changes were small in both the aripiprazole and placebo groups on fasting total cholesterol, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, glucose, and triglycerides.

Report Date: 04 Jan 2013

References:

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