Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole (BMS-337039/OPC-14597)
Clinical Summary for Protocol CN138179
NCT No. 00337571

A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study with Autistic Disorder

Indication:	Autistic Disorder
Clinical Development Phase:	3
Sponsor:	Bristol-Myers Squibb Wallingford, Connecticut US Otsuka Pharmaceuticals Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland US
Trial Initiation Date:	15 Jun 2006
Trial Completion Date:	03 Jun 2008
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: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study with Three Fixed Doses of Aripiprazole in the Treatment of Children and Adolescents with Autistic Disorder

Trial Center(s) by Region: The trial was conducted at 37 centers in the United States.

Clinical Phase/Trial Type: 3/Multi-center, double-blind, randomized therapeutic use trial

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale: Autistic disorder is a neurodevelopmental disorder characterized by abnormalities in social interaction, communication, and the presence of restricted and repetitive behaviors. Although not strictly part of the diagnostic criteria, there are many secondary behavioral features that are commonly associated with autism. These include irritability and tantrums, attention and/or hyperactivity disorders, self-injury, odd responses to sensory stimuli, lack of fear or excessive fearfulness, and many others.

The purpose of this trial was to test the hypothesis that aripiprazole 5 mg, 10 mg, or 15 mg/day was more effective than placebo in treating irritability in children and adolescents with a diagnosis of autistic disorder, as measured by the Irritability Subscale of the Aberrant Behavior Checklist (ABC).

Based on the results of a trial of children and adolescents with conduct disorder and experience with aripiprazole in children and adolescents with Autistic Disorder (AD) and pervasive developmental disorder (PDD), 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 was planned to allow subjects to reach therapeutic dose levels in a minimal timeframe while maintaining good tolerability.

Publications: None to date.

Objectives: The primary objective of this trial was to compare the efficacy of aripiprazole 5 mg, 10 mg, or 15 mg/day with placebo in reducing serious behavioral problems, specifically irritability, agitation, and self-injurious behavior, in children and adolescents with a diagnosis of autistic disorder, as measured by change from baseline to endpoint on the Irritability Subscale of the ABC.

Secondary Objectives:

- To compare the efficacy of aripiprazole with placebo as measured by the clinician-rated Clinical Global Impression of Improvement (CGI-I)
- To compare the efficacy of aripiprazole with that of placebo as measured by other subscales of the ABC (Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate Speech)
- To compare the Response Rate of aripiprazole with placebo (response defined as ≥ 25% reduction from baseline in the ABC Irritability Subscale score and a CGI-I score of 1 [much improved] or 2 [very much improved])
- To compare the effect of aripiprazole with placebo on reduction in compulsive behavior as measured by the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS Compulsion Scale only)
- To compare the tolerability and safety of aripiprazole with placebo

Methodology: This was a double-blind, randomized, placebo-controlled, parallel-group, multicenter 8-week trial. The trial had 2 phases: a screening phase of up to 42 days consisting of a screening visit (Visit 1), a washout period and interim screening visit (Visit 1a) when applicable, and a baseline visit (Visit 2) followed by an 8-week treatment phase. Subjects with a diagnosis of autistic disorder who had clinically significant behavioral problems that were at least moderate in severity (Clinical Global Impression of Severity ([CGI-S] ≥ 4 and ABC Irritability Subscale score ≥ 18) and who continued to meet all other eligibility criteria at the baseline visit began the 8-week, double-blind treatment phase. Subjects were randomized to treatment with aripiprazole 5 mg, 10 mg, or 15 mg/day or placebo in a 1:1:1:1 ratio. Subjects visited the clinic at the end of treatment Weeks 1, 2, 3, 4, 5, 6, and 8, at which time efficacy and safety measures were collected. To assess subject well-being and medication tolerability between visits in the latter half of the double-blind treatment phase, a telephone contact occurred at Week 7. End of trial assessments were performed at the end of Week 8 or at the time of early termination. Subjects who completed the 8-week, double-blind treatment phase were eligible for an open-label, long-term trial that evaluated the safety and tolerability of aripiprazole, flexibly dosed, as a primary endpoint and included evaluations of efficacy and quality of life as secondary endpoints.

Number of Subjects (Planned and Analyzed): Approximately 220 subjects were planned to be randomly assigned to receive aripiprazole 5, 10, or 15 mg/day or placebo at up to approximately 35 sites. A total of 368 subjects were enrolled, with 218 subjects randomized to receive treatment: placebo, 52 subjects; aripiprazole 5 mg, 53 subjects; aripiprazole 10 mg, 59 subjects; and aripiprazole 15 mg, 54 subjects.

Diagnosis and Main Criteria for Inclusion/Exclusion: Subjects were male or female children or adolescents, 6 to 17 years of age, who met current diagnostic criteria for AD (as defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision [DSM-IV-TR] criteria) with serious behavioral problems, such as tantrums, aggression, self-injurious behavior, or a combination of these problems.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration: 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.

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration: Placebo, matching tablets administered orally once daily.

Duration of Treatment: The trial had 2 phases: a screening phase of up to 42 days followed by an 8-week treatment phase.

Trial Assessments:

Efficacy: ABC Irritability Subscale score, CGI-I score, other ABC subscale scores, response rate, and CY-BOCS.

Safety: Adverse events (AEs), serious adverse events (SAEs), discontinuations due to AEs, vital signs, body weight, electrocardiogram (ECGs), routine laboratory tests, physical examinations, Simpson-Angus Scale (SAS) score, the Abnormal Involuntary Movement Scale (AIMS) score, and the Barnes Akathisia Scale.

Criteria for Evaluation:

Efficacy: The primary efficacy outcome measure was the mean change from baseline to endpoint in the ABC Irritability Subscale score. Secondary efficacy outcome measures included the mean CGI-I score, the mean change from baseline to endpoint in the other ABC subscale scores, response rate (response defined as a $\geq$ 25% reduction from baseline to endpoint in the ABC Irritability Subscale score and a CGI-I score of 1 or 2 at endpoint), and the mean change from baseline to endpoint in the CY-BOCS (Compulsion Scale only) and CGI-S.

Safety: Safety outcome measures included the frequency and severity of AEs, SAEs, and discontinuations from the trial due to AEs as well as vital signs, body weight, ECGs, routine laboratory tests, and physical examination. Safety and tolerability of trial medication were evaluated by reports of AEs including clinically significant changes in ECGs, vital signs, clinical laboratory tests, and physical examinations. Safety and tolerability of trial medication was evaluated by the change from baseline in the SAS score, the AIMS score, and the Barnes Akathisia Scale.

Statistical Methods: The planned sample size of 204 evaluable subjects (51 per treatment group) was estimated to provide 92% power to differentiate between placebo and at least 1 or 2 higher dosage aripiprazole treatment groups (10 mg or 15 mg) when the true difference in the mean changes from baseline in the ABC Irritability Subscale score was 7.0. This assumed a standard deviation of 9.42 and a 2-sided test at the 0.025 level of significance (adjusted for 2 comparisons versus placebo to ensure an overall probability of Type 1 error $\leq$ 0.05).

The Randomized Sample included all subjects who were randomized to receive double-blind treatment. The Safety Sample comprised all subjects in the Randomized Sample who took at least 1 dose of trial medication during the double-blind treatment phase, as identified on the dosing record. The Efficacy Sample comprised all subjects who were in the Safety Sample and had at least 1 post-randomization efficacy evaluation and corresponding baseline value (if applicable). The last observation carried forward (LOCF) data set included data recorded at a given timepoint or, if no observation was recorded at that timepoint, data carried forward from the previous timepoint with available data. Baseline data were not carried forward or averaged with the on-treatment data to impute missing values for the LOCF data set. The observed cases (OC) data set consisted of the actual observations at each timepoint.

For continuous measurements, such as the ABC Irritability Subscale score, change scores were evaluated by analysis of covariance (ANCOVA). The ANCOVA models for LOCF data sets included the baseline measure as a covariate and baseline body weight (2 categories: $\geq$ 40 kg and < 40 kg), trial center, and treatment as main effects. The primary presentations of results were the model-based estimates and standard errors (SE) and the 95% confidence intervals (CI) for the treatment differences (aripiprazole-placebo), which were derived from the estimation of the treatment contrast.

Categorical measures such as response were analyzed within the framework of the generalized Cochran-Mantel Haenszel (CMH) procedure. The analyses of the LOCF data set controlled for trial center.

P-values were 2-tailed tests of significance rounded to 3 decimal places. Except for the primary endpoint analysis, all analyses were performed at the 5% significance level.

Safety and tolerability of trial medication were evaluated by reports of AEs including clinically significant changes in ECGs, vital signs, physical examinations, and clinical laboratory tests. The incidence of AEs was tabulated by treatment, according to severity, and drug-attributability.

In addition, weight and body mass index (BMI) were also evaluated in terms of change from baseline. The analytical approaches described for the efficacy analyses were applied to the safety rating scales and weight/BMI evaluations.

All safety analyses were performed on the Safety Sample. For safety analyses, subjects were analyzed by treatment received.

Summary of Results:

Baseline Data, Disposition, and Demographics:
Table 1 displays subject disposition and Table 2 displays demographics and other pertinent baseline characteristics.

Table-1 Disposition of Subjects

Subject Status	Placebo	Aripiprazole 5 mg	Aripiprazole 10 mg	Aripiprazole 15 mg	Total
Enrolled	NA	NA	NA	NA	368
Baseline Failures	NA	NA	NA	NA	150
No. of Subjects included in analysis					
Randomized	52	53	59	54	218
Safety	51	52	59	54	216
Efficacy	49	52	59	53	213
Discontinued from Double-Blind Treatment, n (%)	14 (26.9)	9 (17.0)	10 (16.9)	7 (13.0)	40 (18.3)
Lack of efficacy	3 (5.8)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.4)
Adverse event	4 (7.7)	5 (9.4)	8 (13.6)	4 (7.4)	21 (9.6)
Withdrew consent	2 (3.8)	2 (3.8)	1 (1.7)	0 (0.0)	5 (2.3)
Lost to follow-up	3 (5.8)	1 (1.9)	0 (0.0)	1 (1.9)	5 (2.3)
Poor/non-compliance	1 (1.9)	1 (1.9)	1 (1.7)	1 (1.9)	4 (1.8)
No longer met trial criteria	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.5)
Completed Double-Blind Treatment	38 (73.1)	44 (83.0)	49 (83.1)	47 (87.0)	178 (81.7)

Abbreviations: NA = not applicable

Table-2 Baseline and Demographic Characteristics

	Placebo N = 52	Aripiprazole 5 mg, N = 53	Aripiprazole 10 mg, N = 59	Aripiprazole 15 mg, N = 54	Total N = 218
Mean age (years)	10.2	9.0	10.0	9.5	9.7
Gender, n (%)					
Male	48 (92.3)	47 (88.7)	50 (84.7)	50 (92.6)	195 (89.4)
Female	4 (7.7)	6 (11.3)	9 (15.3)	4 (7.4)	23 (10.6)
Race, n (%)					
White	35 (67.3)	37 (69.8)	41 (69.5)	42 (77.8)	155 (71.1)
Black/African American	13 (25.0)	13 (24.5)	15 (25.4)	9 (16.7)	50 (22.9)
Asian	3 (5.8)	1 (1.9)	2 (3.4)	0 (0.0)	6 (2.8)
Native Hawaiian/Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.5)
Other	1 (1.9)	2 (3.8)	1 (1.7)	2 (3.7)	6 (2.8)
Mean weight (kg)	45.6	38.9	44.8	42.2	42.9

Efficacy Results:

All 3 doses of aripiprazole demonstrated statistically significant improvement compared with placebo on the primary efficacy endpoint, the mean change from baseline to Week 8 LOCF in the ABC Irritability Subscale score. Table 3 summarizes measures related to the primary efficacy endpoint.

Table-3 Summary of Primary Efficacy Endpoint					
Variable		**Placebo**	**Aripirazole**		
			5 mg	**10 mg**	**15 mg**
Primary Efficacy Endpoint					
ABC Irritability Subscale Score[a]	N	49	52	59	53
	Mean baseline (SE)	26.9 (1.04)	28.3 (1.03)	27.6 (0.94)	28.3 (0.99)
	Mean change Wk 8 (SE)	-8.4 (1.39)	-12.4 (1.36)	-13.2 (1.25)	-14.4 (1.31)
	Difference from Placebo[b]		-4.0	-4.8	-6.0
	(95% CI)		(-7.7, -0.4)	(-8.4, -1.3)	(-9.6, -2.3)
	p-value		0.032	0.008	0.001

[a]Results of analyses are model based: ANOVA model, controlling for treatment, baseline weight category (≥ 40 kg and < 40 kg) and trial center, is used for baseline estimates. ANCOVA model, controlling for treatment, baseline weight category (≥ 40 kg and < 40 kg), trial center and baseline value, is used for mean change from baseline comparisons. LS Means, 95% confidence intervals and p-values are based on ANOVA/ANCOVA model.

[b]Treatment difference = difference in adjusted treatment mean changes: aripiprazole-placebo

Aripiprazole demonstrated statistically significant improvement compared with placebo in most of the secondary efficacy endpoints in the 15-mg dose group and in 3 or 4 of the endpoints in the 5- and 10-mg dose groups. All aripiprazole dose groups demonstrated statistically significant improvement compared with placebo in the adjusted mean CGI-I scores at Week 8 LOCF: placebo: 3.3; aripiprazole 5 mg: 2.6, difference -0.7, 95% CI (-1.2, -0.3), $p = 0.003$; 10 mg: 2.5, difference -0.8, 95% CI (-1.3, -0.4), $p < 0.001$; 15 mg: 2.5, difference -0.8, 95% CI (-1.3, -0.3), $p < 0.001$. The response rate at Week 8 LOCF for the placebo group was 34.7% versus 55.8% for the aripiprazole 5-mg group ($p = 0.034$), 49.2% for the 10-mg group ($p = 0.122$), and 52.8% for the 15-mg group ($p = 0.084$). In the mean change from baseline to Week 8 LOCF on the ABC Hyperactivity, Stereotypy, and Inappropriate Speech Subscale scores, all aripiprazole dose groups had statistically significant improvement compared with placebo, except for the 5- and 10-mg groups on the Inappropriate Speech Subscale scores. For the mean changes from baseline to Week 8 LOCF in the CY-BOCS scores, aripiprazole also showed a statistically significant improvement compared with placebo for the 15-mg dose only, and for the CGI-S, 10- and 15-mg aripiprazole doses were statistically significant (Week 8, LOCF; $p \leq 0.05$) compared with placebo. For the remaining secondary efficacy endpoint, the ABC Social Withdrawal Subscale score, results were similar between placebo and all aripiprazole treatment groups.

Safety Results:

Table 4 presents a summary of safety results.

The most frequently (≥ 10%) reported AEs were:

- Placebo: insomnia (11.8%)
- Aripiprazole 5 mg: increased appetite (19.2%), sedation (17.3%), cough (15.4%), and nasopharyngitis (11.5%)
- Aripiprazole 10 mg: sedation (28.8%), fatigue (22.0%), vomiting (20.3%), drooling (13.6%), tremor and pyrexia (11.9% each), and constipation (10.2%)
- Aripiprazole 15 mg: sedation (24.1%), fatigue (18.5%), increased appetite (13.0%), and tremor, extrapyramidal disorder, and salivary hypersecretion (11.1% each)

Table-4 Summary of Safety

	Placebo	Aripiprazole		
Safety Sample	**N = 51**	**5 mg, N = 52**	**10 mg, n = 59**	**15 mg, N = 54**
Deaths, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-emergent SAEs[a], n (%)	0 (0.0)	1 (1.9)	1 (1.7)	0 (0.0)
AEs leading to discontinuation of trial medication, n (%)	4 (7.8)	5 (9.6)	8 (13.6)	4 (7.4)
Treatment-emergent AEs overall, n (%)	37 (72.5)	46 (88.5)	53 (89.8)	46 (85.2)
Treatment-emergent AEs related to trial drug, n (%)	22 (43.1)	37 (71.2)	50 (84.7)	39 (72.2)
Treatment-emergent EPS-related AEs	6 (11.8)	12 (23.1)	13 (22.0)	12 (22.2)
Change from baseline in body weight (kg), Week 8 LOCF	N = 49	N = 52	N = 59	N = 53
Adjusted mean (SE)	0.3 (0.32)	1.3 (0.31)	1.3 (0.29)	1.5 (0.30)
Treatment difference vs placebo (95% CI)		1.0 (0.1, 1.8)	0.9 (0.1, 1.8)	1.2 (0.3, 2.0)
p-value[b]		0.024	0.027	0.007

AE = adverse event, CI = confidence interval, EPS = extrapyramidal symptom, LOCF = last observation carried forward, SAE = serious adverse event, SE = standard error

[a]SAEs were presyncope in an 11-year-old male subject receiving 5-mg aripiprazole and aggression in a 9-year-old female subject receiving 10-mg aripiprazole

[b]ANOVA model, controlling for treatment and trial center, is used for baseline comparisons. ANCOVA model, controlling for treatment, trial center (LOCF only) and baseline value, is used for mean change from baseline comparisons. Means, mean differences, SE of means, 95% confidence intervals for the differences and the p-values are based on ANOVA/ANCOVA model

Conclusions:

At 5-, 10-, and 15-mg/day doses:

- Aripiprazole demonstrated clinically relevant and statistically significant improvement compared with placebo on the primary efficacy endpoint at Week 8 (LOCF), the adjusted mean change from baseline on the ABC Irritability Subscale score. In addition, aripiprazole demonstrated improvements compared with placebo on several secondary efficacy endpoints

- Aripiprazole was safe and well tolerated in this population. There was no evidence of new safety concerns. Statistically significant weight gain was seen in this population for subjects receiving aripiprazole compared with placebo.

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