Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole (BMS-337039/OPC-14597)

Clinical Summary for Protocol CN138178
NCT No. 00332241

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

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:	28 Apr 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, Flexible-Dosed, Parallel-Group Study of Aripiprazole Flexibly Dosed in the Treatment of Children and Adolescents with Autistic Disorder

Trial Centers by Region: The trial was conducted at 20 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: Based on the results of the 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 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).

Key Secondary Objective:

- To compare the efficacy of aripiprazole with placebo as measured by the clinician-rated Clinical Global Impression of Improvement (CGI-I)

Other Secondary Objectives:

- To compare the efficacy of aripiprazole with 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 $\geq$ 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) (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 either aripiprazole (2 to 15 mg/day) or placebo in a 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 evaluates the safety and tolerability of aripiprazole, flexibly dosed, as a primary endpoint and includes evaluations of efficacy and quality of life as secondary endpoints.

Number of Subjects (Planned and Analyzed): Approximately 100 subjects were planned to be randomly assigned to receive aripiprazole (2 to 15 mg) or placebo at up to approximately 20 sites. A total of 164 subjects were enrolled with 98 randomized (51 in the placebo group and 47 in the aripiprazole group).

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 treatment period was 8 weeks in duration.

Trial Assessments:

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

Safety: adverse events (AEs), serious adverse events (SAEs), trial 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. The key secondary efficacy outcome measure was the mean CGI-I score. Secondary efficacy outcome measures included 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 mean change from baseline to endpoint in the CY-BOCS (compulsion scale only).

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 sample size of 90 evaluable subjects (45 per treatment group) was estimated to provide 93% power to differentiate between placebo and the aripiprazole treatment group 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 0.05 level of significance.

The Randomized Sample included all subjects who were randomized to 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. 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: ≥ 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. All analyses were performed at the 5% significance level. For the analysis of the key secondary efficacy endpoint, a hierarchical testing procedure was used in order to protect the overall experiment-wise type I error rate at 0.05. Thus, the CGI-I would be tested only if the aripiprazole treatment group was significantly different versus placebo from the primary efficacy endpoint analysis.

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 Disposition of Subjects

Subject Status	Placebo	Aripiprazole	Total
Enrolled	NA	NA	164
Baseline Failures	NA	NA	66
No. of Subjects included in analyses			
Randomized	51	47	98
Safety	50	47	97
Efficacy	49	46	95

Table 1	**Disposition of Subjects**		
Subject Status	**Placebo**	**Aripiprazole**	**Total**
Discontinued from Double-Blind Treatment, n (%)	15 (29.4)	8 (17.0)	23 (23.5)
Lack of efficacy	6 (11.8)	1 (2.1)	7 (7.1)
Adverse event	3 (5.9)	5 (10.6)	8 (8.2)
Withdrew consent	2 (3.9)	1 (2.1)	3 (3.1)
Lost to follow-up	4 (7.8)	1 (2.1)	5 (5.1)
Completed Double-Blind Treatment	36 (70.6)	39 (83.0)	75 (76.5)

Table 2	**Baseline and Demographic Characteristics**		
	Placebo N = 51	**Aripiprazole N = 47**	**Total N = 98**
Mean age (years)	8.8	9.7	9.3
Gender, n (%)			
Male	44 (86.3)	42 (89.4)	86 (87.8)
Female	7 (13.7)	5 (10.6)	12 (12.2)
Race, n (%)			
White	41 (80.4)	32 (68.1)	73 (74.5)
Black/African American	7 (13.7)	11 (23.4)	18 (18.4)
Asian	0	2 (4.3)	2 (2.0)
Native Hawaiian/Other Pacific Islander	0	1 (2.1)	1 (1.0)
Other	3 (5.9)	1 (2.1)	4 (4.1)
Mean weight (kg)	40.6	43.9	42.2

Efficacy Results: 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 and the key secondary endpoint, the clinician rated CGI-I score, starting at Week 1 and continuing through endpoint (Week 8 LOCF). Table 3 summarizes the primary and key secondary efficacy endpoints.

Table 3	**Summary of Primary and Key Secondary Efficacy Endpoints**		
Variable		**Placebo**	**Aripiprazole**
Primary Efficacy Endpoint			
ABC Irritability Subscale Score[a]	N	49	46
	Mean baseline (SE)	30.8 (1.00)	29.6 (1.01)
	Mean change Wk 8 (SE)	-5.0 (1.43)	-12.9 (1.44)
	Difference from placebo[b]		-7.9
	(95% CI)		(-11.7, -4.1)
	p-value		<0.001

Table 3	**Summary of Primary and Key Secondary Efficacy Endpoints**		
Variable		**Placebo**	**Aripiprazole**
Key Secondary Efficacy Endpoint			
CGI-I[c]	N	49	46
	Mean Week 8 (SE)	3.6 (0.18)	2.2 (0.18)
	Difference from placebo[b]		-1.4
	(95% CI)		(-1.9, -1.0)
	p-value		<0.001

CI = confidence interval, SE = standard error

[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. Least squares (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

[c]Results of analyses of CGI-I are model based: ANCOVA model, controlling for treatment, baseline weight category (≥ 40 kg and < 40 kg), trial center and baseline value of CGI-S, is used for mean improvement score comparisons. LS Means, 95% confidence intervals and p-values are based on ANCOVA model.

Aripiprazole demonstrated statistically significant improvement compared with placebo in most of the other secondary efficacy endpoints. The overall response rate at Week 8 (LOCF) for the placebo group was 14.3% versus 52.2% for the aripiprazole group ($p < 0.001$). Differences between treatment groups in the mean change from baseline to Week 8 (LOCF) in the ABC Hyperactivity, Stereotypy, and Inappropriate Speech Subscale scores were in favor of aripiprazole ($p < 0.001$ each). For the mean changes from baseline to Week 8 (LOCF) in the CGI-S and CY-BOCS scores, there were also differences in favor of aripiprazole (CGI-S: placebo -0.4, aripiprazole -1.2, $p < 0.001$; CY-BOCS: placebo -0.8, aripiprazole -3.8, $p < 0.001$). These statistically significant results in favor of aripiprazole began early in the trial and continued through endpoint (Week 8) in these efficacy measures: the ABC Stereotypy subscale, beginning at Week 1 and at all timepoints on treatment except Week 3; the ABC Hyperactivity subscale, beginning at Week 1 to endpoint; the ABC Inappropriate Speech subscale, beginning at Week 2 to endpoint; and the overall Response Rate beginning at Week 2 and continuing through endpoint. For the remaining secondary efficacy endpoint, the ABC Social Withdrawal Subscale score, results were similar between treatment groups.

Safety Results: Table 4 presents a summary of safety results. The most frequently (≥ 10%) reported AEs in the placebo group were headache (16.0%) and increased appetite, diarrhea, and upper respiratory tract infection (10.0% each), and in the aripiprazole group were fatigue (21.3%), somnolence (17.0%), vomiting and increased appetite (14.9% each), and sedation (10.6%).

Table 4 Summary of Safety		
	Placebo	**Aripiprazole**
Safety Sample	N = 50	N = 47
Deaths, n (%)	0 (0)	0 (0)
Treatment-emergent SAEs, n (%)	0 (0)	0 (0)
AEs leading to discontinuation of trial medication, n (%)	3 (6.0)	5 (10.6)
Treatment-emergent AEs overall, n (%)	36 (72.0)	43 (91.5)
Treatment-emergent AEs related to trial drug, n (%)	25 (50.0)	39 (83.0)
Treatment-emergent EPS-related AEs	4 (8.0)	7 (14.9)
Change from baseline in body weight (kg), Week 8 LOCF	N = 49	N = 45
Adjusted mean (SE)	0.8 (0.29)	2.0 (0.30)
Treatment difference vs placebo (95% CI)		1.2 (0.4, 2.0)
p-value[a]		0.004

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

[a] ANCOVA model, controlling for treatment 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:

When flexibly dosed (2 to 15 mg/day):

- Aripiprazole demonstrated clinically relevant and statistically significant improvement compared with placebo on the primary efficacy endpoint, the adjusted mean change from baseline on the ABC Irritability Subscale, starting at Week 1 and continuing through endpoint (Week 8 LOCF).
- Aripiprazole demonstrated clinically relevant and statistically significant improvement compared with placebo on the key secondary efficacy endpoint, the clinician rated CGI-I score, starting at Week 1 and continuing through endpoint (Week 8 LOCF). In addition, aripiprazole demonstrated statistically significant improvement compared with placebo on 5 secondary efficacy endpoints.
- Aripiprazole was safe and well tolerated in this population. There was no evidence of new safety concerns. Somnolence, sedation, fatigue, extrapyramidal symptoms, and weight gain were observed more frequently in subjects treated with aripiprazole relative to those treated with placebo.

Report Date: 21 Oct 2008