Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole (BMS-337039/OPC-14597)

Clinical Summary for Protocol CN138180
NCT No. 00365859

A 52-Week, Open-label, Multicenter Study of the Safety and Tolerability 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, CT US Otsuka Pharmaceuticals Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland US
Trial Initiation Date:	20 Sep 2006
Trial Completion Date:	05 Jun 2009
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 (OPC-14597)

Protocol Title: A 52-Week, Open-label, Multicenter Study of the Safety and Tolerability of Aripiprazole Flexibly Dosed in the Treatment of Children and Adolescents with Autistic Disorder

Trial Center(s) by Region: The trial was conducted at 53 centers in the United States.

Clinical Phase/Trial Type: 3/Open-label, multi-center, noncomparative 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:

Primary Objective

The primary objective of this trial was to evaluate long-term safety and tolerability of aripiprazole flexibly dosed in the treatment of serious behavioral problems in children and adolescents with a diagnosis of autistic disorder. Safety and tolerability were assessed by vital sign measurements, body weight/body mass index (BMI), electrocardiograms (ECGs), clinical laboratory evaluations, physical examinations, adverse events (AEs), and treatment discontinuations.

In addition to the measurements of the primary objective specified above, extrapyramidal side effects were evaluated using the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Global Clinical Assessment and the Simpson-Angus Scale (SAS).

Secondary Objectives

Secondary objectives of the trial were:

- To evaluate efficacy using the Aberrant Behavior Checklist (ABC) and Clinical Global Impression of Severity (CGI-S)

- To evaluate the long-term effect of aripiprazole flexibly dosed on health-related quality of life in children and adolescents with a diagnosis of autistic disorder, as measured by the Pediatric Quality of Life (PedsQL) 4.0

Methodology: This was an open-label, multicenter safety investigation of aripiprazole, flexibly dosed, in children and adolescents with a diagnosis of AD. Subjects who completed either of the antecedent double-blind, parallel-group studies of aripiprazole in comparison to placebo (protocols CN138178 or CN138179) were eligible to enter this 52-week trial, provided that continuation of treatment was clinically warranted, as judged by the investigator, and there were no clinically relevant AEs that would preclude inclusion in the trial. Since the trial blind from the antecedent trials was not broken prior to subjects entering this trial, the investigator's decision to allow a subject to rollover into the CN138180 trial was based on his clinical judgment of the subject's condition. De novo subjects (ie, subjects who did not participate in protocols CN138178 or CN138179) were also eligible, provided that they met the entry criteria specified in the protocol. Sites were not permitted to enroll de novo subjects who were eligible to enroll in CN138178 or CN138179 until they had completed enrolling subjects in those studies, unless approved by the sponsor/contract research organization (CRO). De novo subjects included children or adolescents (with or without current treatment) who were either currently exhibiting or had a history of serious behavioral problems with a diagnosis of AD. The decision to switch a subject from current medication (psychotropics) other than aripiprazole to trial therapy was to be based on either an inadequate response or tolerability issues. De novo subjects with a history of serious behavioral problems who currently were being treated with aripiprazole and were doing well could have been enrolled in this trial if, in the investigator's clinical judgment, the evaluations could facilitate the subject's medical care.

Number of Subjects: It was anticipated that 300 subjects would receive open-label treatment with aripiprazole in this trial; 330 subjects actually received open-label treatment on the completion of enrollment into the trial. Of the 330 treated subjects, there were 244 (74%) rollover (placebo: 70, aripiprazole: 174) and 86 (26%) de novo subjects.

Diagnosis and Main Criteria for Inclusion/Exclusion: Subjects who completed participation in protocol CN138178 or CN138179 and continued to meet all inclusion criteria and none of the exclusion criteria were eligible for this trial provided that continuation of treatment was clinically warranted, as judged by the investigator, and there were no clinically relevant AEs that precluded inclusion in the trial. De novo subjects (who did not participate in protocols CN138178 or CN138179) were to be a male/female child or adolescent aged from 6 to 17 years (with a documented mental age of at least 18 months) who met the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition, Text Revision (DSM-IV-TR) diagnostic criteria for autistic disorder with either or both of the following conditions: current behavioral problems or history of behavioral problems currently being treated with psychotropic medications.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration: Aripiprazole (oral tablet) flexibly dosed (2 to 15 mg/day) taken once daily at the same time each day without regard to meals. Because the antecedent double-blind protocols (CN138178 or CN138179) were still blinded, all subjects were started at 2 mg/day aripiprazole, which began on Day 1 of this open-label, long-term trial.

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration: Not Applicable.

Duration of Treatment: Individual subject duration was 52 weeks.

Trial Assessments:

Efficacy: ABC, Clinical Global Impression-Improvement (CGI-I), CGI-S, and Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).

Safety: AEs, physical examinations, vital signs, body weight/BMI, ECGs, clinical laboratory evaluations, and extrapyramidal symptom (EPS) measures including the AIMS, Barnes Akathisia Scale, and SAS.

Other: Pediatric Quality of Life (PedsQL), Caregiver Strain Questionnaire (CGSQ), and Autism Diagnostic Interview-Revised (ADI-R).

Criteria for Evaluation:

Efficacy: Efficacy variables included the ABC and CGI-S.

Safety: Safety variables included AEs, physical examinations, vital signs, body weight/BMI, ECGs, clinical laboratory evaluations, and EPS measures including the AIMS, Barnes Akathisia Scale, and SAS.

Other: Other criteria for evaluation included the PedsQL.

Statistical Methods: The Enrolled Sample consisted of all subjects in the trial (ie, all subjects who signed the informed consent). The Safety Sample included all enrolled subjects who received at least 1 dose of open-label trial medication. This was the primary sample for evaluating safety during this 52-week trial. The efficacy sample included subjects in the safety sample who had at least 1 post-treatment (open-label) efficacy evaluation. This was the primary sample for the descriptive efficacy summaries during this trial.

The evaluation of efficacy and quality of life in this open-label trial was of secondary importance. Safety and tolerability of trial medication, which was of primary importance, was evaluated by reports of AEs including clinically relevant changes in ECGs, vital signs, body weight, physical examinations, clinical laboratory tests, and EPS

measures. Descriptive statistics were presented including mean, standard deviation, median, and ranges for continuous variables, and frequency and percent frequency for categorical variables. Comparisons were made to baseline when appropriate. For rollover subjects, baseline measurements were the last available observations from either CN138178 or CN138179 protocols that were on or before Day 1 (start of trial medication in CN138180).

BMI and body weight z-score analyses were conducted over time. The body weight and BMI z-scores are by age and gender-standardized values (corresponding to a normal distribution with mean 0 and a standard deviation of 1) of the actual weight and BMI measurements, based on the growth charts provided by the Centers for Disease Control and Prevention (CDC). These growth charts consist of a series of percentile curves that reflect the distribution of selected body measurements, such as weight and BMI, in the overall United States (US) pediatric population between the ages of 2 to 20 years.

Summary of Results:

Baseline Data, Disposition, and Demographics: Table 1 presents a summary of subject disposition

Table-1 Subject Disposition

	De Novo	Placebo Rollover	Aripiprazole Rollover	Overall
No. of subjects enrolled	109	70	174	353
Screen Failures	23	0	0	23
Entered Treatment Phase	86	70	174	330
No. of subjects completing treatment (52 weeks)	55 (64.0)	37 (52.9)	107 (61.5)	199 (60.3)
No. of subjects discontinued, n (%)[a]	31 (36.0)	33 (47.1)	67 (38.5)	131 (39.7)
Lack of efficacy	8 (9.3)	5 (7.1)	7 (4.0)	20 (6.1)
Adverse event[b]	9 (10.5)	11 (15.7)	15 (8.6)	35 (10.6)
Subject withdrew consent	7 (8.1)	5 (7.1)	15 (8.6)	27 (8.2)
Lost to follow-up	2 (2.3)	8 (11.4)	21 (12.1)	31 (9.4)
Poor/noncompliance	2 (2.3)	1 (1.4)	2 (1.1)	5 (1.5)
Subject no longer met trial criteria	1 (1.2)	0 (0)	1 (0.6)	2 (0.6)
Administrative reason	1 (1.2)	1 (1.4)	2 (1.1)	4 (1.2)
Other	1 (1.2)	2 (2.9)	4 (2.3)	7 (2.1)

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

[b]For 2 rollover subjects, the AEs leading to discontinuation started prior to the start of the CN138180 trial.

Table 2 presents a summary of baseline and demographic characteristics.

Table-2	**Baseline and Demographic Characteristics, Safety Sample**			
	De Novo N = 86	**Placebo Rollover N = 70**	**Aripiprazole Rollover N = 174**	**Overall N = 330**
Age (years)				
Mean (SD)	9.7 (3.13)	9.6 (2.95)	9.5 (3.00)	9.6 (3.02)
Range	6 - 17	6 - 17	6 - 17	6 - 17
Gender, n (%)				
Male	70 (81.4)	62 (88.6)	155 (89.1)	287 (87.0)
Female	16 (18.6)	8 (11.4)	19 (10.9)	43 (13.0)
Race, n (%)				
White	65 (75.6)	53 (75.7)	117 (67.2)	235 (71.2)
Black	14 (16.3)	12 (17.1)	44 (25.3)	70 (21.2)
Asian	0 (0.0)	2 (2.9)	4 (2.3)	6 (1.8)
Other[a]	7 (8.1)	3 (4.3)	9 (5.2)	19 (5.8)
	N = 86	**N = 70**	**N = 170**	**N = 326**
Weight (kg)				
Mean(SD)	42.2 (23.02)	44.8 (20.36)	45.3 (21.75)	44.4 (21.78)
Range	17 - 127	20 - 112	17 - 139	17 - 139
Weight Z-Score[b]				
Mean (SD)	0.47 (1.669)	0.95 (1.112)	0.98 (1.388)	0.84 (1.429)
Range	-8.1, 3.7	-1.6, 3.4	-3.1, 4.2	-8.1, 4.2
Body Mass Index (kg/m^2)				
Mean (SD)	19.97 (6.270)	20.96 (5.152)	21.55 (6.378)	21.01 (6.124)
Range	12.0 - 45.4	13.8 - 37.5	12.1 - 48.1	12.0 - 48.1
Body Mass Index Z-Score[b]				
Mean (SD)	0.43 (1.573)	0.98 (0.997)	1.00 (1.236)	0.85 (1.310)
Range	-5.3, 2.9	-1.6, 2.8	-4.1, 3.3	-5.3, 3.3

[a]Other includes other races, American Indian/Alaskan Native, and Native Hawaiian/Other Pacific Islander

[b]Population norms to derive Z-scores were obtained from www.cdc.gov/nchs/about/major/nhanes/growthcharts/datafiles.htm

Abbreviations: kg = kilogram, m = meter, SD = standard deviation

Efficacy Results: A summary of ABC irritability and CGI-S objectives is presented in Table 3.

Table-3	**Summary of Efficacy Endpoints**			
Variable	**De Novo**	**Placebo Rollover**	**Aripiprazole Rollover**	**Overall**
Efficacy Endpoints				
ABC Irritability Subscale Score[a]	N = 80	N = 68	N = 166	N = 314
Mean baseline	23.2	21.5	15.0	18.5
Mean change endpoint (LOCF) (SD)	-6.5 (11.12)	-6.1 (11.25)	0.7 (9.72)	-2.6 (10.98)
CGI Severity Score[b]	N = 84	N = 69	N = 169	N = 322
Mean baseline	4.8	4.2	3.9	4.2

Table-3 Summary of Efficacy Endpoints				
Variable	**De Novo**	**Placebo Rollover**	**Aripiprazole Rollover**	**Overall**
Mean change endpoint (LOCF) (SD)	-0.8 (0.85)	-0.4 (1.06)	-0.0 (1.01)	-0.3 (1.04)

[a] ABC Irritability Subscale Score is from 0 to 45. A negative change score signifies improvement.
[b] CGI-S Score is from 1 to 7. A negative change score signifies improvement.
Abbreviations: LOCF = last observation carried forward, SD = standard deviation

Safety Results: A summary of safety results is presented in Table 4.

Table-4 Summary of Safety				
	Number (%) of Subjects			
	De Novo	**Placebo Rollover**	**Aripiprazole Rollover**	**Total**
	N = 86	N = 70	N = 174	N = 330
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-emergent SAEs, n (%)	3 (3.5)	1 (1.4)	5 (2.9)	9 (2.7)
Treatment-emergent AEs leading to discontinuation, n (%)	9 (10.5)	10 (14.3)	14 (8.0)	33 (10.0)
Overall treatment-emergent AEs, n (%)	75 (87.2)	63 (90.0)	148 (85.1)	286 (86.7)
Treatment-emergent EPS-related AEs	16 (18.6)	6 (8.6)	26 (14.9)	48 (14.5)
Mean change from baseline by time period in body weight z-score[a]				
Baseline mean (SD)	0.47 (1.687)	0.95 (1.112)	0.98 (1.392)	0.84 (1.434)
Change from baseline, mean (SD)				
≤ 3 months	0.13 (0.283)	0.10 (0.204)	0.09 (0.300)	0.10 (0.277)
3 - 6 months	0.24 (0.433)	0.26 (0.331)	0.20 (0.327)	0.22 (0.359)
6 - 9 months	0.31 (0.570)	0.28 (0.367)	0.23 (0.407)	0.26 (0.448)
> 9 months	0.33 (0.580)	0.23 (0.399)	0.24 (0.465)	0.26 (0.486)
Mean change from baseline by time period in BMI z-score[a]				
Baseline mean (SD)	0.44 (1.591)	0.98 (0.997)	1.01 (1.236)	0.86 (1.313)
Change from baseline, mean (SD)				
≤ 3 months	0.17 (0.436)	0.12 (0.268)	0.09 (0.500)	0.12 (0.443)
3 - 6 months	0.29 (0.625)	0.28 (0.388)	0.18 (0.549)	0.23 (0.543)
6 - 9 months	0.36 (0.647)	0.24 (0.438)	0.18 (0.643)	0.24 (0.611)
> 9 months	0.33 (0.768)	0.15 (0.476)	0.14 (0.775)	0.19 (0.725)

[a] The body weight and BMI z-scores are by age and gender-standardized values (corresponding to a normal distribution with mean 0 and a standard deviation of 1) of the actual weight and BMI measurements, based on the growth charts provided by the CDC
Abbreviations: AE = adverse event; EPS = extrapyramidal symptoms, LOCF = last observation carried forward, SAE = serious adverse event, SD = standard deviation

There were no deaths. There were a total of 13 treatment-emergent serious adverse events reported in 9 subjects (2.7%), the majority of which were in the category of psychiatric disorders. Suicidal ideation in the midst of a tantrum was reported in one subject (0.3%). Discontinuations due to treatment-emergent AEs occurred in 10.0% of subjects, with the most common AEs being increased weight (2.1%) and aggression (2.1%). The types of AEs reported in this trial were consistent with those observed in previous studies of aripiprazole in pediatric populations. The most common treatment-emergent AEs (occurring in ≥ 10.0% of subjects) were increased weight (23.0%), vomiting (18.8%), nasopharyngitis (13.3%), increased appetite (13.0%), pyrexia (11.8%), upper respiratory tract infection (11.5%), and insomnia (10.0%). EPS-related events occurred in 14.5% of subjects; tremor was the most common (3.0%).

There were minimal changes observed from baseline to endpoint (last observation carried forward [LOCF]) in the SAS, AIMS or Barnes Akathisia EPS scales. There were no clinically relevant ECG abnormalities, changes in vital signs or changes in metabolic laboratory parameters.

Serum prolactin levels decreased during the trial. The mean change from baseline in serum prolactin (total aripiprazole exposure data) for subjects in the trial less than 3 months was -5.6 and -6.3 for subjects in the trial greater than 9 months. There is no known clinical consequence of this change. There were no reports of hyperprolactinemia.

Other Results: Improvements were reported in all cohort groups on the PedsQL (all age groups, combined scales) at endpoint (LOCF).

Conclusions:

- There were no new safety findings in this open-label trial and the results are consistent with the known drug profile of aripiprazole and illness profile of autistic disorder.
- There were no clinically relevant changes observed in laboratory parameters (including metabolic results), vital signs, or ECGs.
- Early weight gain was observed, but based on BMI and weight z-scores, this change reached a plateau at 3-6 months, and weight gain was not associated with clinically relevant increases in metabolic laboratory parameters or the development of metabolic syndrome.
- The efficacy results are consistent with durable treatment effects.

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