Bristol-Myers Squibb Company

Aripiprazole (BMS-337039/OPC-14597)
Clinical Summary for Protocol CN138014

Tolerability, Pharmacokinetics and Pharmacodynamics of Aripiprazole During Oral Administration in Children and Adolescents with Conduct Disorder

Indication:	Schizophrenia and Conduct Disorder
Clinical Development Phase:	1
Sponsor:	Department of Clinical Discovery Bristol-Myers Squibb Pharmaceutical Research Institute Bristol-Myers Squibb Company Princeton, NJ Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, MD US
Trial Initiation Date:	17 Feb 2000
Trial Completion Date:	03 Sep 2003
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: Tolerability, Pharmacokinetics and Pharmacodynamics of Aripiprazole During Oral Administration in Children and Adolescents with Conduct Disorder

Trial Centers by Region: Site 1: University Hospitals of Cleveland, Cleveland, OH; Site 2: Children's Hospital Medical Center, Cincinnati, OH; Site 3: Children's Mercy Hospital, Kansas City, MO.

Clinical Phase: 1

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale: Aripiprazole (BMS-337039, OPC-14597), a dihydrocarbostyril quinolinone derivative, is a novel antipsychotic being developed as a collaborative project between Otsuka Pharmaceutical Company, Ltd., and Bristol-Myers-Squibb (BMS). Biochemically, aripiprazole has been shown to be a partial agonist at members of the D2 family of dopamine (DA) receptors. In vitro, aripiprazole exhibits a D2 partial agonist profile in the inhibition of prolactin release from primary cultured anterior pituitary cells. In vivo, aripiprazole has been shown to exhibit antagonist properties in animal models of dopaminergic hyperactivity (blockade of apomorphine-induced stereotypy) and agonist activity in an animal model of dopaminergic hypoactivity (blockade of increased dopamine synthesis in reserpine-treated rats). The major circulating metabolite of aripiprazole, dehydro-aripiprazole (OPC-14857, BMS-337044), is equipotent to aripiprazole at the D2 receptor.[1] As a result, dehydro-aripiprazole is likely to contribute to the pharmacological effects of aripiprazole.

Aripiprazole tablets are approved by the Food and Drug Administration for the treatment of schizophrenia and for the treatment of bipolar disorder and by The European Agency for the Evaluation of Medicines for schizophrenia.

Conduct Disorder (CD) is a condition characterized by inappropriately aggressive behavior towards people and/or property. To date no medications have been indicated for use in CD in children and adolescents. However, anti-psychotics, including haloperidol, chlorpromazine and thioridazine, have shown some promise in the treatment of aggression.[2] Most recently, risperidone demonstrated efficacy in the treatment of aggression in a small trial with 20 pediatric subjects aged 5 to 14 years.[3] This trial was designed to provide preliminary safety, pharmacokinetic and pharmacodynamic results in children and adolescents with CD to support the design of pivotal safety and efficacy studies.

Publications: Poster Presentations at Annual Meetings: European College of Neuropsychopharmacology 2003, American Academy of Child and Adolescent Psychiatry 2003, American College of Neuropsychopharmacology 2003, Collegium

Internationale Neuro-Psychopharmacologium 2004 (citation: Findling RL, Blumer JL, Kauffman R, et al. Pharmacokinetic effects of aripiprazole in children and adolescents with CD. Int J Neuropsychopharmacol. 2004;7 (Suppl 1):S441.

Objectives:

Primary Objective:

The primary objective of this trial was to determine the multiple dose pharmacokinetics of aripiprazole in children and adolescents with CD.

Secondary Objective:

The secondary objective of this trial was to assess the safety profile and pharmacodynamics of aripiprazole in these subjects.

Methodology: This was an open-label, 15 day, 3-center trial (Phase A) with an optional 36 month open-label safety extension (Phase B). Children ages 6 to 12 years and adolescents ages 13 to 17 years, with a diagnosis of CD and a score of 2 to 3 on the Rating of Aggression Against People and/or Property (RAPP), were to be enrolled.

For Phase A (Screening to Day 15), subjects were to receive daily doses of approximately 0.1 mg/kg aripiprazole starting on Day 1 and continuing through Day 14. Specifically, subjects weighing less than 25 kg were to receive 1 mg, subjects weighing between 25 and 50 kg were to receive 2 mg, subjects weighing between 50 and 70 kg were to receive 5 mg, and subjects weighing more than 70 kg were to receive 10 mg. If doses of 2 to 10 mg aripiprazole were poorly tolerated, subsequent doses may have been reduced at the Investigator's discretion. During Phase A, subjects were to report to the Investigator's clinic at least twice before receiving their first dose of aripiprazole, once for screening and training on neuropsychological tests, and a second time for the collection of baseline data on neuropsychological tests. If preferred, the screening and training procedures may have been performed at separate visits. Dosing was to commence on Day 1. Prior to dosing on Days 1 and 14, subjects were to be admitted to the Investigator's clinic, where they were to remain for 24 h post-dosing (overnight). In addition, subjects were to report to the clinical facility for outsubject visits in the morning on Days 7 and 10. On days when subjects did not report to the clinic, they were to take their daily dose of aripiprazole at home. On these days, caregivers were asked to note dosing time in a diary. Safety, pharmacokinetic and pharmacodynamic assessments were to be performed at selected times throughout Phase A portion of the trial. Safety assessments included adverse events (AEs), physical examinations, orthostatic vital sign measurements, 12-lead electrocardiograms (ECG), clinical laboratory evaluations (including prolactin) and, to assess extrapyramidal symptoms (EPS), the Abnormal Involuntary Movement Scale (AIMS), the Simpson-Angus Neurologic Rating Scale (SAS) and the Barnes Akathisia Rating Scale (BARS). Pharmacodynamic assessments included the RAAPP, the Clinical Global Impression (CGI) scale, and a battery of

neuropsychological tests (Wisconsin Card Sort Test [WCST], Connors' Continuous Performance Test [CPT] and Verbal Fluency Test [VFT]). Following discharge from the clinic on Day 15, subjects were permitted to enter the open-label extension period (Phase B) with no interruption of dosing.

During Phase B, subjects were to visit the clinic during Months 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36 for safety and pharmacodynamic assessments and possible dose adjustment. As in Phase A, safety assessments were to include AE monitoring, ECGs, orthostatic vital signs, clinical laboratory tests including prolactin, a urine screen for drugs of abuse, physical examination (including BMI measurements at each scheduled clinic visit), AIMS, SAS and BARS. Pharmacodynamic assessments were to include RAAPP, CGI scale, and a battery of neuropsychological tests (WCST, CPT and VFT). Throughout Phase B, doses were permitted to be adjusted as needed at the discretion of the Investigator; however, in no case was a dose of greater than 15 mg/day to be administered.

Number of Subjects: A total of 23 (12 children and 11 adolescents) subjects were enrolled in this trial and 5 (2 children and 3 adolescents) subjects completed the trial.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Inclusion: Otherwise healthy children and adolescents with a confirmed diagnosis of CD as defined in DSM IV, with or without co-morbid Attention Deficit Hyperactivity Disorder, as defined in DSM IV, or Oppositional Defiant Disorder, as defined in DSM IV, and a score of 2 or 3 on the RAAPP Scale.

Exclusion: Significant deviations from normal in physical examination, clinical laboratory, or ECG assessments made at screening, an IQ ≥ 70 based on the Wechsler Intelligence Scale for Children, or any Axis I psychiatric diagnosis.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration: Aripiprazole was provided in a tablet formulation at dosage strengths of 1, 5, 10 and 15 mg. The initial dose was based on body weight according to the guidelines provided in Table 1.

Table 1:Dosing Guidelines

Body Weight	Initial Dose
≤ 25 kg	1 mg/day
> 25 kg but ≤ 50 kg	2 mg/day
> 50 kg but ≤ 70 kg	5 mg/day
> 70 kg	10 mg/day

Doses were to be administered once daily with 8 oz of room temperature water, without regard for food. The daily dosing time was to remain constant for each subject unless a change in dosing time was necessitated by AEs. Subjects who elected to participate in the outsubject extension (Phase B) were to receive a dose of trial medication on Day 15 of

Phase A; however, for subjects who did not elect to participate in Phase B, the final dose of aripiprazole was to be administered on Day 14.

For subjects with body weights of greater than 25 kg, if the initial dose of aripiprazole was poorly tolerated, subsequent doses were permitted to be reduced at the Investigator's discretion. During Phase B, doses were permitted to be either decreased or increased at the Investigator's discretion. The following guidelines were to be followed when making dose adjustments:

- Dose adjustments between 5 and 15 mg were to be made in 5 mg increments. Dose adjustments between 1 and 5 mg were to be made in 1 mg increments.
- During Phase B, dose titrations were permitted to be made every 2 weeks. More frequent dose titrations were not to be allowed without the permission of the Sponsor.
- The maximum dose to be administered to any subject in this trial was to be 15 mg per day.

Subjects were to visit the Investigator's clinic for all dose adjustments.

Duration of Treatment: Fourteen (14) days of outsubject treatment (Phase A), followed by an optional 18-month open-label outsubject extension (Phase B) which was extended to an optional total of 36-months.

Trial Assessments: Trial assessments included safety and tolerability assessments, as well as pharmacokinetic and pharmacodynamic assessments.

Criteria for Evaluation:

Safety, Tolerability: AEs, physical examinations, vital signs, clinical laboratory results (including prolactin), ECGs and assessments of SAS, AIMS and BARS.

Pharmacokinetics: The pharmacokinetic outcome measures were maximum plasma concentration (Cmax), minimum plasma concentration (Cmin), time to maximum plasma concentration (Tmax), area under the concentration curve [AUC](TAU) and apparent oral clearance (CLT/F). Serial blood samples were to be collected prior to and for 24 h post-dosing on Days 1 and 14. Additional blood samples were to be collected on Days 7 and 10 for the determination of Cmin. The pharmacokinetic outcome measures were Cmax, Cmin, Tmax, AUC(Tau), and CL/F.

Pharmacodynamics: Pharmacodynamic assessments were to include the RAAPP rating, the CGI rating, and a battery of neuropsychological tests (WCST, CPT, and VFT). To assess EPS, subjects were to be rated using the SAS, the BARs, and AIMS at screening, during Phase A on Days 1 and 14 (4 h post-dose), and on Day 7 (2 h post-dose); during Phase B, at the month 1 through 6 clinic visits and at trial discharge (Month 36). In addition, EPS assessments were to be performed tri-monthly if the subject showed any evidence of EPS.

Statistical Methods:

Safety: All AEs recorded during the trial were listed and tabulated by group, body system and primary term. Any serious adverse event (SAE) was identified. All laboratory abnormalities meeting predefined criteria were listed and tabulated by treatment and laboratory test. ECG recordings were evaluated by the Investigator and abnormalities, if present, were listed. AIM scores were listed by trial day and group.

Pharmacokinetics: Pharmacokinetic parameters of aripiprazole, dehydro-aripiprazole, DM-1452, OPC-3373 and DCPP were listed and summary statistics were tabulated by trial day and dose of aripiprazole for children and adolescents, respectively.

Pharmacodynamics: Frequency distributions of the RAAPP, the CGI Rating Scale variables, count data from the neuropsychological test battery (WCST, CPT, and VFT), and corresponding changes from baseline were tabulated by age group and visit (visit Days 1, 7 and 14 of Phase A, and monthly visits of Phase B). Summary statistics were to be provided for the hit mean reaction time and percentage data in Connor's CPT, the results of the fluency test, and the corresponding changes from baseline by age group and visit.

To explore the relationship between pharmacodynamic responses (RAAPP, CGI improvements and neuropsychological test changes) by the end of Phase A and aripiprazole pharmacokinetics, Day 14 changes from baseline in these pharmacodynamic responses were plotted against Day 14 aripiprazole AUC(TAU).

Summary of Results:

Baseline Data, Disposition, and Demographics:

A total of 23 subjects (12 children and 11 adolescents) were enrolled into this trial. All completed Period A and continued on into Period B. Of the 23 subjects randomized to treatment in this trial, 5 subjects (21.7%, 2 children and 3 adolescents) completed and 18 subjects (78.3%) were discontinued from the trial.

Safety Results: There were no deaths or other SAEs. Eighteen (18) subjects (10 children and 8 adolescents) of 23 enrolled were discontinued from the trial. No subjects were discontinued due to AEs, 6 subjects discontinued due to non-compliance, 3 subjects withdrew consent, 7 subjects were lost to follow-up, and 2 subjects were discontinued for "other" reasons. One (1) subject discontinued due to lack of efficacy and the other due to lack of efficacy at the maximum dose allowed by the protocol.
A total of 132 AEs that counted occurred in 17 of 23 (73.9%) subjects who received any aripiprazole treatment. A total of 70 AEs occurred in 10 of 12 (83.3%) children and a total of 62 AEs occurred in 9 of 11 (81.8%) adolescents. The AE profiles were generally

similar in children and adolescents with most of the AEs occurring in gastrointestinal disorders and nervous system disorders system organ classes.

For children, the most frequent AEs reported were: somnolence (n=6 [50.0%] in Phase A and 2 in Phase B [16.7%]); vomiting (n=5 [41.7%] in Phase A and 2 [16.7%] in Phase B); decreased appetite (n=2 [16.7%] in Phase A and 3 [25.0%] in Phase B); increased appetite (n=4 [33.3%] in Phase B); nausea (n=1 [8.3%] in Phase A and 2 [16.7%] in Phase B); cough (n=3 [25.0%] in Phase B); skin laceration (n=2 [16.7%] in Phase A); headache, upper abdominal pain, and influenza (n=1 [8.3%] each in Phases A and B).

For adolescents, the most frequent AEs reported: somnolence (n=4 [36.4%] in Phase A and 3 [27.3%] in Phase B);abdominal pain upper (n=3 [27.3%] each in Phases A and B); headache (n=5 [45.5%] in Phase B); vomiting (n=3 [27.3%] in Phase A and 1 [9.1%] in Phase B); dizziness (n=2 [18.2%] in Phase A and 1 [9.1%] in Phase B); diarrhea (n=1 [9.1%] in Phase A and 2 [18.2%] in Phase B); pharyngolaryngeal pain (n=2 [18.2%] in Phase A); and dysmenorrhea and influenza (n=2 [18.2%] each in Phase B).

There were 8 subjects (4 children and 4 adolescents) who experienced 11 marked laboratory abnormalities (MAs). One (1) of these was reported as an AE. One (1) child had an AE of increased hepatic enzymes reported. The subject had elevations in both ALT and AST that were considered MAs. Other MAs included an additional subject with increased ALT, 3 subjects with decreased hemoglobin, 2 subjects with increased urinary glucose, and 1 subject each with increased alkaline phosphatase, uric acid and eosinophils.

Pharmacokinetic Results: Pharmacokinetic parameters were calculated for aripiprazole, dehydro-aripiprazole, DM-1452, OPC-3373 and DCPP for children and adolescents. Summary statistics for the pharmacokinetic parameters are tabulated by demographic group for aripiprazole analyte in Table 2.

Table 2: Summary Statistics for Aripiprazole Pharmacokinetic Parameters								
Age Group *	**Dose (mg)**	**Trial Day**	**n**	**Cmax (ng/mL) Geo. Mean (CV%)**	**Tmax (h) Median (Min, Max)**	**AUC[a] (ng·h/mL) Geo. Mean (CV%)**	**CLT/F (L/h) Mean (SD)**	**Weight Normalized CLT/F (L/h/kg) Mean SD**
C	1	1	3	8.9 (54)	4.0 (3.0, 8.0)	151 (52)	-	-
		14	3	21.8 (73)	4.0 (0.0, 6.0)	47[b] (a)	2.59[b] (c)	0.11[b] (c))
	2	1	4	16.5 (40)	3.0 (2.0, 8.0)	226 (37)	-	-
		14	5	48.8 (53)	2.0 (1.0, 4.0)	827 (62)	2.66 (1.07)	0.07 (0.04)
	5	1	5	50.0 (25)	1.0 (1.0, 4.0)	669 (21)	-	-
		14	3	138.0 (22)	2.0 (1.0, 3.0)	2217 (23)	2.31 (0.61)	0.05 (0.02)
A	2	1	2	14.3 (c)	2.5 (2.0, 3.0)	211 (c)	-	-
		14	2	43.8 (a)	2.0 (2.0, 2.0)	800 (c)	2.50 (c)	0.05 (c)
	5	1	5	23.7 (13)	3.0 (2.0, 8.0)	411 (2.89)	-	-
		14	5	73.1 (53)	4.0 (2.0, 6.0)	1340 (57)	4.09 (1.77)	0.07 (0.03)
	10	1	3	37.7 (48)	2.0 (2.0, 6.0	553 (30)	-	-
		14	3	136.0 (23)	3.0 (2.0, 24.0)	2387 (37)	4.36 (1.43)	0.05 (0.02)
	15	1	1	59.9 (N/A)	2.0 (2.0, 2.0)	602 (N/A)	-	-
		14	1	194.2 (N/A)	2.0 (2.0, 2.0)	3879 (N/A)	3.87 (N/A)	0.03 (N/A)

-Clearance parameters not calculated on Day 1
*Age Group Code: A=Adolescent, C=Child
N/A: not applicable
[a]Represents AUC(0-T) on Day 1 and AUC(TAU) on Day 14
[b]n=2
[c]SD and CV% not reported because n=2

Pharmacodynamic Results: Results of the assessment of the effects of multiple doses of aripiprazole on pharmacodynamic parameters (RAAPP, CGI, and a battery of neuropsychological tests [WCST, CPT and VFT]) based on frequency distributions and plots may be summarized as follows:

RAAPP: These scores appeared improved by Day 14 of Phase A, when both groups had a typical (median) score of 2, observed in 7 children and 7 adolescents among the 11 studied in each group. The scores continued to improve in Phase B with the typical (median) score varying between 1 and 2, with more scores of 1 (no aggression) seen for children, and somewhat more scores of 2 (mild aggression) seen for adolescents. There

appeared to be no clear trend over time, but the sample sizes were small especially after 18 months.

CGI: On Day 7 of dosing (Phase A), the typical (median) CGI improvement score was 3 (minimally improved) for both groups, and on Day 14 it was 3 (minimally improved) for adolescents and 2 (much improved) for children. In Phase B, typical scores seen were 'very much' or 'much improved' with the exception of the 1st and 18th month for children (median scores of 2.5 and 3, respectively) and the 15 month for adolescents (median score of 2.5). In the trial overall, improvement in CGI scores was observed earlier (by Day 14) in children, while starting by Month 1 and up to Month 3 there appeared to be additional improvement in adolescents. There were no apparent differences overall between the two age groups from Month 4 and later.

Neuropsychological Test Battery (WCST, CPT, VFT): For WCST and CPT there appeared to be some improvements in the scores with time, especially in the early part of the trial. Improvements may have been more pronounced in children than adolescents. For VFT also there appeared to be improvements in the performance over time; again, improvements may have been more noticeable for children in early phase. It should be noted that an assessment of improvement in these results was difficult due to the small number of subjects, and the results should be interpreted with caution.

Conclusions:

- The extent of accumulation of aripiprazole on Day 14 compared to Day 1 (2.4 to 6.4 times) was similar for children and adolescents, and was consistent with the extent of accumulation observed in adults.
- Steady state was attained within 14 days of once daily aripiprazole dosing in both children and adolescents, similar to the time to steady-state in adults.
- The apparent oral clearance of aripiprazole was similar in adolescents and adults and values appeared to be independent of aripiprazole dose. Although apparent oral clearance values were approximately one third lower in children, apparent oral clearance values for aripiprazole were similar among children, adolescents, and adults when normalized for body weight.
- The overall metabolic profile following oral dosing of aripiprazole was similar in children and adolescents. As with adults, dehydro-aripiprazole (BMS-337044, OPC-14857) was the predominant circulating metabolite in the plasma of children and adolescents with mean exposure values approximately one-third those of parent aripiprazole.
- The body weight-adjusted pharmacokinetics of orally administered aripiprazole was similar in children and adolescents compared to adults.
- Aripiprazole appears to be generally safe and well-tolerated following multiple-dose administration of appropriate doses to children and adolescents with CD.

Report Date: 30 July 2006

[1] Hirose T. The binding affinities of OPC-14587, a main metabolite of OPC-14597, on various receptors. Otsuka In-House Report Number 012561. Bristol-Myers Squibb Pharmaceutical Research Institute, 2001. BMS Control Number 920001538.

[2] Findling RL, Schulz SC, Reed MD and Blumer JL. The antipsychotics: a pediatric perspective. Pediatr Clin North Am. 1998;45(5):1205-32.

[3] Findling RL, McNamara NK, Branicky LA, O'Riordan MA, Lemon E., Schlucter M and Blumer JL. Risperidone in children with conduct disorder. Presented at the Annual Meeting of the American Psychiatric Association, 1999.