Otsuka Maryland Research Institute, Inc.
Maryland Clinical Research

Aripiprazole (OPC-14597, BMS-337039)

Clinical Summary for Protocol 31-03-238
NCT No. 00102479

An Open-label Dose Escalation Study to Assess the Safety, Tolerability, and Pharmacokinetics of Orally Administered Aripiprazole Tablets in Children and Adolescent Patients

Indication:	Schizophrenia and Acute Mania
Clinical Development Phase:	1
Sponsor:	Otsuka Maryland Research Institute, Inc. 2440 Research Boulevard Rockville, MD, USA Bristol-Myers Squibb Company
Trial Initiation Date:	26 Jul 2004
Trial Completion Date:	08 Jul 2005
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, BMS-337039)

Protocol Title: An Open-label Dose Escalation Study to Assess the Safety, Tolerability, and Pharmacokinetics of Orally Administered Aripiprazole Tablets in Children and Adolescent Patients

Trial Center(s) by Region: Multicenter (3 sites in the United States).

Clinical Phase/Trial Type: 1/ Open-label, Multicenter, Non-comparative trial

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale: In a previous trial conducted in children and adolescents with conduct disorder, aripiprazole doses up to 15 mg once daily (QD) were well tolerated. However, a maximum tolerated dose (MTD) in the pediatric population was not determined since it was not a defined objective of the protocol. The purpose of this trial was to evaluate the safety and tolerability of doses greater than 15 mg and up to 30 mg in the pediatric population. Doses in excess of 30 mg were not studied due to limitations based upon the no-effect doses established in nonclinical toxicity studies in the most sensitive species.

Establishing an MTD in the pediatric population was desirable because additional studies are planned to assess the efficacy of aripiprazole in the treatment of schizophrenia and mania in the pediatric population.

Publications:
Findling RL, Kauffman RE, Sallee FR, Carson WH, Nyilas M, Mallikaarjun S, Shoaf SE, Forbes RA, Boulton DW, Pikalov A. Tolerability and pharmacokinetics of aripiprazole in children and adolescents with psychiatric disorders: an open-label, dose-escalation study. J Clin Psychopharmacol. 2008 Aug;28(4):441-6.

Objectives: The objectives of this trial were to assess the safety, tolerability, and pharmacokinetics (PK) of repeated doses of aripiprazole following oral administration to children and adolescent patients preferentially with a primary schizophrenia diagnosis or bipolar spectrum disorder. Additional pediatric diagnoses could be included at the discretion of the investigator. Though not specifically mentioned in the trial objectives, efficacy was also assessed in this trial.

Methodology: This tolerability trial was a multicenter, open-label, sequential cohort, dose escalation trial of multiple doses of aripiprazole ranging from 2 mg to 30 mg. After subjects were screened and deemed eligible to participate, they entered the dose-escalation phase of the trial. Subjects were administered aripiprazole for up to 12 days (depending upon the maximum dose for the cohort) using a forced titration scheme to achieve one of the following dose levels: 20 mg, 25 mg, or 30 mg. Following the dose-escalation phase, subjects entered the fixed-dose phase and were administered

the maximum dose for that cohort for 14 days. Subjects participated in PK sampling on Days 14 and 15 of the fixed-dose phase.

All participating investigators evaluated each subject in each cohort to assess the subject's tolerability to the dose. Dose toleration was defined as follows: during the course of the trial the subject does not experience any untoward events or potentially clinically significant changes from baseline in laboratory values, vital signs, electrocardiogram (ECG) tracings, or extrapyramidal symptom (EPS) ratings, that are assessed as possibly related to the drug, and would warrant adjustment or discontinuation of the trial drug. A dose level was judged to have been tolerated if 4 out of 6 (67%) of the subjects in a cohort with that maximum dose tolerated the dose. Therefore, dose tolerability for a cohort could have been assessed after the first 4 subjects enrolled in the cohort completed the fixed-dose phase. Once a dose level was determined to be tolerated, enrollment in the next dose level was opened.

Subjects who did not tolerate the 20-mg dose were given the option of being dosed at 15 mg for 14 days. If the 20-mg dose was tolerated, a separate cohort of 6 subjects was started and was titrated to a maximum dose level of 25 mg. If the 25-mg dose was tolerated, a separate cohort of 6 subjects was started and was titrated to a maximum dose level of 30 mg. If any dose level was not tolerated, the previous dose level that was tolerated would have been identified as the MTD. At the discretion of the sponsor, an additional separate cohort of 6 subjects could have been tested to confirm the MTD.

Subject participation could have lasted up to 71 days: screening up to 14 days, dose escalation up to 12 days, fixed-dose phase up to 15 days, and follow-up contact 30 days after the last clinic visit.

Number of Subjects: A maximum of 24 children and adolescents were planned to be enrolled in this trial. Twenty-one subjects actually enrolled in the trial and received at least one dose of trial medication: 8 subjects in the aripiprazole (ARIP) 20-mg cohort, 7 subjects in the ARIP 25-mg cohort, and 6 subjects in the ARIP 30-mg cohort. Seventeen subjects (81%) completed both the dose-escalation and fixed-dose phases. All 21 subjects were analyzed for safety and 20 subjects were analyzed for efficacy.

Diagnosis and Main Criteria for Inclusion/Exclusion: Male or female children or adolescents between 10 and 17 years, inclusive, with a primary schizophrenia spectrum diagnosis or bipolar spectrum disorder were eligible to participate in this trial. Subjects with additional pediatric diagnoses were included at the investigator's discretion. Subjects must have been in good physical health as determined by medical history, clinical laboratory tests, ECG, and physical examinations.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration: The aripiprazole tablets manufactured for this trial consisted of 2-mg clinical presentation tablets and 5-mg, 10-mg, and 15-mg commercial presentation tablets. Doses were administered as follows: 5 mg = 1 × 5 mg tablet; 10 mg = 1 × 10 mg

tablet; 15 mg = 1×15 mg tablet; 20 mg = 2×10 mg tablets; 25 mg = 1×10 mg and 1×15 mg tablets; and 30 mg = 2×15 mg tablets. All medication was administered orally.

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

Duration of Treatment: Subjects were administered aripiprazole for up to 12 days during the dose-escalation phase and for 14 days during the fixed-dose phase.

Trial Assessments:
Safety and Tolerability:
Subject safety and tolerability were assessed based on adverse events (AEs), clinical laboratory data, physical examination findings, vital signs, ECGs, and EPS ratings.

Pharmacokinetics:
Blood was collected for the determination of aripiprazole plasma concentrations.

Efficacy:
The investigators conducted a clinical interview and administered the Clinical Global Impression Scale (CGI), measuring CGI-Severity and CGI-Improvement.

Criteria for Evaluation:
Primary outcome variables: The primary outcome variables were tolerability, safety, and PK. Investigators judged the dose tolerability of individual subjects based on AEs, ECGs, vital signs, clinical laboratory tests, physical examination findings, and EPS ratings. The EPS rating scales included the Simpson-Angus Scale (SAS), the Abnormal Involuntary Movement Scale (AIMS), and the Barnes Akathisia Rating Scale (BARS). The EPS ratings were assessed based on the SAS Total Score, the AIMS Movement Rating Score, and the BARS Global Score.

A Safety Council, comprising all trial investigators, met via teleconference when at least 4 subjects in a cohort completed the fixed-dose phase. Each trial investigator provided his opinion of the dose tolerability for each subject, and final assessments were reached by majority vote. A dose level was judged to have been tolerated if 4 out of 6 (67%) of the subjects in a cohort with that maximum dose tolerated the dose.

Safety: Safety was assessed on the basis of AEs, ECGs, vital signs, clinical laboratory tests, physical examination findings, and EPS ratings.

Pharmacokinetics: The primary PK variables were maximum steady-state plasma concentration ($C_{ss,max}$) and area under the concentration-time curve during a dosage interval (τ) at steady-state (AUC_{τ}) on Day 14 of the fixed-dose phase. Other variables assessed were the time to maximum plasma concentration (t_{max}) and steady state oral clearance (Cl_{ss}/F).

Efficacy: Efficacy was evaluated as a secondary outcome variable based on the CGI-Severity and the CGI-Improvement.

Pharmacokinetic Methods:
Bioanalytical: Aripiprazole and dehydro-aripiprazole plasma concentrations were quantified by a validated assay using high performance liquid chromatography with tandem mass spectrophotometric detection (HPLC-MS/MS).

Pharmacokinetics: Plasma concentrations of aripiprazole and dehydro-aripiprazole were analyzed using noncompartmental methods.

Statistical Methods: Plasma concentrations by time point, PK parameters, and changes from baseline in safety and efficacy endpoints were summarized by descriptive statistics for each dose cohort. No formal inferential comparisons among cohorts were planned or performed. For the efficacy analysis (ie, change from baseline in CGI-Severity score; and CGI-Improvement score) and analysis of the EPS data (ie, change from baseline in SAS Total Score, AIMS Movement Rating Score, and BARS Global Score), both observed cases (OC) and last observation carried forward (LOCF) datasets were used at the Day 14 visit in the fixed-dose phase.

Summary of Results:

Baseline Data, Disposition, and Demographics: In terms of baseline diagnosis, one subject (4%) had schizophrenia and 12 subjects (57%) had bipolar disorder. Of the remaining 8 subjects (38%), 5 had Tourette's syndrome, and one each had pervasive developmental disorder, obsessive compulsive disorder, and attention deficit hyperactivity disorder with conduct disorder. Medical history was similar among the subjects.

Thirty-one subjects were screened for this trial, of whom 21 were enrolled and received at least one dose of trial medication: 8 subjects in the ARIP 20-mg cohort; 7 subjects in the ARIP 25-mg cohort; and 6 subjects in the ARIP 30-mg cohort. Four subjects (19%) discontinued prematurely from the trial, 2 (2/8; 25%) in the ARIP 20-mg cohort for a protocol deviation and withdrawal of consent, and 2 (2/7; 29%) in the ARIP 25-mg cohort due to an AE and withdrawal of consent. In the first cohort, both discontinued subjects were replaced by subjects who went on to complete the trial. In the second cohort, Subject 003-1007 was replaced by Subject 001-1107 who later withdrew because of an AE. Overall, 17 subjects (81%) completed both the dose-escalation and fixed-dose phases. All 21 subjects were analyzed for safety and 20 subjects were analyzed for efficacy.

The demographics were not comparable across treatment cohorts; the ARIP 30-mg cohort included the youngest children with the lowest body mass index (BMI). The majority of subjects overall were male Caucasians who were not of Latino descent.

Tolerability Results: The Safety Council determined dose tolerability in each subject and the overall dose tolerability of a cohort. During the trial, the Safety Council met 3 times to assess subject tolerability: 08 October 2004 to evaluate the 6 subjects who had completed the fixed-dose phase of the ARIP 20-mg cohort, 05 January 2005 to evaluate the 5 subjects who had completed the fixed-dose phase of the ARIP 25-mg cohort, and on 21 June 2005 to evaluate the 6 subjects who had completed the fixed-dose phase of the ARIP 30-mg cohort. Individual subject tolerability was based on majority vote following review and discussion of subject records. Results are summarized as follows:

- In the ARIP 20-mg cohort, 5 of the 6 evaluated subjects tolerated aripiprazole up to the 20-mg dose. Subject 002-1101 down-titrated from 20 mg to 15 mg on Trial Day 14 (Day 6 of the fixed-dose phase) after experiencing a mild dystonic reaction predominately on the right side with trigeminal rash several days after starting the 20-mg dose. The subject completed the remainder of the fixed-dose phase on 15 mg. Since 83% (5/6) of the cohort had tolerated the highest dose, the ARIP 25-mg cohort was subsequently initiated.

- In the ARIP 25-mg cohort, 4 out of 5 evaluated subjects tolerated aripiprazole up to the 25-mg dose. Subject 001-1107 tolerated only up to the 20-mg dose. This subject terminated on Trial Day 16 after experiencing an AE of an acute dystonic reaction on Trial Day 12 which lasted one day; the subject's last dose of trial medication was taken on Trial Day 11 (Day 1 of the fixed-dose phase). Since 80% (4/5) of the cohort had tolerated the highest dose, the ARIP 30-mg cohort was subsequently initiated.

- In the ARIP 30-mg cohort, 6 out of 6 evaluated subjects (100%) tolerated aripiprazole up to the 30-mg dose.

Safety Results: Twenty-one subjects were enrolled in the trial and received at least one dose of trial medication. One subject each in the ARIP 20-mg cohort and ARIP 25-mg cohort terminated the trial (ie, both withdrew consent) before reaching the fixed-dose phase. The average daily dose of trial drug in the fixed-dose phase of the trial was 17.4 mg, 25 mg, and 30 mg for the 20-, 25-, and 30-mg treatment cohorts, respectively. The lower-than expected average daily dose for the 20-mg cohort reflects the dosing of one subject who took a 10-mg daily dose during the fixed-dose phase and was terminated for noncompliance.

The most common treatment-emergent adverse events (TEAEs) (reported by ≥ 2 subjects overall) included headache (9/21, 43%), upper abdominal pain (5/21, 24%), vomiting (4/21, 19%), dizziness (4/21, 19%), musculoskeletal stiffness (3/21, 14%), blurred vision (2/21, 10%), nausea (2/21, 10%), fatigue (2/21, 10%), pyrexia (2/21, 10%), dystonia (2/21, 10%), sedation (2/21 10%), somnolence (2/21, 10%), tremor (2/21, 10%), insomnia (2/21, 10%), epistaxis (2/21, 10%), and acne (2/21, 10%). No clear dose-related trends were observed. With the exception of one report of severe muscle

rigidity in the ARIP 20-mg cohort and one report of severe influenza in the ARIP 25-mg cohort, all TEAEs were mild to moderate in nature.

There were no subject deaths or serious adverse events (SAEs). One subject in the ARIP 25-mg cohort withdrew from the trial on Trial Day 16 because of an AE of moderate dystonia that was considered by the investigator to be definitely related to the trial medication.

Overall in each cohort, no clinically relevant changes from baseline were observed over time in any of the clinical laboratory values, vital signs, or ECG parameters. Clinically significant abnormalities were observed in some subjects in clinical laboratory values (creatine phosphokinase [CPK], glucose), vital signs (standing and supine systolic and diastolic blood pressure), and ECG results (QTcB). However, no abnormal chemistry laboratory values, vital signs values, or ECG results were reported as AEs, and no subjects discontinued from the trial due to abnormalities in these assessments.

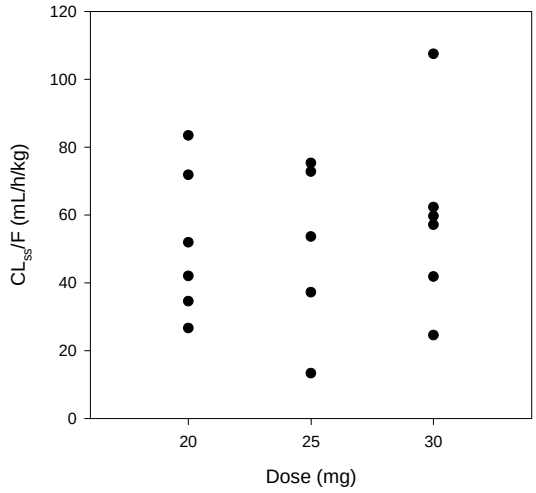
At baseline, according to EPS rating scale scores, symptoms of parkinsonism, dyskinesia, and akathisia were absent in all subjects. On Days 1 and 14 of the fixed-dose phase, subjects showed no change to minimal increase in symptoms.

Pharmacokinetic Results: A summary of aripiprazole plasma PK parameters is presented in the table below. A plot of steady state oral clearance (CL_{ss}/F) values versus dose is presented in the figure below.

Mean (SD) Plasma Pharmacokinetic Parameters for Aripiprazole Following Multiple Oral QD Dosing of Aripiprazole in Children and Adolescent Subjects

Parameter	20 mg (N = 6)	25 mg (N = 5)	30 mg (N = 6)
$C_{ss,max}$ (ng/mL)	435 (137)	529 (341)	653 (213)
t_{max} (h)[a]	2.00 (1.00-24.08)	2.05 (1.00-4.02)	2.00 (1.00- 8.00)
AUC_{τ} (ng·h/mL)	8031 (3745)	9488 (7001)	12770 (5444)
CL_{ss}/F (mL/h/kg)	51.7 (22.0)	50.4 (25.9)	58.8 (27.7)

[a] Values are median (minimum -maximum)



Values of Steady State Oral Clearance (CL_{SS}/F) Versus Dose Following Multiple Oral QD Dosing of Aripiprazole in Children and Adolescent Subjects

Efficacy Results: The baseline mean CGI-Severity scores were similar among all cohorts, with mean scores ranging from 3.5 to 4.0, characterizing the subjects as being mildly to moderately ill. Change from baseline scores at Day 1 and Day 14 (OC) of the fixed-dose phase showed progressive improvement over time in CGI-Severity in each cohort. The magnitude of improvement over time was least in the 20-mg group (-0.86 at Day 1 and -1.50 at Day 14 [OC]) and highest in the 30-mg group (-2.00 at Day 1 and -2.33 at Day 14 [OC]). The Day 14 LOCF results were similar, except that these data did not show greater improvement over the observed Day 1 score for the ARIP 25-mg cohort.

Compared to screening, improvement in subjects' conditions as measured by the CGI-Improvement score was seen in all cohorts at Day 1 and Day 14 (OC) of the fixed-dose phase, as indicated by scores ranging from 1.33 to 2.29, which are characterized by the scale as "very much improved" to "much improved." The magnitude of improvement over time was least in the 20-mg group (2.29 at Day 1 and 1.67 at Day 14 [OC]) and highest in the 30-mg group (1.33 at both Day 1 and at Day 14 [OC]). The Day 14 LOCF results were similar, except that these data did not show greater improvement over the observed Day 1 score for the ARIP 25-mg cohort.

Conclusions:

- Orally administered aripiprazole at dosages of 20 mg QD, 25 mg QD, and 30 mg QD for 14 days preceded by an 8 to 12 day dose-escalation phase appears to be safe and well tolerated in children and adolescent subjects aged 10 to 17 years with psychiatric disorders who participated in this trial.

- Aripiprazole PK is linear in children and adolescent subjects aged 10 to 17 years.
- Aripiprazole clearance (adjusted for body weight) in children and adolescent subjects is similar to that in adult subjects.
- Aripiprazole C_{max} values in children and adolescent subjects aged 10 to 17 years are higher compared with adults due to differences in body weight.
- The AUC_{τ} ratio of active metabolite dehydro-aripiprazole to aripiprazole in children and adolescent subjects aged 10 to 17 years is similar to that in adult subjects.
- Based on observed cases analysis, subjects in all cohorts showed improvements in their symptoms based on CGI-Severity and CGI-Improvement scores, with the greatest improvement observed at the highest assessed fixed dose, 30 mg QD, and the least improvement observed at the lowest assessed fixed dose, 20 mg QD.

Report Date: 30 Jan 2006