Bristol-Myers Squibb Company

Aripiprazole (BMS-337039/OPC-14597)

Clinical Summary for Protocol CN138020

Assessment of the In Vivo Release Characteristics and Safety of an Intramuscular Depot Formulation of Aripiprazole in Subjects with Schizophrenia or Schizoaffective Disorder

Indication:	Schizophrenia
Clinical Development Phase:	1
Sponsor:	Bristol-Myers Squibb Pharmaceutical Research & Development Princeton, NJ, USA Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland, USA
Trial Initiation Date:	19 Sep 2003
Trial Completion Date:	02 Dec 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 (BMS-337039/OPC-14597)

Protocol Title: Assessment of the In Vivo Release Characteristics and Safety of an Intramuscular Depot Formulation of Aripiprazole in Subjects with Schizophrenia or Schizoaffective Disorder

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

Clinical Phase/Trial Type: 1/ Open-label, Two-phase, Ascending Dose Trial

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale: This was the first clinical ascending dose trial with aripiprazole (BMS-337039) intramuscular (IM) depot formulation. The purpose was to present an estimation of an in vivo release rate of aripiprazole following single doses of 15, 50, 100, 200, 300, and 400 mg aripiprazole IM depot formulation.

ABILIFY® (aripiprazole), a partial agonist at members of the D2 family dopamine receptors, is a novel and atypical antipsychotic agent approved in tablet form for the treatment of schizophrenia based on the establishment of efficacy in short-term (4- and 6-week) trials in schizophrenic subjects. The approval was followed by a supplemental New Drug Application with data demonstrating that ABILIFY® delays the time to relapse and the rate of relapse in stable schizophrenic subjects followed for up to 26 weeks.[1]

Bristol-Myers Squibb and Otsuka Pharmaceuticals, Inc., have developed formulations of aripiprazole that may be used as alternatives to the tablet formulation based on subject and physician preferences (ie, oral solution, orally disintegrating tablets) and new formulations that are suited to specific clinical needs (ie, immediate-release IM injection for agitation). In addition, an IM depot formulation of aripiprazole has been developed which may provide a useful alternative to tablets in patients stabilized on ABILIFY® tablets in the acute setting who would benefit from continued treatment with aripiprazole where compliance may be problematic.

Publications: None to date.

Objectives:
Primary Objective: To estimate the in vivo release rate of aripiprazole following single doses of 15, 50, 100, 200, 300, and 400 mg aripiprazole IM depot formulation.

Secondary Objective: To assess the safety and tolerability of single doses of 15, 50, 100, 200, 300, and 400 mg aripiprazole IM depot formulation and single doses of 5 mg aripiprazole standard IM formulation.

Methodology: This was an open-label, two-phase, non-randomized, ascending dose, sequential panel trial in subjects with a diagnosis of schizophrenia or schizoaffective disorder. After enrollment and signing the approved informed consent form, subjects received a single dose of 5 mg aripiprazole standard IM formulation (Phase 1) followed by safety and pharmacokinetic (PK) monitoring. After ≥ 28 day washout interval, subjects who qualified based on no significant adverse events (AEs) or clinical laboratory abnormalities returned to the clinical facility to receive a single dose of either 15, 50, 100, 200, 300 or 400 mg aripiprazole IM depot formulation (Phase 2), followed by safety and PK monitoring. Subjects were allowed to continue receiving medication for the treatment of schizophrenia or schizoaffective disorder during this trial (if the specific medication was not listed in the exclusion criteria). The location of the injection site alternated such that the standard IM formulation was administered deep into the triceps muscle in the dominant arm and the IM depot formulation was administered in the non-dominant arm. For the 200-, 300-, or 400-mg doses, the IM depot formulations were administered deep in the mid-lateral thigh muscle.

For each phase, subjects were admitted to the clinical facility one day (Day -1) prior to drug administration and were confined to the facility for a minimum of 48 hours post-dose.

Following sequential IM administration of standard and ascending depot doses of aripiprazole (Phase 1 and Phase 2, respectively), blood samples were collected for PK analysis up to 23 days (528 hours) post-dose. In addition, for Phase 2, PK samples were collected weekly during Weeks 4-6; once every two weeks during Weeks 6-12 and once-a-month during Weeks 16-28 until plasma concentrations of aripiprazole were less than the lower limit of quantification (LLQ) of the assay. Subjects were discharged from the trial when plasma concentrations of aripiprazole were less than LLQ for 2 consecutive visits.

Blood samples were obtained for creatine phosphokinase (CK) and aldose concentration on Days -1, 1, 2, and 3 in Phases 1 and 2. CK was measured during each return visit to the clinical facility for PK sample collection in both phases of trial.

Following trial drug administration, the Investigator assessed the injection site for signs of local irritation and inflammation. If the Investigator and Medical Monitor determined that the standard IM formulation was well-tolerated (no significant AEs or clinical laboratory abnormalities), the subject returned for Phase 2 to receive the IM depot formulation. Approximately 2 weeks after dosing, preliminary AEs for each subject were sent to all sites involved in the trial to review prior to dose escalation. Subjects in the 200-, 300-, or 400-mg dosing schedules did not receive the IM depot injection until safety data from all subjects in the previous panel were reviewed by the Investigator and Medical Monitor.

Number of Subjects: Thirty (30) subjects were screened; 21 subjects were enrolled and treated (9 screen failures); 10 completed the trial as designed (11 subjects discontinued).

Diagnosis and Main Criteria for Inclusion/Exclusion: This trial enrolled subjects with chronic, stable schizophrenia or schizoaffective disorder, as defined by Diagnostic and Statistical Manual of Mental Disorders (4th Edition), who were otherwise considered healthy as determined by medical history, physical examination, 12-lead electrocardiogram (ECG), and clinical laboratory evaluations. Subjects taking stable doses of any non-excluded antipsychotic medications for the treatment of schizophrenia or schizoaffective disorder were allowed to participate. The use of lithium and valproate was permitted. Subjects receiving chronic stable medications for diabetes, thyroid disorders and those on hormone replacement therapy were also allowed to participate. Enrolled women were not nursing, pregnant or of childbearing potential.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration: Each subject was administered a single 5-mg dose of aripiprazole standard IM formulation (Phase 1). Following ≥ 28 day washout interval, each subject received a single dose of the aripiprazole IM depot formulation of 15, 50, 100, 200, 300 or 400 mg (Phase 2).

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

Duration of Treatment: A single 5-mg dose of aripiprazole standard IM formulation (Phase 1) and a single dose of the aripiprazole IM depot formulation of 15, 50, 100, 200, 300 or 400 mg (Phase 2).

Trial Assessments:
Safety and Tolerability: AEs, vital signs, ECGs, physical examinations, and clinical laboratory tests.

Pharmacokinetics: Plasma aripiprazole and dehydro-aripiprazole metabolite concentrations.

Criteria for Evaluation:
Safety and Tolerability: Safety assessments were based on medical review of AE reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests. The incidence of AEs was tabulated and revised for potential significance and clinical importance.

Pharmacokinetics: The following PK parameters were measured (Cmax, Tmax, AUC (0-T), AUC (INF), T-HALF and Frel) for aripiprazole and its major active metabolite, dehydro-aripiprazole, were derived from plasma concentration versus time data:

Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration

AUC (0-T)	Area under the plasma concentration-time curve from time zero to the last sample time point
AUC (INF)	Area under the plasma concentration-time curve from time zero extrapolated in infinite time
T-HALF	Plasma half-life
Frel	Absorption of the depot formulation relative to standard IM

The PK results were determined using a validated noncompartmental analysis and an exploratory deconvolution analysis to determine the rate and extent of aripiprazole absorption from the two IM formulations.

Pharmacokinetic/pharmacodynamic Methods:
Bioanalytical: Plasma samples were assayed for aripiprazole and dehydro-aripiprazole by a validated LC/MS/MS method.[2] Spiked analytical quality control samples were analyzed along with the trial samples in order to assess the accuracy and precision of each analytical run.

Pharmacokinetics: Plasma aripiprazole and dehydro-aripiprazole concentration versus time data were analyzed using compartmental and noncompartmental methods, as well as deconvolution analysis.

Statistical Methods: The number of subjects was not based on statistical power considerations. Summary statistics were tabulated by treatment for the PK parameters. Geometric means and coefficients of variation were presented for Cmax, AUC (INF), AUC (0-T) and Frel. Medians, minima, and maxima were presented for Tmax by treatment. Means and standard deviations were tabulated for the absorption parameters describing in vivo release rate.

Summary of Results:

Baseline Data, Disposition, and Demographics: Thirty (30) subjects with documented chronic, stable schizophrenia or schizoaffective disorder were screened for the trial; 21 were enrolled and 9 discontinued prior to enrollment in the trial. Of the 21 subjects enrolled, 10 completed the protocol as designed (of the 11 subjects who discontinued: 3 were lost to follow-up; 3 withdrew consent; 2 were non-compliant; 1 lacked efficacy; 1 did not meet the trial criteria and 1 subject left partial hospitalization program).

Subjects were predominantly male (86%) with a mean age of 39 years (range 19-57 years); 10 subjects were black (48%), 8 subjects were white (38%) and 3 subjects were “other” (14%; 1 Egyptian and 2 Hispanic subjects); the mean body mass index (BMI) was 29 kg/m^2 (range 22.4-35.4 kg/m^2).

Pharmacokinetic Results:
Aripiprazole: Following administration of aripiprazole IM depot formulation, the mean Cmax values of aripiprazole increased approximately equal to the increment in dose with

doses up to 200 mg and increased less than the increment in dose between the 200 and 400 mg doses. Mean AUC (0-T) values of aripiprazole appeared to increase greater than the increment in aripiprazole dose between the 15 and 400 mg dose groups. Mean T-HALF ranged from 252 to 824 hr. Following single 15 to 400 mg doses of aripiprazole in the IM depot formulation, the estimated time required to absorb 50% of dose ranged between 240 to 840 hr (10 to 35 days). Deconvolution analysis showed the cumulative fraction of aripiprazole absorbed from the IM depot formulation approached unity, suggesting complete absorption of aripiprazole from the depot formulation relative to the standard IM formulation.

Dehydro-aripiprazole: Following administration of single 15 to 400 mg doses of aripiprazole IM depot, the mean Cmax values of dehydro-aripiprazole appeared to increase less than the increment in aripiprazole dose with aripiprazole dose, and mean AUC (0-T) values of dehydro-aripiprazole appeared to increase more than the increment in aripiprazole dose over the 15 to 400 mg dose range.

Safety Results: There were no deaths or discontinuation due to AEs. Most AEs were mild to moderate in intensity. None of the AEs appeared to be dose related for the IM depot formulation. The types of AEs described by a particular preferred term were not different after treatment with IM depot formulation compared to the IM standard formulation. There were 2 serious AEs considered to be unrelated to trial therapy (suicide attempt and exacerbation of schizophrenia) and neither event resulted in discontinuation of trial therapy. The most common treatment-emergent AE was headache occurring in 4 subjects (19%), followed by anxiety occurring in 3 subjects (14%). All other AEs occurred in 2 or fewer subjects. Overall, 4 laboratory marked abnormalities (MA) occurred, 3 of which were considered AEs by the Investigator; elevated CK (~8 x upper limit of normal [ULN]), elevated blood glucose (142 mg/dL) and hypertriglyceridemia. All AEs were resolved by trial discharge. The other MA was a mildly elevated leukocytes count (17.3 x 10^3 c/μL), which resolved 3 days later (14.1 x 10^3 c/μL). No subject had an AE related to the ECG findings. Most ECG abnormalities were either present at pre-dose only or both pre-dose and post-dose. There was no evidence that aripiprazole had any clinically relevant effects on physical examinations, injection sites or vital sign measurements, including orthostatic vital sign assessments.

Conclusions:

- Absorption of aripiprazole from the IM depot formulation was complete relative to the IM standard formulation based on dose adjusted AUC (0-T) values and maximum cumulative fraction of dose absorbed as determined by deconvolution analysis.

- Following single dose of aripiprazole in the IM depot formulation, the estimated time required to absorb 50% of the aripiprazole dose ranged between 10 to 35 days over the dose range of 15 to 400 mg.

- Single doses of aripiprazole IM depot over the range of 15 mg to 400 mg were generally safe and well tolerated by subjects with schizophrenia or schizoaffective disorder in this trial.

Report Date: 27 Jun 2007

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[1] Approved 2004 Abilify (aripiprazole) US package insert, Physician's desk reference. July, 2004.

[2] Pierson, Sharon, Alta Validation Report AR337A, "Method Validation for the Determination of BMS-337039 and BMS-337044 in Human Plasma (K_3EDTA) Using LC-API/MS/MS." Bristol Myers Squibb Pharmaceutical Research Institute; 2001. BMS Document Control No. 920010507.