Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole (OPC-14597)

Clinical Summary for Protocol 31-11-289
NCT No. 01552772

An Open-label, Safety and Tolerability Trial of Aripiprazole IM Depot Treatment Initiation in Adult Subjects with Schizophrenia Stabilized on Atypical Oral Antipsychotics Other Than Aripiprazole

Indication:	Schizophrenia
Clinical Development Phase:	1
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. Rockville, Maryland, United States
Trial Initiation Date:	27 Jan 2012
Trial Completion Date:	11 May 2012
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: An Open-label, Safety and Tolerability Trial of Aripiprazole IM Depot Treatment Initiation in Adult Subjects with Schizophrenia Stabilized on Atypical Oral Antipsychotics Other Than Aripiprazole

Trial Center(s) by Region: Multicenter (12 centers in the United States)

Clinical Phase/Trial Type: Phase 1 Adjunct therapy safety and tolerability.

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale: The dosing paradigm in the two completed phase 3 trials (Trial 31-07-246 and Trial 31-07-247) of aripiprazole IM depot 400/300 mg included an oral aripiprazole stabilization run-in phase, followed by administration of monthly aripiprazole intramuscular (IM) depot 400 mg injections. Along with the first IM depot injection, oral aripiprazole was co-administered for the first 14 consecutive days. However, safety and tolerability data were not available for subjects who were treated with an oral antipsychotic medication other than aripiprazole before and concomitant (for the first 14 days) to the first injection of aripiprazole IM depot. Thus, the current trial aimed to assess the safety and tolerability of aripiprazole IM depot after treatment initiation in schizophrenic subjects who were stabilized on atypical oral antipsychotics other than aripiprazole**.**

Publications: None to date.

Objectives:

Primary: Safety: To determine the safety and tolerability of a single dose of aripiprazole IM depot following treatment initiation in schizophrenic subjects currently stabilized on atypical oral antipsychotics other than aripiprazole.

Secondary: Pharmacokinetics (PK): To determine plasma concentrations of aripiprazole and its metabolite, dehydro aripiprazole, at Day 7, Day 14, and Day 28 following administration of aripiprazole IM depot.

Efficacy: To determine the efficacy of aripiprazole IM depot based on the Positive and Negative Syndrome Scale (PANSS; total, positive, and negative subscales), Clinical Global Impression Severity (CGI S), and Clinical Global Impression Improvement (CGI I) scores.

Methodology: Trial 31-11-289 was an open label, single dose, multicenter trial to assess the safety and tolerability of aripiprazole IM depot as adjunctive therapy in adults with schizophrenia who were currently stabilized on atypical oral antipsychotics other than

aripiprazole. The trial consisted of a screening phase of up to 30 days, a treatment phase of 28 days, and a follow up at 30 days after the last trial visit.

Aripiprazole IM depot (400 mg) was administered to subjects stabilized on atypical oral antipsychotic medications other than aripiprazole. Subjects entering the trial must have been clinically stable on any of the following atypical oral antipsychotic medications for at least 14 days before the administration of aripiprazole IM depot: risperidone, olanzapine, quetiapine, ziprasidone, or paliperidone (atypical long acting IM depot antipsychotic medications were not allowed). Concomitant to the aripiprazole IM depot injection, subjects continued to receive their current atypical oral antipsychotic medication for 14 days. During this period, investigators were to consider reducing the dose of the oral antipsychotic medication to the mid to lower recommended dose range described in the prescribing information, as the initiation of aripiprazole IM depot treatment added an additional antipsychotic medication to the subject's treatment. The dose of oral antipsychotic medication could be further adjusted at the discretion of the investigator based on the subject's symptoms, as well as the observed safety and tolerability profile for the subject.

This was an outpatient trial and, after the administration of aripiprazole IM depot at the trial site, the subjects returned to the site on Day 7 (± 1 day), Day 14 (± 1 day), and Day 28 (± 1 day) for efficacy assessments, safety assessments, and collection of laboratory and PK samples. Subjects who completed all trial visits through the Day 28 visit were offered after care, including appropriate schizophrenia therapy at the investigator's discretion, and were followed to monitor for safety events. Blood samples were collected at Day 7 (± 1 day), Day 14 (± 1 day), and Day 28 (± 1 day) for aripiprazole and dehydro aripiprazole concentration measurements.

Number of Subjects: Approximately 60 adult subjects in the United States with schizophrenia were to be enrolled in this trial. A total of 75 subjects were screened and 60 subjects were enrolled. All 60 (100%) enrolled subjects received one injection of aripiprazole IM depot 400 mg as planned and represent the safety population

Diagnosis and Main Criteria for Inclusion/Exclusion: The trial population included male and female subjects, 18 to 64 years of age, inclusive, with a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, (DSM-IV-TR) criteria. Subjects must have had a history of tolerating aripiprazole and must have been stable for at least 14 days on one of the following atypical oral antipsychotic medications before administration of aripiprazole IM depot: risperidone, olanzapine, quetiapine, ziprasidone, or paliperidone. Subjects were excluded if: they met DSM-IV-TR criteria for substance abuse or dependence within the past 180 days; including alcohol and benzodiazepines, (excluding caffeine and nicotine); they had a positive drug screen for cocaine or other drugs of abuse (excluding stimulants and other prescribed medications and marijuana), required prohibited concomitant therapy during the trial, and use of any CYP2D6 and CYP3A4 inhibitors, or CYP3A4 inducers within 14 days before dosing and for the duration of the trial; had a

significant risk of committing suicide based on history, routine psychiatric status examination, investigator's judgment, or who had an answer of "yes" on questions 4 or 5 (current or over the last 30 days) on the baseline version of the C-SSRS; had a history of neuroleptic malignant syndrome or clinically significant tardive dyskinesia as assessed by the investigator, or men and women who were sexually active and refused to commit to utilizing 2 of the approved birth control methods or who would not remain abstinent during the trial and for 180 days (men) or 150 days (women) after the last dose of trial medication. Women who were pregnant were also excluded.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration: Aripiprazole IM depot 400 mg was administered as a single injection into the gluteal muscle on Day 1 of the trial. Aripiprazole IM depot (400 mg) was supplied as vials of lyophilized powder reconstituted with a designated quantity of sterile water for injection before administration.

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

Duration of Treatment: The planned treatment phase of the trial was 28 days.

Trial Assessments: These included the incidence of adverse events (AEs), vital sign measurements, electrocardiogram (ECG) findings, clinical laboratory test results (serum chemistry, hematology, and urinalysis), physical examination findings, extrapyramidal symptoms (EPS), and suicidality. The EPS rating scales completed during the trial were the Simpson Angus Scale (SAS), the Abnormal Involuntary Movement Scale (AIMS), and the Barnes Akathisia Rating Scale (BARS). Extrapyramidal symptoms were assessed based on the SAS Total Score, the AIMS Movement Rating Score, and the BARS Global Score. Suicidality was assessed based on the C SSRS data. Efficacy was based on changes in PANSS (total score, and positive and negative subscale scores), and CGI S, and CGI I scores. For PK, bioanalytical assessments included plasma samples (analyzed for determination of aripiprazole and its major metabolite, dehydro-aripiprazole, concentrations using high performance liquid chromatography with tandem mass spectrometry (HPLC MS/MS).

Criteria for Evaluation:

Efficacy: Efficacy Endpoints included changes from baseline score in PANSS total score, changes from Baseline score in PANSS positive subscale score, changes from Baseline score in PANSS negative subscale score, and changes from Baseline score in CGI-S and CGI-I score.

Pharmacokinetics: PK endpoints were the aripiprazole and dehydro-aripiprazole plasma concentrations at predose on Day 1, and on Day 7 (±1 day), Day 14 (±1 day), and Day 28 (±1 day) were reported. No further PK analysis was performed.

Safety: Safety endpoints were AEs, vital signs, ECGs, clinical laboratory monitoring (ie, serum chemistry, hematology, urinalysis), physical examinations, EPS, and suicidality assessments. Suicidality data collected from the C SSRS assessments were summarized for the treated sample reporting suicidality; suicidal behavior only, emergence of suicidal behavior; suicidal ideation only, emergence of suicidal ideation; emergence of serious suicidal ideation; and worsening of suicidal ideation.

Statistical Methods: The methods used for each type of analysis are described by parameter. *Efficacy*: The dataset for all efficacy analyses consisted of data from all enrolled subjects who had at least 1 efficacy measurement. Both observed case data (OC) and last observation carried forward (LOCF) data for these subjects were included. The LOCF method was used to impute missing data at visits after Baseline for the efficacy analysis and for the safety EPS assessment scales. Baseline measurements of effectiveness variables except CGI-I were defined as their measurements before the first dose of aripiprazole IM depot on Day 1. Change from Baseline data of effectiveness variables and original score at each visit were summarized using descriptive statistics for each atypical antipsychotic used before trial and for each visit.

Pharmacokinetics/pharmacogenomics: The dataset for the PK analysis consisted of all evaluable aripiprazole PK parameters from enrolled subjects. No data imputation was done for missing data (ie, missing data remained missing for the analyses). Plasma was analyzed for aripiprazole and dehydro-aripiprazole concentrations. Pharmacokinetic parameters were determined using the compartmental method. A separate report on the pharmacogenomics of the individual subjects was prepared as an appendix to the study report.

Safety: The dataset for all safety analyses consisted of data from all enrolled subjects who received 1 dose of trial medication, regardless of any protocol violation. All observed data for these subjects were included. In general, summary statistics of changes from Baseline and incidence of events were provided for safety variables. Data from unscheduled visits were not used in the mean change from baseline calculation, but were included in the incidence calculation. Baseline measurements of safety variables were defined as the last measurements before the first dosing of trial medication (aripiprazole IM depot 400 mg).

Summary of Results:

Baseline Data, Disposition, and Demographics: Seventy-five subjects were screened and 60 subjects entered the trial. All 60 subjects were treated with aripiprazole IM depot. Fifty-eight (96.7%) subjects completed 25-32 days in the trial. Subject 008S0804 on quetiapine discontinued on Day 25, thus he is included in the total of 58 subjects who completed 25-32 days (Week 4) because he discontinued at the start of that week. Three other subjects withdrew during the trial: Subject 011S1108 completed 11-17 days

(Week 2); Subject 009S0906 completed 18-24 days (Week 3); and Subject 010S1005 was lost to follow-up but is included in the 33-44 days (> Week 4) group.

Subjects were taking the following atypical oral antipsychotic medications at trial entry: quetiapine (28 subjects), risperidone (24 subjects), ziprasidone (5 subjects), and olanzapine (3 subjects). Of the 60 subjects treated, 56 (93.3%) completed the trial and 4 (6.7%) discontinued. The reasons for discontinuation were lost to follow-up (2/60 subjects, 3.3%), AE (1/60 subjects, 1.7%), and protocol deviation (1/60 subjects, 1.7%). Demographic and baseline characteristics were similar between the atypical oral antipsychotic medication groups. Most subjects were male (50/60 subjects, 83.0%) and black/African American (49/60 subjects, 82.0%). The mean age was 43.2 years (range: 21.0 to 57.0 years). The mean PANSS total score at baseline was 64.5, with a mean PANSS positive subscore of 16.7 and a mean PANSS negative subscore of 17.0. The CGI-S score at baseline was 3.3. The mean age at the time of first diagnosis was 27.0 years (range: 8 to 56 years). All 60 subjects (100%) were taking a baseline medication.

In addition to the 5 atypical antipsychotic medications that were required for inclusion in the trial (risperidone [24/60 subjects, 40.0%], olanzapine [3/60 subjects, 5.0%], quetiapine fumerate [28/60 subjects, 46.7%], ziprasidone [5/60 subjects, 8.3%], and paliperidone [0 subjects]), the most prevalent baseline medication was benzatropine mesilate (7/60 subjects, 11.7%). Subjects were also on the following psycholeptic baseline medications: zolpidem tartrate (4/60 subjects, 6.7%), and lithium and diphenhydramine hydrochloride (3/60 subject each, 5.0%). Other baseline medications taken by ≥ 5% of total subjects included: ibuprofen (5/60 subjects, 8.3%), multivitamin (4/60 subjects, 6.7%), hydrochlorothiazide (4/60 subjects, 6.7%), lisinopril (3/60 subjects, 5.0%), amlodipine besylate (3/60 subjects, 5.0%), metformin (3/60 subjects, 5.0%), and trazodone (3/60 subjects, 5.0%). There were no remarkable differences among the baseline medications compared by atypical antipsychotic medication.

Efficacy Results: Fifty-nine (98.3%) enrolled subjects who had at least one efficacy measurement were included in the effectiveness analyses. While the analyses were not powered for efficacy, subjects' results did show numerical improvement in the PANSS total score, the positive and negative subscales, and the CGI S and the CGI I.

Pharmacokinetic/pharmacodynamic Results:

Bioanalytical: The HPLC MS/MS method used for the determination of aripiprazole and dehydro aripiprazole in plasma had adequate linearity, specificity, sensitivity, and accuracy and the methods and other details were described in a separate report.

Pharmacokinetics: Observed aripiprazole and dehydro-aripiprazole plasma concentrations were comparable to the observed concentrations in previous trials.

Pharmacogenomics: A separate report of the pharmacogenomics results was prepared as an appendix to the study report. The individual results by subject showed that 36 subjects had extensive metabolism of the P450 CYP2D6 isozyme, 22 subjects samples showed intermediate metabolism, and samples from 2 subjects showed poor metabolism.

Safety Results: All 60 (100%) enrolled subjects received one injection of aripiprazole IM depot 400 mg as planned and represent the safety population. Overall, 35/60 (58.3%) subjects treated with aripiprazole IM depot reported 77 treatment emergent adverse events (TEAEs). All TEAEs were reported as mild or moderate.

The most common TEAEs (overall incidence ≥ 5%) were injection site pain and toothache (4/60 subjects each, 6.7%); and dystonia, fatigue, increased blood creatine phosphokinase, insomnia, and restlessness (3/60 subjects each, 5.0%).

No subject died during the trial. One of 60 subjects (1.7%) reported a serious TEAE (suicide attempt) on Day 52 during the safety follow-up period, which was considered unrelated to trial medication by both the investigator and the sponsor. No subjects discontinued trial treatment because of TEAEs; however, 1/60 subject (1.7%) was discontinued from the trial because of a TEAE (insomnia). The most common potentially trial medication-related TEAEs ≥ 5% were dystonia, increased blood creatine phosphokinase, injection site pain, and restlessness (3/60 subjects each, 5.0%).

Treatment with aripiprazole IM depot did not result in any clinically relevant mean changes in clinical laboratory values, vital signs, or ECG parameters in this population of subjects with schizophrenia.

A weight gain ≥ 7% from baseline occurred during the trial for 2/60 subjects (3.3%) overall. No subjects experienced a weight loss ≥ 7% from baseline.

The analysis of the SAS, AIMS, and BARS scales did not suggest any increase in the severity of EPS during the trial. No subject had a post-baseline suicidal event during the treatment period as assessed by C-SSRS. As noted above, one subject attempted suicide during the safety follow-up period. All results for this subject's C SSRS assessment indicated no suicidal ideation, behavior, or attempts from Screening through Day 28.

There was a protocol deviation during the trial. The requirement to maintain the assigned atypical antipsychotic for 14 (± 1) days after IM depot administration was not followed for 26/60 subjects (43.3%) during the trial: 23 subjects took less than 13 days and 3 subjects took > 15 days of atypical oral antipsychotic medication. Thirty-four of 60 subjects (57%) received the protocol-specified treatment of 13 to 15 days of concomitant atypical oral antipsychotic. The safety profile was consistent for subjects who took < 13 days oral antipsychotic treatment compared with subjects who took the protocol-compliant 13 to 15 days of oral antipsychotic treatment.

Conclusions:

- A single monthly injection of aripiprazole IM depot 400 mg with 2 weeks of concomitant atypical oral antipsychotic treatment was safe and well-tolerated when given to subjects who were previously stabilized on atypical oral antipsychotic treatment other than aripiprazole.
- Aripiprazole concentrations on Day 28 were comparable to those concentrations observed in other trials when subjects took 2 weeks of oral aripiprazole with the initial aripiprazole IM depot administration.
- Subjects' results showed numerical improvement in the PANSS total score, the positive and negative subscales, and the CGI-S and the CGI-I.

Report Date: Report Issued: 19 Sep 2012
Date of Amendment 1 Issue: 14 Mar 2013
Date of Amendment 2 Issue: 18 Feb 2014