Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole (OPC-14597 IMD)

Clinical Summary for Protocol 31-10-002

Indication:	Schizophrenia
Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Co., Ltd. 3-2-27 Otedori, Chuo-ku Osaka, Japan
Trial Initiation Date:	29 Sep 2011
Trial Completion Date:	12 Dec 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 IMD)

Protocol Title: Multicenter Open-label Study Investigating the Pharmacokinetics of Aripiprazole IM Depot Formulation (OPC-14597 IMD) During Repeated Administration to Patients with Schizophrenia

Trial Center(s) by Region: 16 sites in Japan

Clinical Phase/Trial Type: Phase 3/Open-label, multicenter, repeated-dose, pharmacokinetics trial

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale: Aripiprazole intramuscular (IM) depot formulation is being developed as an intramuscular formulation for switching from oral aripiprazole in patients whose mental state is stable or adequately maintained by aripiprazole. The recommended dosage of oral aripiprazole approved in Japan is 6 to 24 mg/day. After switching to aripiprazole IM depot formulation, it is necessary to achieve a similar plasma concentration to that obtained during treatment with the oral formulation of aripiprazole in order to maintain clinical efficacy.

Based on the pharmacokinetic (PK) profile obtained from the single-dose trial (031-07-002)[1] conducted in Japan, the plasma drug concentration-time profile of aripiprazole after repeated administration of IMD was simulated and was compared with the plasma drug concentration in Japanese subjects when aripiprazole tablets was administered repeatedly at 6 to 24 mg/day. The plasma drug concentration-time profile after repeated administration of IMD at 300 or 400 mg was estimated to be in the trough concentration range obtained with aripiprazole tablets at 6 to 24 mg/day. Based on these results, the sponsor consulted with the Pharmaceuticals and Medical Devices Agency and is now conducting a non-inferiority trial of aripiprazole IM depot formulation versus aripiprazole tablets (031-08-003). However, this confirmatory trial is not designed to obtain information on the PK parameters during repeated administration.

Considering the above background, in order to make a more detailed investigation of the steady state plasma drug concentration-time profile after repeated administration of aripiprazole IM depot formulation, we have planned a repeated-dose trial in Japanese subjects with schizophrenia. The doses of aripiprazole IM depot formulation to be investigated are 300 mg and 400 mg, for which efficacy and safety are being evaluated in overseas confirmatory studies (31-07-246, 31-07-247) and an Asian registration trial (031-08-003) is being performed for Japanese regulatory filing purposes. A total of 5 doses will be administered, with this number being selected from the results of a simulation of the plasma drug concentration-time profile after repeated administration of aripiprazole IM depot formulation based on data from a domestic single-dose trial (031-07-002)[1] and the results of an overseas repeated-dose trial (31-05-244).[2] It is

considered that a steady state plasma drug concentration will be reached after 5 doses of aripiprazole IM depot formulation.

With regard to safety, no particularly significant AEs have been identified in the overseas single-dose trial (CN138-020),[3] overseas repeated-dose trial (31-05-244), and domestic single-dose trial (031-07-002)[1] as well as the ongoing overseas confirmatory studies (31-07-246, 31-07-247), overseas long-term trial (31-08-248), and Asian confirmatory trial (031-08-003) for Japanese registration, at doses of up to 400 mg. Thus, the sponsor considers that the safety of the subjects can be ensured.

Publications: None to date.

Objectives: To assess the PK and safety after repeated administration of a total of 5 doses of 300 mg or 400 mg of aripiprazole IM depot formulation at 4-week intervals in subjects with schizophrenia.

Methodology: This was a multicenter open-label trial performed in subjects with schizophrenia diagnosed as defined by *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR). This trial consisted of an aripiprazole IM depot formulation treatment period and a post-treatment observation period. An investigator or subinvestigator obtained written informed consent from subjects in whom schizophrenia was diagnosed based on DSM-IV-TR and whose mental condition had been stable or well maintained on Abilify® (aripiprazole tablets) monotherapy for more than 2 weeks, and then performed a screening examination of the subjects. Subjects judged to be appropriate for the trial entered the aripiprazole IM depot formulation treatment period.

During the aripiprazole IM depot formulation treatment period, subjects received IM injections of aripiprazole IM depot formulation in the gluteal region at a dose of either 300 mg or 400 mg once every 4 weeks for a total of 5 doses. The ratio of subjects in the 300-mg group and 400-mg group was 1:1. For 2 weeks after the first dose of aripiprazole IM depot formulation, in order to maintain an adequate plasma aripiprazole concentration, aripiprazole tablets (6 mg/day or 12 mg/day) were also administered. The duration of the IM depot treatment period was 20 weeks from the first injection. The post-treatment observation period was set as a period of 4 weeks after completion of the aripiprazole IM depot formulation treatment period.

Number of Subjects:
300-mg group:
Planned: 8; treated: 12; PK analysis: 12; safety analysis: 12
400-mg group:
Planned: 8; treated: 16; PK analysis: 16; safety analysis: 16

Diagnosis and Main Criteria for Inclusion/Exclusion:

1) Subjects with a diagnosis of schizophrenia as defined by DSM-IV-TR (295.30, 295.10, 295.20, 295.90, 295.60)
2) Subjects who gave written informed consent by themselves (If the subject was a minor, written consent from a legal representative was obtained in addition to the subject's own written informed consent.)
3) Subjects, both male and female, aged 18 years or older, but younger than 65 years, at the time of giving informed consent (provided that the subject did not turn 65 years old during the trial period)
4) Subjects with a body mass index (BMI) of 18.5 or higher and lower than 35.0
5) Subjects who had received aripiprazole tablet(s) monotherapy with no change of the dosage and administration for more than 2 weeks prior to giving informed consent (1-2 times a day, 6 to 24 mg/day*) and whose mental condition was stable or well maintained

*Permitted dosages of aripiprazole tablets were 6, 9, 12, 15, 18, 21, or 24 mg/day and subjects who received any other daily doses were excluded.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration:

1) Trial drug: Aripiprazole IM Depot Formulation (IMD)
2) Code name: OPC-14597 IMD
3) Content and dosage form: An injectable formulation consisting of a vial containing 400 mg of aripiprazole hydrate in anhydrous form*

*Aripiprazole IM depot formulation was supplied as a lyophilized formulation of an aqueous suspension (in a vial). Just prior to administration, 2.0 mL of water for injection was injected into the 400-mg vial to prepare an aripiprazole suspension. After the addition of water for injection, 2.5 mL of suspension was prepared in the vial. When 400 mg of aripiprazole was to be administered, 2.0 mL of aripiprazole suspension was injected intramuscularly, and for a 300 mg administration of aripiprazole, 1.5 mL of aripiprazole suspension was injected.

To the subjects in each group, a single dose of aripiprazole IM depot formulation (300 mg or 400 mg) was injected into the gluteal muscles once every 4 weeks for a total of 5 doses.

During the trial period, the dosage of aripiprazole IM depot formulation was not changed. For 2 weeks after the first injection of aripiprazole IM depot formulation, aripiprazole tablets were administered concomitantly. The dosage of oral aripiprazole tablets was determined as follows, based on the dose of aripiprazole tablets prior to administration of aripiprazole IM depot formulation.

- Subjects whose dose of aripiprazole tablets prior to administration of aripiprazole IM depot formulation was in the range of 6 to 15 mg/day (once or twice a day): 6 mg/day (once a day).

- Subjects whose dose of aripiprazole tablets prior to administration of aripiprazole IM depot formulation was in the range of 18 to 24 mg/day (once or twice a day): 12 mg/day (once a day).

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration:

1) Other trial drug: Aripiprazole tablets
2) Code name: OPC-14597
3) Content and dosage form: White plain tablets containing 6 mg of aripiprazole in each tablet

Duration of Treatment:
20 weeks (the treatment period was defined as lasting until 4 weeks after the fifth dose of aripiprazole IM depot formulation)

Trial Assessments:
Efficacy evaluation:
Clinical Global Impression-Severity of Illness (CGI-S), Global Impression–Improvement (CGI-I)

Pharmacokinetic evaluation:
Blood collection for measurement of the plasma drug concentration prior to administration of aripiprazole IM depot formulation.

Safety evaluation:
Adverse events (AEs), clinical laboratory tests, vital signs, weight, height, BMI, electrocardiograms (ECGs), Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS), Columbia–Suicide Severity Rating Scale (C-SSRS), and injection site reaction prior to administration of aripiprazole IM depot formulation (excluding the first dose).

Criteria for Evaluation:
Efficacy:
CGI-S, CGI-I

Pharmacokinetics:

1) Plasma concentration-time profiles of aripiprazole and its main metabolite OPC-14857
2) Total plasma molar concentration profiles of the active compounds (aripiprazole and its main metabolite OPC-14857)
3) C_{672h} of aripiprazole and its main metabolite OPC-14857 before the first administration of aripiprazole IM depot formulation and after doses 1-5
4) Pharmacokinetic parameters of aripiprazole and its main metabolite OPC-14857 after the fifth dose of aripiprazole IM depot formulation: C_{max}, t_{max}, AUC_{672h}, λ_z, $t_{1/2,z}$, CL/F*, CL/F/BW*, V_z/F*, V_z/F/BW*, C_{max}/D, and AUC_{672h}/D (*only calculated for aripiprazole)

5) Ratio of the AUC_{672h} of the main metabolite OPC-14857 to that of aripiprazole after the fifth dose of aripiprazole IM depot formulation (metabolite ratio)

Safety:
Adverse events, clinical laboratory tests, vital signs, body weight, 12-lead ECG, DIEPSS, C-SSRS, and reactions at the injection site

Statistical Methods: *Efficacy*: List tables were prepared for CGI-S and CGI-I.

Pharmacokinetics
For each of the PK endpoints 1) to 3) above, descriptive statistics were calculated at each blood collection time point (number of subjects, arithmetic mean, standard deviation, coefficient of variation, geometric mean, minimum, median, and maximum; the same hereafter). When preparing figures, the arithmetic mean and standard deviation were used.

Concerning PK endpoint 4) above, the descriptive statistics for each parameter were calculated by compound and dose. When preparing figures, the arithmetic mean and standard deviation were used.

Concerning PK endpoint 5) above, descriptive statistics were calculated for each dose. When preparing figures, the arithmetic mean and standard deviation were used.

Safety:
All AEs were classified according to System Organ Class and Preferred Terms of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by overall incidence, treatment group, dose level, severity, time of onset, duration, and causality. Serious adverse events (SAEs) and AEs leading to discontinuation were summarized and reported similarly. Extrapyramidal system AEs and injection sited reactions were also summarized by treatment group, dose, and overall incidence. The number of subjects discontinuing due to extrapyramidal AEs or injection site reactions was also reported.

Laboratory test result values were summarized as descriptive statistics for each treatment group and dose at each time point and for the change from baseline to each time point. Shift tables for changes from baseline were presented. The incidence of clinically significant abnormal laboratory values was presented in shift tables.

Vital signs measurements were summarized for each dose level and presented as descriptive statistics and the incidence of abnormal values was determined and summarized. Descriptive statistics of the body weight values at each point and changes from the baseline were calculated for each dose level, as were summaries of BMI categories. Shift tables were prepared for the incidence of normal and abnormal findings in 12-lead ECG measures at each time point and dose level.

Scores for the DIEPSS and C-SSRS were summarized for each item at each time period and dose level.

Summary of Results:

Baseline Data, Disposition, and Demographics:

- A total of 28 subjects were enrolled; 12 subjects were treated with 300 mg aripiprazole IM depot formulation and 16 subjects were treated with 400 mg aripiprazole IM depot formulation. All subjects treated were included in both the PK and the safety analyses.
- The total of 28 subjects comprised 15 males and 13 females. Mean age was 38.6 ± 11.4 years (mean ± SD; same below), body weight was 64.67 ± 13.49 kg, and BMI was 24.10 ± 3.95. Mean age at onset of schizophrenia was 27.1 ± 8.7 years.
- The 300-mg group comprised 3 male and 9 female subjects, with a greater number of female subjects. The 400-mg group comprised 12 male and 4 female subjects, with a greater number of male subjects. Mean body weight was 62.64 ± 10.94 kg in the 300-mg group and 66.19 ± 15.30 kg in the 400-mg group and BMI was 24.13 ± 3.95 in the 300-mg group and 24.08 ± 4.07 in the 400-mg group, with both parameters being comparable between the two groups. Of the other baseline characteristics, the dose of aripiprazole tablets showed a notable difference with respect to the trend of distribution between the two groups, but there were no other parameters that showed a notable difference between the two groups.

Efficacy Results:

No efficacy analysis was performed.

Pharmacokinetic/pharmacodynamic Results:

- The PK analysis set consisted of 12 subjects in the 300-mg group and 16 subjects in the 400-mg group.
- The mean plasma concentrations of aripiprazole and OPC-14857 appeared to reach a steady state prior to the fourth dose of aripiprazole IM depot formulation (12 weeks [84 days] after initiation).
- The median trough concentration of aripiprazole after the first injection of aripiprazole IM depot formulation (300 mg and 400 mg) was in the range from the median plasma trough concentration of aripiprazole at the steady state following administration of aripiprazole tablets at 6 mg/day to the median C_{max} of aripiprazole at the steady state following administration of aripiprazole tablets at 24 mg/day.
- The mean C_{max} after the fifth dose of 300 mg or 400 mg of aripiprazole IM depot formulation was lower than mean C_{max} of aripiprazole at the steady state following administration of aripiprazole tablets at 24 mg/day. The median t_{max} of the 300-mg group and the 400-mg group was 120.30 hours (5.01 days) and 95.70 hours (3.99 days), respectively, while the mean $t_{1/2,\,z}$ was 657 hours (27.4 days) and 1340 hours (55.8 days), respectively.

- Median t_{max} of OPC-14857 after the fifth dose of aripiprazole IM depot formulation was 263.25 hours (10.97 days) in the 300-mg group and 119.92 hours (5.00 days) in the 400-mg group, while mean $t_{1/2,z}$ was 1080 hours (45.0 days) and 1660 hours (69.2 days), respectively.
- The mean AUC_{672h} ratio of OPC-14857 to aripiprazole after the fifth dose of aripiprazole IM depot formulation was 0.336 in the 300-mg group and 0.354 in the 400-mg group. The mean total plasma molar concentration-time profiles of the two active compounds combined after the fifth dose of aripiprazole IM depot formulation showed trends similar to the changes of the mean plasma molar concentration-time profiles of aripiprazole.

Safety Results:

- The safety analysis set consisted of 12 subjects in the 300-mg group and 16 subjects in the 400-mg group.
- Adverse events occurred in 83.3% of the 300-mg group (10/12 subjects) and 87.5% of the 400-mg group (14/16 subjects). Potentially drug-related AEs occurred in 75.0% of the 300-mg group (9/12 subjects) and 62.5% of the 400-mg group (10/16 subjects). Adverse events that occurred in at least 2 subjects in each dose group were nasopharyngitis in 4 subjects and akathisia, abnormal hepatic function, injection site pain, and increased blood prolactin in 2 subjects each in the 300-mg group, while in the 400-mg group there was only nasopharyngitis in 2 subjects. All events in the 300-mg group were mild, while the events in the 400-mg group were either mild or moderate, but most were mild. Potentially drug-related AEs that occurred in at least 2 subjects were akathisia and injection site pain in 2 subjects each from the 300-mg group, while there were no potentially drug-related AEs that occurred in at least 2 subjects from the 400-mg group.
- There were no deaths reported. In 1 subject from the 400-mg group, a SAE that occurred was attempted suicide and AEs that led to discontinuation were delusions of reference and suicidal ideation. In 1 subject from the 300-mg group, mastitis was an AE that led to discontinuation.
- Adverse events related to the extrapyramidal system were observed in 2/12 subjects in the 300-mg group and 4/16 subjects in the 400-mg group. All of these were mild and did not result in discontinuation. In 1 subject from the 400-mg group the event was due to another drug and a relation to the trial drug was ruled out. Adverse events related to injection site reactions were observed in 3/12 subjects in the 300-mg group and 2/16 subjects in the 400-mg group. All events were mild and did not result in discontinuation.
- Concerning the shift table for changes of clinical laboratory test results before and after treatment, some parameters were within the reference range at baseline but exceeded the reference range after treatment and changes of the descriptive statistics were noted. However, no clinically significant consistent trends were observed.
- No clinically significant consistent trends were observed in relation to vital signs, body weight, and 12-lead ECG findings.

- When aripiprazole IM depot formulation (300 mg or 400 mg) was administered once every 4 weeks, there were no significant safety concerns and good tolerability was verified.

Conclusions:
Concerning PK, the mean plasma concentrations of aripiprazole and OPC-14857 reached a steady state prior to the fourth dose of aripiprazole IM depot formulation [12 weeks (84 days) after initiation]. In addition, the median plasma trough concentration of aripiprazole after the first dose of aripiprazole IM depot formulation (300 mg and 400 mg) was in the range from the median trough concentration of aripiprazole at the steady state after administration of aripiprazole tablets at 6 mg/day to the median C_{max} of aripiprazole at the steady state after administration of aripiprazole tablets at 24 mg/day.

Concerning safety, all AEs that occurred after the administration of aripiprazole IM depot formulation were either mild or moderate and there were no deaths. Other SAEs included 1 case of attempted suicide in the 400-mg group, but a relation to the trial drug was ruled out. Concerning AEs that led to discontinuation, the one subject with the SAE in the 400-mg group also developed delusions of reference and suicidal ideation, and 1 subject in the 300-mg group developed mastitis; however, these events resolved or improved. Adverse events related to the extrapyramidal system and related to injection site reactions were observed in both the 300-mg group and the 400-mg group, but all of these events were mild. Based on the laboratory test results, there were no clinically significant consistent trends of abnormalities. In conclusion, when aripiprazole IM depot formulation (300 mg or 400 mg) was administered once every 4 weeks, there were no significant safety issues and good tolerability was demonstrated.

Report Date: 24 June 2013

References:

[1] Otsuka Pharmaceutical Co., Ltd. An Investigation of the pharmacokinetics, tolerability, and safety of a single-dose of aripiprazole IM depot in patients with schizophrenia (clinical pharmacology trial). Clinical Study Report for study 031-07-002, 2009.

[2] Otsuka Pharmaceutical Development & Commercialization, Inc. An Open-label, Parallel Arm, Multiple Dose Tolerability, Pharmacokinetics and Safety Study in Adult Patients with Schizophrenia Following Administration of Aripiprazole Intramuscular (IM) Depot Formulation Once Every Four Weeks. Clinical Report Protocol No. 31-05-244, 2009.

[3] Bristol-Myers Squibb Company. Assessment of the In Vivo Release Characteristics and Safety of an Intramuscular Depot Formulation of Aripiprazole in Subjects with Schizophrenia or Schizoaffective Disorder. Final Clinical Study Report for Study CN138020, 2007.