Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole (OPC-14597)

Clinical Summary for Protocol 31-11-284
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A Multicenter, Open-label Study to Assess Hospitalization Rates in Adult Subjects with Schizophrenia Treated Prospectively for 6 Months with Aripiprazole IM Depot Compared With 6-month Retrospective Treatment with Oral Antipsychotics in a Naturalistic Community Setting in Europe, Canada, and Asia

Indication:	Schizophrenia
Clinical Development Phase:	3b
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland, United States
Trial Initiation Date:	30 Jan 2012
Trial Completion Date:	11 Oct 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: A Multicenter, Open-label Study to Assess Hospitalization Rates in Adult Subjects with Schizophrenia Treated Prospectively for 6 Months with Aripiprazole IM Depot Compared With 6-month Retrospective Treatment with Oral Antipsychotics in a Naturalistic Community Setting in Europe, Canada, and Asia

Trial Center(s) by Region: Multicenter (38 activated sites; 11 of those sites with subjects on trial); Multinational in Europe, Canada, and Asia

Clinical Phase/Trial Type: 3b/Multi-center, Open-label

Trial Interruption: This trial was terminated early by the sponsor. The reason for trial closure was not related to safety because no signals or items of concern were identified.

Scientific Background and Explanation of Rationale: Schizophrenia is a chronic condition that requires continual treatment to maintain adequate cognitive and social functioning.

ABILIFY®(aripiprazole) oral tablets are approved in the US for the treatment of adults and adolescents with acute schizophrenia, maintenance of stability in adults with schizophrenia, treatment of acute manic episodes associated with bipolar I disorder in adults and pediatric patients, maintenance of efficacy in adults with bipolar I disorder, and as adjunctive treatment of major depressive disorder (MDD). Aripiprazole is also approved for the treatment of schizophrenia in the European Union (EU), Australia, and a number of countries in Asia, Europe, and Latin America. The aripiprazole immediate release IM injection formulation is approved for agitation in schizophrenia and bipolar mania in the US and EU. In addition, an oral solution formulation and orally disintegrating (dispersible) tablets have been approved and marketed in the US and EU. The favorable side effect profile of oral aripiprazole, including its low incidence of extrapyramidal symptoms (EPS), low risk of prolactin elevation, decreased adrenergic and anticholinergic side effects, and minimal weight gain, makes it an excellent candidate for a long-acting depot formulation. The efficacy, safety, and tolerability of an IM depot formulation of aripiprazole are being examined for the treatment of schizophrenia in 2 pivotal phase 3 trials, and another phase 3 trial is being conducted to supplement the safety data and to provide additional efficacy data for the maintenance treatment of patients with schizophrenia.

The aim of this current trial was to evaluate the effects of once-monthly injections with aripiprazole IM depot treatment on inpatient psychiatric hospitalization rates (proportion of subjects with ≥ 1 inpatient psychiatric hospitalization[s]), and to further evaluate the long-term safety and tolerability of aripiprazole IM depot formulation.

Publications: None to date.

Objectives: The primary objective was to compare inpatient psychiatric hospitalization rates (proportion of subjects with ≥ 1 inpatient psychiatric hospitalization[s]) between Months 4 to 6 (Weeks -12 to -24) of the retrospective period while the subject was receiving oral standard of care antipsychotic treatment(s) with those of Months 4 to 6 (Weeks 12 to 24) of the prospective period after the switch to aripiprazole IM depot in adult subjects with schizophrenia. The secondary objective was to further evaluate long-term safety and tolerability of aripiprazole IM depot in adult subjects with schizophrenia.

Methodology: This was a multicenter, open-label trial consisting of a screening phase and 3 treatment phases: a Tolerability Assessment Phase (if applicable), an Open-label Aripiprazole IM Depot Treatment Phase, and an Open-label Aripiprazole IM Depot Treatment Extension Phase (if eligible). This was to be a 6-month retrospective followed by 6-month prospective trial to assess the inpatient psychiatric hospitalization rates of subjects receiving oral standard of care (6-month retrospective hospitalization[s]) and that of subjects receiving once-monthly aripiprazole IM depot injections prospectively for 6 months (6 months prospective hospitalization[s]). Inpatient psychiatric hospitalization rates in the last 3 months of oral standard of care were to be compared with those in the last 3 months of aripiprazole IM depot treatment. This trial was terminated early by the sponsor. The reason for trial closure was not related to safety because no signals or items of concern were identified.

Number of Subjects: Approximately 700 subjects were to be screened at approximately 125 sites in Europe, Canada, and Asia to enroll an estimated sample size of 500 subjects to be able to detect a difference of 15% or higher between pre-switch and post-switch hospitalization rates. After 250 subjects completed the Open-label Aripiprazole IM Depot Treatment Phase, an interim analysis was to be conducted. This trial was terminated early by the sponsor. The reason for trial closure was not related to safety because no signals or items of concern were identified. As a result of the early termination of the trial, the number of subjects enrolled was significantly less than the projected sample size. A total of 33 subjects were screened for the trial, and 30 subjects were treated.

Diagnosis and Main Criteria for Inclusion/Exclusion: Male and female subjects, aged 18 to 65 years, inclusive, with a diagnosis of schizophrenia as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria and a history of the illness for at least 1 year (12 months) prior to screening, who had at least one inpatient psychiatric hospitalization within the 2 years (24 months) prior to screening but had been managed on an outpatient basis during the 4 weeks prior to signing the Informed Consent Form and during the screening period, who had been prescribed oral antipsychotic treatment in the last 7 months prior to screening (with at least 7 months retrospective data by records or a reliable source, pertaining to all hospitalizations and interventions) and showed a response to the treatment (other than clozapine) according to the investigator's opinion, and who would have required a change in treatment for any

reason (eg, lack of efficacy, poor compliance, or side effects) and would have potentially benefited from extended treatment with a long-acting injectable formulation.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration: The investigational products were aripiprazole IM depot 400 mg supplied as lyophilized vials and aripiprazole oral tablets. Both doses of aripiprazole IM depot used in this trial (400 mg and 300 mg) were obtained from the 400 mg lyophilized vials. Aripiprazole IM depot was to be administered every month (28 days ± 2 days during the Open-label Aripiprazole IM Depot Treatment Phase and 28 [-2/+10] days during the Open-label Aripiprazole IM Depot Treatment Extension Phase). All doses of aripiprazole IM depot were injected into the gluteal muscle, and care was taken to avoid inadvertent injection into a blood vessel.

Oral aripiprazole tablets were supplied as round, white tablets containing 5 mg, 10 mg or 15 mg of aripiprazole packaged in child-resistant blister cards to assess tolerability during the Tolerability Assessment Phase (if needed), during the Open-label Aripiprazole IM Depot Treatment Phase for the first 14 days as concomitant treatment with the first 400 mg aripiprazole IM depot injection, and for administration as rescue therapy at daily doses recommended in the protocol or adjusted by the investigator.

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

Duration of Treatment: The duration of this trial from first subject enrolled to last subject completed was originally estimated to be up to 37 months, including an estimated 1.5-year enrollment period. The total length of participation in the trial (from a minimum of 7 months and 2 days to a maximum of 9 months) for an individual subject depended on the screening duration (2 to 28 days), Tolerability Assessment Phase duration (0 to 1 month), Open-label Aripiprazole IM Depot Treatment Phase duration (6 months) and a 30-day follow-up. All subjects who completed the Open-label Aripiprazole IM Depot Treatment Phase had the option to enter the Open-label Aripiprazole IM Depot Treatment Extension Phase. The Open-label Aripiprazole IM Depot Treatment Extension Phase of the trial was to continue until 31 Dec 2014 or until aripiprazole IM depot was commercially available in the respective country, whichever occurred sooner. Due to the early termination of the trial, sites placed subjects on appropriate therapy per the investigator's judgment before discontinuing IM depot; Canadian subjects were offered enrollment into Trial 31-11-283.

Trial Assessments:

Efficacy: Hospitalization, Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression – Severity (CGI-S), and the Clinical Global Impression – Improvement (CGI-I).

Other: Drug Attitude Inventory (DAI), Quality of Life Scale (QLS), Impact of Weight on Quality of Life – Lite (IWQoL-L), Subjective Well-being Under Neuroleptic Treatment – short version (SWN-S), and the Investigator's Assessment Questionnaire (IAQ).

Safety: adverse events (AEs), clinical laboratory tests (serum chemistry, hematology, and urinalysis), physical examination, vital signs, body weight, body mass index (BMI), waist circumference, electrocardiogram (ECG), EPS, (Simpson-Angus Scale [SAS], Abnormal Involuntary Movement Scale [AIMS], and Barnes Akathisia Rating Scale [BARS]), suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS), and injection site evaluation.

Criteria for Evaluation: The criteria for evaluation listed below were to be analyzed per protocol. Data presented were limited to trial discontinuations due to AEs, serious adverse events (SAEs), laboratory data, ECG, and deaths based on data collected. This trial was discontinued early by the sponsor. The reason for trial closure was not related to safety because no signals or items of concern were identified.

Primary Efficacy Endpoint: The primary endpoint of this trial was to be the comparison of inpatient psychiatric hospitalization rates (proportion of subjects with ≥ 1 inpatient psychiatric hospitalization[s]) between Months 4 to 6 (Weeks -12 to -24) of the retrospective period while the subject was receiving oral standard of care antipsychotic treatment(s) with those of Months 4 to 6 (Weeks 12 to 24) of the prospective period after the switch to aripiprazole IM depot. The comparison was to be the proportion of pre-switch (to aripiprazole IM depot) inpatient psychiatric hospitalization to the proportion of post-switch inpatient hospitalization. Hospitalization data of the last 3 months of the retrospective and prospective treatment periods were to be compared. The retrospective treatment period refers to the treatment period with oral standard of care prior to the 4-week outpatient treatment period before screening.

Other Endpoints: The last 3 months of the retrospective and prospective (Open-label Aripiprazole IM Depot Treatment Phase) treatment periods were to be compared for the following endpoints:

- Number of inpatient psychiatric hospitalizations per subject
- Cumulative duration of inpatient psychiatric hospitalizations
- Mean duration of inpatient psychiatric hospitalizations
- Number and mean duration of all other (non-inpatient) psychiatric treatment visits including, but not limited to, partial hospitalizations, intensive outpatient programs, assertive community treatment programs, emergency room visits, hospitalizations for psychosocial reasons, etc
- Number of inpatient nonpsychiatric hospitalizations per subject
- Cumulative duration of inpatient nonpsychiatric hospitalizations
- Mean duration of inpatient nonpsychiatric hospitalizations

- Number and mean duration of all other (outpatient or non-inpatient) nonpsychiatric treatment visits including, but not limited to, emergency room visits

In addition, the following endpoints were to be assessed in the Open-label Aripiprazole IM Depot Treatment Phase:

- Mean change from baseline (Day 0) to Week 24 in PANSS total score
- Mean change from baseline (Day 0) to Week 24 in PANSS positive and negative subscale scores
- Mean change from baseline (Day 0) to Week 24 in CGI-S score
- Mean CGI-I score at Week 24
- Discontinuation rate due to all causes
- Time to discontinuation due to all causes
- Proportion of responders (ie, defined as ≥ 30% decrease from baseline in PANSS total score or a score of 1 [very much improved] or 2 [much improved] on the CGI-I scale)
- Mean change from baseline (Day 0) to Week 24 in QLS score
- Mean change from baseline (Day 0) to Week 24 in SWN-S score
- Mean change from baseline (Day 0) to Week 24 in DAI total score
- Mean change from baseline (Day 0) to Week 24 in IWQoL-L total score
- Mean change from baseline (Day 0) to Week 24 in IAQ total score

Safety: AEs were examined by frequency, severity, seriousness, and discontinuation (all-cause and due to AEs). The C-SSRS was to be completed at baseline and all subsequent visits to assess the risk of suicide events and to classify reported suicide events.

The incidence of clinically significant changes was calculated for vital signs and routine laboratory tests. Mean change from baseline and incidence of clinically significant changes were calculated for ECG parameters, prolactin concentrations, lipid/metabolic profile (fasting glucose, fasting total cholesterol, fasting high density lipoprotein , fasting low density lipoprotein , fasting triglycerides), and body weight. A central ECG service was utilized to review all ECGs to standardize interpretations for the safety analysis.

Extrapyramidal symptoms were evaluated by calculating the mean change from baseline in SAS, AIMS, and BARS scores when applicable. Injection site pain was evaluated by mean Visual Analogue Scale scores as reported by the subject after each injection and at each trial visit. The investigator ratings of localized pain, redness, swelling, and induration at the injection site were also tabulated for post-injection site evaluations at each visit. By-subject listings of physical examination findings were reviewed as a further assessment of safety.

Statistical Methods: Data summaries were limited to tabulations of trial discontinuations due to AEs, SAEs, and deaths and data listings for trial discontinuations due to AEs, SAEs, and deaths.

Summary of Results:

Baseline Data, Disposition, and Demographics: A total of 33 subjects were screened for the trial, and 30 subjects were treated. Three subjects completed the trial. The most frequent reason for subject discontinuation from the trial was that the sponsor discontinued the trial. Of the 30 subjects enrolled in the trial, 19 subjects entered Phase A, and 19 subjects entered Phase B. Phase B consisted of the 8 subjects from Phase A and 11 entered Phase B directly from Screening. Three subjects completed Phase B and entered Phase C.

In the Safety Sample, there were twice as many males as females (20 and 10, respectively) and all were white, non-Hispanic or Latino.

Efficacy and Other Results: Due to the low number of enrolled subjects and the sponsor's early termination of the trial, the primary efficacy and other endpoints were not evaluated.

Safety Results: A total of 33 subjects were screened and 30 subjects were treated. In Phase B, 10 of 19 subjects (52.6%) experienced at least 1 treatment-emergent adverse event (TEAE), and the total number of TEAEs reported was 23. The most common TEAEs (≥ 10% of subjects) in Phase B were fatigue (2 of 19 subjects [10.5%]) and insomnia (3 of 19 subjects [15.8%]). In Phase C, 1 of 3 subjects (33.3%) experienced one TEAE. The only TEAE in Phase C was diabetes mellitus, which was reported in 1 subject (33.3%). The majority of TEAEs were reported to be mild or moderate in severity. One subject in Phase B experienced 2 SAEs (schizophrenia and drug-induced liver injury), both of which were considered severe. The event of drug-induced liver injury as called by the investigator was not supported by the lab value (eg, total bilirubin was within normal limits). No other SAEs were reported.

Overall, 6 of 19 subjects in Phase B experienced a potentially drug-related TEAE. The most common potentially drug-related TEAEs (incidence ≥ 10% of subjects) were fatigue (2 of 19 subjects [10.5%]), and insomnia (3 of 19 subjects [10.5%]).

Overall, only 1 subject in Phase B experienced any AE leading to discontinuation (schizophrenia). No deaths, Hy's Law cases, or pregnancies were reported during the trial.

The most common potentially clinically relevant laboratory test abnormalities reported during the trial were elevated fasting triglycerides (Phase B and C; the subject who experienced the SAE of drug-induced liver injury was not part of this group), elevated total fasting cholesterol (Phase B), elevated fasting glucose (Phase B and C), elevated fasting low-density lipoprotein cholesterol calculation (Phase B), and elevated creatine phosphokinase (Phase B).

There were no clinically relevant abnormalities in vital signs reported in Phase A, B, or C. Two subjects experienced potentially clinically relevant ECG abnormalities. One subject experienced an event of supraventricular premature beat in Phase B. The subject had an associated AE of heart palpitations beginning on Day 49, which was mild and continuing. One subject experienced an event of symmetrical T-wave inversion in Phase B. This subject did not have any other associated AEs.

Conclusions:

- Due to the low number of enrolled subjects and the sponsor's early termination of the trial, the primary efficacy and other endpoints outlined in the protocol were not evaluated.
- In Phase B, 10 of 19 subjects (52.6%) experienced at least 1 TEAE. One of three subjects in Phase C (33.3%) experienced one TEAE.
- The most common TEAEs in Phase B (≥ 10% of subjects) were fatigue (10.5%) and insomnia (15.8%). The only TEAE in Phase C was diabetes mellitus, which was reported in 1 subject (33.3%). The majority of TEAEs were reported as mild or moderate in severity.
- One subject in Phase B experienced 2 SAEs (schizophrenia and drug-induced liver injury), both of which were considered severe. The event of drug-induced liver injury as called by the investigator was not supported by the lab value (eg, total bilirubin was within normal limits).
- No other SAEs were reported.
- Overall, 6 of 19 subjects in Phase B experienced a potentially drug-related TEAE. The most common potentially drug-related TEAEs (≥ 10% of subjects) were fatigue (10.5%), and insomnia (10.5%).
- The most common potentially clinically relevant laboratory test abnormalities reported during the trial were elevated fasting triglycerides, elevated total fasting cholesterol, elevated fasting glucose, elevated fasting low density lipoprotein cholesterol calculation, and elevated creatine phosphokinase.
- There were no clinically relevant abnormalities in vital signs reported. Two subjects experienced potentially clinically relevant ECG abnormalities.

Report Date: 21 Feb 2013