Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole Intramuscular Depot (OPC-14597, Lu AF41155)

Clinical Summary for Protocol 31-12-297
Eudra CT No. 2012-003806-28
NCT No. 01683058

A 26-week, Multicenter, Open-label, Extension Study of Aripiprazole Intramuscular Depot (OPC-14597, Lu AF41155) in Patients with Schizophrenia

Indication:	Schizophrenia
Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland, USA H. Lundbeck A/S (Lundbeck)
Trial Initiation Date:	10 Jan 2013
Trial Completion Date:	17 Feb 2014
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 intramuscular (IM) depot (OPC-14597, Lu AF41155)

Protocol Title: A 26-week, Multicenter, Open-label, Extension Study of Aripiprazole Intramuscular Depot (OPC-14597, Lu AF41155) in Patients with Schizophrenia

Trial Center(s) by Region: 38 sites in the US, Croatia, and Latvia.

Clinical Phase/Trial Type: 3/Multicenter, Open-label, Extension

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale: This was a multicenter, open-label trial designed to continue to provide aripiprazole IM depot (400 mg or 300 mg) to eligible subjects with schizophrenia who met the completion criteria in registrational Trial 31-12-291. The trial design and population were appropriate for an extension trial to evaluate tolerability of aripiprazole IM depot.

In this trial, all subjects received aripiprazole IM depot 400 mg or 300 mg as the initial dose per the investigator's discretion.

Publications: None to date.

Objectives: The primary objective of this open-label trial was to evaluate the safety and tolerability of aripiprazole IM depot administered for 26 weeks to subjects with schizophrenia.

Methodology: This was a multicenter, open-label trial designed to continue to provide aripiprazole IM depot (400 mg/300 mg) to eligible subjects with schizophrenia who had met the completion criteria in registrational Trial 31-12-291 for the acute treatment of adults with schizophrenia.

Eligible subjects entered this trial directly after completing the Week 12 visit of Trial 31-12-291. The Week 12 evaluations conducted at the last trial visit for Trial 31-12-291 served as the baseline evaluations for Trial 31-12-297.

Subjects were to receive aripiprazole IM depot every 28 days, as prescribed by the investigator.

Subjects returned to the trial site monthly through the Week 24/early termination (ET) visit (at Day 168, − 2/+ 10 days, or upon ET) for assessment of safety. At each visit, all assessments, except for postinjection evaluations, were performed prior to the aripiprazole IM depot injection. A posttreatment follow-up telephone call was performed 14 ± 2 days after the last trial visit and included the recording of adverse events (AEs) that occurred and any concomitant medications taken since the last visit.

Number of Subjects: Approximately 125 subjects were planned to be rolled over into Trial 31-12-297 from Trial 31-12-291; the actual number of subjects treated in Trial 31-12-297 was 74 (68 from the United States, and 6 from Europe).

Diagnosis and Main Criteria for Inclusion/Exclusion: The trial population included male and female subjects between 18 and 66 years of age, inclusive, with a diagnosis of schizophrenia (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition Text Revision) who completed Trial 31-12-291.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration: The investigational medicinal product (IMP) was aripiprazole IM depot 400 mg supplied as lyophilized vials. Both doses of aripiprazole IM depot used in this trial (400 mg and 300 mg) were obtained from the 400-mg lyophilized vials.

The investigator determined the appropriate dose (400 mg or 300 mg) for the subject at each monthly visit (trial months were every 4 weeks, defined as 28 (- 2/+ 10) days). The monthly dose may have been modified, either reduced from 400 mg to 300 mg to address tolerability or increased from 300 mg to 400 mg to address efficacy, at the discretion of the investigator.

Concomitant with the first 14 days of aripiprazole IM depot treatment in Trial 31-12-297, subjects received either double-blind concomitant oral aripiprazole tablets (10-20 mg/day) or matching oral placebo tablets based on their randomized treatment in Trial 31-12-291. Oral treatment in Trial 31-12-297 was blinded to maintain the double-blind treatment assignment in Trial 31-12-291.

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 estimated to be approximately 16 months. Individual participation for subjects was expected to be approximately 182 days, consisting of 24 weeks of open-label treatment and 14 (± 2) days of safety follow-up after completion of open-label treatment.

Trial Assessments: Safety was assessed by AE reporting, vital sign collection, clinical laboratory tests, urinalysis, urine pregnancy tests (followed by a serum pregnancy test if urine test was positive), 12-lead electrocardiograms (ECG), and physical examinations. In addition, body weight, waist circumference, and extrapyramidal symptoms (EPS) were assessed. The Columbia Suicide Severity Rating Scale (C-SSRS) was completed to classify reported suicidal events and to assess suicidal ideation.

Criteria for Evaluation:
Primary Outcome Variables:
Safety:

- Frequency and severity of treatment-emergent adverse events (TEAEs), serious TEAEs (clinical and laboratory), and discontinuation from IMP due to TEAEs.
- Suicide risk as assessed and classified by the C-SSRS.
- Extrapyramidal symptoms evaluated using the Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS).
- Vital signs, laboratory tests, ECG parameters, body weight, and physical examination findings.

Statistical Methods: Due to the open-label, single-arm nature of the trial, all data were summarized using descriptive statistics.

Summary of Results:

Baseline Data, Disposition, and Demographics: A total of 74 subjects were enrolled in the trial at 38 centers in the US, Croatia, and Latvia. Forty-five (60.8%) subjects completed the trial, and 29 (39.2%) subjects were discontinued. Most subjects were male (56/74 subjects, 75.7%), black or African American (45/74 subjects, 60.8%), and not Hispanic or Latino (66/74 subjects, 89.2%). The mean age was 43.0 years (range 19-64 years), and mean body mass index (BMI) at baseline was 29.9 kg/m^2 (range 18.9-46.7 kg/m^2).

Safety Results:

- Aripiprazole IM depot 400 mg/300 mg administered once monthly was well tolerated by adult subjects with schizophrenia.
- No deaths occurred during the trial. Serious TEAEs and TEAEs resulting in discontinuation of IMP were reported for 6.8% (5/74) and 8.1% (6/72) of subjects, respectively. The only serious TEAEs reported in ≥ 2% of subjects were depression and schizophrenia (each in 2/74 subjects, 2.7%). The only TEAEs resulting in discontinuation of IMP in ≥ 2% of subjects was depression (2/74 subjects, 2.7%).
- Overall, 49/74 (66.2%) subjects had TEAEs. The majority of TEAEs were mild to moderate in severity. Treatment-emergent AEs reported for of ≥ 5% of subjects were weight increased (22/74 subjects, 29.7%), akathisia (9/74 subjects, 12.2%), headache (6/74 subjects, 8.1%), weight decreased (6/74 subjects, 8.1%), and hyperlipidemia (4/74 subjects, 5.4%).

- There was minimal variation from baseline in EPS rating scale scores (BARS, AIMS, SAS).

- There was one TEAE related to suicidality (suicidal ideation) during the trial, with minimal mean changes in the C-SSRS suicidal ideation intensity score. Potential suicide events were reported by 6/74 (8.1%) subjects, all events were suicidal ideation (6/74, 8.1%) as assessed by the Columbia Classification Algorithm of Suicide Assessment (C-CASA)/C-SSRS.

- There were 2 TEAEs related to changes in ECG QT interval, both events were ECG QT prolonged. No subjects had a new onset QTc interval > 500 milliseconds or a change from baseline ≥ 60 milliseconds, regardless of the correction method used.

- There was one TEAE related to WBC (neutropenia), and one TEAE related to orthostasis (dizziness postural). There were no TEAEs related to lipid parameters, glucose metabolism, prolactin, or injection site.

- There were no other clinically relevant findings with regard to vital signs, injection site, or laboratory values.

Conclusions:

- Aripiprazole IM depot 400 mg/300 mg administered once monthly was well tolerated by adult subjects with schizophrenia.

- There was a low rate of subject discontinuation due to TEAEs or lack of efficacy as determined by the investigator.

- Increases in body weight and EPS-related TEAEs were observed, but are consistent with the known safety profile of aripiprazole.

- The safety and tolerability profile of aripiprazole IM depot showed no new safety concerns, with respect to TEAEs, suicidality, EPS, vital signs, laboratory findings, ECG parameters, or physical examination findings.

Report Date: 10 May 2014