Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole Intramuscular Depot (OPC-14597, Lu AF41155)

**Clinical Summary for Protocol 31-12-291**
**IND No. 67,380**
**Eudra CT No. 2012-003805-86**
**NCT No. 01663532**

A 12-week, Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Aripiprazole Intramuscular Depot (OPC-14597, Lu AF41155) in the Acute Treatment of Adults with Schizophrenia

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|---|---|
| Indication: | Schizophrenia |
| Clinical Development Phase: | 3 |
| Sponsor: | Otsuka Pharmaceutical Development & Commercialization, Inc.<br>2440 Research Boulevard<br>Rockville, Maryland, USA<br><br>H. Lundbeck A/S (Lundbeck) |
| Trial Initiation Date: | 12 Oct 2012 |
| Trial Completion Date: | 30 Aug 2013 |
| 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 Depot (OPC-14597, Lu AF41155)

**Protocol Title:** A 12-week, Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Aripiprazole Intramuscular Depot (OPC-14597, Lu AF41155) in the Acute Treatment of Adults with Schizophrenia

**Trial Center(s) by Region:** Fifty-five trial sites worldwide (46 in United States [US], 5 in Croatia, and 4 in Latvia) were approved to receive investigational medicinal product (IMP) for this trial. Of these, 51 trial sites (45 in US, 2 in Croatia, and 4 in Latvia) were open for enrollment, 44 trial sites (40 in the US, 2 in Croatia, and 2 in Latvia) screened subjects, and 41 trial sites (37 in the US, 2 in Croatia, and 2 in Latvia) enrolled subjects.

**Clinical Phase/Trial Type:** 3/Multicenter, Randomized, Double-blind, Placebo-controlled

**Trial Interruption:** There was no unplanned trial interruption.

**Scientific Background and Explanation of Rationale:** Trial 31-12-291 is part of the aripiprazole intramuscular (IM) depot clinical development program and was designed to demonstrate the efficacy and safety of aripiprazole IM depot for the treatment of adult subjects with an acute episode of schizophrenia. A 12-week double-blind Acute Treatment Phase was considered to be of adequate length to determine whether an antipsychotic effect has been demonstrated. Since efficacy in schizophrenia is dependent on both treatment duration and dose, a fixed-dose, parallel group approach represents the optimal trial design to evaluate efficacy.

To minimize any potential bias that might occur, the investigator and subject were blinded to the timing of the primary endpoint for efficacy evaluation (ie, Week 10). Although the preplanned endpoint for the primary analysis was defined as Week 10 in the statistical analysis plan (SAP), this information was not included in the protocol or communicated to site staff during the trial. The choice of the Week 10 time point for primary efficacy evaluation was discussed and agreed upon with the Food and Drug Administration (FDA) (correspondence date 15 Mar 2013).

The treatment group receiving a placebo is typically the standard control group requested by the FDA in clinical trials, including efficacy trials of antipsychotics in subjects with schizophrenia.

During the Screening Phase and for 2 weeks after the first injection in the Acute Treatment Phase, inpatient hospitalization was required given the acute symptoms of the illness. Inpatient hospitalization was left to the discretion of the investigator for the remainder of the trial.

**Publications:** None to date.

**Objectives:** Primary: To evaluate the overall efficacy of aripiprazole IM depot as acute treatment in subjects with schizophrenia.

Secondary: To evaluate the safety and tolerability of aripiprazole IM depot as acute treatment in subjects with schizophrenia.

**Methodology:** This was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of aripiprazole IM depot for treatment of acute episodes of schizophrenia in adult subjects. The trial included a 13-day Screening Phase and a 12-week Acute Treatment Phase with a 14 (± 2)-day Safety Follow-up.

Screening Phase: Subjects entered a pretreatment Screening Phase of up to 13 days to assess eligibility criteria. If subjects had been exposed to aripiprazole in the past (ie, tolerability had been established), then subjects entered a washout period for 7 days from prior antipsychotic medications and other prohibited concomitant medications. If subjects had not been exposed to aripiprazole in the past (ie, tolerability had not been established), oral aripiprazole 10 mg daily was given for 3 days to establish tolerability prior to the 7-day washout period from prior antipsychotic medications and other prohibited medications. Subjects were required to be hospitalized during the entire Screening Phase. If not already hospitalized, the subject was to be hospitalized from the time of the signing of the informed consent form (ICF) onward during the Screening Phase.

12-week Acute Treatment Phase: Subjects who met the entrance criteria and were diagnosed with schizophrenia as defined by criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) and confirmed by the Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders Studies were considered for enrollment. All subjects must have had an acute psychotic episode as defined by both of the following at screening and baseline:

1) Currently experiencing an acute exacerbation of psychotic symptoms accompanied by significant deterioration in the subject's clinical and/or functional status from their baseline clinical presentation with a Positive and Negative Syndrome Scale (PANSS) total score ≥ 80 and

2) Specific psychotic symptoms on the PANSS as measured by a score of > 4 on each of the following items (possible scores of 1 to 7 for each item):

- Conceptual disorganization (P2)
- Hallucinatory behavior (P3)
- Suspiciousness/persecution (P6)
- Unusual thought content (G9)

At baseline, eligible subjects were randomized in a 1:1 ratio to either aripiprazole IM depot or placebo, stratified by trial site. For 14 days beginning with the first injection, subjects randomized to aripiprazole IM depot received concomitant oral aripiprazole and subjects randomized to placebo received concomitant oral placebo in a blinded fashion. During the first 2 weeks of the Acute Treatment Phase, all subjects must have remained as inpatients; however, during the remainder of the Acute Treatment Phase a subject may have been either an inpatient or outpatient, based on the investigator's judgment of the subject's clinical status. Subjects who were outpatients returned to the clinic for trial visits biweekly through Week 12 (even numbered weeks) and were contacted by phone on a biweekly basis (odd numbered weeks).

Safety Follow-up: Except for subjects who continued into Trial 31-12-297 after completing the Week 12 visit, all subjects were followed-up for safety via telephone contact 14 (± 2) days after the last trial visit.

**Number of Subjects:** Planned: Approximately 565 subjects were planned to be screened at approximately 150 trial sites worldwide (45 in US and remainder in rest of world [ROW]) with 310 subjects randomized (1:1) to aripiprazole IM depot 400 mg or matching placebo.

Analyzed: Fifty-five trial sites worldwide (46 in US, 5 in Croatia, and 4 in Latvia) were approved to receive IMP for this trial. Although 150 sites were planned, only 55 sites were included as subject enrollment was faster than anticipated. Fifty-one of these 55 sites (45 in US, 2 in Croatia, and 4 in Latvia) were open for enrollment and 44 (40 in the US, 2 in Croatia, and 2 in Latvia) screened subjects. A total of 506 subjects were screened from 44 sites with 340 subjects randomized from 41 sites (168 to aripiprazole IM depot 400 mg [162 from US, 5 from Croatia, and 1 from Latvia] and 172 to matching placebo [165 from US, 6 from Croatia, and 1 from Latvia]).

Of the 340 subjects randomized, 339 (167 aripiprazole IM depot 400 mg subjects and 172 placebo subjects) received at least one injection of double-blind IMP and were analyzed for safety (ie, Safety Sample). All 339 subjects also had at least one postbaseline efficacy assessment and were included in the modified intent-to-treat (mITT) population and analyzed for efficacy (ie, Efficacy Sample).

**Diagnosis and Main Criteria for Inclusion/Exclusion:** Male and female subjects between 18 and 65 years of age, inclusive, with a DSM-IV-TR diagnosis of schizophrenia for at least 1 year prior to screening, who would benefit from hospitalization or continued hospitalization for the treatment of a current acute relapse of schizophrenia were enrolled in this trial. All subjects must have had an acute psychotic episode at screening and baseline as defined in the methodology section of this summary.

**Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration:** Aripiprazole IM depot was supplied as 400 mg lyophilized vials for

doses of 400 mg or 300 mg every 4 weeks (ie, once monthly). All doses of double-blind IMP were injected into the gluteal muscle.

All subjects received aripiprazole IM depot 400 mg (or matching placebo) as the initial dose with a single decrease to aripiprazole IM depot 300 mg (or matching placebo) permitted for tolerability per the investigator's judgment. A single return to the 400 mg dose (or matching placebo) for efficacy reasons was allowed.

**Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration:** Matching placebo injections were dosed identically to aripiprazole IM depot.

For 14 days beginning with the first injection, subjects randomized to aripiprazole IM depot also received concomitant double-blind oral aripiprazole (10 mg to 20 mg daily, based on the investigator's clinical judgment) and subjects randomized to placebo received concomitant double-blind oral matching placebo tablets. Oral aripiprazole was administered using 10 mg and 15 mg tablets.

**Duration of Treatment:** 12 weeks.

**Trial Assessments:**
*Efficacy:* PANSS (total, positive, and negative), Clinical Global Impression – Severity (CGI-S), Clinical Global Impression - Improvement (CGI-I), and Personal and Social Improvement (PSP) scales.

*Safety*: Adverse events (AEs), concomitant medications, mean dose of concomitant benzodiazepines, physical examination, weight, waist circumference, body mass index (BMI), vital signs, clinical laboratory assessments, electrocardiogram (ECG), Simpson Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), Columbia-Suicide Severity Rating Scale (C-SSRS), subject assessment of injection site pain using a Visual Analog Scale (VAS), and investigator assessment of injection site.

**Criteria for Evaluation:**
*Efficacy*:
Primary Efficacy Endpoint: Change from baseline to endpoint (Week 10) in PANSS total score
Key Secondary Efficacy Endpoint: Change from baseline to endpoint (Week 10) in CGI-S scale
Other Secondary Efficacy Endpoints:

- Change from baseline to endpoint (Week 10) in PANSS positive and negative subscale scores
- Change from baseline to endpoint (Week 10) in PSP score
- CGI-I scale score at endpoint (Week 10)
- Responder rate at endpoint (Week 10) (response defined by ≥ 30% reduction from baseline in PANSS total score)

*Safety*: AEs were examined by frequency, relationship to IMP, severity, seriousness, and as cause of discontinuation from the trial. AEs of special interest were tabulated separately. The incidence of suicidality was assessed using data collected from the C-SSRS and summarized overall, by type, and by change from baseline in the Suicidal Ideation Intensity (SSI) score. Injection site pain was evaluated by mean VAS scores as reported by the subject after each injection and at the last visit. The investigator rating of pain, swelling, redness, and induration at the injection site was also tabulated for post injection site evaluations at each visit. Mean changes from baseline and the incidence of clinically relevant changes were calculated for vital signs (including weight), ECG parameters, routine laboratory tests and prolactin concentrations. Extrapyramidal symptoms (EPS) were evaluated by calculating mean change from baseline in SAS total, AIMS movement rating, and BARS global scores. Subject listings of physical examination findings were reviewed as a further assessment of safety.

**Statistical Methods:**
*Efficacy*: All efficacy analyses were carried out using the mITT population, defined as all subjects in the randomized sample (intent-to-treat population) who had at least one injection of double-blind IMP (aripiprazole IM depot or placebo) and had at least one postbaseline efficacy assessment. The trial sites were pooled geographically by region for efficacy analyses. The primary efficacy endpoint was the change from baseline to endpoint (Week 10) in PANSS total score. The primary statistical comparison was performed using Mixed Model Repeated Measure (MMRM) analysis with a restricted maximum likelihood approach. The analyses included categorically fixed effects of treatment, region (pooled sites), trial week, and treatment-by-week interaction, as well as the continuously fixed covariates of baseline score-by-week interaction. An unstructured covariance structure was used to model the within-subject errors and Kenward-Rodger degree of freedom was used to test the fixed effects. In addition, analyses of covariance (ANCOVA) including baseline value as covariate, and treatment group and region as factors, were performed using last observation carried forward (LOCF) and observed cases (OC) data for change from baseline in PANSS total score at each trial week. To explore the robustness of the primary efficacy analysis under the assumption of missing-at-random, sensitivity analyses were performed using the pattern mixture approach, with multiple imputations (based on the discontinuation reasons) under the assumption of missing-not-at-random, in addition to the model-based methods using the shared parameter model and the random coefficient pattern mixture model. The key secondary efficacy endpoint was the change from baseline to endpoint (Week 10) in CGI-S score. The key secondary efficacy endpoint was analyzed by fitting the similar MMRM model described in the analysis of the primary efficacy endpoint in addition to similar sensitivity analyses. A hierarchal testing procedure was used for the key secondary efficacy endpoint so that the overall type I error rate was maintained at 0.05.

Analyses identical to the analysis of the primary efficacy endpoint were applied to the change from baseline in PANSS positive and negative subscales. Similar analyses (ie, ANCOVA) for change from baseline in PSP score were performed for both LOCF and

OC datasets at Week 10 and Week 12. CGI-I score at endpoint (Week 10) was analyzed using the Cochran-Mantel-Haenszel row mean score test (van Elteren test) controlling for region. The comparison was performed by trial week using both the LOCF and OC datasets. Responder rate was analyzed using the Fisher's Exact test for both the LOCF and OC datasets. Responder rate was also analyzed using the Cochran-Mantel-Haenszel general association test controlling for region for both the LOCF and OC datasets. Ninety-five percent confidence intervals (CIs) for difference in responder rates were provided.

*Safety*: All safety analyses were carried out using the Safety Sample (ie, all randomized subjects receiving at least one injection of double-blind IMP). Safety data including AEs, vital signs, clinical laboratory results, ECG parameters, special interest AEs, injection site pain, and Columbia Classification Algorithm of Suicide Assessment (C-CASA) categories using C-SSRS assessments were summarized using descriptive statistics. In addition, trial medication exposure, concomitant medication, compliance with IMP, and protocol deviations were summarized using descriptive statistics. Change from baseline in EPS rating scales (SAS, AIMS, and BARS), weight, and prolactin levels were analyzed using the ANCOVA model with treatment group as a factor and baseline value as a covariate. The Breslow-Day test of the homogeneity of the odds ratios was performed across demographic subgroups for gender, age, and race for treatment-emergent adverse events (TEAEs) reported for at least 5% of aripiprazole IM depot 400 mg/300 mg subjects at a rate at least twice the placebo rate.

**Summary of Results:**

**Baseline Data, Disposition, and Demographics:** Baseline disease characteristics were comparable between the 2 treatment groups. As expected based on entry criteria, these subjects were markedly ill. Inclusion criteria required a PANSS total score of ≥ 80 and scores of > 4 in the defined PANSS categories. In the enrolled population, mean overall PANSS total scores were 103 (range 82-144), and mean P2, P3, P6, and G9 scores were all > 5. Mean CGI-S scores were 5.2 (range 4-7) and mean PSP total scores were 42.6 (range 21-81). All subjects had been diagnosed with schizophrenia for ≥ 1 year and less than half (42.6%) had been previously exposed to oral aripiprazole.

Subject disposition in the 12-week Acute Treatment Phase is summarized in the following table.

| Subject Disposition | | | |
|---|---|---|---|
| | **Aripiprazole IM Depot 400/300mg** | **Placebo (N=172)** | **Total (N=340)** |
| **SUBJECTS** | **n (%)** | **n (%)** | **n (%)** |
| SCREENED | | | 506 |
| SCREEN FAILURE | | | 166 |
| RANDOMIZED | 168 (100.0) | 172 (100.0) | 340 (100.0) |
| COMPLETED | 94 (56.0) | 65 (37.8) | 159 (46.8) |
| DISCONTINUED | 74 (44.0) | 107 (62.2) | 181 (53.2) |
| ANALYZED FOR SAFETY | 167 (99.4) | 172 (100.0) | 339 (99.7) |
| ANALYZED FOR EFFICACY | 167 (99.4) | 172 (100.0) | 339 (99.7) |

Note: Subjects who were randomized and received at least one dose of IMP were included in safety analysis. Subjects who were randomized and received at least one dose of IMP and had at least one postbaseline efficacy assessment were included in efficacy analysis. One subject who was randomized did not receive any dose of IMP.

Note: Subjects who completed the evaluation of the last scheduled visit (Week 12) were defined as trial completers.

The demographic characteristics for randomized subjects were similar in the aripiprazole IM depot and placebo groups. Most subjects randomized were male (269/340, 79.1%), Black/African American (223/340, 65.6%), and non-Hispanic/Latino (307/340, 90.3%). The mean age was 42.4 years (range 18-65 years) and mean BMI was 28.5 $kg/m^2$ (range 17.5-40.5 $kg/m^2$). Most subjects (96.2%) were enrolled in the US.

**Efficacy Results:** Aripiprazole IM depot 400 mg/300 mg administered as a monthly injection was effective for the treatment of an acute episode of schizophrenia in adult subjects as demonstrated by superiority to placebo in the primary efficacy endpoint, change from baseline to endpoint (Week 10) in PANSS total score.

Results for the key secondary endpoint, change from baseline to endpoint (Week 10) in CGI-S score, also showed superiority of aripiprazole IM depot 400 mg/300 mg to placebo.

The changes from baseline in both the PANSS total score and the CGI-S score were greater, indicating more improvement in the subjects' condition, in the aripiprazole IM depot 400 mg/300 mg group than in the placebo group and the treatment differences were statistically significant at all time points during the trial (Weeks 1 through 12).

Results of all other efficacy analyses supported those from the primary and key secondary results and demonstrated superiority of aripiprazole IM depot 400 mg/300 mg to placebo.

A summary of primary, key secondary, and other secondary efficacy results at Week 10 is provided in the following table.

**Summary of Efficacy Results at Week 10 (Trial 31-12-291; Efficacy Sample)**

| Efficacy Endpoint | Trial Week | Arip IM depot 400/300 mg | | Placebo | | Comparison Arip IM depot 400/300 mg vs Placebo | |
|---|---|---|---|---|---|---|---|
| | | N | Value | N | Value | Difference (95% CI) | P-value |
| PANSS Total Score (MMRM) | Baseline (Mean [SD]) | 162 | 102.4 (11.4) | 167 | 103.4 (11.1) | - | - |
| | Week 10 (LSMean Change) | 99 | −26.8 | 81 | −11.7 | −15.1 (−19.4, −10.8) | <0.0001 |
| CGI-S (MMRM) | Baseline (Mean [SD]) | 162 | 5.2 (0.5) | 168 | 5.2 (0.5) | - | - |
| | Week 10 (LSMean Change) | 99 | −1.4 | 81 | −0.6 | −0.8 (−1.1, −0.6) | <0.0001 |
| PANSS Positive Subscale Score (MMRM) | Baseline (Mean [SD]) | 162 | 29.5 (3.3) | 167 | 29.4 (3.0) | - | - |
| | Week 10 (LSMean Change) | 99 | −10.0 | 81 | −4.9 | −5.1 (−6.4, −3.7) | <0.0001 |
| PANSS Negative Subscale Score (MMRM) | Baseline (Mean [SD]) | 162 | 23.7 (4.7) | 167 | 24.6 (4.5) | - | - |
| | Week 10 (LSMean Change) | 99 | −4.5 | 81 | −1.6 | −2.8 (−4.1, −1.6) | <0.0001 |
| PSP Score (LOCF) | Baseline (Mean [SD]) | 144 | 43.7 (9.4) | 149 | 42.6 (9.7) | - | - |
| | Week 10 (LSMean Change) | 136 | 12.3 | 146 | 5.2 | 7.1 (4.1, 10.1) | <0.0001 |
| CGI-I (LOCF) | Week 10 (Mean [SD]) | 162 | 2.7 (1.2) | 168 | 3.7 (1.3) | Not calculated | <0.0001 |
| Responder Rate PANSS Total Score (LOCF) | Week 10 (n/N [%]) | 162 | 60/162 (37.0) | 167 | 24/167 (14.4) | 22.7 (12.9, 32.4) | <0.0001 |

Arip = aripiprazole

Note: A MMRM model analysis was used for PANSS scores and CGI-S (OC data); an ANCOVA model was used for PSP score (LOCF data); a Cochran–Mantel–Haenszel row mean score differ test controlling for region (pooled sites) was used for CGI-I (LOCF data), and a Fisher's exact test was used for responder rates (LOCF data).

The median time to discontinuation for all causes was significantly longer for the aripiprazole IM depot 400 mg/300 mg group than for the placebo group.

Results of multiple sensitivity analyses for the primary and key secondary efficacy endpoints demonstrated the overall robustness of the efficacy results.

The results of subgroup analyses were similar to the results of the overall population, indicating there were no groups with deviating efficacy outcomes.

**Safety Results:** Aripiprazole IM depot 400 mg/300 mg administered once monthly was well tolerated by adult subjects with an acute episode of schizophrenia. The majority of subjects in each treatment group (aripiprazole IM depot: 161/167 [96.4%] subjects; placebo: 168/172 [97.7%] subjects) had no change in their starting dose (400 mg) of aripiprazole IM depot/placebo.

Treatment-emergent AEs were reported for 79.6% of aripiprazole IM depot 400 mg/300 mg subjects and 70.9% of placebo subjects. Treatment-emergent AEs reported for ≥ 5% of aripiprazole IM depot 400 mg/300 mg subjects and at least twice the incidence of placebo were increased weight (16.8% vs 7.0%), akathisia (11.4% vs 3.5%), injection site pain (5.4% vs 0.6%), and sedation (5.4% vs 1.2%). Generally, these events were mild in severity. No report of these events was classified as a serious TEAE or was associated with IMP discontinuation. No statistically significant differences in odds ratios (ie, aripiprazole IM depot 400 mg/300 mg group vs placebo group) were noted between demographic subgroup categories when these TEAEs were examined by age, gender, and race using the Breslow-Day test of homogeneity.

No deaths occurred during the trial, and the incidence of serious TEAEs (4.8% of aripiprazole IM depot 400 mg/300 mg subjects vs 3.5% of placebo subjects) and discontinuations of IMP (4.2% of aripiprazole IM depot 400 mg/300 mg subjects vs 7.6% of placebo subjects) due to TEAEs were low.

There were significant treatment differences in mean change from baseline in prolactin values between aripiprazole IM depot 400 mg/300 mg and placebo at Week 12 ($p = 0.0176$) and at the last visit ($p = 0.0002$), with larger mean decreases in the aripiprazole IM depot 400 mg/300 mg group compared with placebo. Similar treatment differences were noted for male subjects at Week 12 ($p = 0.0012$) and at the last visit ($p < 0.0001$), but no significant treatment differences were noted for female subjects. Differences in mean change in prolactin values between the aripiprazole IM depot 400 mg/300 mg group and placebo group were not considered to be clinically relevant. The overall incidence of potentially clinically relevant prolactin values (> 1 × upper limit of normal) was lower in the aripiprazole IM depot 400 mg/300 mg group (2.8%) than in the placebo group (11.4%). No subjects in either treatment group had a TEAE related to prolactin.

Metabolic changes in the aripiprazole IM depot 400 mg/300 mg group compared with the placebo group included a larger incidence of subjects with potentially clinically relevant shifts from baseline in fasting glucose levels from < 126 mg/dL to ≥ 126 mg/dL (6.6% vs 2.8%, respectively), any increase ≥ 40 mg/dL in fasting total cholesterol (12.3% vs 5.5%, respectively), and any increase ≥ 30 mg/dL in fasting calculated LDL-cholesterol levels (14.2% vs 8.7%, respectively). No differences were observed for changes in triglycerides between the 2 treatment groups.

Mean increases from baseline in weight were noted in both treatment groups at Week 12 (aripiprazole IM depot 400 mg/300 mg: 3.5 kg; placebo: 0.8 kg) and at the last visit (aripiprazole IM depot 400 mg/300 mg: 2.8 kg; placebo: 0.8 kg), with significantly larger increases in the aripiprazole IM depot 400 mg/300 mg group than in the placebo group (Week 12: $p = 0.0018$; last visit: $p = 0.0003$). The incidence of potentially clinically relevant weight gain (defined as ≥ 7% change from baseline) at Week 12 and at the last visit during the Acute Treatment Phase was 28.3% and 21.5%, respectively, for aripiprazole IM depot 400 mg/300 mg subjects and 12.1% and 8.5%, respectively, for placebo subjects.

Aripiprazole IM depot 400 mg/300 mg treated subjects also had a higher incidence of EPS-related TEAEs (19.2%) than placebo subjects (8.1%). Except for akathisia (11.4% vs 3.5%, respectively) and tremor (3.0% vs 0.6%, respectively), the incidence of EPS-related TEAEs was comparable between the treatment groups.

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

**Conclusions:**

- Aripiprazole IM depot 400mg/300 mg administered as a monthly injection was efficacious for the treatment of an acute episode of schizophrenia in adult subjects as demonstrated by superiority to placebo in the primary efficacy endpoint, change from baseline to endpoint (Week 10) in PANSS total score.

- Results of the key secondary and all other efficacy analyses supported those from the primary results and demonstrated superiority of aripiprazole IM depot 400 mg/300 mg to placebo.

- Aripiprazole IM depot 400 mg/300 mg administered once monthly was well tolerated by adult subjects with an acute episode of schizophrenia. No deaths were reported during the trial, and the incidence of serious TEAEs and discontinuations of IMP due to TEAEs were low.

- The safety and tolerability profile of aripiprazole IM depot showed no unexpected side effects and no clinically relevant effect on vital signs, QTc prolongation, prolactin, or suicidality. Increases in weight and a higher incidence of EPS-related TEAEs were noted in subjects treated with aripiprazole IM depot 400 mg/300 mg compared with placebo. Metabolic changes included increases in fasting glucose levels, total cholesterol and calculated LDL-cholesterol levels compared with placebo. No differences were observed for changes in triglycerides between treatment groups.

**Report Date:** 16 Dec 2013