Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole intramuscular depot (OPC-14597)

**Clinical Summary for Protocol 31-07-247**
**NCT No. 00706654**

# A 38-week, Multicenter, Randomized, Double-blind, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of an Intramuscular Depot Formulation of Aripiprazole (OPC-14597) as Maintenance Treatment in Patients with Schizophrenia "ASPIRE EU" (Aripiprazole Intramuscular Depot Program in Schizophrenia)

Indication: Schizophrenia

Clinical Development Phase: 3

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| Sponsor: | Otsuka Pharmaceutical Development & Commercialization, Inc.<br>Rockville, Maryland, United States |
| Trial Initiation Date: | 26 September 2008 |
| Trial Completion Date: | 31 August 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 intramuscular (IM) depot (OPC-14597)

**Protocol Title:** A 38-week, Multicenter, Randomized, Double-blind, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of an Intramuscular Depot Formulation of Aripiprazole (OPC-14597) as Maintenance Treatment in Patients with Schizophrenia "ASPIRE EU" (Aripiprazole Intramuscular Depot Program in Schizophrenia)

**Trial Center(s) by Region:** 105 centers in Austria, Belgium, Bulgaria, Chile, Croatia, Estonia, France, Hungary, Italy, South Korea, Poland, South Africa, Thailand, and United States (US).

**Clinical Phase/Trial Type:** Phase 3, Therapeutic non-inferiority trial.

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

**Scientific Background and Explanation of Rational:** The favorable safety profile of oral aripiprazole makes it a viable candidate for long-term use as an Intramuscular (IM) depot injection. A phase 1 clinical trial (Trial CN138-020) determined that the IM depot formulation of aripiprazole was well tolerated and that peak aripiprazole plasma concentrations in most subjects were observed after approximately 100 hours. Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) simulated aripiprazole plasma concentration-time profiles based on the assessed pharmacokinetic (PK) parameters from Trial CN138-020 and from previous oral steady state studies. These simulations included a proposed switching regimen in which oral dosing was tapered off with concomitant administration of 100, 200, 300, and 400 mg aripiprazole IM depot monthly (ie, every 28 days). Data from these simulations indicated that the lower 95% confidence interval (CI) for minimum plasma concentration ($C_{min}$) for 400 mg/300 mg aripiprazole IM depot would be expected to be above (or very close to) the steady-state $C_{min}$ of daily dosing with aripiprazole 10 mg, and below the mean steady-state maximum plasma concentration ($C_{max}$) of daily dosing with aripiprazole 30 mg at all times, including tapering off oral dosing.

Trial 31-05-244 was a phase 1b trial conducted by OPDC to assess the safety, tolerability and PK of aripiprazole IM depot formulation following multiple (ie, 5) doses of aripiprazole IM depot (400 mg, 300 mg, and 200 mg) administered once every 4 weeks to subjects with schizophrenia. Subjects receiving aripiprazole 10 mg at screening were to continue oral treatment at the 10-mg dose for 14 days prior to randomization. Subjects who were on other antipsychotics or were receiving aripiprazole doses higher than 10 mg were switched or down-titrated (as appropriate) to aripiprazole 10 mg over a 14-day period and then stabilized on oral aripiprazole 10 mg for an additional 14 days before receiving aripiprazole IM depot. Oral treatment (10 mg daily) was administered along with the first aripiprazole IM depot dose and was continued for 14 days post-randomization to maintain adequate plasma concentrations. Subsequent doses of

aripiprazole IM depot were given at Months 1, 2, 3, and 4, and subjects were assessed up to 28 weeks post-randomization. Once-monthly administration of the 200 mg IM depot injections did not result in mean aripiprazole trough plasma concentrations that were comparable to the therapeutic concentrations of 10 mg to 30 mg oral aripiprazole administered daily to schizophrenic subjects. In this multiple-dose trial and in another single-dose trial (Trial CN138-020), the PK profiles and clinical data for aripiprazole IM depot 400 mg/300 mg suggested that these doses would be efficacious and tolerable, and thus, both were further investigated in the phase 3 trials.

The current trial, Trial 31-07-247, was a pivotal phase 3 registrational trial designed to evaluate the efficacy, safety, and tolerability of a long-acting IM depot formulation of aripiprazole administered to adult subjects with a diagnosis of schizophrenia as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). The research hypothesis was that a comparable proportion of subjects with a DSM-IV-TR diagnosis of schizophrenia who achieve stability of symptoms on oral aripiprazole (10 to 30 mg), and maintain the response for a minimum of 8 consecutive weeks, will experience an impending relapse by end of 26 weeks of treatment from the date of randomization in the Double-blind, Active-controlled Phase, when randomized to treatment with aripiprazole IM depot (400 mg/300 mg) monthly compared with subjects randomized to daily treatment with oral aripiprazole (10 to 30 mg). In order to maintain plasma concentrations within the effective range for oral aripiprazole (ie, 10 to 30 mg), all subjects received aripiprazole IM depot 400 mg as the initial dose with concurrent administration of oral aripiprazole for the first 14 days of IM depot treatment. Aripiprazole IM depot 50 mg (with option to decrease to 25 mg) was included as a low-dose aripiprazole group in this trial (Trial 31-07-247) to test assay sensitivity for the non-inferiority design.

The non-inferiority design of this trial is in accordance with the 2003 European Medical Agency (EMA) appendix (CPMP/EWP/49/01) to the existing note for guidance on clinical trial methodology concerning the development of depot preparations of approved medicinal products in schizophrenia, and the 2006 EMA guideline on the choice of the non-inferiority margin (European Medicines Agency (EMA), effective date Jan 2006) and has been used for the evaluation of oral and depot formulations of other antipsychotic medications. Accordingly, Trial 31-07-247 examined the proportion of stabilized subjects (at least 8 consecutive weeks in Oral Stabilization Phase) who experienced an impending relapse during the first 26 weeks of maintenance treatment (Double-blind, Active-controlled Phase) as a clinically relevant endpoint for evaluation of maintenance treatment.

**Publications:** None to date.

**Objectives:** The primary objective of this trial was to evaluate the efficacy of aripiprazole IM depot compared with oral aripiprazole, as measured by proportion of subjects experiencing exacerbation of psychotic symptoms/impending relapse (hereafter referred to as impending relapse) by end of 26 weeks of double-blind treatment, in

subjects with schizophrenia who have maintained stability on oral aripiprazole for at least 8 consecutive weeks during the Oral Stabilization Phase before initiating treatment with aripiprazole IM depot.

The secondary objective was to evaluate the safety and tolerability of aripiprazole IM depot as maintenance treatment in subjects with schizophrenia.

**Methodology:** This was a randomized, double-blind, active-controlled trial consisting of a screening phase and 3 treatment phases: Conversion Phase, Oral Stabilization Phase, and Double-blind, Active-controlled Phase. The non-inferiority design of this trial is in accordance with the 2003 EMA appendix (CPMP/EWP/49/01) to the existing note for guidance on clinical trial methodology concerning the development of depot preparations of approved medicinal products in schizophrenia.

*Interim Analysis*: No interim analysis was prespecified.

*Screening Phase:* Eligibility was determined during a screening period of 2 to 42 days. Subjects who were receiving oral treatment with any antipsychotic(s) other than aripiprazole, aripiprazole in combination with any other antipsychotic(s), or generic aripiprazole entered the Conversion Phase. Subjects who were already receiving a stable dose of aripiprazole monotherapy (not inclusive of generic forms of aripiprazole, where available) entered directly into the Oral Stabilization Phase, provided that the prescribed aripiprazole dose did not exceed 30 mg daily at screening. In addition, subjects with a lapse in aripiprazole or other antipsychotic treatment at the time of trial entry ("lapse" was defined as > 3 consecutive days without medication), entered directly into the Oral Stabilization Phase.

*Conversion Phase:* During weekly visits in the Conversion Phase, subjects had their dose converted from other antipsychotic(s) to oral aripiprazole monotherapy (trial medication) over a minimum of 4 weeks and a maximum of 6 weeks. A recommended conversion scheme was described in the protocol; however, the investigator was to decide the best scheme based on the subject's clinical need. For subjects receiving aripiprazole in combination with other antipsychotic(s) at screening, the Conversion Phase was used to taper the subjects off the other antipsychotic(s). The goal of the Conversion Phase was for all subjects to achieve a daily monotherapy starting dose target of 10 or 15 mg/day oral aripiprazole by Week 4 and no later than Week 6 of the Conversion Phase; higher target starting doses were acceptable based on the investigator's judgment and the subject's clinical need.

*Oral Stabilization Phase*: Subjects who successfully converted to oral aripiprazole monotherapy and subjects who were already receiving oral aripiprazole as monotherapy for schizophrenia at screening or who had a lapse in treatment with aripiprazole or other antipsychotic treatment prior to trial entry ("lapse" defined as > 3 consecutive days without medication), regardless of time off aripiprazole treatment, entered the Oral Stabilization Phase. Subjects who received recent treatment with an approved IM depot

formulation of an antipsychotic drug were to be initiated on oral aripiprazole in the Oral Stabilization Phase, but only after one cycle plus 14 days had elapsed from the date of the last IM depot injection (eg, 2-week cycle plus an additional 14 days for risperidone long-acting injection) or 60 days since the last injection of an investigational IM depot formulation. During Oral Stabilization Phase, which was a minimum of 8 weeks and a maximum of 28 weeks in duration, subjects were assessed biweekly and stabilized on an oral dose of aripiprazole ranging from 10 to 30 mg daily. Stability was defined as fulfillment of ALL of the following criteria for 8 consecutive weeks (4 consecutive biweekly visits), with the possibility of one excursion from stability criteria during the 8-week period, as long as the excursion did not occur on the final visit of the Oral Stabilization Phase:

1. Outpatient status **AND**
2. Positive and Negative Syndrome Scale (PANSS) Total Score ≤ 80 **AND**
3. Lack of 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
   - suspiciousness
   - hallucinatory behavior
   - unusual thought content, **AND**
4. Clinical Global Impression of Severity (CGI-S) ≤ 4 (moderately ill) **AND**
5. Clinical Global Impression of Severity of Suicide (CGI-SS) ≤ 2 (mildly suicidal) on Part 1 and ≤ 5 (minimally worsened) on Part 2.

*Double-blind, Active-controlled Phase:* Subjects eligible for the 38-week Double-blind, Active-controlled Phase were randomly assigned via an interactive voice response system (IVRS) and/or an interactive web response (IWR) system in a 2:2:1 ratio to double-blind treatment to one of 3 treatment groups, stratified by region (US and non-US):

1. aripiprazole IM depot 400 mg/300 mg,
2. the stabilization dose of oral aripiprazole, or
3. aripiprazole IM depot 50 mg/25 mg.

The aripiprazole IM depot 50 mg/25 mg dose was included as a low-dose aripiprazole group to test assay sensitivity for the non-inferiority design. Each subject randomized to oral aripiprazole was randomly assigned to a placebo group to match the administration procedure for either the aripiprazole IM depot 400 mg/300 mg group (high-dose IM depot placebo) or the aripiprazole IM depot 50 mg/25 mg group (low-dose IM depot placebo). Subjects assigned to treatment with IM depot received oral matching placebo tablets, and those assigned to oral aripiprazole tablets received IM depot matching placebo (either high-dose IM depot placebo or low-dose IM depot placebo). Subjects randomized to either dose of aripiprazole IM depot (400 mg or 50 mg) continued to receive oral aripiprazole 10 mg to 20 mg daily (dispensed as double-blind trial medication) for the first 14 days of the Double-blind, Active-controlled Phase to maintain therapeutic plasma concentrations.

Beginning at Week 4, modifications to the Double-blind, Active-controlled Phase starting dose were permitted as follows:

For subjects randomized to aripiprazole IM depot 400 mg, a one-time decrease in dose to aripiprazole IM depot 300 mg and a one-time return to aripiprazole IM depot 400 mg was permitted.

- For subjects randomized to aripiprazole IM depot 50 mg, a one-time decrease in dose to aripiprazole IM depot 25 mg and a one-time return to aripiprazole IM depot 50 mg was permitted.
- For subjects randomized to oral aripiprazole, a one-time change in dose (increase or decrease) and a one-time reversal of the change (decrease in dose if previously increased or increase in dose if previously decreased) was permitted as long as the dose remains within the range of 10 to 30 mg daily.

All IM depot injections (aripiprazole 400 mg, aripiprazole 300 mg, aripiprazole 50 mg, aripiprazole 25 mg, and placebo) were administered monthly (every 28 days).

During the Double-blind, Active-controlled Phase, subjects were assessed weekly in the clinic for the first 4 weeks and then biweekly to Week 38. Subjects were evaluated for impending relapse at every clinic visit and at all unscheduled clinic visits during the Double-blind, Active-controlled Phase. In addition, subjects were contacted by phone between visits to determine whether or not the scheduled visit should be moved forward, based upon the subject's clinical need. Any subject withdrawn for lack of efficacy in the Double-blind, Active-controlled Phase met at least one of the criteria for impending relapse:

1. Clinical Global Impression of Improvement (CGI-I) of ≥ 5 (minimally worse)

**AND**

- an increase on any of the following individual PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score > 4 with an absolute increase of ≥ 2 on that specific item since randomization **OR**
- an increase on any of the following individual PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content to a score > 4 and an absolute increase of ≥ 4 on the combined 4 PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) since randomization.

**OR**

2. Hospitalization due to worsening of psychotic symptoms (including partial hospitalization programs), but excluding hospitalization for psychosocial reasons

**OR**

3. CGI-SS score of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2

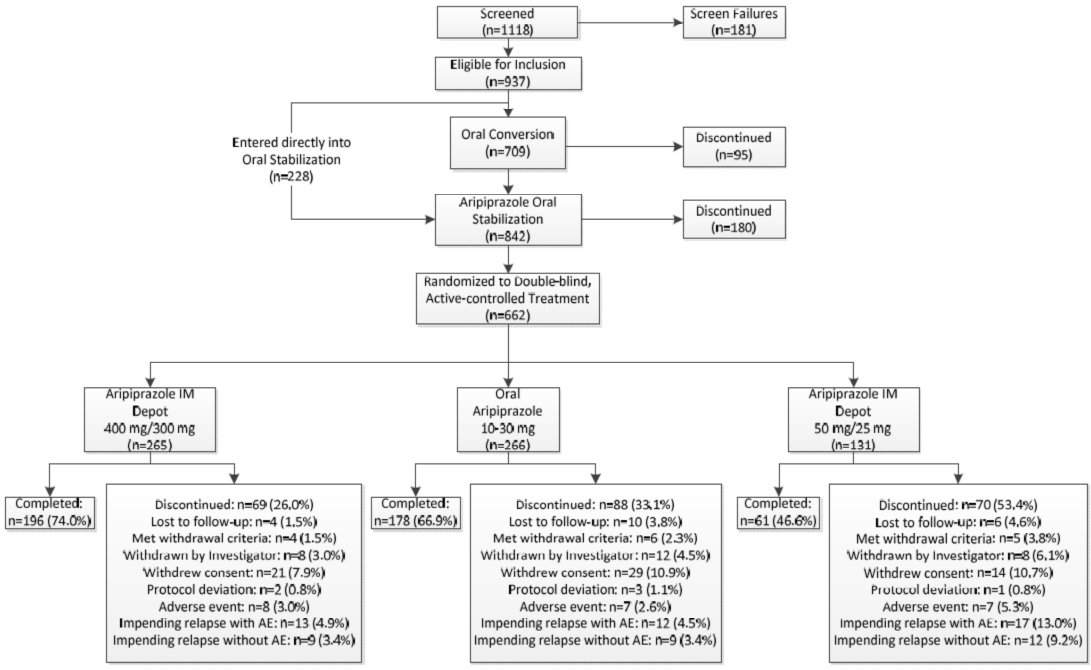
**OR**

4. Violent behavior resulting in clinically relevant self-injury, injury to another person, or property damage.

The following options were available to trial participants after completion or discontinuation from the trial:

- Subjects who discontinued the trial for any reason during the Double-blind, Active-controlled Phase or who completed the full 38-week Double-blind, Active-controlled Phase may have been offered entry into a 52-week open-label rollover trial (Trial 31-08-248).
- Subjects not electing to enter the open-label trial and those who were discontinued or withdrawn during other phases of this trial were to be prescribed appropriate antipsychotic treatment by the investigator or the subject's primary care physician and were followed up for safety. Subjects were to return for safety assessments 2 weeks (± 3 days) and 4 weeks (± 3 days) after the last trial visit.
- In addition, subjects who received at least one dose of aripiprazole IM depot (or matching placebo) and discontinued the trial for any reason, and subjects who completed the Double-blind, Active-controlled Phase, were to attend a safety follow-up clinic visit 12 weeks (± 3 days) after the last trial visit and receive follow-up phone calls at 20 and 26 weeks (± 5 days) after the last trial visit for evaluation of safety.

**Number of Subjects:** Originally it was estimated that approximately 1500 subjects at approximately 120 sites worldwide (estimated distribution was 40 sites in the US and the remainder in the rest of the world) would be enrolled in the trial. Approximately 260 subjects were expected to be randomized to aripiprazole IM depot (400 mg/300 mg), 260 subjects to oral aripiprazole (10 to 30 mg), and 130 subjects to aripiprazole IM depot (50 mg/25 mg). The actual number of subjects screened, randomized, and discontinued from 98 enrolling sites of 105 initiated sites (including 37 enrolling sites of 41 initiated sites in Europe) are shown in the figure below




All randomized subjects were included in the intent-to-treat population and were analyzed for efficacy. Six hundred sixty-two randomized subjects were treated and analyzed for safety in the Double-blind, Active-controlled Phase.

**Diagnosis and Main Criteria for Inclusion/Exclusion:** Male and female subjects, ages 18 to 60 years with a current diagnosis of schizophrenia as defined by DSM-IV-TR criteria and a history of the illness for at least 3 years prior to screening who have a history of symptom exacerbation with interruption or discontinuation of antipsychotic treatment, who are currently being treated with one or more antipsychotic(s) other than clozapine and who, in the investigator's judgment, require chronic treatment with an antipsychotic medication and would benefit from treatment with an aripiprazole IM depot formulation were enrolled. Prior to entry into the Double-blind, Active-controlled Phase of the trial, subjects were required to be clinically stable on oral aripiprazole for 8 consecutive weeks based on the criteria previously defined in the methodology section.

Subjects were excluded if they had a current DSM-IV-TR diagnosis other than schizophrenia (including schizoaffective disorder, major depressive disorder, bipolar disorder, delirium, dementia, amnestic or other cognitive disorders); were diagnosed with borderline, paranoid, histrionic, schizotypal, schizoid, or antisocial personality disorder; were, according to the investigator's opinion, experiencing acute depressive symptoms within the 30 days prior to screening that required treatment with an antidepressant; had schizophrenia that was considered resistant/refractory to antipsychotic treatment by history; or had a history of failure to clozapine treatment or response to clozapine treatment only. Also excluded were subjects with a significant risk of violent behavior or

a significant risk of committing suicide based on history or the investigator's judgment; those who currently met DSM-IV-TR criteria for substance dependence; including alcohol and benzodiazepines, but excluding caffeine and nicotine; those with known hypothyroidism or hyperthyroidism (unless their condition had been stabilized with medications for at least the past 90 days); those who had a history or evidence of a medical condition that would expose them to an undue risk of a significant adverse event (AE) or interfere with assessments of safety or efficacy during the course of the trial, including but not limited to hepatic, renal, respiratory, cardiovascular, endocrine, neurologic, hematologic, or immunologic disease as determined by the clinical judgment of the investigator and those with epilepsy or a history of seizures, except for a single childhood febrile seizure, post traumatic, alcohol withdrawal, etc. Sexually active subjects who refused to comply with requirements for contraceptive use while in this trial and female subjects who were pregnant or nursing were also excluded.

**Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration:** Aripiprazole IM depot was supplied as 400 mg, 200 mg, and placebo lyophilized vials. The 400 mg vial was used to prepare the 400 mg and 300 mg doses, and the 200 mg vial was used to prepare the 50 mg and 25 mg doses of trial medication. An unblinded Site Trial Drug Manager prepared and administered the double-blind IM depot trial medication because of differences in appearance of reconstituted aripiprazole IM depot (milky white suspension) vs placebo (clear solution). All doses of IM depot (active and placebo) were to be injected into the gluteal muscle.

**Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration:** Aripiprazole oral tablets and matching placebo tablets were used during the Double blind, Active controlled Phase. In addition to those subjects randomized to receive aripiprazole oral tablets 10 30 mg, subjects randomized to either dose of aripiprazole IM depot (400 mg or 50 mg) also received oral aripiprazole 10 mg to 20 mg daily (dispensed as double blind trial medication) for the first 14 days of the Double blind, Active controlled Phase to maintain therapeutic plasma concentrations. Oral trial medication was dispensed by an Unblinded Site Trial Drug Manager at weekly and biweekly visits, as appropriate. Double blind oral aripiprazole was administered at doses of 10 mg to 30 mg daily using 10 mg and 15 mg tablets. Oral placebo tablets were dosed identically to the active medication within each treatment group. Aripiprazole oral tablets were also used for converting subjects from other antipsychotic medications during the Conversion Phase and Oral Stabilization Phase. Open label oral aripiprazole was given at doses of 10 mg to 30 mg daily using 5 mg, 10 mg, and 15 mg tablets.

**Duration of Treatment:** Subjects were planned to be on trial for up to 38 weeks and were followed for two weeks after their last dose for safety. (Actual subject exposure is described in the results section). Subjects may have also received oral aripiprazole for 4-6 weeks during the conversion phase and 8-28 weeks during the oral stabilization phase.

**Trial Assessments:** PANSS, CGI-S, Personal and Social Performance (PSP), Trails A total score, Tower of London item scores, University of Maryland: Letter-Number Span total score (hereafter referred to as Letter-Number Span), Drug Attitude Inventory (DAI), Medication Adherence Questionnaire (MAQ), Investigator's Assessment Questionnaire (IAQ), physical examination, height, vital signs, body weight, waist circumference, body mass index (BMI), 12-lead electrocardiogram (ECG), clinical laboratory tests (hematology, serum chemistry, urinalysis), prolactin level, pregnancy test for Women of Child Bearing Potential(WOCBP), drug screen, blood alcohol test, Simpson-Angus Scale(SAS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), CGI-SS, CGI-S, CGI-I, Columbia Suicide Severity Rating Scale (C-SSRS), resource utilization questionnaire, AEs, prior and concomitant medications, blood draw for metabolic profiling (cytochrome P450 [CYP] 2D6 isozyme), visual analog scale (VAS), investigator rating of injection site, and Patient Satisfaction with Medication Questionnaire (PSMQ)-Modified, and pharmacokinetics (PK).

**Criteria for Evaluation:**

*Primary Efficacy Endpoint*: The primary endpoint of this trial was the estimated proportion of subjects experiencing impending relapse by end of 26 weeks of treatment from the date of randomization in the Double-blind, Active-controlled Phase, in subjects with schizophrenia who had maintained stability on oral aripiprazole for at least 8 consecutive weeks in the Oral Stabilization Phase of the trial before the first monthly IM injection.

*Secondary Efficacy Endpoints*: The secondary efficacy endpoints in the Double-blind, Active-controlled Phase were as follows:

- Time to impending relapse from the date of randomization in the Double-blind, Active controlled Phase
- Percentage of responders at endpoint in the Double-Blind, Active-controlled Phase (ie, response defined as meeting stability criteria)
- Percentage of subjects achieving remission, where remission was defined as a score of $\leq 3$ on each of the following specific PANSS items, maintained for a period of 6 months: delusions (P1), unusual thought content (G9), hallucinatory behavior (P3), conceptual disorganization (P2), mannerism/posturing (G5), blunted affect (N1), social withdrawal (N4), and lack of spontaneity (N6)

Other secondary endpoints evaluated for the Double-blind, Active-controlled Phase were as follows:

- Mean change from baseline to endpoint in PANSS total score
- Mean change from baseline to endpoint in CGI-S
- Mean change from baseline to endpoint in PANSS positive and negative subscale scores
- Mean CGI-I score at endpoint
- Time to discontinuation from all causes

*Other Outcome Variables:* Outcomes were assessed for the Oral Stabilization Phase and the Double-blind, Active controlled Phase by mean change from baseline in the PSP Scale, Trails A total score, Tower of London item scores, Letter-Number Span, DAI score, MAQ score, and IAQ total score. In addition, the proportion of subjects hospitalized for exacerbation of psychotic symptoms and the frequency of outpatient visits not required per the protocol were tabulated as measures of healthcare resource utilization. Frequency distributions were provided from responses to the PSMQ-Modified for treatment satisfaction and subject-rated side effects.

*Safety Endpoints*: AEs were examined by frequency, severity, seriousness, and discontinuation from the trial. Discontinuations from all causes were also summarized. Suicidality was summarized by change from baseline in CGI-SS (Part 1) and mean CGI-SS score (Part 2), and the C-SSRS. The Columbia Classification Algorithm of Suicide Assessment (C-CASA), a standardized system for categorizing suicidality, was used to classify potential suicidality events at baseline and during the trial. Injection site pain was evaluated by mean VAS scores as reported by the subject before and after each injection and at each trial visit. The investigator rating of pain, redness, swelling, and induration at the injection site was also tabulated for pre and post-injection site evaluations at each visit.

The incidence of clinically relevant changes was calculated for vital signs and routine laboratory tests. Mean change from baseline and incidence of clinically relevant changes were calculated for ECG parameters, prolactin concentrations, and body weight. Extrapyramidal symptoms (EPS) were evaluated by calculating mean change from baseline in SAS total, AIMS movement rating, and BARS global scores. By-subject listings of physical examination findings were reviewed as a further assessment of safety.

**Statistical Methods:** The primary efficacy endpoint of this trial was the estimated proportion of subjects experiencing impending relapse by end of 26 weeks of treatment from the date of randomization into the Double-blind, Active-controlled Phase in subjects with schizophrenia who maintained stability on oral aripiprazole for at least 8 consecutive weeks in the Oral Stabilization Phase of the trial. The objective of the statistical analysis was to demonstrate non-inferiority of aripiprazole IM depot (400 mg/300 mg) to oral aripiprazole tablets (10 to 30 mg) with regard to the primary efficacy endpoint of the estimated proportion of subjects experiencing impending relapse by end of 26 weeks of treatment from the date of randomization, which was estimated from the time-to-event Kaplan-Meier curve at Week 26 (Day 182).

*Primary Efficacy Endpoint Analysis*: For the primary analysis of estimated proportion of subjects experiencing impending relapse by end of 26 weeks from the date of randomization in the Double-blind, Active-controlled Phase, all subjects belonging to the ITT dataset were included. The test of non-inferiority of aripiprazole IM depot (400 mg/300 mg) to oral aripiprazole (10 to 30 mg) was performed using a 95% confidence interval (CI; 2-sided) for the difference in the estimated proportion of subjects meeting impending relapse criteria by end of Week 26 (aripiprazole IM depot

400 mg/300 mg vs oral aripiprazole tablets 10 mg to 30 mg). Non-inferiority was considered confirmed if the upper bound of the 2-sided 95% CI was below the predefined margin, 11.5%. Data from a previous trial (CN138-047) which compared time to relapse for oral aripiprazole to placebo, were taken into consideration in setting the non-inferiority margin. Once non-inferiority was declared by the preceding test, superiority of IM depot 400 mg/300 mg over IM depot 50 mg/25 mg was tested by examining the difference in the estimated proportions of subjects meeting impending relapse criteria between IM depot 400 mg/300 mg and IM depot 50 mg/25 mg by end of Week 26 using z-statistic for statistical significance at the 0.05 significance level (2-sided) as assay sensitivity analysis. In addition, a similar test was performed to compare oral aripiprazole tablets 10-30 mg with aripiprazole IM depot 50 mg/25 mg.

Although the primary efficacy analysis was based on the ITT population, a similar analysis for the primary efficacy endpoint was also performed by excluding subjects who were unblinded or potentially unblinded at site level and excluding duplicate-entry subjects with overlapping aripiprazole oral tablets/IM depot injections.

*Secondary Efficacy Endpoint Analysis*: The secondary efficacy endpoints for the Double blind, Active-controlled Phase were time to impending relapse, percentage of responders in each treatment group, and percentage of subjects achieving remission. The Cox Proportional Hazard model in the model was fitted to the time to impending relapse event data with treatment as factor. The 95% CIs for the hazard ratios (aripiprazole IM depot 400 mg/300 mg to oral aripiprazole, aripiprazole IM depot 400 mg/300 mg to aripiprazole IM depot 50 mg/25 mg) were provided. The log-rank test was performed to test the equality of survival curves (aripiprazole IM depot 400 mg/ 300 mg vs aripiprazole IM depot 50 mg/25 mg) at the 0.05 significance level (2-sided).

In addition, the percentage of subjects meeting the impending relapse criteria was summarized by treatment group for the Double-blind, Active-controlled Phase Efficacy Sample in the Double-blind, Active-controlled Phase (ie, Week 38). Chi-squared tests were performed.

The percentage of subjects meeting PANSS items remission criteria was also summarized biweekly and at the last visit in the Double-blind, Active-controlled Phase. The percentage of responders at the endpoint of the Double-blind, Active-controlled Phase and percentage of subjects achieving remission were analyzed using the Chi-squared test.

*Other Secondary Efficacy Variables and Analysis*: Other variables included the following:

1. Mean change from baseline to endpoint in PANSS total score
2. Mean change from baseline to endpoint in CGI-S score
3. Mean change from baseline to endpoint in PANSS positive subscale total score
4. Mean change from baseline to endpoint in PANSS negative subscale total score
5. Mean CGI-I score
6. Time to discontinuation due to all causes

The mean changes from baseline for variables (1) - (4) were summarized using descriptive statistics by treatment group and visit for the Double-blind, Active-controlled Phase Efficacy Sample in the Double-blind, Active-controlled Phase. The mean CGI-I score was summarized using descriptive statistics by treatment group and visit for the Double-blind, Active controlled Phase Efficacy Sample in the Double-blind, Active-controlled Phase. Descriptive statistics for variables (1) - (5) were also summarized by visit for the Double-blind, Active-controlled Phase Efficacy Sample in the Oral Stabilization Phase. Secondary efficacy variables (1) - (4) were analyzed by fitting an analysis of covariance (ANCOVA) model for the change scores with treatment as a factor and baseline value as a covariate. Variable (5) was analyzed by using the Cochran-Mantel-Haenszel method based on row mean score statistics. Analyses of the other secondary efficacy variables (1) - (5) were performed for the Double-blind, Active-controlled Phase Efficacy Sample using both last observation carried forward (LOCF) and observed case (OC) datasets by visit. Additionally, changes from baseline in PANSS total score and CGI-S score were analyzed by the Mixed Model Repeated Measures approach using OC datasets. The mixed model included fixed effects of treatment, visit, and interaction of treatment by visit with baseline as a covariate. The unstructured covariance matrix for observations within a subject was used. Alternatively, if convergence issues occurred fitting the model, a first order autoregressive covariance structure was used. Kaplan-Meier curves for the time to discontinuation due to all causes were plotted and analyzed using the log-rank test.

*Subgroup Efficacy Analyses*: Subgroup analyses of the Double-blind, Active-controlled Phase Efficacy Sample in time to event of impending relapse, percentage of subjects meeting the impending relapse criteria, percentage of responders, percentage of subjects achieving remission, mean change from baseline to endpoint in PANSS total score, PANSS positive subscale score, PANSS negative subscale score, CGI-S score, and mean CGI-I score at the endpoint of the Double-blind, Active-controlled Phase were provided by region (US, non-US), sex, race (Caucasian, non-Caucasian), age (< 45 years, ≥ 45 years), ethnicity (Hispanic/Latino, Non- Hispanic/Latino), and BMI (> 28 $kg/m^2$, > 28 $kg/m^2$).

Descriptive statistics were provided for the mean change from baseline to the end of the Oral Stabilization Phase in the PANSS total score, PANSS positive and negative subscale scores, and CGI-S score. The mean CGI-I score at the end of the Oral Stabilization Phase was summarized. These efficacy endpoints were also summarized by visit for treatment with oral aripiprazole tablets for the Oral Stabilization Phase Efficacy Sample. A listing of these efficacy endpoints was provided for subjects enrolled into the Conversion Phase. Change from baseline in other outcome variables (if applicable) from the Double-blind, Active controlled Phase were analyzed using an ANCOVA model with terms for treatment and baseline value as a covariate. In addition, descriptive statistics were provided for other outcome assessments.

*Safety*: Safety data from the Conversion Phase were listed; data from the Oral Stabilization Phase and the Double-blind, Active-controlled Phase were tabulated,

summarized by descriptive and/or inferential statistics. In addition, changes in the following parameters were analyzed over the period from the end of the Oral Stabilization Phase to the end of the Double-blind, Active-controlled Phase using an ANCOVA model with treatment as a factor and baseline as covariate: prolactin concentration, body weight, and SAS total, BARS global, and AIMS movement rating scores.

*Pharmacokinetic Methods*: Blood samples collected from 244 subjects during the End of Oral Stabilization Phase visit and at Weeks 4, 12, 16, and 20 during Double-blind, Active-controlled Phase were analyzed for aripiprazole and dehydro-aripiprazole and results were reported. Samples collected from subjects for CYP 2D6 isozyme metabolism status were analyzed and results were also reported.

**Summary of Results:**

**Baseline Data, Disposition, and Demographics:** A total of 1118 subjects were screened with 181 screen failures. A total of 709 subjects underwent the Conversion Phase cross-titration and 842 subjects were entered into the Oral Stabilization Phase, including 228 subjects who did not require conversion and entered directly into the Oral Stabilization Phase after screening. A total of 662 subjects entered the Double-blind, Active-controlled Phase, including 265 subjects randomized to receive aripiprazole IM depot 400 mg/300 mg, 266 subjects to receive oral aripiprazole tablets 10-30 mg, and 131 to receive aripiprazole IM depot 50 mg/25 mg.

A larger proportion of subjects (196/265 subjects, 74.0%) in the aripiprazole IM depot 400 mg/300 mg group completed the trial than in the oral aripiprazole tablets 10-30 mg group (178/266 subjects, 66.9%) or the aripiprazole IM depot 50 mg/25 mg group (61/131 subjects, 46.6%). Subject withdrawal of consent was the most common reason overall for trial discontinuation (64/662 subjects, 9.7%).

Most of the subjects randomized into the Double-blind, Active-controlled Phase were male (406/662, 61.3%) and Caucasian (387/662, 58.5%). The mean age of randomized subjects was 41.2 years (range 18 to 60 years). The mean age at first diagnosis was 27.3 years. The mean PANSS total score and CGI-S scores were 62.6 and 3.4, respectively at baseline of the Oral Stabilization Phase, and 57.1 and 3.1, respectively, at baseline of the Double-blind, Active-controlled Phase.

**Efficacy Results:** The results of analysis of the primary efficacy endpoint, the estimated proportion of subjects experiencing impending relapse by end of Week 26 of the Double-blind, Active-controlled Phase, showed that aripiprazole IM depot 400 mg/300 mg is not inferior to aripiprazole oral tablets 10-30 mg. The estimated relapse rate by end of Week 26 was 7.12% in the aripiprazole IM depot 400 mg/300 mg group and 7.76% in the oral aripiprazole tablets 10-30 mg group, a difference of −0.64%. The 95% CI (−5.26, 3.99) for the difference in the estimated proportion of subjects experiencing impending relapse by end of Week 26 excluded the predefined non-inferiority margin, 11.5%. Therefore,

aripiprazole IM depot 400 mg/300 mg is non-inferior to the aripiprazole oral tablets 10-30 mg formulation. The estimated proportion of subjects experiencing impending relapse by end of Week 26 for the aripiprazole IM depot 400 mg/300 mg group was 7.12%, which was statistically significantly lower than in the aripiprazole IM depot 50 mg/25 mg group (21.80%; p = 0.0006). Thus, superiority of aripiprazole IM depot 400 mg/300 mg over aripiprazole IM depot 50 mg/25 mg was established and the validity of the trial design was confirmed. Further substantiation of assay sensitivity was provided by the demonstration that the difference (−14.04%) between oral aripiprazole tablets 10-30 mg and aripiprazole IM depot 50 mg/25 mg in estimated proportion of subjects experiencing impending relapse by end of Week 26 was statistically significant in favor of oral aripiprazole tablets (p = 0.0012).

The secondary efficacy endpoint, time to impending relapse during the 38-week Double-blind, Active-controlled Phase, was similar in the aripiprazole IM depot 400 mg/300 mg group and the oral aripiprazole tablets 10-30 mg group (p = 0.9920). The risk of impending relapse was similar in the aripiprazole IM depot 400 mg/300 mg group and the oral aripiprazole tablets 10-30 mg group (hazard ratio = 0.991, 95% CI = 0.545, 1.803). However, the time to impending relapse was statistically significantly delayed (ie, improved) in the aripiprazole IM depot 400 mg/300 mg group compared with the aripiprazole IM depot 50 mg/25 mg group (p < 0.0001). The aripiprazole IM depot 50 mg/25 mg group had a 3.158-fold higher risk of relapse than the aripiprazole IM depot 400 mg/300 mg group (95% CI = 1.813, 5.502).

During Trial 31-07-247, it was discovered that 12 subjects were either enrolled in Trial 31-07-247 at 2 different sites or enrolled in Trial 31-07-247 and another trial investigating aripiprazole IM depot (Trial 31-07-246 or Trial 31-08-248).

There were also 13 confirmed individual subject unblindings during the course of this trial, including 2 intentional and 11 unintentional unblindings. Results of analysis of the primary efficacy endpoint and time to impending relapse were similar whether including or excluding these subjects who were unblinded or potentially unblinded at site level and had overlapping aripiprazole oral tablets/IM depot injections due to duplicate entry.

A summary of the results of secondary efficacy endpoints during the Double-blind, Active controlled Phase are presented in the following table: mean change from baseline to endpoint (up to Week 38) in PANSS total score, PANSS positive and negative subscale scores, and CGI-S score; as well as mean CGI-I score at endpoint. The stability of symptoms established in the Oral Stabilization Phase (ie, with oral aripiprazole tablets 10-30 mg) was maintained throughout the Double-blind, Active-controlled Phase with aripiprazole IM depot 400 mg/300 mg. At Week 38, the PANSS total scores had improved compared with baseline in the aripiprazole IM depot 400 mg/300 mg group (change of −1.66) while they remained stable in the oral aripiprazole tablets 10-30 mg group (change of 0.58) (p = 0.0272). This same pattern was seen for the CGI scores. Statistically significant differences in favor of aripiprazole IM depot 400 mg/300 mg were seen for PANSS total score, CGI-S, and CGI-I for comparisons with both of the

other treatment groups, and for the PANSS positive subscale score in the comparison with aripiprazole IM depot 50 mg/25 mg.

**Summary Results of PANSS and CGI scales (Double-blind, Active-controlled Phase Efficacy Sample; LOCF)**

| Parameter | Visit | LS Mean (SE)[a] Change From Baseline | | | Comparison Arip IM Depot 400/300 mg vs Oral Arip | | Comparison Arip IM Depot 400/300 mg vs Arip IM Depot 50/25 mg | |
|---|---|---|---|---|---|---|---|---|
| | | Arip IM Depot 400/300 mg (N = 265) | Oral Arip 10-30 mg (N = 266) | Arip IM Depot 50/25 mg (N = 131) | Difference 95% CI[a] | P-value[a] | Difference 95% CI[a] | P-value[a] |
| PANSS Total Score | Baseline[b] | 57.94 (0.786) n = 263 | 56.57 (0.782) n = 266 | 56.08 (1.114) n = 131 | 1.37 (−0.81, 3.55) | 0.2179 | 1.85 (−0.83, 4.53) | 0.1751 |
| | Week 38 | −1.66 (0.718) n = 263 | 0.58 (0.714) n = 266 | 3.08 (1.017) n = 131 | −2.24 (−4.23, −0.25) | 0.0272 | −4.74 (−7.19, −2.30) | 0.0002 |
| PANSS Positive Subscale Score | Baseline[b] | 12.76 (0.230) n = 263 | 12.15 (0.228) n = 266 | 11.80 (0.326) n = 131 | 0.60 (−0.03, 1.24) | 0.0634 | 0.96 (0.17, 1.74) | 0.0168 |
| | Week 38 | −0.12 (0.249) n = 263 | 0.52 (0.247) n = 266 | 1.46 (0.352) n = 131 | −0.64 (−1.33, 0.05) | 0.0675 | −1.58 (−2.43, −0.73) | 0.0003 |
| PANSS Negative Subscale Score | Baseline[b] | 16.79 (0.312) n = 263 | 16.93 (0.310) n = 266 | 17.10 (0.442) n = 131 | −0.14 (−1.00, 0.73) | 0.7544 | −0.31 (−1.37, 0.75) | 0.5689 |
| | Week 38 | −0.74 (0.220) n = 263 | −0.15 (0.219) n = 266 | −0.19 (0.312) n = 131 | −0.59 (−1.20, 0.02) | 0.0572 | −0.56 (−1.31, 0.19) | 0.1449 |
| CGI-S | Baseline[b] | 3.12 (0.050) n = 259 | 3.09 (0.049) n = 263 | 2.95 (0.071) n = 129 | 0.02 (−0.11, 0.16) | 0.7262 | 0.16 (−0.01, 0.33) | 0.0605 |
| | Week 38 | −0.13 (0.049) n = 259 | 0.05 (0.049) n = 263 | 0.23 (0.070) n = 129 | −0.17 (−0.31, −0.04) | 0.0123 | −0.36 (−0.52, −0.19) | < 0.0001 |
| CGI-I[c] | Week 38 | 3.27 (1.16) n = 263 | 3.66 (1.16) n = 266 | 4.02 (1.32) n = 131 | NA | 0.0002 | NA | < 0.0001 |

Arip = aripiprazole; CGI-I = Clinical Global Impression of Improvement; CGI-S = Clinical Global Impression of Severity; CI = Confidence Interval; Diff = difference; IM = intramuscular; LOCF = last observation carried forward; LS = least squares (mean); NA = Not applicable; PANSS = Positive and Negative Symptom Scale; SE = standard error

Note: Except for CGI-I, subjects with baseline and at least one postbaseline assessment are included. For CGI-I, subjects with at least one postbaseline assessment are included.

[a] The LS means (adjusted mean), SE, difference, 95% CIs, and p-values are derived from an analysis of variance model with treatment as term for the baseline value and an analysis of covariance model with treatment as term and baseline as covariate for change from baseline.

[b] Actual LS mean values and standard errors are shown for baseline.

[c] Mean values and standard deviations are shown for CGI-I.

The proportion of responders (ie, subjects who met the stability criteria) at endpoint (up to Week 38) in the Double-blind, Active-controlled Phase was 89.8% (237/264) in the aripiprazole IM depot 400 mg/300 mg group compared with 89.4% (235/263) in the oral aripiprazole tablets 10- 30 mg group, and 75.2% (97/129) in the aripiprazole IM depot 50 mg/25 mg group. There was no significant difference in the proportion of responders between the aripiprazole IM depot 400 mg/300 mg group and the oral aripiprazole tablets

10-30 mg group (p = 0.8750); however, the proportion of responders was statistically significantly higher in the aripiprazole IM depot 400 mg/300 mg group than in the aripiprazole IM depot 50 mg/25 mg group (p = 0.0001).

Remission was defined as a score of ≤ 3 on each of the following specific PANSS items, maintained for a period of 6 months: delusions (P1), unusual thought content (G9), hallucinatory behavior (P3), conceptual disorganization (P2), mannerisms/posturing (G5), blunted affect (N1), social withdrawal (N4), and lack of spontaneity (N6). The proportion of subjects achieving remission was 48.8% (105/215) in the aripiprazole IM depot 400 mg/300 mg group compared with 53.2% (107/201) in the oral aripiprazole tablets 10-30 mg group, and 59.7% (43/72) in the aripiprazole IM depot 50 mg/25 mg group. Only those subjects who remained in the trial for at least 6 months were included in the calculation of remission rates, hence the denominators for this analysis are smaller than the numbers of subjects randomized into each treatment group. The differences between the aripiprazole IM depot 400 mg/300 mg group and oral aripiprazole tablets 10 30 mg group, and between the aripiprazole IM depot 400 mg/300 mg and aripiprazole IM depot 50 mg/25 mg groups were not statistically significant (p = 0.3700 and p = 0.1097, respectively). The proportions of subjects achieving a score of ≤ 3 at last visit (LOCF) on each of the specific PANSS items defined above were 65.0% (171/263) in the aripiprazole IM depot 400 mg/300 mg group compared with 63.5% (169/266) in the oral aripiprazole tablets 10-30 mg group, and 55.7% (73/131) in the aripiprazole IM depot 50 mg/25 mg group.

Of the 265 subjects randomly assigned to treatment with aripiprazole IM depot 400 mg/300 mg in the Double-blind, Active-controlled Phase, 67 discontinued due to all reasons by Day 280, resulting in a discontinuation rate of 25.28%. In the oral aripiprazole tablets 10-30 mg group, 266 subjects were randomly assigned to treatment in the Double-blind, Active-controlled Phase; 87 discontinued by Day 280, a discontinuation rate of 32.71%. There was a statistically significant difference in time to discontinuation due to all reasons between the 2 groups (p = 0.0484) in favor of the aripiprazole IM depot 400 mg/300 mg treatment group. In the aripiprazole IM depot 50 mg/25 mg group, 70 of the 131 subjects randomly assigned to treatment discontinued, for a discontinuation rate of 53.44%. The median time to discontinuation was 234 days and there was a statistically significant difference between the aripiprazole IM depot 400 mg/300 mg and the aripiprazole IM depot 50 mg/25 mg groups (p < 0.0001) in favor of the aripiprazole IM depot 400 mg/300 mg treatment group.

**Other Outcome Results**:
*PSP Total Score*: The PSP scale is a validated clinician-rated scale that measures personal and social functioning in 4 domains: socially useful activities (eg, work and trial), personal and social relationships, self-care, and disturbing and aggressive behaviors. For subjects in the IM depot 400 mg/300 mg and oral aripiprazole tablets 10-30 mg groups, the PSP score remained relatively stable from baseline to the last visit of the Double-blind, Active-controlled Phase (0.45 and 0.08 point increases for the aripiprazole IM depot 400 mg/300 mg and oral aripiprazole tablets 10-30 mg groups,

respectively). There was no significant difference in the magnitude of the change between the 2 treatment groups (p = 0.9946). For subjects in the aripiprazole IM depot 50 mg/25 mg group, the PSP total score decreased from baseline to the last visit during the Double-blind, Active-controlled Phase (−2.39 points), indicating a decrease in social functioning The difference in the change from baseline to last visit in the PSP score was statistically significant between the aripiprazole IM depot 50 mg/25 mg group and the aripiprazole IM depot 400 mg/300 mg group (p = 0.0266).

*Cognition Assessments*: Cognition was evaluated using the Trails A (attention and psychomotor speed), the Tower of London (reasoning and problem solving ability), and the Letter-Number Span assessments (evaluates working memory).

Mean decreases from baseline to the last visit in the Double-Blind, Active-controlled Phase in the Trails A scores were −3.16, −2.16, and −4.94 for the aripiprazole IM depot 400 mg/ 300 mg, oral aripiprazole tablets 10-30 mg group, and aripiprazole IM depot 50 mg/25 mg groups, respectively. For the Tower of London assessments, mean total move scores changed by −2.79, −0.93, and 1.84, and mean execution time scores decreased by −25.73, −29.71, and −11.53 seconds, in the aripiprazole IM depot 400 mg/300 mg, oral aripiprazole tablets 10-30 mg, and aripiprazole IM depot 50 mg/25 mg groups, respectively. Mean Letter-Number Span scores declined slightly in all treatment groups (−0.18, −0.13, and −0.66 in the aripiprazole IM depot 400 mg/300 mg, oral aripiprazole tablets 10-30 mg, and aripiprazole IM depot 50 mg/25 mg groups, respectively). There were no statistically significant differences between treatment groups for any of the cognitive assessments.

*Drug Attitude Inventory Score*: The DAI is a validated self-report instrument used to evaluate the subject's attitude toward treatment. A positive total final score meant a positive subjective response and negative total score meant a negative subjective response. There were minimal changes at the last visit in the DAI total score for the aripiprazole IM depot 400 mg/300 mg, oral aripiprazole tablets 10-30 mg, and aripiprazole IM depot 50 mg/25 mg groups during the Double-blind, Active-controlled Phase (−0.53, −0.27, and −0.56 points, respectively). The change from baseline to last visit in the DAI score was not statistically significantly different between the aripiprazole IM depot 400 mg/300 mg and oral aripiprazole tablets 10-30 mg group (p = 0.6034) or between the aripiprazole IM depot 400 mg/300 mg group and the aripiprazole IM depot 50 mg/25 mg group (p = 0.5168).

*Medication Adherence Questionnaire Total Score*: The MAQ total score ranges from 0 to 4 with higher scores indicating a lower level of adherence to medication regimens. The mean MAQ score was less than 1 (indicating adherence to medication) for most visits during the entire trial. Changes from baseline to last visit in the MAQ total score during the Double-blind, Active controlled Phase were minimal (−0.08, −0.02, and −0.07 for the aripiprazole IM depot 400 mg/300 mg, oral aripiprazole tablets 10-30 mg, and aripiprazole IM depot 50 mg/25 mg groups, respectively) and not significantly different between treatment groups (p = 0.8793 and p = 0.9911 for the comparisons of

aripiprazole IM depot 400 mg/300 mg vs oral aripiprazole tablets 10-30 mg and vs aripiprazole IM depot 50 mg/25 mg, respectively).

*Investigator's Assessment Questionnaire Total Score*: The IAQ is a 12-item questionnaire completed by investigators that assesses relative effectiveness (efficacy, safety, and tolerability) of antipsychotic medications in subjects with schizophrenia. Each item is scored on a scale of 1 (much better) to 5 (much worse); therefore, lower scores represent greater overall improvement. For subjects in the aripiprazole IM depot 400 mg/300 mg and oral aripiprazole tablets 10-30 mg groups, the IAQ score remained relatively stable from baseline to last visit during the Double-blind, Active-controlled Phase (changes of 0.08 and 0.35 points, respectively), with no statistically significant differences between groups in the magnitude of the change ($p = 0.5007$). However, for subjects in the aripiprazole IM depot 50 mg/25 mg group, the increase was larger (2.04 points), indicating worsening, and the difference was significantly worse compared with the aripiprazole IM depot 400 mg/300 mg group ($p = 0.0017$).

*Patient Satisfaction with Medication Questionnaire-Modified*: The PSMQ-Modified was used by the investigator to assess subject satisfaction with treatment, subject perception of the frequency of side effects, and subject preference of current vs previous antipsychotic medication (ie, those taken at screening). At the baseline of the Double-blind, Active-controlled Phase, the majority of subjects (76.8% to 78.7%) in all treatment groups reported that they were very satisfied or extremely satisfied with their current treatment compared with the antipsychotic medication they were taking at the time of screening. At the last visit in the Double-blind, Active-controlled Phase, this level of treatment satisfaction remained stable in the aripiprazole IM depot 400 mg/300 mg, and oral aripiprazole tablets 10-30 mg treatment groups (78.7% and 79.1%, respectively), but had declined in the aripiprazole IM depot 50 mg/25 mg group (67.5%). The percentage of subjects in each category of treatment side effects was similar in the aripiprazole IM depot 400 mg/300 mg and oral aripiprazole tablets 10-30 mg groups at baseline and at the last visit of the Double-blind, Active-controlled Phase. The percentage of subjects in both treatment groups in each category of side effects remained relatively stable throughout the Double-blind, Active-controlled Phase for both of these treatment groups. A larger percentage of subjects in the aripiprazole IM depot 50 mg/25 mg group reported "no side effects" at baseline and at the last visit, than in either of the other 2 treatment groups. At baseline of the Double-blind, Active-controlled Phase, most subjects (91.9%, 92.9%, and 92.8% in the aripiprazole IM depot 400 mg/300 mg, oral aripiprazole tablets 10-30 mg, and aripiprazole IM depot 50 mg/25 mg groups, respectively) preferred their current double-blind treatment to the antipsychotic treatment they received prior to enrolling in the trial. This remained stable at the last visit for the aripiprazole IM depot 400 mg/300 mg and oral aripiprazole tablets 10-30 mg groups (91.0% and 91.7%, respectively) but decreased in the aripiprazole IM depot 50 mg/25 mg group (82.4%).

*Health Care Utilization Evaluation*: Most subjects did not have outpatient visits (other than scheduled outpatient trial visits) during the Oral Stabilization Phase (76.3%) or during the Double-blind, Active-controlled Phase (> 69% in each group). The percentage

of subjects with no outpatient visits was similar in the aripiprazole IM depot 400 mg/300 mg and oral aripiprazole tablets 10-30 mg groups (69.1% and 71.1%, respectively) and higher in the aripiprazole IM depot 50 mg/25 mg group (77.9%). Few subjects (18.9%, 24.1%, and 18.5%, in the aripiprazole IM depot 400 mg/300 mg, oral aripiprazole tablets 10-30 mg, or aripiprazole IM depot 50 mg/25 mg groups, respectively) had paid jobs at baseline of the Double-blind, Active controlled Phase. At the last visit, the proportions of subjects with paid jobs had increased slightly in the aripiprazole IM depot 400 mg/300 mg and oral aripiprazole tablets 10-30 mg groups and decreased in the aripiprazole IM depot 50 mg/25 mg group (19.5%, 24.9%, and 16.8%, respectively).

**Pharmacokinetic Results:** The recommended oral dose of aripiprazole for the maintenance treatment of schizophrenia in adult subjects is 10 mg to 30 mg administered daily. Based on the observed concentrations after IM depot administration in this trial, it was confirmed that aripiprazole concentrations consistent with those expected following a 10 mg to 30 mg daily oral dose of aripiprazole were achieved after the first and subsequent IM depot administrations monthly. Specifically, mean aripiprazole trough plasma concentrations after the first IM depot administration in the Double-blind, Active-controlled Phase were maintained above that of 10 mg daily oral aripiprazole with mean aripiprazole trough plasma concentrations gradually increasing by the fourth IM depot administration to steady state levels. There was no correlation noted between aripiprazole and dehydro-aripiprazole plasma concentrations and the observation of serious AEs (SAEs). Examination of plasma concentrations from those subjects who required dose decrease for tolerability showed no correlation with IM depot aripiprazole concentrations.

**Safety Results:** Aripiprazole IM depot was generally well tolerated by subjects with schizophrenia who received doses of 400 mg or 300 mg monthly for up to 38 weeks during the Double-blind, Active-controlled Phase. All subjects began treatment at a dose of 400 mg with an option to decrease once to 300 mg if they did not fully tolerate the 400 mg dose. Most subjects treated with aripiprazole IM depot 400 mg had no variation in their aripiprazole IM depot dose during the Double-blind, Active-controlled Phase; 246/265 (92.8%) subjects starting aripiprazole IM depot 400 mg remained on their starting dose throughout the phase. Similarly, most subjects treated with aripiprazole IM depot 50 mg had no variation in their aripiprazole IM depot dose during the Double-blind, Active-controlled Phase; 130/131 (99.2%) subjects starting aripiprazole IM depot 50 mg remained on their starting dose throughout the phase. For subjects treated with oral aripiprazole tablets 10-30 mg during the Double-blind, Active-controlled Phase most had no change in the dose of their IM depot placebo (high-dose IM depot placebo: 128/133, 96.2%; low-dose IM depot placebo: 127/133, 95.5%).

During the Double-blind, Active-controlled Phase, the majority of treatment-emergent AEs (TEAEs) were reported as mild or moderate in severity. The incidence of TEAEs reported for ≥5% of aripiprazole IM depot 400 mg/300 mg subjects was comparable to or less than that reported for subjects treated with oral aripiprazole tablets 10-30 mg or

aripiprazole IM depot 50 mg/25 mg with the exception of akathisia (10.6% vs 6.8% vs 8.4%), decreased weight (9.8% vs 6.0% vs 9.2%), injection site pain (7.5% vs 2.3% vs 0.8%), and upper respiratory tract infection (6.8% vs 4.1% vs 3.8%). TEAEs of akathisia, decreased weight, injection site pain, and upper respiratory tract infection were generally mild in severity. No report of akathisia, decreased weight, injection site pain, or upper respiratory tract infection was considered to be a serious TEAE or associated with discontinuation of treatment.

Two deaths occurred during the trial; both during the Double-blind, Active-controlled Phase. One death was due to cardiac arrest in a subject randomized to oral aripiprazole tablets 10-30 mg and the other death was due to a completed suicide in a subject randomized to aripiprazole IM depot 50 mg/25 mg. Neither event leading to death was considered by the investigator to be related to trial medication. One additional subject died (cause unknown) during the screening period before receiving any trial medication.

During the Double-blind, Active-controlled Phase, 15/265 (5.7%) aripiprazole IM depot 400 mg/300 mg subjects, 15/266 (5.6%) oral aripiprazole tablets 10-30 mg subjects, and 11/131 (8.4%) aripiprazole IM depot 50 mg/25 mg subjects reported serious TEAEs. The only serious TEAEs reported for ≥ 1% of aripiprazole IM depot 400 mg/300 mg subjects were schizophrenia (5/265, 1.9%) and psychotic disorder (4/265, 1.5%). The serious TEAEs of schizophrenia and psychotic disorder were reported for 2/266 (0.8%) and 2/266 (0.8%) oral aripiprazole tablets 10- 30 mg subjects, respectively, and 3/131 (2.3%) and 4/131 (3.1%) aripiprazole IM depot 50 mg/25 mg subjects, respectively.

Other serious TEAEs reported during the Double-blind, Active-controlled Phase included acute myocardial infarction, pneumonia, schizophrenia (paranoid type), suicidal ideation, and suicide attempt each reported by 2 subjects; and the following events that were reported by one subject each: cardiac arrest, cardiac failure congestive, chest pain, fatigue, cholecystitis chronic, appendicitis perforated, sepsis, ankle fracture, radius fracture, ovarian epithelial cancer, ovarian fibroma, convulsion, neuroleptic malignant syndrome, agitation, completed suicide, drug abuse, acute respiratory distress syndrome, asthma, and organizing pneumonia.

Blood samples for PK analysis were obtained from 6 of the 41 subjects who experienced serious TEAEs during the Double-blind, Active controlled Phase. No correlation between aripiprazole and dehydro-aripiprazole plasma concentrations and the observation of serious TEAEs was noted in these subjects.

During the Double-blind, Active-controlled Phase, 21/265 (7.9%) aripiprazole IM depot 400 mg/300 mg, 19/266 (7.1%) oral aripiprazole tablets 10-30 mg, and 24/131 (18.3%) aripiprazole IM depot 50 mg/25 mg subjects discontinued treatment due to TEAEs. Treatment emergent AEs resulting in trial medication discontinuation reported for ≥ 1% of aripiprazole IM depot 400 mg/300 mg subjects were schizophrenia (8/265, 3.0%) and psychotic disorder (4/265, 1.5%). The events of schizophrenia and psychotic disorder resulting in trial medication discontinuation occurred in 5/266 (1.9%) and 5/266 (1.9%)

oral aripiprazole tablets 10-30 mg subjects, respectively, and 9/131 (6.9%) and 8/131 (6.1%) aripiprazole IM depot 50 mg/25 mg subjects, respectively.

Other TEAEs leading to discontinuation during the Double-blind, Active controlled Phase included schizophrenia (paranoid type) and suicidal ideation, each reported by 3 subjects; tremor and insomnia, each reported by 2 subjects; and the following events that were reported by one subject each: cardiac arrest, chest pain, alanine aminotransferase increased, electrocardiogram ST segment elevation, liver function test abnormal, dyskinesia, dystonia, neuroleptic malignant syndrome, agitation, completed suicide, depression, drug abuse, visual hallucinations, suicide attempt, and acute respiratory distress syndrome.

During the Double-blind, Active-controlled Phase, treatment-emergent EPS and EPS-related TEAEs were reported for 58/265 (21.9%) aripiprazole IM depot 400 mg/300 mg, 31/266 (11.7%) oral aripiprazole tablets 10-30 mg, and 16/131 (12.2%) aripiprazole IM depot 50 mg/25 mg subjects. The most commonly reported EPS and EPS-related events in each group were akathisia events (aripiprazole IM depot 400 mg/300 mg group: 29/265, 10.9%; oral aripiprazole tablets 10-30 mg group: 18/266, 6.8%; aripiprazole IM depot 50 mg/25 mg group: 11/131, 8.4%) followed by parkinsonism events (15/265, 5.7%; 11/266, 4.1%; 7/131, 5.3%; respectively). The percentage of subjects using anticholinergic medications can be used as a proxy measure for EPS. During the Double-blind, Active-controlled Phase, 52/265 (19.6%) aripiprazole IM depot 400 mg/300 mg subjects, 46/266 (17.3%) oral aripiprazole tablets 10-30 mg subjects, and 18/131 (13.7%) aripiprazole IM depot 50 mg/25 mg subjects received an anticholinergic agent.

There was minimal variation in EPS symptoms during the Double-Blind, Active-controlled Phases as assessed by mean changes from baseline in the SAS, AIMS, and BARS rating scales. There were statistically significant differences between aripiprazole IM depot 400 mg/300 mg and oral aripiprazole tablets 10-30 mg and between aripiprazole IM depot 400 mg/ 300 mg and aripiprazole IM depot 50 mg/25 mg in BARS global score with mean decreases in the oral aripiprazole tablets 10-30 mg and aripiprazole IM depot 50 mg/25 mg groups compared with mean increases in the aripiprazole IM depot 400 mg/300 mg. However, the changes were not considered to be clinically relevant.

In this trial, injection site reactions observed were generally mild in severity, and decreased over time. Furthermore, subject- and investigator-rated assessments of injection site supported the overall favorable tolerability with minimal discomfort at the injection site. During the Double-blind, Active-controlled Phase, 24/265 (9.1%) aripiprazole IM depot 400 mg/300 mg, 7/266 (2.6%) oral aripiprazole tablets 10-30 mg, and 1/131 (0.8%) aripiprazole IM depot 50 mg/25 mg subjects experienced TEAEs related to the injection site.

During the Double-blind, Active-controlled Phase, investigators rated pain, redness, swelling, and induration at the current injection site as absent in 81.4% to 98.1% of subjects treated with aripiprazole IM depot 400 mg/300 mg after the first injection, and as absent in 88.3% to 98.9% after the last injection. Similar results were observed for oral aripiprazole tablets 10-30 mg subjects: 83.3% to 98.5% (first injection), and 90.2% to 99.6% (last injection). Investigators rated pain, redness, swelling, and induration in subjects treated with aripiprazole IM depot 50 mg/25 mg as absent in 90.7% to 99.2% (first injection), and 90.0% to 99.2% (last injection) of subjects.

During the Double-blind, Active-controlled Phase, the mean pain score reported by aripiprazole IM depot 400 mg/300 mg subjects using the VAS (0 = no pain to 100 =unbearably painful) was 5.6 after the first injection and improved to 3.7 after the last injection. Similar mean pain score results were observed for oral aripiprazole tablets 10-30 mg subjects using a VAS: 4.9 (first injection), and 3.5 (last injection). The mean pain score reported by aripiprazole IM depot 50 mg/25 mg subjects using the VAS was 3.3 after the first injection and improved to 2.4 after the last injection.

During the Double-blind, Active-controlled phase, 2/265 (0.8%) aripiprazole IM depot 400 mg/300 mg, 1/266 (0.4%) oral aripiprazole tablets 10-30 mg, and 3/131 (2.3%) aripiprazole IM depot 50 mg/25 mg subjects had a TEAE that was considered related to suicidal ideation/suicide. Treatment-emergent AEs considered related to suicidal ideation/suicide included suicidal ideation (1/265 [0.4%] aripiprazole IM depot 400 mg/300 mg; and 2/131 [1.5%] aripiprazole IM depot 50 mg/25 mg subjects [3 events in 2 subjects]), attempted suicide (1/265 [0.4%] aripiprazole IM depot 400 mg/300 mg and 1/266 [0.4%] oral aripiprazole tablets 10-30 mg subjects), and completed suicide (1/131 [0.8%] aripiprazole IM depot 50 mg/25 mg subjects). As assessed by C-CASA/ C-SSRS, suicidal events were experienced by 9/265 (3.4%) subjects in the aripiprazole IM depot 400 mg/300 mg group, 7/266 (2.6%) subjects in the oral aripiprazole tablets 10-30 mg group, and 4/131 (3.1%) subjects in the aripiprazole IM depot 50 mg/25 mg group.

Criteria for determining the clinical relevance of laboratory, vital sign, and ECG data were prespecified and were provided in the protocol.

During the Double-blind, Active-controlled Phases, treatment with aripiprazole IM depot 400 mg/300 mg (up to 10 monthly injections of 400 mg or 300 mg, including co-administration of oral aripiprazole for the first 14 days of the first IM depot injection) did not result in any clinically relevant mean changes in clinical laboratory test (hematology and serum chemistry) results in this population of subjects with schizophrenia.

There was a mean decrease in prolactin levels relative to the Double-blind, Active-controlled Phase baseline in the aripiprazole IM depot 400 mg/300 mg group (−0.33 ng/mL) compared with a mean increase in the oral aripiprazole tablets 10-30 mg (0.79 ng/mL; $p < 0.01$) and aripiprazole IM depot 50 mg/25 mg (1.11 ng/mL; $p < 0.01$) groups. The incidence of aripiprazole IM depot 400 mg/300 mg subjects with prolactin

levels above the upper limit of normal range (ULN) at any assessment during the Double-blind, Active-controlled Phase was 14/260 (5.4%) compared with 9/260 (3.5%) of oral aripiprazole tablets 10-30 mg, and 6/128 (4.7%) of aripiprazole IM depot 50 mg/25 mg subjects, with more males having an increase above the ULN than females in each treatment group.

Overall, no clinically relevant changes from baseline were observed in lipid or glucose parameters during the Double-blind, Active-controlled Phase. No clinically relevant trends were observed in the incidences of abnormalities for fasting triglyceride levels, calculated fasting low density lipoprotein cholesterol levels, fasting high-density lipoprotein cholesterol levels, or fasting glucose levels.

During the Double-blind, Active-controlled Phase, treatment with aripiprazole IM depot 400 mg/300 mg did not result in any clinically relevant mean changes in vital signs or ECG parameters. The incidence of potentially clinically relevant weight gain (defined as ≥ 7% change from baseline) at the last visit during the Double-blind, Active-controlled Phase was 9.5% (25/264) for aripiprazole IM depot 400 mg/300 mg, 11.7% (31/266) for oral aripiprazole tablets 10-30 mg and 4.6% (6/131) for aripiprazole IM depot 50 mg/25 mg, and the incidence of potentially clinically relevant weight loss (defined as ≥ 7% change from baseline) was 10.2% (27/264) for aripiprazole IM depot 400 mg/ 300 mg, 4.5% (12/266) for oral aripiprazole tablets 10-30 mg, and 9.9% (13/131) for aripiprazole IM depot 50 mg/25 mg. The mean changes in weight at the end of the Double-blind, Active-controlled Phase were −0.2 kg, −1.1 kg, and 0.7 kg for the aripiprazole IM depot 400 mg/300 mg, oral aripiprazole tablets 10-30 mg, and aripiprazole IM depot 50 mg/25 mg groups, respectively. Although there were some statistically significant treatment differences in mean change from baseline in weight between aripiprazole IM depot 400 mg/300 mg and oral aripiprazole tablets 10-30 mg and between aripiprazole IM depot 400 mg/300 mg and aripiprazole IM depot 50 mg/25 mg during the Double-blind, Active-controlled Phase, these changes were not considered clinically relevant.

**Conclusions:**

- Aripiprazole IM depot 400 mg/300 mg administered as monthly injections was effective for the maintenance treatment of schizophrenia in adult subjects as demonstrated by non-inferiority to oral aripiprazole tablets 10-30 mg in the estimated proportion of subjects with impending relapse by end of Week 26. In addition, aripiprazole IM depot 400 mg/300 mg was superior to aripiprazole IM depot 50 mg/25 mg (low-dose arm to test assay sensitivity for the non-inferiority design) in the primary efficacy endpoint, thus confirming validity of the trial design.
- Results of the efficacy analysis of time to impending relapse during the 38-week Double-blind, Active-controlled Phase also showed that time to impending relapse was similar in the aripiprazole IM depot 400 mg/300 mg and oral aripiprazole tablets 10-30 mg groups, and was significantly delayed compared with aripiprazole IM depot 50 mg/25 mg.

- The proportions of responders (ie, subjects who met the stability criteria) at endpoint in the Double-blind, Active-controlled Phase were similar in the aripiprazole IM depot 400 mg/300 mg and oral aripiprazole tablets 10-30 mg groups, and significantly higher in the aripiprazole IM depot 400 mg/300 mg group than in the aripiprazole IM depot 50 mg/25 mg group.
- The stability of symptoms established in the Oral Stabilization Phase (ie, with oral aripiprazole tablets 10-30 mg) was maintained throughout the Double-blind, Active-controlled Phase with aripiprazole IM depot 400 mg/300 mg at a level comparable to oral aripiprazole tablets 10-30 mg. Efficacy assessments, including the PSP total score, cognitive function assessments, and IAQ score were supportive of the non-inferior efficacy of treatment with aripiprazole IM depot 400 mg/300 mg compared with treatment with oral aripiprazole tablets 10-30 mg.
- The time to discontinuation for all causes was statistically significantly delayed in the aripiprazole IM depot 400 mg/300 mg group compared with both the oral aripiprazole tablets 10-30 mg group and the aripiprazole IM depot 50 mg/25 mg group.
- The observed aripiprazole concentrations in this trial were within those of 10 mg to 30 mg daily oral doses of aripiprazole after the first and subsequent monthly IM depot injections.
- Aripiprazole IM depot 400 mg/300 mg administered monthly was well tolerated by subjects with schizophrenia. The AE profile of aripiprazole IM depot 400 mg/300 mg was similar to that seen with oral aripiprazole tablets 10-30 mg daily and aripiprazole IM depot 50 mg/25 mg monthly. Most TEAEs were either mild or moderate in severity.
- Treatment-emergent AEs reported for ≥ 5% of subjects were comparable across treatment groups except for akathisia, decreased weight, injection site pain, and upper respiratory tract infection, which occurred at a higher incidence in the aripiprazole IM depot 400 mg/300 mg group than in the oral aripiprazole tablets 10-30 mg or aripiprazole IM depot 50 mg/25 mg groups.
- Two deaths occurred during the Double-blind, Active-controlled Phase of the trial. One subject in the oral aripiprazole tablets 10-30 mg group died due to cardiac arrest and one subject in the aripiprazole IM depot 50 mg/25 mg group died due to a completed suicide; neither event leading to death was considered related to trial treatment.
- Mean prolactin levels decreased in the aripiprazole IM depot 400 mg/300 mg group and increased in the oral aripiprazole tablets 10-30 mg and aripiprazole IM depot 50 mg/25 mg groups overall and by sex. The incidence of potentially clinically relevant prolactin values (> 1 x ULN) was similar across treatment groups.
- Overall, no clinically relevant changes from baseline were observed in lipid or glucose parameters during the Double-blind, Active-controlled Phase. No clinically relevant trends were observed in the incidences of abnormalities for fasting triglyceride levels, calculated fasting low-density lipoprotein cholesterol levels, fasting high-density lipoprotein cholesterol levels, or fasting glucose levels.
- Except for incidence of weight change ≥ 7%, there were no clinically relevant findings with regard to vital signs, ECG findings, EPS, suicidality, injection site, and laboratory values.

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