Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole intramuscular (IM) depot (OPC-14597)

Clinical Summary for Protocol 31-07-246

NCT No. 00705783

A 52-week, Multicenter, Randomized, Double-blind, Placebo-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 US"

(**A**ripiprazole Intramu**s**cular De**p**ot Program **i**n Schizoph**re**nia)

Indication:	Schizophrenia
Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. Rockville, MD, United States
Trial Initiation Date:	30 July 2008
Early Termination Date:	03 February 2011
Trial Summary Date:	23 December 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)

Protocol Title: A 52-week, Multicenter, Randomized, Double-blind, Placebo-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 US" (**A**ripiprazole Intramu**s**cular De**p**ot Program **i**n Schizoph**re**nia)

Trial Center(s) by Region: 108 sites in the United States, Mexico, Argentina, Bulgaria, Romania, Serbia, Slovakia, Russia, India, Taiwan, Malaysia, and the Philippines.

Clinical Phase/Trial Type: Phase 3 Interventional

Trial Interruption: The trial was monitored for both efficacy and safety under the supervision of a Data Monitoring Committee (DMC). The trial design included 2 prespecified interim analyses for efficacy in order to minimize continued exposure to placebo and the risk of relapse; one was to occur after accrual of 50% of the 125 targeted events (63 events) and the second was to occur after 75% accrual of the events (94 events). The DMC was responsible for ongoing safety monitoring and evaluation of efficacy from the prespecified interim analyses. The second interim analysis was to be performed only if the first was not positive.

Based on the results of the first interim analysis, the DMC recommended early termination of the trial, as per protocol, because the objectives of the trial had been achieved based upon the prespecified interim analysis, precluding any continued exposure of subjects to placebo. When the trial was prematurely terminated by the sponsor based on positive efficacy results as prespecified per the protocol, all subjects who remained in the trial at that time point, regardless of phase, could be offered entry into the 52-week open-label Trial 31- 08-248 based on the investigator's discretion.

Scientific Background and Explanation of Rationale: Prior to the conduct of the Phase 3 trials for the intramuscular (IM) depot formulation, two phase 1 trials were conducted to assess the pharmacokinetic (PK) profile of different doses of IM depot formulations after single (CN138-020) and multiple doses (31-05-244) in patients with schizophrenia.

Pharmacokinetic data from the phase 1 single dose IM depot trial and from previous oral steady state trials were modeled to simulate various dose and administration frequency combinations of oral and IM depot aripiprazole administration.

Based on the simulations, a switching regimen from oral to IM depot formulation was proposed in which oral dosing was continued for two weeks with concomitant administration of 200, 300, and 400 mg aripiprazole IM depot once every 4 weeks. Data

from these simulations indicated that the minimum plasma concentration (C_{min}) for 300 mg and 400 mg aripiprazole IM depot was expected to be very close to or above the steady state minimum plasma concentrations observed with daily dosing with aripiprazole 10 mg, and below the steady state maximum plasma concentrations (C_{max}) of daily dosing with aripiprazole 30 mg. Simulated aripiprazole concentrations for the 200 mg aripiprazole IM depot were initially below the C_{min} of 10 mg daily aripiprazole but increased with subsequent doses. Therefore, the 400 mg, 300 mg and the 200 mg doses were selected to be studied in a Phase 1b multiple dose trial in subjects with schizophrenia, who were randomized to a dose level of the IM depot injections once monthly for 5 months, while concomitantly receiving 10 mg oral aripiprazole for 2 weeks after the first IM depot injection. The results from the Phase 1b trial indicated that the 400 mg and 300 mg IM depot injections resulted in mean aripiprazole trough and average plasma concentrations that were comparable to the aripiprazole plasma concentrations between 10 mg to 30 mg oral aripiprazole administered daily to schizophrenic subjects which is the recommended range for oral dosing.

The PK profiles and available clinical data for aripiprazole IM depot 300 mg and 400 mg from Phase 1b multiple dose trial suggested that these doses would be efficacious and tolerable, however the 400 mg was selected for starting dose in the pivotal phase 3 trial (31-07-246) since it resulted in higher aripiprazole C_{min} in the Phase 1b multiple dose trial, with 300 mg being allowed for subjects not fully tolerating the 400-mg dose. Similar to the Phase1b multiple dose trial, all subjects received concurrent administration of oral aripiprazole for the first 2 weeks of aripiprazole IM depot injection, however the oral dosing regimen was changed to 10-20 mg daily to maintain plasma concentrations within the effective range for oral aripiprazole (i.e., 10 to 30 mg) after the first aripiprazole IM depot injection and subsequent dose where aripiprazole IM depot were given once every 4 weeks.

The current trial, Trial 31-07-246, was a pivotal phase 3 registrational trial designed to evaluate the efficacy, safety, and tolerability of the 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 subjects with a DSM-IV-TR diagnosis of schizophrenia who achieved stability of symptoms on aripiprazole IM depot (400 mg or 300 mg), and maintained the response for a minimum of 12 weeks, would experience an exacerbation of psychotic symptoms or impending relapse significantly later than subjects stabilized for 12 weeks on aripiprazole IM depot and subsequently treated with placebo. This trial design, which included both a 12-week stabilization phase and a placebo-controlled phase for assessment of relapse, was developed based on discussions with the US Food and Drug Administration (FDA) at the aripiprazole IM depot pre-investigational new drug (IND) meeting of 04 March 2003.

Publications: Kane JM, Sanchez R, Perry PP, Jin N, Johnson BR, Forbes RA, et al. Aripiprazole Intramuscular Depot as Maintenance Treatment in Patients with

Schizophrenia: A 52-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study. J Clin Psychiatry. 2012;73(5):617-24.

Objectives: The primary objective of the trial was to evaluate the efficacy of aripiprazole IM depot compared with placebo, as measured by time to exacerbation of psychotic symptoms/impending relapse, in schizophrenic subjects who had maintained stability on aripiprazole IM depot for at least 12 weeks.

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

Methodology: This was a randomized, double-blind, placebo-controlled trial consisting of a screening phase and 4 treatment phases: Conversion, Oral Stabilization, IM Depot Stabilization, and Double-blind Placebo-controlled. Note that in the protocol, these phases are referred to numerically, ie, Phase 1, 2, 3, and 4, respectively; however, in the clinical study report the full phase names are used for clarity and to differentiate between the clinical phases of drug development.

Screening Phase

Eligibility was determined during a Screening Phase 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 (this did not include generic forms of aripiprazole, where available) entered directly into the Oral Stabilization Phase. 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, provided that the prescribed aripiprazole dose did not exceed 30 mg daily at screening.

Conversion Phase

During weekly visits in the Conversion Phase, subjects had their dose cross-titrated from other antipsychotic(s) to oral aripiprazole monotherapy (trial medication) over a minimum of 4 weeks and a maximum of 6 weeks. A recommended cross-titration scheme was described; 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 other antipsychotic(s). The goal of the Conversion Phase was for all subjects to achieve a monotherapy target dose of 10 or 15 mg/day oral aripiprazole at Week 4 and no later than Week 6 of the Conversion Phase, although higher target doses were acceptable based on the investigator's judgment and the subject's clinical need.

Oral Stabilization Phase

Subsequently, subjects successfully converted to oral aripiprazole monotherapy, subjects with a lapse of antipsychotic treatment of > 3 consecutive days, and subjects who were already receiving oral aripiprazole as monotherapy for schizophrenia (excluding generic formulations) at screening entered the Oral Stabilization Phase. Subjects who had 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 last injection for an investigational IM depot formulation.

During the Oral Stabilization Phase, which was a minimum of 4 weeks and a maximum of 12 weeks in duration, subjects were assessed biweekly and stabilized on an oral dose of aripiprazole ranging from 10 mg to 30 mg daily. Stability was defined as fulfillment of all of the following criteria for 4 consecutive weeks (2 consecutive biweekly visits), and was required for the subject to continue into the IM Depot 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

IM Depot Stabilization Phase

Subjects fulfilling the oral stabilization requirement in the Oral Stabilization Phase were assigned to receive, in a single-blind fashion, aripiprazole IM depot 400 mg and began an IM Depot Stabilization Phase for a minimum of 12 weeks and a maximum of 36 weeks. All subjects received aripiprazole IM depot 400 mg as the initial dose in the IM Depot Stabilization Phase, irrespective of the final oral dose in the Oral Stabilization Phase. During the IM Depot Stabilization Phase, a single decrease to aripiprazole IM depot 300 mg was permitted for tolerability, as was a single return to the original aripiprazole IM depot 400 mg dose, if required. Oral dosing with aripiprazole (10 mg to 20 mg/day) continued for the first 2 weeks concomitant to the first IM depot injection in the IM Depot Stabilization Phase to achieve therapeutic plasma concentrations of aripiprazole. An unblinded Trial Drug Manager was responsible for dispensing open-label oral aripiprazole, as directed by the interactive voice response system and/or an interactive web response (IVRS/IWR). Subjects attended weekly visits for the first 4 weeks of the

IM Depot Stabilization Phase and biweekly visits thereafter. At each biweekly visit, subjects were assessed for stability using the same criteria employed for the Oral Stabilization Phase (see above). Subjects were dosed with aripiprazole IM depot monthly (every 28 days) during the IM Depot Stabilization Phase. The minimum allowable interval between IM depot injections was 26 days.

To proceed to the Double-blind, Placebo-controlled Phase, subjects had to meet stability criteria on single-blind aripiprazole IM depot 400 or 300 mg for 12 consecutive weeks (6 consecutive biweekly visits). A period of up to 36 weeks was permitted to maximize the possibility of achieving the required duration of symptom stability. Subjects were allowed one excursion from meeting stability criteria during the 12-week period, as long as the excursion did not occur on the final visit of the IM Depot Stabilization Phase. An excursion occurred when stability criteria were not met at a biweekly visit or if a scheduled visit was missed (ie, the visit occurred outside of the protocol-defined visit window). Therefore, stability criteria were assessed at a visit only if the visit fell within the protocol-defined window. Assessments for stability criteria continued until it was clear that the subject could not meet the criteria for 6 consecutive biweekly visits (including one excursion) on or before Week 36. An investigator may have chosen to conduct one or more interim unscheduled visits following an excursion in order to assess the clinical status of the subject and the feasibility of the subject's continuation in the trial; however, no rating scale assessments were to be conducted during these unscheduled visit(s). Any subject with consecutive excursions at Weeks 26 and 28 was withdrawn from the trial at Week 28 since he/she would not have been able to meet the stability requirement by Week 36. Subjects not meeting the stability criteria for 6 consecutive biweekly visits by Week 36 were withdrawn.

Double-blind, Placebo-controlled Phase

Subjects eligible for the Double-blind, Placebo-controlled Phase were randomly assigned via an IVRS/IWR system in a 2:1 ratio to double-blind treatment with aripiprazole IM depot or placebo, respectively. It was projected that the target number of impending relapse events (125) could be observed with 225 subjects randomized into this phase. The initial IM depot dose (aripiprazole or placebo) for the Double-blind, Placebo-controlled Phase was the stabilization dose of aripiprazole IM depot from the IM Depot Stabilization Phase (last dose in the IM Depot Stabilization Phase). All IM depot injections (aripiprazole 400 mg, aripiprazole 300 mg, and placebo) were administered monthly (ie, every 28 days) by an unblinded Trial Drug Manager who was utilized to maintain the blind for individuals involved with trial assessments since this IM depot formulation could not be blinded given that a matching placebo was not available (the matching placebo was clear, not milky white). During the Double-blind, Placebo-controlled Phase, subjects were evaluated biweekly in the clinic and at any unscheduled visits for signs of exacerbation of psychotic symptoms/impending relapse (criteria outlined in Criteria for Evaluation section of this synopsis; hereafter referred to as impending relapse) and were contacted by phone between visits to determine whether or not the scheduled visit should be moved to an earlier time, based upon the subject's

clinical need. The appearance of any or all of the signs of exacerbation of psychotic symptoms/impending relapse criteria resulted in withdrawal from the trial. Any subject withdrawn for lack of efficacy in the Double-blind, Placebo-controlled Phase had to meet at least one of the criteria for exacerbation of psychotic symptoms/impending relapse.

Subjects who discontinued the trial for any reason during the Double-blind, Placebo-controlled Phase or completed the Double-blind, Placebo-controlled Phase may have been offered entry into the 52-week open-label Trial 31-08-248. Subjects not electing to enter the open-label trial and those who were discontinued or withdrawn during other trial phases were to be prescribed appropriate antipsychotic treatment by the investigator or the subject's primary care physician and were followed up for safety. When the trial was prematurely terminated by the sponsor based on positive efficacy results as prespecified per the protocol, all subjects who remained in the trial at that time point, regardless of phase, could be offered entry into the 52-week open-label Trial 31-08-248 based on the investigator's discretion.

Number of Subjects: Approximately 1500 subjects at an estimated 120 sites were to be enrolled into the trial. The projected total number of subjects to be randomly assigned to treatment in the trial was 225. Using a 2:1 randomization ratio, the number of subjects to be randomly assigned to treatment in the aripiprazole IM depot group was 150 and for the placebo group was 75. Due to the lower than expected impending relapse rate, enrollment and randomization continued beyond the planned estimates (225 planned; 403 actual) to achieve the target number of impending relapse events.

A total of 1025 subjects were screened and 403 subjects were randomly assigned to treatment in the Double-blind, Placebo-controlled Phase, with 269 subjects randomly treatment with aripiprazole IM depot and 134 subjects randomly assigned to treatment with placebo. All randomized subjects were included in the intent-to-treat population and were analyzed for efficacy. All randomized subjects were treated and analyzed for safety. The number of subjects enrolled into each trial phase was as follows:

- Conversion Phase - 633
- Oral Stabilization Phase - 710
- IM Depot Stabilization Phase - 576
- Double-blind, Placebo-controlled Phase – 403

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. Prior to entry into the IM Depot Stabilization Phase, subjects were required to meet stability criteria for at least 4 consecutive weeks on oral aripiprazole. Subsequently, subjects had to meet stability criteria for at least 12 consecutive weeks prior to being randomized in the Double-blind, Placebo-controlled Phase of the trial. Stability criteria are as outlined in the Oral Stabilization Phase above. Subjects with diagnosis other than schizophrenia, including schizoaffective disorder, major depressive disorder, bipolar disorder, delirium,

dementia, amnestic or other cognitive disorders, those diagnosed with borderline, paranoid, histrionic, schizotypal, schizoid, or antisocial personality disorders, those with a history of substance or alcohol dependence were excluded from the trial. Those with a history of seizure disorders, or other medical conditions that would expose them to undue risk of a significant AE or interfere with trial assessments, those who had the following laboratory, vital sign and ECG results at Screening were also excluded from the trial:

1. Platelets ≤ 75,000/mm^3
2. Hemoglobin ≤ 9 g/dL
3. Neutrophils, absolute ≤ 1000/mm^3
4. Aspartate aminotransferase > 3x upper limit of normal
5. Alanine aminotransferase > 3x upper limit of normal
6. Creatinine ≥ 2 mg/dL
7. Diastolic blood pressure > 105 mmHg
8. QTc > 475 msec using either the QTcB (Bazett) or QTcF (Fridericia) corrections on 2 of 3 time points of triplicate ECGs performed

All subjects were required to agree to use an approved contraceptive for the duration of the trial and for 180 days following the last trial dose. Those who refused to agree, and female subjects who were pregnant or nursing were excluded.

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 monthly (every 28 days). An unblinded Trial Drug Manager licensed to reconstitute the solution and to give intramuscular injections prepared and administered the single-blind and double-blind IM depot trial medications due to differences in appearance of reconstituted aripiprazole IM depot (milky white suspension) vs placebo (IM clear solution). Aripiprazole oral tablets (5 mg, 10 mg, and 15 mg) were used for conversion of subjects from other antipsychotic medications during the Conversion Phase.

Open-label oral aripiprazole was given at doses of 10 mg to 30 mg daily during the Oral Stabilization Phase using tablets of 10 mg and 15 mg. In addition, oral aripiprazole was given at doses of 10 mg to 20 mg daily for the first 2 weeks of the IM Depot Stabilization Phase (concomitant to the first IM depot injection) using tablets of 10 mg and 15 mg.

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration: Placebo was dosed identically to aripiprazole IM depot within each treatment group.

Duration of Treatment: The trial was scheduled to continue for 52 weeks.

Trial Assessments: Personal and social functioning was measured using the Personal and Social Performance (PSP) Scale. Cognition was evaluated objectively using the Trails A, Tower of London, and University of Maryland: Letter-Number Span assessments. University of Maryland hereafter referred to as Letter-Number Span assessment. The acceptability of treatment was measured from the subject's perspective

using the Drug Attitude Inventory (DAI), Medication Adherence Questionnaire (MAQ), and Patient Satisfaction with Medication Questionnaire (PSMQ)-Modified. The investigators' overall satisfaction with treatment, taking into consideration both efficacy and tolerability, was scored based on responses to the Investigator's Assessment Questionnaire (IAQ). The proportion of subjects hospitalized for exacerbation of psychotic symptoms (including emergency department visits) was tabulated as a measure of healthcare resource utilization. The frequency of outpatient visits to various healthcare providers (eg, primary care physicians, psychiatrists, other mental health practitioners) was also examined.

Criteria for Evaluation:

Primary Efficacy Endpoint: The primary efficacy endpoint of the trial was the time from randomization to exacerbation of psychotic symptoms/impending relapse in the Double-blind, Placebo-controlled Phase, defined as meeting any or all of the following 4 criteria:

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 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 significant self-injury, injury to another person, or property damage

Secondary Efficacy Endpoints: The following key secondary efficacy endpoint was compared in the Double-blind, Placebo-controlled Phase between the aripiprazole treatment group and the placebo group:

- Percentage of subjects meeting exacerbation of psychotic symptoms/impending relapse criteria

Other secondary endpoints evaluated in the Double-blind, Placebo-controlled Phase included the following:

- Proportion of responders (ie, response defined as meeting stability criteria, as outlined in the Oral and IM Depot Stabilization Phases) at endpoint
- Proportion of subjects achieving remission, where remission is 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), lack of spontaneity (N6)

- 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 subscales
- Mean CGI-I score at endpoint
- Time to discontinuation due to all causes

Other Outcome Variables: In addition to the personal and social functioning assessments described earlier, the proportion of subjects hospitalized for exacerbation of psychotic symptoms (including emergency department visits) was tabulated as a measure of healthcare resource utilization. The frequency of outpatient visits to various healthcare providers (eg, primary care physicians, psychiatrists, other mental health practitioners) was also examined.

Pharmacokinetics/pharmacogenomics: A sample to assess the CYP2D6 isozyme metabolism status of the subject was taken at the end of the Conversion Phase for subjects undergoing cross-titration from other antipsychotics in the Conversion Phase or at the Oral Stabilization Phase baseline visit for subjects who entered the Oral Stabilization Phase directly after screening.

Blood sampling for population PK analysis was performed at Weeks 1, 2, 4, 8, 12, and 36/End of Phase during the IM Depot Stabilization Phase (single-blind IM depot stabilization) and at Weeks 2, 4, 6, and 8 during the Double-blind, Placebo-controlled Phase (double-blind IM depot maintenance). In addition, a sample was drawn in the event of any serious AEs (SAEs) as soon as possible after the occurrence of the event. Four milliliter (4 mL) samples were drawn.

Safety Endpoints: Adverse events (AEs) were examined by frequency, severity, seriousness, and discontinuation (all causes and due to AEs).

The CGI-SS and the Columbia Suicide Severity Rating Scale (C-SSRS) were used to assess the risk of suicidal events and to classify reported suicide events. In the original protocol, the C-SSRS was administered at baseline and post-baseline to further classify suicidal events if the CGI-SS score at any post-baseline visit was 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2. The protocol was amended (Protocol Amendment 2 dated 18 November 2009) to include completion of the C-SSRS at each visit.

The Columbia Classification Algorithm of Suicide Assessment (C-CASA) was used to classify potential suicidality events recorded on the AE form. Kelly Posner, PhD, of Columbia University and the Research Foundation for Mental Hygiene, conducted a separate analysis of AEs for potential suicidality according to C-CASA criteria on all subjects without a C-SSRS completed at each visit.

Injection site pain was assessed by using a visual analog scale (VAS) as reported by the subject before and 1 hour (± 15 minutes) after each injection during the IM Depot Stabilization Phase and the Double-blind, Placebo-controlled Phase. The investigator rating of pain, redness, swelling, and induration at the injection site of IM depot was also assessed at these time points.

The incidence of potentially clinically relevant changes was calculated for vital sign abnormalities (including body weight) and laboratory test abnormalities. Mean change from baseline and incidence of potentially clinically relevant changes were calculated for electrocardiogram (ECG) parameters, insulin, fasting insulin, and prolactin. A central ECG service was utilized to review all ECGs in order to standardize interpretations for the safety analysis. Extrapyramidal symptoms (EPS) were evaluated by calculating mean change from baseline on the Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and the Barnes Akathisia Rating Scale (BARS). By-subject listings of physical examination findings were reviewed as a further assessment of safety.

Pharmacokinetic/pharmacogenomic Methods: Blood samples were collected from 542 subjects during the IM Depot Stabilization Phase and during the Double-blind, Placebo-controlled Phase of the trial, and were analyzed for aripiprazole and dehydro-aripiprazole concentrations. Samples collected from subjects for cytochrome P450 (CYP) 2D6 isozyme metabolism status were analyzed and results were reported.

Statistical Methods:

Efficacy: The primary efficacy analysis was based on the ITT population consisting of all randomized subjects. The primary endpoint compared the efficacy of aripiprazole IM depot (400 mg or 300 mg) with that of placebo with regard to time to impending relapse. This was analyzed using a log-rank test comparing the 2 treatment groups (aripiprazole IM depot 400 mg or 300 mg vs placebo) at 90% power and an overall nominal significance level of 0.05 (2-sided) following a group sequential procedure giving assumptions that the 6-month impending relapse rate was 55% for placebo and 35% for aripiprazole IM depot (based on an earlier placebo-controlled, long-term oral aripiprazole maintenance trial of a different design). Interim analyses were prespecified to be performed at approximately 50% (63 events) and 75% (94 events) of event accrual time points using Haybittle-Peto group sequential boundaries and an alpha level of 0.001 at each of the 2 interim analyses. Additionally, a 95% confidence interval (CI) for the hazard ratio (aripiprazole IM depot vs placebo) was provided using the Cox Proportional Hazard model with terms for treatment in the model. The trial was to be discontinued if efficacy was established (at a significance level of 0.001) at either of the prespecified interim analyses. Otherwise, the trial was to continue. The alpha level for the final analysis was 0.0498. The resulting total number of events satisfying these design constraints was 125.

To assess the sensitivity of the primary efficacy analysis results due to potential informative censoring prior to the scheduled duration of follow-up of 12 months,

4 approaches of sensitivity analyses were adopted. These were: (1) use of subimpending relapse criteria, (2) treating 20% of randomly selected discontinued subjects only from the IM depot group as events, (3) treating all discontinuations as events, and (4) multiple imputation of censored observations. Subjects who were discontinued in the Double-blind, Placebo-controlled Phase due to the trial being terminated early were not imputed in the final analysis.

The statistical criteria for trial discontinuation based on the interim analysis, including sensitivity analyses, are shown in the following table.

Interim Analysis Statistical Criteria for Trial Discontinuation

Number	Criteria	p-value
1	P-value of primary endpoint: time to impending relapse	< 0.001
2	P-value of time to event analysis by sub-impending relapse criteria	< 0.001
3	P-value of sensitivity analysis in which 20% of IM depot discontinuations (other than relapse) will be randomly selected and will be treated as events one day after the date of discontinuation and all discontinuations in placebo will be treated as censored on the date of discontinuation. Multiple Imputation of the 20% censored discontinuations will be used	< 0.05
4	P-value of sensitivity analysis in which all discontinuations (regardless of treatment group) will be treated as events	< 0.01
5	All p-values (for theta values = 0.95, 0.975, 1, 1.025, 1.05) using multiple imputation	< 0.01

The key secondary efficacy endpoint in this trial was the percentage of subjects meeting impending relapse criteria at the endpoint of the Double blind, Placebo-controlled Phase. To preserve the overall type I error rate at the 0.05 level, the following testing procedure was used. If the primary hypothesis of comparing time to impending relapse between aripiprazole IM depot and placebo was rejected at an overall nominal alpha level of 0.05, then the key secondary endpoint was tested at the 0.05 level.

Change from baseline in the secondary efficacy variables from the Double-blind, Placebo controlled Phase (ie, PANSS total and subscale and CGI-S scores) were analyzed using an analysis of covariance model with terms for treatment and baseline value as a covariate. CGI-I scores were analyzed for the Double-blind, Placebo-controlled Phase using the Cochran Mantel-Haenszel method. Additionally, for the Double-blind, Placebo-controlled Phase, PANSS total score and CGI-S score were analyzed by the Mixed Model Repeated Measures. Kaplan-Meier curves were plotted for time to discontinuation due to all causes other than termination of trial due to prespecified interim analysis results and analyzed using the log-rank test. The percentage of responders and percentage of subjects achieving remission were analyzed using the Chi-square test. CGI-I scores at endpoint, as well as changes from baseline to endpoint in PANSS total and subscale scores and in CGI-S, were also summarized using descriptive statistics.

Change from baseline in other outcome variables (if applicable) from the Double-blind, Placebo-controlled Phase were analyzed using an analysis of covariance model with

terms for treatment and baseline value as a covariate. In addition, descriptive statistics were provided for other outcome assessments.

Pharmacokinetics/ pharmacogenomics: All the plasma concentrations presented in this report and the supportive tables including descriptive statistics are presented in 3 significant figures.

Safety: Safety endpoints were summarized by descriptive and/or inferential statistics for the Oral Stabilization, IM Depot Stabilization, and Double-blind, Placebo-controlled Phases.

Summary of Results:

Baseline Data, Disposition, and Demographics: The first prespecified interim analysis (after 50% of events had occurred) was conducted by the DMC using a data cut-off date of 08 June 2010. At the time of the interim analysis, 971 subjects had been screened for the trial with 172 screen failures and 775 subjects enrolled into the trial. There were 24 subjects in screening, 29 subjects in the Conversion Phase, 26 subjects in the Oral Stabilization Phase, 121 subjects in the IM Depot Stabilization Phase, and 207 subjects in the Double-blind, Placebo-controlled Phase. Approximately half of the subjects (374/775, 48.3%) had discontinued from the trial and 18/775 subjects (2.3%) had completed the trial (defined as completing the Week 52 visit in the Double-blind, Placebo-controlled Phase). The interim data analyzed included 344 subjects in the Double-blind, Placebo-controlled Phase (230 in the aripiprazole IM depot group and 114 in the placebo group).

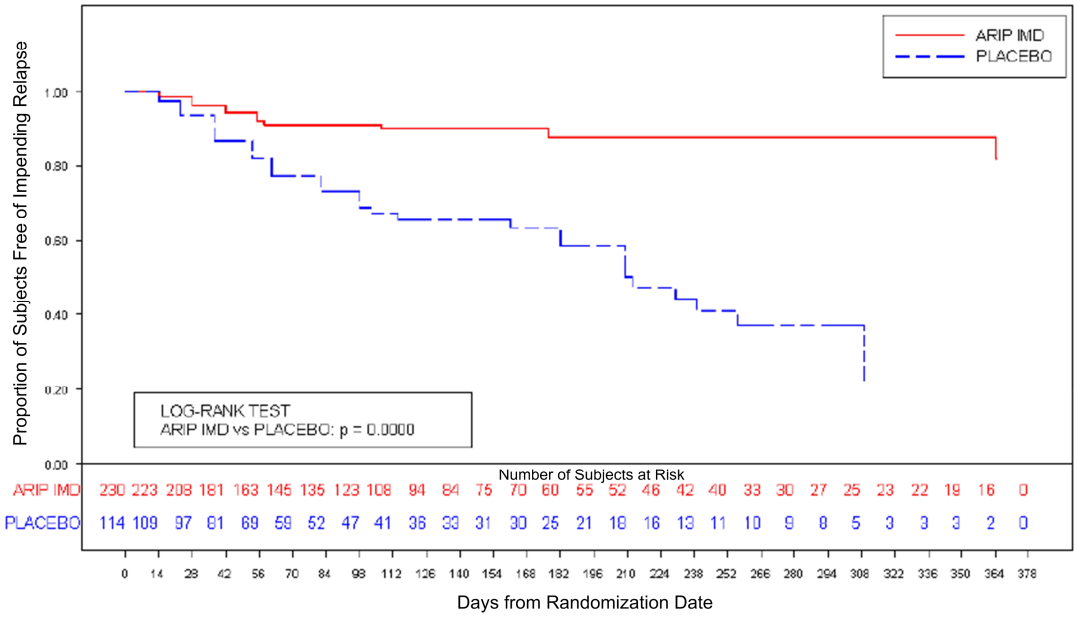
The DMC reported that the stopping rules had been met and recommended termination of the trial, as per protocol. This resulted in the sponsor's termination of the trial on 26 July 2010 because the prespecified efficacy endpoint criteria were met. Investigative site personnel were informed of the decision to terminate the trial and instructed to have subjects return to the clinic for discontinuation and the option to enroll in Trial 31-08-248. The last randomized subject was discontinued from the trial on 24 August 2010 and the final subject from a nonrandomized trial phase on 30 August 2010.

During the time period from 08 June 2010 to 24 August 2010, an additional 16 impending relapse events occurred and therefore the number of impending relapse events in the final analysis was 80. At the time of final analysis, 1025 subjects had been screened and 843 subjects had entered the trial. Of these, 633 subjects entered the Conversion Phase, 710 subjects entered the Oral Stabilization Phase (subjects who did not require conversion to oral aripiprazole could enter directly into Oral Stabilization Phase), 576 subjects entered the IM Depot Stabilization Phase, and 403 subjects were randomized to the Double-blind, Placebo-controlled Phase. A total of 269 subjects were randomized to receive aripiprazole IM depot and 134 to receive placebo.

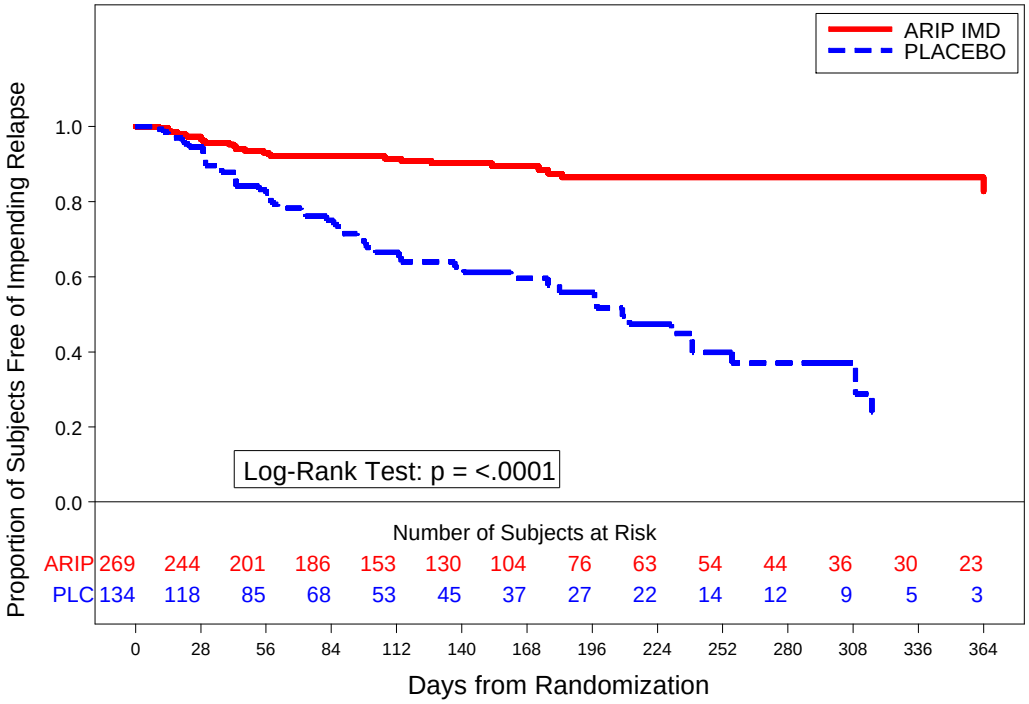
The majority of randomized subjects (237/403, 58.8%) were discontinued from the trial due to the sponsor-initiated termination based on the positive outcome of the interim analysis as recommended by the DMC. Demographic and baseline characteristics were well balanced between the randomized groups (interim and final analyses). For the final analysis, most subjects were male (241/403, 59.8%) and Caucasian (244/403, 60.5%). The mean age of randomized subjects was 40.6 years (range 18 to 61 years). The mean age at first diagnosis was 26.0 years. The mean PANSS total score and CGI-S score at the Oral Stabilization Phase baseline (66.4 and 3.5, respectively) and IM Depot Stabilization Phase baseline (59.4 and 3.2, respectively) suggest that the population was symptomatically stable. Furthermore, in the Double-blind, Placebo-controlled Phase, at baseline, a mean PANSS total score of 54.5 and a mean CGI-S score of 2.9 demonstrate a symptomatically stable population resulting from the IM Depot Stabilization Phase.

Efficacy Results: The prespecified interim analysis of efficacy data included 344 randomized subjects and 64 events of impending relapse (08 June 2010). Results of the interim analysis showed that time to impending relapse was significantly shorter for subjects randomized to placebo compared with subjects randomized to aripiprazole IM depot in the Double-blind, Placebo-controlled Phase ($p < 0.0001$; log-rank test). The hazard ratio from the Cox proportional hazard model for the placebo to aripiprazole IM depot comparison was 4.72 (95% CI = 2.81, 7.94), thus subjects in the placebo group had a 4.72-fold greater risk of experiencing impending relapse than subjects in the aripiprazole IM depot group. The hazard ratio from the Cox proportional hazard model for the aripiprazole IM depot to placebo comparison was 0.212 (95% CI = 0.126, 0.357).

The final efficacy analysis included 403 randomized subjects and 80 impending relapse events. The results from the final analysis were consistent with the interim analysis results in showing that the time to impending relapse was significantly shorter for subjects in the placebo group compared with subjects in the aripiprazole IM depot group (hazard ratio = 5.03, $p < 0.0001$; log-rank test). The hazard ratio from the Cox proportional hazard model for the placebo to aripiprazole IM depot comparison was 5.029 (95% CI = 3.154, 8.018), thus subjects in the placebo group had a 5.03-fold greater risk of experiencing impending relapse than subjects in the aripiprazole IM depot group. The hazard ratio from the Cox proportional hazard model for the aripiprazole IM depot to placebo comparison was 0.199 (95% CI = 0.125, 0.317). Kaplan-Meier plots depicting these results for the interim and final analyses are shown in the following figures. Note that in the Kaplan-Meier plots, the term “risk” refers to “risk of impending relapse.”



Kaplan-Meier Product Limit Plot of Time to Impending Relapse (Double-blind, Placebo-controlled Phase Efficacy Sample) - Interim Analysis (64 Events)
ARIP IMD = aripiprazole IM depot.
Note: P-value in legend represents a p value < 0.0001.



Kaplan-Meier Product Limit Plot of Time to Impending Relapse (Double-blind, Placebo-controlled Phase Efficacy Sample) - Final Analysis (80 Events)
ARIP and ARIP IMD = aripiprazole IM depot; PLC = placebo.

The key secondary efficacy endpoint, percentage of subjects meeting the impending relapse criteria, was significantly lower in the aripiprazole IM depot group (interim analysis, 9.6%; final analysis, 10.0%; $p < 0.0001$) than in the placebo group (interim analysis: 36.8%; final analysis: 39.6%). For both treatment groups (interim and final analyses), the most common criterion for impending relapse that was met was the CGI-I + PANSS scores criterion.

A summary of the results of secondary efficacy endpoints during the Double-blind, Placebo-controlled Phase are presented in the following table:

Summary Results of PANSS and CGI scales (Double-blind, Placebo-controlled Phase Efficacy Sample; LOCF)								
Parameter	**Visit**	**Mean (SD)**		**Change From Baseline LS Mean (SE)[a]**		**Difference[a]**	**95% CI[a]**	**P-value[a]**
		Arip IM Depot (N=269)	**Placebo (N=134)**	**Arip IM Depot (N=269)**	**Placebo (N=134)**			
PANSS Total Score	Baseline	54.54 (12.01) n=269	54.35 (11.59) n=134	-	-	-	-	-
	Week 52	55.84 (14.58) n=266	65.90 (18.16) n=134	1.43 (0.76) n=266	11.55 (1.07) n=134	−10.11	−12.68, −7.54	<0.0001[a]
PANSS Positive Subscale Score	Baseline	11.97 (3.42) n=269	11.79 (3.22) n=134	-	-	-	-	-
	Week 52	12.37 (4.62) n=266	16.06 (6.15) n=134	0.44 (0.27) n=266	4.25 (0.37) n=134	−3.82	−4.72, −2.91	<0.0001[a]
PANSS Negative Subscale Score	Baseline	15.88 (4.16) n=269	15.72 (4.43) n=134	-	-	-	-	-
	Week 52	16.00 (4.60) n=266	17.28 (5.00) n=134	0.19 (0.20) n=266	1.55 (0.28) n=134	−1.36	−2.04, −0.67	0.0001[a]
CGI-S	Baseline	2.89 (0.83) n=269	2.87 (0.82) n=134	-	-	-	-	-
	Week 52	3.02 (0.97) n=266	3.53 (1.20) n=134	0.14 (0.05) n=266	0.66 (0.07) n=134	−0.52	−0.70, −0.35	<0.0001[a]
CGI-I	Week 52	3.70 (1.05) n=266	4.53 (1.23) n=133	N/A	N/A	N/A	N/A	<0.0001[b]

Arip = aripiprazole; CGI-I = Clinical Global Impression of Improvement; CGI-S = Clinical Global Impression of Severity; CI = Confidence Interval; IM = intramuscular; LOCF = last observation carried forward; LS = least squares (mean); N/A = Not applicable; PANSS = Positive and Negative Symptom Scale; SD = standard deviation; 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 (aripiprazole IM depot vs placebo) 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]P-value (aripiprazole IM depot vs placebo) is derived from Cochran-Mantel-Haenszel method based on raw mean score statistics.

The percentage of responders (ie, subjects who continued to meet the stability criteria) at the last visit in the Double-blind, Placebo-controlled Phase was 87.6% (234/267 subjects) in the aripiprazole IM depot group compared with 56.0% (75/134 subjects) in the placebo group, a statistically significant difference ($p < 0.0001$).

The percentage of subjects achieving remission (defined as the proportion of subjects meeting criteria and maintaining them for at least 6 months as outlined in the secondary endpoints of the Double-blind, Placebo-controlled Phase) was 52.9% in the aripiprazole IM depot group compared with 38.7% in the placebo group, a numerically greater but not statistically significant difference ($p = 0.1756$).

The trial was terminated by the sponsor once efficacy was established by the DMC based on the positive results of the first prespecified interim analysis after accrual of 50% of impending relapse events, ie, 64 events. Subjects who were discontinued from the trial at the time it was terminated by the sponsor in response to the positive results of the interim analysis are not considered as discontinued in the analyses of time to discontinuation for all causes. Of the 269 subjects randomly assigned to treatment with aripiprazole IM depot in the Double-blind, Placebo-controlled Phase, 67 discontinued the trial for all causes (except for termination of the trial based on positive results of interim analysis), resulting in a discontinuation rate of 24.9%. In the placebo group, 134 subjects were randomly assigned treatment in the Double-blind, Placebo-controlled Phase; 73 discontinued treatment, for a discontinuation rate of 54.5%. The median time to discontinuation was 162 days for the placebo group and not estimatable for the aripiprazole IM depot group, a statistically significant difference between the 2 groups ($p < 0.0001$).

Other Outcome Results:

PSP Total Score: For subjects in the aripiprazole IM depot group, the PSP total scores minimally changed from baseline to last visit of the Double-blind, Placebo-controlled Phase (−1.74 points). However, for subjects in the placebo group, the scores decreased (indicating a decrease in social functioning) during the Double-blind, Placebo-controlled Phase (−6.20 points). The decrease from baseline to last visit in the PSP score was significantly greater in the placebo group than in the aripiprazole IM depot group ($p = 0.0002$).

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).

For the Trails A assessment, lower scores indicate higher levels of cognitive function. In the Double-blind, Placebo-controlled Phase, there was a decrease (−1.55 seconds, SD = 16.46) from baseline to last visit in the Trails A score for the aripiprazole IM depot group, whereas there was an increase (0.87 seconds, SD = 16.88) for the placebo group, representing a decline in cognitive function. The change from baseline to last visit in the Trails A score was not significantly different between the placebo and aripiprazole IM depot groups ($p = 0.1435$).

For the parameters described here, lower Tower of London scores represent greater levels of cognitive function. Decreases were observed in the Tower of London total move and

execution time scores from baseline to the last visit during the Double-blind, Placebo-controlled Phase in the aripiprazole IM depot group; in contrast, increases in these items were observed in the placebo group. None of the changes from baseline to last visit in the Tower of London total score categories were significantly different between the placebo and aripiprazole IM depot groups (total move score $p = 0.3388$, total execution time score $p = 0.5410$).

The Letter-Number Span total score ranged from 0 to 24 with higher scores representing a higher degree of cognitive function. In the Double-blind, Placebo-controlled Phase, there were minimal changes from baseline to last visit in Letter-Number Span total score for the aripiprazole IM depot group. However, the Letter-Number Span total score declined from baseline to last visit (indicating worsening) during the Double-blind, Placebo-controlled Phase for the placebo group. The decrease from baseline to last visit in the Letter-Number Span total score was significantly greater (indicating worsening) in the placebo group than in the aripiprazole IM depot group ($p < 0.0001$). Letter-Number Span assessments were reanalyzed excluding data from 6 Russian sites (site 122 and sites 124 through 128), and 7 Bulgarian sites (site 100 and sites 102 through 107) because these data had been collected using unvalidated translations of the instrument. Results of the Letter-Number Span analysis were similar regardless of whether data from the affected sites in Russia and Bulgaria were included or excluded.

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 from baseline to the last visit in the DAI total score for both the aripiprazole IM depot and placebo groups during the Double-blind, Placebo-controlled Phase. The change from baseline to last visit in the DAI score was not significantly different between the placebo and aripiprazole IM depot groups ($p = 0.4019$).

Medication Adherence Questionnaire Total Score: The MAQ total score ranges from 0 to 4 with higher scores indicating greater nonadherence to medication regimens. The mean MAQ total score was < 1 (indicating adherence to medication) and stable during the entire trial. The change from baseline to last visit in the MAQ total score during the Double-blind, Placebo-controlled Phase was minimal and was not significantly different between the placebo and aripiprazole IM depot groups ($p = 0.3341$).

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 patients 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 group, the IAQ score increased from baseline to last visit during the Double-blind, Placebo-controlled Phase (1.32 points). However, for subjects in the placebo group, the increase was greater (3.78 points), indicating worsening. The increase from baseline to

last visit in the IAQ score was significantly greater in the placebo group than in the aripiprazole IM depot group ($p < 0.0001$).

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 treatment. The percentage of subjects with each category of treatment satisfaction was similar in the aripiprazole IM depot and placebo groups at baseline, with 82.1% and 81.3% of subjects, respectively, reporting they were extremely or very satisfied with their treatment. By the last visit in the Double-blind, Placebo-controlled Phase, the percentage of subjects reporting each level of treatment unsatisfaction (somewhat, very, and extremely unsatisfied) was higher in the placebo group than in the aripiprazole IM depot group. The proportion of subjects reporting they were extremely or very satisfied with their treatment was similar at baseline (82.1%) and the last visit (76.6%) for subjects in the aripiprazole IM depot group but was decreased for subjects in the placebo group (81.3% vs 66.1% for baseline and last visit, respectively).

Health Care Utilization Evaluation: Most subjects (79.4%) did not have outpatient visits (other than scheduled outpatient visits) during the Double-blind, Placebo-controlled Phase. However, the proportion of subjects with outpatient visits was higher for the placebo group (29.9%) than for the aripiprazole IM depot group (16.0%). Most subjects (93.5%) were not hospitalized during the Double-blind, Placebo-controlled Phase. However, the proportion of subjects with hospitalization was higher for the placebo group (9.0%) than for the aripiprazole IM depot group (5.2%). Few subjects were employed at baseline of the Double-blind, Placebo-controlled Phase in either the aripiprazole IM depot or placebo group (21.6% and 19.4%, respectively). These proportions were similar at the last visit (18.9% and 20.5%). The mean total number of paid and unpaid hours in the week before the baseline visit and in the week before the final visit in the Double-blind, Placebo-controlled Phase were similar in the aripiprazole IM depot and placebo groups.

Pharmacokinetic/pharmacodynamic Results: The recommended oral dose of aripiprazole for the maintenance of schizophrenia in patients 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 within the range typically achieved following a 10 mg to 30 mg daily oral dose of aripiprazole, were achieved after the first and subsequent IM depot administrations monthly (every 28 days). Specifically, mean aripiprazole trough plasma concentrations after the first IM depot administration in the IM Depot Stabilization 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. Mean aripiprazole plasma concentrations in placebo subjects in the Double-blind, Placebo-controlled Phase were maintained above mean aripiprazole trough concentrations of 10 mg oral daily aripiprazole greater than 4 weeks after the last IM depot administration in the IM Depot Stabilization Phase. Based on the mean plasma concentrations observed in this trial, no

meaningful accumulation in aripiprazole and dehydro-aripiprazole plasma concentrations were observed after the fourth IM depot administration. There was no correlation noted between aripiprazole and dehydro-aripiprazole plasma levels and the observation of serious AEs (SAEs). Examination of plasma concentrations levels from those subjects who required dose increases for efficacy or dose decreases for safety 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 (every 28 days) for up to 36 weeks during the IM Depot Stabilization Phase and up to 52 weeks during the Double-blind, Placebo-controlled Phase. All subjects began treatment at a dose of 400 mg during the IM Depot Stabilization Phase with an option to decrease once to 300 mg if they did not fully tolerate the 400 mg dose. Most subjects (518/576, 89.9%) had no variation in their aripiprazole IM depot dose during the IM Depot Stabilization Phase (ie, they started as planned on 400 mg and remained on 400 mg). During the Double-blind, Placebo-controlled Phase, 235/244 (96.3%) subjects starting aripiprazole IM depot 400 mg and 16/25 (64.0%) subjects starting aripiprazole IM depot 300 mg remained on their starting doses throughout the phase.

During the IM Depot Stabilization and Double-blind, Placebo-controlled Phases, the majority of treatment-emergent AEs (TEAEs) were reported as mild or moderate in severity. Treatment-emergent AEs that occurred at an incidence ≥ 2% in aripiprazole IM depot subjects during the IM Depot Stabilization Phase were insomnia (46/576, 8.0%), increased weight (40/576, 6.9%), anxiety (38/576, 6.6%), akathisia (36/576, 6.3%), headache (34/576, 5.9%), injection site pain (34/576, 5.9%), tremor (21/576, 3.6%), somnolence (15/576, 2.6%), diarrhea (14/576, 2.4%), cough (13/576, 2.3%), nausea (13/576, 2.3%), and vomiting (12/576, 2.1%).

Treatment-emergent AEs that occurred at an incidence ≥ 2% in aripiprazole IM depot subjects and occurred more frequently than in placebo subjects during the Double-blind, Placebo-controlled Phase included insomnia (27/269 [10.0%] aripiprazole IM depot vs 12/134 [9.0%] placebo subjects, respectively), headache (16/269 [5.9%] vs 7/134 [5.2%]), tremor (16/269 [5.9%] vs 2/134 [1.5%]), decreased weight (9/269 [3.3%] vs 4/134 [3.0%]), vomiting (8/269 [3.0%] vs 3/134 [2.2%]), sedation (7/269 [2.6%] vs 1/134 [0.7%]), toothache (7/269 [2.6%] vs 3/134 [2.2%]), upper respiratory tract infection (7/269 [2.6%] vs 3/134 [2.2%]), arthralgia (6/269 [2.2%] vs 1/134 [0.7%]), and fatigue (6/269 [2.2%] vs 1/134 [0.7%]).

The only TEAE reported by ≥ 5% of aripiprazole IM depot subjects and at least twice the incidence of placebo was tremor (5.9% of aripiprazole IM depot subjects vs 1.5% of placebo subjects). Adverse events of tremor were generally mild in severity. No report of tremor was classified as an SAE or was associated with discontinuation of treatment.

Two deaths occurred during the trial. One was due to coronary artery insufficiency during the IM Depot Stabilization Phase and the other was due to pancreatic carcinoma in

a subject randomized to aripiprazole IM depot during the Double-blind, Placebo-controlled Phase. Neither event leading to death was considered by the investigator to be related to treatment with aripiprazole IM depot.

During the IM Depot Stabilization Phase, 25/576 (4.3%) subjects reported serious TEAEs. The only serious TEAE reported by ≥ 1% of subjects during the IM Depot Stabilization Phase was that of schizophrenia (9/576 subjects, 1.6%). During the Double-blind, Placebo-controlled Phase, 11/269 (4.1%) aripiprazole IM depot subjects and 9/134 (6.7%) placebo subjects reported serious TEAEs, respectively. The only serious TEAE reported for ≥ 1% of aripiprazole IM depot subjects was psychotic disorder, which occurred in 4/269 (1.5%) aripiprazole IM depot subjects compared with 4/134 (3.0%) placebo subjects.

During the IM Depot Stabilization Phase, TEAEs resulting in discontinuation of trial medication were reported by 28/576 (4.9%) subjects. The only TEAE resulting in discontinuation of trial medication reported for ≥ 1% of subjects during the IM Depot Stabilization Phase was that of schizophrenia (8/576, 1.4%). During the Double-blind, Placebo-controlled Phase, 19/269 (7.1%) aripiprazole IM depot and 18/134 (13.4%) placebo subjects discontinued treatment due to TEAEs. The only TEAE resulting in trial medication discontinuation reported for ≥ 1% of aripiprazole IM depot subjects was psychotic disorder (7/269 [2.6%] vs 8/134 [6.0%] placebo subjects).

During the IM Depot Stabilization Phase, treatment-emergent EPS and EPS-related AEs were reported for 75/576 (13.0%) subjects. These were most commonly Parkinsonism events (39/576, 6.8%), primarily tremor in 21/576 (3.6%) subjects, followed by akathisia events (36/576, 6.3%). During the Double-blind, Placebo-controlled Phase, treatment emergent EPS and EPS-related AEs were reported for 40/269 (14.9%) aripiprazole IM depot and 13/134 (9.7%) placebo subjects. The most commonly reported EPS-related symptoms during this phase were parkinsonism events (22/269 [8.2%] of aripiprazole IM depot and 4/134 [3.0%] of placebo subjects), primarily tremor in 16/269 (5.9%) aripiprazole IM depot and 2/134 (1.5%) placebo subjects, and akathisia events (15/269 [5.6%] aripiprazole IM depot and 8/134 [6.0%] placebo subjects).

There was minimal variation in EPS symptoms during the IM Depot Stabilization and Double-Blind, Placebo-controlled Phases as assessed by mean changes from baseline in the SAS, AIMS, and BARS rating scales. There were no statistically significant differences between aripiprazole IM depot and placebo at endpoint for any of these scales.

The IM administration of the aripiprazole depot formulation was well tolerated by subjects during the IM Depot Stabilization Phase and the Double-blind, Placebo-controlled Phase. During the IM Depot Stabilization Phase, 36/576 (6.3%) subjects experienced TEAEs related to the injection site. During the Double-blind, Placebo-controlled Phase, 13/269 (4.8%) aripiprazole IM depot and 5/134 (3.7%) placebo subjects experienced TEAEs related to the injection site.

After the first and last injections during the IM Depot Stabilization Phase, investigators rated pain, redness, swelling, and induration at the current injection site as absent in 73.8% to 95.8% of subjects, and 76.5% to 96.3%, respectively. During the Double-blind, Placebo-controlled Phase for all randomized subjects on active treatment (non-placebo), investigators rated pain, redness, swelling, and induration at the current injection site as absent in 80.1% to 98.1% of subjects, and 84.4% to 98.5% after the first and last injections, respectively. Similar results were observed for all randomized subjects on placebo during the Double-blind, Placebo-controlled Phase: 72.2% to 97.7% (first injection), and 77.3% to 97.7% (last injection). Assessments of pain, redness, swelling, and induration at the most recent injection site (the site of the previous injection) were reanalyzed excluding data from all 5 sites in Mexico due to errors in assessment of the previous injection site. This reanalysis did not change the current injection site results presented above, and only minimally affected the investigator assessments of previous injection sites; results were similar with or without data from the Mexican sites.

During the IM Depot Stabilization Phase, the mean intensity of injection pain reported by subjects using a VAS (0 = no pain to 100 = unbearably painful) was 6.1 after the first injection and improved to 4.9 after the last injection. During the Double-blind, Placebo-controlled Phase, the mean VAS score reported by subjects on active treatment was 5.1 after the first injection and improved to 4.0 after the last injection. Similar mean pain score results were observed for subjects on placebo using a VAS: 5.1 (first injection), and 4.9 (last injection). The VAS for subject-reported pain at most recent injection site (the site of the previous injection) was reanalyzed, excluding data from all 5 sites in Mexico due to errors in assessment of the previous injection site. There were no appreciable changes in results when previous injection site VAS data from sites in Mexico were excluded.

During the IM Depot Stabilization Phase, 1/576 (0.2%) subject had suicidal ideation reported as a TEAE. Suicidal events were reported by 6/576 (1.0%) subjects as assessed by C-CASA / C-SSRS; all events were suicidal ideation. During the Double-blind, Placebo-controlled phase, 1.5% aripiprazole IM depot subjects (1 suicide attempt and 7 suicide ideations in a total of 7 subjects) and no placebo subjects had a TEAE that was considered related to suicidal ideation/suicide. Suicidal events were reported by 7/269 (2.6%) of aripiprazole IM depot subjects compared with 0/134 (0%) placebo subjects as assessed by C-CASA / C-SSRS.

During both the IM Depot Stabilization and Double-blind, Placebo-controlled Phases, treatment with aripiprazole IM depot (up to 18 monthly injections of 400 mg or 300 mg, including co-administration of oral aripiprazole for the first 2 weeks of the first IM depot treatment in the IM Depot Stabilization Phase) did not result in any clinically meaningful mean changes in clinical laboratory test results in this population of subjects with schizophrenia.
In the IM Depot Stabilization Phase, there was a mean decrease from baseline in prolactin values at the last visit (−0.05 ng/mL) of this phase. There was a mean decrease

in prolactin levels relative to the Double-blind, Placebo-controlled Phase baseline in the aripiprazole IM depot group (−0.38 ng/mL) compared with a mean increase in the placebo group (1.67 ng/mL) ($p < 0.001$). The incidence of aripiprazole IM depot subjects with prolactin levels greater than upper limit of normal range (ULN) at any assessment during the Double-blind, Placebo-controlled Phase was 1.9% compared with 7.1% of placebo subjects, with more males having an increase than females in both treatment groups.

Overall, no clinically meaningful changes from baseline were observed in lipid or glucose parameters during the IM Depot Stabilization Phase or during the Double-blind, Placebo-controlled Phase compared with placebo. No clinically meaningful 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 IM Depot Stabilization and Double-blind, Placebo-controlled Phases, treatment with aripiprazole IM depot did not result in any clinically meaningful 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, Placebo-controlled Phase was 6.4% for aripiprazole IM depot and 5.2% for placebo subjects, and the incidence of potentially clinically relevant weight loss (defined as ≥ 7% change from baseline) was 6.4% for aripiprazole IM depot and 6.7% for placebo. The incidence of potentially clinically relevant weight gain (defined as ≥ 7% change from baseline) at any visit during the Double-blind, Placebo-controlled Phase was 10.1% for the aripiprazole IM depot group and 7.5% for the placebo group, and the incidence of potentially clinically relevant weight loss (defined as ≥ 7% change from baseline) was 8.2% for both groups. The mean changes in weight at the end of the Double-blind, Placebo-controlled Phase were −0.2 kg and −0.4 kg for the aripiprazole IM depot and placebo groups, respectively. There were no statistically significant between-group differences in the change from baseline in weight during the Double-blind, Placebo-controlled Phase.

Conclusions:

- Aripiprazole IM depot 400 or 300 mg administered as monthly injections was effective for the maintenance treatment of schizophrenia in adults as demonstrated by a statistically significant difference, compared with placebo, in the primary efficacy endpoint of time to impending relapse.
- The percentage of subjects who met the criteria for impending relapse was significantly lower in the aripiprazole IM depot group than in the placebo group. The maintenance of stability was also demonstrated by statistically significant differences favoring aripiprazole IM depot in PANSS and CGI scores that remained significant throughout the Double-blind, Placebo-controlled Phase. In addition, the PSP total score, cognitive function assessments, and IAQ score are supportive of the efficacy of aripiprazole IM depot treatment.

- Aripiprazole IM depot was well tolerated by adult subjects with schizophrenia as demonstrated by an AE profile similar to placebo. Most TEAEs were either mild or moderate in severity. The only TEAE reported by ≥ 5% of subjects receiving aripiprazole IM depot and at least twice the incidence of placebo was tremor.
- The increased rate of tremor over placebo treatment is consistent in trials with oral aripiprazole, as also reported in the aripiprazole product labeling. Generally, tremor occurred with a low frequency throughout the trial. Adverse events of tremor were generally mild in severity. No report of tremor was classified as an SAE or was associated with discontinuation of treatment.
- There were no clinically relevant findings with regard to laboratory values, vital signs, weight, ECG findings, EPS, suicidality, or injection site.
- 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.

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