Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole (OPC-14597)

Clinical Summary for Protocol 31-05-244
NCT No. 01870999

An Open-label, Parallel Arm, Multiple Dose Tolerability, Pharmacokinetics and Safety Study in Adult Patients with Schizophrenia Following Administration of Aripiprazole Intramuscular (IM) Depot Formulation Once Every Four Weeks

Indication:	Schizophrenia
Clinical Development Phase:	1b
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. Rockville, Maryland, United States
Trial Initiation Date:	07 Nov 2007
Trial Completion Date:	20 Oct 2008
Summary Issued:	23 Dec 2014

This summary is for public dissemination of information in accordance with local regulatory requirements.
These results are supplied for informational purposes only. Prescribing decisions should be made based on the approved package insert.
This trial was conducted in compliance with Good Clinical Practice guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research subjects, no trial procedures were performed on trial candidates until written consent or assent had been obtained from them and/or their legally acceptable representative. The informed consent form, protocol, and amendments for this trial were submitted to and approved by the institutional review board or ethics committee at each respective trial center.

Name of Investigational Medicinal Product: Aripiprazole (OPC-14597)

Protocol Title: An Open-label, Parallel Arm, Multiple Dose Tolerability, Pharmacokinetics and Safety Study in Adult Patients with Schizophrenia Following Administration of Aripiprazole Intramuscular (IM) Depot Formulation Once Every Four Weeks

Trial Center(s) by Region: Multicenter (7 centers; United States initiated and enrolled subjects)

Clinical Phase/Trial Type: Phase 1b/ Open Label, Parallel Arm, Multiple Dose

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale: Aripiprazole is a marketed oral atypical antipsychotic that functions as a partial agonist at dopamine D_2 (D_2) and serotonin 5-HT1A receptors and is also a serotonin 5-HT2A receptor antagonist. Animal models show that the receptor affinity profile is unique in that aripiprazole serves as a D_2 receptor antagonist when dopamine is in excess and as a D_2 receptor agonist in hypodopaminergic states. Unlike other antipsychotics with a primary mechanism of D_2 receptor antagonism, aripiprazole has demonstrated a low incidence of extrapyramidal symptoms (EPS), low potential for weight gain and metabolic disturbances, and lack of induced elevations in prolactin levels in patients with schizophrenia. Thus, the favorable side effect profile of oral aripiprazole makes it an excellent candidate for a long-acting depot formulation.

One clinical trial (Protocol CN138020) with an intramuscular (IM) depot formulation of aripiprazole was conducted to assess the safety, tolerability, and pharmacokinetics (PK) of single doses of the aripiprazole IM depot formulation in subjects with schizophrenia or schizoaffective disorder. In that trial, single IM doses ranging from 15 mg to 400 mg of aripiprazole were administered to subjects. The IM depot formulation appeared to be well tolerated. Peak aripiprazole plasma concentrations in most subjects were observed after approximately 100 hours. Consequently, the current trial was conducted to assess the safety, tolerability, and PK of the aripiprazole IM depot formulation following multiple administrations of this IM depot formulation (once every 4 weeks) in subjects with schizophrenia.

Publications: None to date.

Objectives: This trial assessed the safety, tolerability, effectiveness, and PK of aripiprazole IM depot following IM administration once every 4 weeks to adult subjects with schizophrenia.

Methodology: This trial was an open-label, parallel-arm, multiple-dose, multicenter trial that included three groups of subjects with a diagnosis of schizophrenia.

After titration/stabilization on oral aripiprazole, the following doses of aripiprazole IM depot were to be administered every 4 weeks for 5 months (total of IM injections per subject in each group):

Dose Level 1: 400 mg dose group (Group 1)
Dose Level 2: 300 mg dose group (Group 2)
Dose Level 3: 200 mg dose group (Group 3)

Initially, up to 32 subjects were to be randomized to either Group 1 (400 mg) or Group 2 (300 mg). Once randomization had completed for Groups 1 and 2, 10 to 12 subjects were to be enrolled in Group 3 (200 mg). To ensure an adequate number of subjects for PK analysis, at least 5 subjects within each dose group were to receive a minimum of 3 injections of aripiprazole IM depot and have PK samples collected through at least 672 hours following the last dose.

Subjects considered for enrollment were to be stable for at least 28 days on their current antipsychotic medication or were to be receiving oral aripiprazole at a minimum dose of 10 mg daily prior to screening.

Before enrollment in a treatment arm, subjects entered a titration/stabilization period of up to 28 days (Day −28 to Day −1) that consisted of one of the following:

1. For subjects already on oral aripiprazole 10 mg at screening, no titration was needed, but these subjects were to demonstrate stability on oral aripiprazole 10 mg for 14 days prior to randomization/treatment assignment.

2. For subjects not currently taking oral aripiprazole at screening, antipsychotic treatment was switched to oral aripiprazole 10 mg daily over a 14-day period and the subjects were to demonstrate stability at that dose for a minimum of 14 days prior to randomization/treatment assignment.

3. For subjects currently on doses of oral aripiprazole higher than 10 mg daily at screening, the dose of oral aripiprazole was to be down-titrated to 10 mg over a 14-day period in step sizes at the discretion of the investigator. This was to be followed by an additional 14 days at the 10-mg dose to demonstrate continued stability prior to randomization/treatment assignment.

Following the titration/stabilization phase, eligible subjects were randomized to aripiprazole IM depot 400 mg or 300 mg or were assigned to aripiprazole IM depot 200 mg (Day 1) and received the first injection of aripiprazole IM depot. In addition, subjects received oral aripiprazole 10 mg beginning on the day of the injection (concomitantly with the first injection) and continuing for 14 days after the injection (Day 1 to Day 14). Both the IM depot and oral doses of aripiprazole were to be given in the morning without regard to food. The concomitant use of oral aripiprazole 10 mg was discontinued after Day 14. Subsequent injections of aripiprazole IM depot occurred every 4 weeks (beginning of Weeks 5, 9, 13, and 17).

Subjects continued to have weekly outpatient visits through Week 21, including an additional mid-week visit at Week 18.5 during Month 5. Subjects had visits at Weeks 23, 24, and 25 during Month 6. Although the last IM depot injection occurred at Week 17, Week 24 was the protocol-defined End of Treatment Visit.

Every effort was to be made to perform the Week 24 assessments at the final evaluation for any subject who terminated the trial prematurely. Subjects completing the trial were contacted by phone to assess AEs at Week 28, approximately 11 weeks after the last dose of IM depot. A similar follow-up contact was made 30 days after the early termination (ET) Visit for subjects who discontinued the trial for any reason. Hospitalization of subjects while enrolled in the trial was at the discretion of the principal investigator, but approval from the medical monitor was required.

Number of Subjects: This trial planned to enroll 44 subjects. A total of 41 subjects were randomized to the aripiprazole IM depot 400 mg group (14 subjects) or 300 mg group (16 subjects) or were assigned to the aripiprazole IM depot 200 mg group (11 subjects). Two of these subjects (one in the aripiprazole IM depot 300 mg group and one in the aripiprazole IM depot 200 mg group) were randomized or assigned to treatment in error and did not receive any injections of aripiprazole IM depot. Therefore, the safety analyses included the 39 subjects who received at least one injection of aripiprazole IM depot (14, 15, and 10 dosed with aripiprazole IM depot 400 mg, 300 mg, and 200 mg, respectively). The exploratory evaluation of potential effectiveness was based on the intent to treat principle and included all randomized subjects with baseline and post baseline data for at least one effectiveness parameter, irrespective of treatment. In this trial, 40 subjects were analyzed for effectiveness, including one of the subjects who was randomized to treatment (aripiprazole IM depot 300 mg), but not injected with the IM depot formulation.

Diagnosis and Main Criteria for Inclusion/Exclusion: Subjects between the ages of 18 and 64, inclusive, with a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria were enrolled. Subjects who consumed alcoholic beverages routinely or during the screening period, those who had a recent (6 month) history of alcohol or drug abuse, those who used any antipsychotic medication, other prohibited psychotropic medication, any CYP2D6 and CYP3A4 inhibitors, or CYP3A4 inducers (as defined in the protocol) within 14 days prior to dosing and for the duration of the trial, those with current hepatitis, or a history of hepatitis or as a carrier of HBsAg and/or antibodies to hepatitis C virus, and sexually active subjects unwilling to use approved methods of contraception during the trial and for 30 days (females) to 90 days (males) after the last dose of trial medication were excluded from the trial, as were pregnant or nursing women.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration: Subjects received 400 mg, 300 mg, or 200 mg aripiprazole IM depot formulation as a monthly injection for 5 months. In addition, subjects received open-label oral aripiprazole 10 mg during the titration/stabilization period before

randomization/ treatment assignment and for 14 days after randomization/treatment assignment (concomitant with the first IM depot dose). Aripiprazole IM depot was manufactured by Otsuka Pharmaceutical Co, Ltd (Japan) and was supplied in vials containing either 200 mg or 400 mg lyophilized aripiprazole powder for injection. Oral aripiprazole tablets used during the titration/stabilization period and for the first 14 days of the dosing period after randomization/treatment assignment were manufactured by Bristol-Myers Squibb Company (Puerto Rico).

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

Duration of Treatment: Twenty-four weeks.

Trial Assessments:
Tolerability and Safety: Adverse events (AEs), clinical laboratory tests (serum chemistry, hematology, and urinalysis), physical examinations, vital signs, electrocardiograms (ECGs), and extrapyramidal symptoms (EPS) assessments (Simpson Angus Scale [SAS], Abnormal Involuntary Movement Scale [AIMS], and Barnes Akathisia Rating Scale [BARS]). A serum pregnancy test was performed at screening for all female subjects and urine pregnancy tests were to be performed monthly before each IM depot injection during the treatment period and at Week 24. Urine drug and alcohol screens were performed at screening and Week 13.

Pharmacokinetic (PK):
Plasma aripiprazole and dehydro-aripiprazole metabolite concentrations.

Effectiveness:
Clinical Global Impression - Severity of Illness (CGI-S) Score, Clinical Global Impression – Improvement (CGI-I) Score, Positive and Negative Syndrome Scale (PANSS) Total Score, PANSS Positive and Negative Subscale Scores, and hospitalization for “worsening schizophrenia” (ie, hospitalization for any AE pertaining to the exacerbation of schizophrenic symptoms).

Criteria for Evaluation:

Primary Outcome Variables:

Tolerability and Safety: Tolerability and safety evaluations for individual subjects were based on AE reporting (including injection site reactions), clinical laboratory tests (serum chemistry, hematology, and urinalysis), physical examinations, vital signs, ECGs, and EPS assessments (change from baseline in SAS Total Score, BARS Global Score, and AIMS Movement Rating Score).

PK: Aripiprazole maximum (peak) steady-state drug concentration in the plasma during a dosing interval ($C_{ss,max}$), aripiprazole minimum steady-state drug concentration in the

plasma during a dosing interval ($C_{ss,min}$), and aripiprazole area under the concentration-time curve during a dosing interval (τ) at steady-state (AUC_{τ}).

Secondary Outcome Variables:

PK: Aripiprazole time to maximum (peak) plasma concentration (t_{max}), aripiprazole average steady-state drug concentration in the plasma during a dosing interval ($C_{ss,avg}$), aripiprazole apparent terminal-phase disposition rate constant (first-order) (λ_z), and aripiprazole terminal-phase elimination half-life ($t_{½,z}$). Dehydro-aripiprazole $C_{ss,max}$, $C_{ss,min}$, AUC_{τ}, and t_{max}.

Effectiveness: Change from baseline for PANNS Total Score, PANSS Positive Subscale Score, PANSS Negative Subscale Score, and CGI-S Score by visit; mean CGI-I data by visit; and hospitalizations categorized by reason (ie, "worsening schizophrenia" recorded as any AE pertaining to the exacerbation of schizophrenic symptoms versus hospitalization for other reasons).

Pharmacokinetic/pharmacodynamic Methods:

Bioanalytical: Plasma samples were analyzed for aripiprazole and its metabolite, dehydro-aripiprazole, using a validated high performance liquid chromatography with tandem mass spectrometric detection method. The method was linear over the range between 0.500 and 250 ng/mL for aripiprazole and dehydro-aripiprazole.

PK: Aripiprazole and dehydro-aripiprazole plasma concentration-time data were analyzed using a noncompartmental method at steady state. Actual blood sample times were used for PK calculations.

Statistical Methods: No formal statistical analysis was performed. Plasma concentration data were summarized by treatment and time point using descriptive statistics; summary values were reported as three significant figures. PK parameters were summarized by treatment using descriptive statistics.

Effectiveness: To explore the potential effectiveness of aripiprazole IM depot for the treatment of schizophrenia, mean scores and mean changes from baseline in PANSS Total Score, PANSS Positive and Negative Subscale Scores, and CGI-S Score and mean CGI-I Score were summarized by treatment group and visit using descriptive statistics. Effectiveness variables were analyzed using both the last observation carried forward (LOCF) and observed case (OC) data sets. The incidence of hospitalization for "worsening schizophrenia" versus other reasons was summarized by treatment group. Worsening schizophrenia was determined from AE reports pertaining to the exacerbation of schizophrenic symptoms.

Safety: Safety data were summarized by descriptive statistics, as appropriate. All AEs were coded from verbatim terms to system organ class and preferred terms using the

Medical Dictionary for Regulatory Activities (MedDRA), Version 9.1. The incidence of treatment-emergent adverse events (TEAEs) was summarized by treatment group for all TEAEs, TEAEs by severity, potentially drug-related TEAEs, serious TEAEs, and discontinuations due to TEAEs. TEAEs occurring during co-administration of aripiprazole IM depot and oral aripiprazole were summarized separately. For continuous safety variables (clinical laboratory tests, vital sign measurements, ECG parameters, and EPS scales), descriptive statistics were used to summarize original values, changes from baseline at each visit, and changes from baseline to the last scheduled visit. Potentially clinically significant changes in clinical laboratory parameters, vital signs, weight, and ECG findings were identified using prospectively-defined criteria.

QT intervals corrected for heart rate (QTc) were obtained using formulae from the following sources: Bazett (QTcB), Fridericia (QTcF), and Neuropharm Division of the Food and Drug Administration (FDA; QTcN).

Suicidal behavior was assessed at screening using Item 10 of the Montgomery Asberg Depression Rating Scale (MADRS) to ensure that enrolled subjects did not represent a significant risk of committing suicide. This trial was completed before the requirement by the FDA to include suicidality assessment at every visit, preferably using the Columbia-Suicide Severity Rating Scale.

Summary of Results:

Baseline Data, Disposition, and Demographics: A total of 41 subjects were randomized into the trial and 39 received at least one dose of aripiprazole IM depot. Two of these subjects (one in the aripiprazole IM depot 300 mg group and one in the aripiprazole IM depot 200 mg group) were randomized or assigned to treatment in error and did not receive any injections of aripiprazole IM depot. Therefore, the safety analyses included the 39 subjects who received at least one injection of aripiprazole IM depot (14, 15, and 10 dosed with aripiprazole IM depot 400 mg, 300 mg, and 200 mg, respectively).

Subject 0010029 received oral aripiprazole in the titration/stabilization phase and was randomized to aripiprazole IM depot 300 mg, but did not receive the depot injection due to mild ongoing cellulitis of the right leg that had been present at screening and baseline and did not improve during the titration/stabilization phase. The subject eventually withdrew from the trial for an SAE of severe venous thrombosis. CGI-I was rated at the early termination visit. In addition, baseline and post-baseline (early termination) data were collected for CGI-S. Therefore, data for these parameters are included in the effectiveness analysis. The subject's safety data are presented in data listings, but are not tabulated in the safety analyses because he never received aripiprazole IM depot. Subject 0153007 also received oral aripiprazole in the titration/stabilization phase. This subject was assigned to aripiprazole IM depot 200 mg before all screening assessment scales were complete. When scales were performed predose on Day 1, the subject was shown to be in acute relapse. As such, he did not qualify for the trial and did not receive

aripiprazole IM depot. No post-baseline data were collected for this subject, so he is not included in any analyses of safety or effectiveness. Although the last injection of aripiprazole IM depot was administered at the Week 17 visit, subjects were to continue to attend visits through the end of treatment visit at Week 24, and if possible, to return to the clinic for a final PK sample at Week 25. Approximately half of the subjects (53.7%) completed the trial through Week 24 (10 [71.4%], 8 [50.0%], and 4 [36.4%] in the aripiprazole IM depot 400 mg, 300 mg, and 200 mg groups, respectively). Overall, withdrawn consent was the most common reason for discontinuation of trial subjects (7/41 subjects, 17.1%). Withdrawal of consent occurred most frequently among subjects assigned to aripiprazole IM depot 200 mg Overall, 5 (12.2%) subjects withdrew due to AEs. Four of the AE withdrawals occurred in the aripiprazole IM depot 300 mg group; however, 1 of these withdrawals was due to an SAE that occurred after randomization, but before administration of aripiprazole IM depot (Subject 0010029 described above). Overall, 5 (12.2%) subjects met withdrawal criteria (ie, 3 subjects were noncompliant, 1 relocated, and 1 became pregnant). The investigator withdrew one subject in the aripiprazole IM depot 400 mg group for lack of efficacy. One subject (0153007 described above) who was assigned to the aripiprazole IM depot 200 mg group in error was withdrawn for a protocol violation before receiving the depot injection because he did not meet entrance criteria. All 22 subjects who completed the trial received five doses of aripiprazole IM depot, continued PK sampling through at least the 672-hour time point, and were included in the PK analysis group.

PK Sample Demographics

The 400 mg dose PKT-1 sample included a total of 14 subjects (7 male and 7 female). Of these subjects, 6 were black, six were white. One subject each was identified as Asian and Other, respectively. The median age for these subjects was 48 years (range 28 to 60 years). The 300 mg dose PKT-2 sample included 13 subjects (10 male, and 3 female). Of these, 9 were black and 4 were white. The median age was 47 (range 23 to 61 years). The 200 mg dose PKT-3 sample included 10 subjects (9 male and 1 female). Of these, 6 were black, 3 were white and one was identified as Other.

The overall majority of subjects in this trial were male (71.0%) and not Hispanic (95.0%). Slightly more than half of the population was Black or African American (54.0%) and 37% of trial participants were white. Three (7.0%) subjects were reported as being of “other” race, specifically one each reporting mixed-race, Hispanic, and Mexican. The remaining subject was Asian (2.0%). The mean age of the trial population was 45.2 years (range, 19 to 62 years) and the mean age was comparable across the three treatment groups. Mean weight was slightly higher for the aripiprazole IM depot 300 mg group (92.8 kg) compared with the 400 mg (80.6 kg) and 200 mg (84.3 kg) groups; however, BMI was similar in each of the three treatment groups. The overall BMI was 28.7 kg/m^2

All subjects enrolled into the trial had been previously treated for schizophrenia. PANSS and CGI-S Scores at baseline were similar for each of the three treatment groups and indicated mild illness. As required per the protocol, none of the subjects exhibited

clinically significant suicidal behavior at enrollment, as indicated by MADRS suicide item scores ≤ 1 in each treatment group at screening.

Effectiveness Results: The analyses for potential effectiveness included 40 subjects with baseline and post-baseline data for at least one effectiveness measure (14 and 16 subjects randomized to aripiprazole IM depot 400 mg and 300 mg, respectively, and 10 subjects assigned to aripiprazole IM depot 200 mg). The mean changes from baseline in PANSS and CGI-S Scores are summarized for Weeks 12 and 24 in the table below.

Change From Baseline in PANSS and CGI-S Scores (LOCF)

Parameter Visit Week	Aripiprazole IM Depot 400 mg (N = 14)			Aripiprazole IM Depot 300 mg (N = 16)			Aripiprazole IM Depot 200 mg (N = 11)		
	n	Mean Score	Mean Change (SD)	n	Mean Score	Mean Change (SD)	n	Mean Score	Mean Change (SD)
PANSS Total Score									
Baseline	13	69.3	-	14	64.6	-	10	63.8	-
Week 12	13	69.3	0.0 (20.2)	14	65.7	1.1 (12.1)	10	62.5	−1.3 (4.8)
Week 24	13	68.5	−0.8 (20.9)	14	63.0	−1.6 (14.1)	10	62.5	−1.3 (5.3)
PANSS Positive Subscale									
Baseline	13	18.5	-	14	16.2	-	10	15.4	-
Week 12	13	17.3	−1.2 (6.1)	14	17.5	1.3 (4.0)	10	14.4	−1.0 (1.2)
Week 24	13	16.8	−1.6 (6.1)	14	16.6	0.4 (4.5)	10	14.4	−1.0 (1.6)
PANSS Negative Subscale									
Baseline	13	17.1	-	14	16.1	-	10	18.1	-
Week 12	13	18.2	1.1 (4.4)	14	16.3	0.1 (3.2)	10	18.1	0.0 (2.0)
Week 24	13	17.5	0.5 (4.2)	14	16.1	−0.1 (3.7)	10	17.5	−0.6 (2.0)
CGI-S Score									
Baseline	14	3.3	-	16	3.1	-	10	3.0	-
Week 12	14	3.2	−0.1 (0.5)	16	3.1	0 (0.6)	10	2.8	−0.2 (0.4)
Week 24	14	3.1	−0.1 (0.5)	16	3.1	−0.1 (0.7)	10	2.8	−0.2 (0.4)

Note: A decrease in score indicates improvement.

The mean CGI-I Scores at Week 24 (3.7 in the aripiprazole IM depot 400 mg and 200 mg groups and 3.4 in the aripiprazole IM depot 300 mg group) corroborated what was observed with the mean CGI-S scores (ie, no change from baseline). Additionally, results of the OC analysis supported the results of the LOCF analysis.

Overall, 7/41 (17.1%) subjects were hospitalized during the course of the trial (1 in the aripiprazole IM depot 400 mg group, 5 in the aripiprazole IM depot 300 mg group, and 1 in the aripiprazole IM depot 200 mg group). However, only one subject (aripiprazole IM depot 300 mg group) was hospitalized for an AE of worsening schizophrenic symptoms. All subjects who were hospitalized during the trial began the trial as outpatients and completed the trial as outpatients.

PK Results: The PK dataset consisted of 22 subjects who completed the trial, including PK sampling through at least the 672-hour time point after the fifth IM depot injection

(10, 8, and 4 subjects in the aripiprazole IM depot 400 mg, 300 mg, and 200 mg groups, respectively). A summary of aripiprazole PK parameters is presented in the tables below:

Mean (SD) Aripiprazole Pharmacokinetic Parameters in Subjects with Schizophrenia

PK Parameter	Aripiprazole IM Depot 400 mg [a]	Aripiprazole IM Depot 300 mg [b]	Aripiprazole IM Depot 200 mg [c]
$C_{ss,max}$ (ng/mL)	316 (160)	269 (128)	100 (68.4)
t_{max} (day)[d]	7.1 (3.0-11.2)	6.5 (0.5-21.2)	5.0 (4.0-27.9)
AUC_{τ} (µg·h/mL)	163 (88.8)	140 (58.4)	54.5 (39.4)
$t_{1/2,z}$ (day)	46.5 (10.8)[e]	29.9 (8.0)[f]	ND
$C_{ss,min}$ (ng/mL)[g]	212 (113)	156 (67.7)	95.0 (86.2)
$C_{ss,avg}$ (ng/mL)	242 (132)	208 (87.0)	81.1 (58.7)

NA = not applicable; ND = not determined; SD = standard deviation.
[a] n = 10
[b] n = 8
[c] n = 4
[d] Median (minimum-maximum)
[e] n = 6
[f] n = 4
[g] $C_{ss,min}$ = aripiprazole concentration at 672 hours.

A summary of dehydro-aripiprazole PK parameters is presented in the table below:

Mean (SD) Dehydro-aripiprazole Pharmacokinetic Parameters in Subjects with Schizophrenia

PK Parameter	Aripiprazole IM Depot 400 mg [a]	Aripiprazole IM Depot 300 mg [b]	Aripiprazole IM Depot 200 mg [c]
$C_{ss,max}$ (ng/mL)	89.4 (37.9)	74.7 (20.8)	30.3 (19.8)
t_{max} (day)[d]	6.6 (3.00-14.0)	12.5 (0.5-22.2)	5.5 (0.0-27.9)
AUC_{τ} (µg·h/mL)	47.8 (19.1)	38.9 (13.2)	14.7 (9.47)
$C_{ss,min}$ (ng/mL)[e]	64.1 (27.0)	54.1 (21.1)	26.2 (24.7)

NA = not applicable; SD = standard deviation.
[a] n = 10
[b] n = 8
[c] n = 4
[d] Median (minimum-maximum)
[e] $C_{ss,min}$ = dehydro-aripiprazole concentration at 672 hours.

Safety Results

Extent of Exposure: Of the 41 enrolled subjects, 39 (95.1%) received at least one injection of aripiprazole IM depot and constituted the safety population. Exposure to aripiprazole IM depot was greatest in the aripiprazole IM depot 400 mg group, where 12/14 (85.7%) subjects received all 5 planned injections. However, two of these subjects (randomized to aripiprazole IM depot 400 mg) withdrew from the trial during the last month prior to completing the required duration of PK sampling, and thus, were excluded from the PK analysis. In the aripiprazole IM depot 300 mg group, 9/16 (56.3%) subjects received the second depot injection and 8/16 (50.0%) continued to receive the third, fourth, and fifth injections. The percentage of subjects who received injections of aripiprazole IM depot 200 mg decreased at each visit. Four of 11 (36.4%) subjects in the aripiprazole IM depot 200 mg group received all five planned injections.

All subjects who received the first injection of aripiprazole IM depot also received oral aripiprazole during the first week of the trial at an average daily dose of 10 mg. During the second week of the trial, at least 81% of subjects in each treatment group received the concurrent oral aripiprazole at an average dose of 10 mg daily. Cumulative exposure to oral aripiprazole during co-administration with IM depot was 196, 205, and 129 subject-days in the aripiprazole IM depot 400 mg, 300 mg, and 200 mg groups, respectively.

Adverse Events:

Overall, 26 (66.7%) subjects who received ≥ 1 injection of aripiprazole IM depot reported at least one TEAE. The incidence of TEAEs was slightly higher in the aripiprazole IM depot 300 mg group (11/15 subjects; 73.3%) than in the aripiprazole IM depot 400 mg group (9/14 subjects; 64.3%) and aripiprazole IM depot 200 mg group (6/10 subjects; 60.0%). The most common TEAEs (overall incidence) were vomiting (4 subjects), injection site pain (4 subjects), upper respiratory tract infection (URTI; 4 subjects), and tremor (4 subjects). Injection site pain and tremor were more common in the aripiprazole IM depot 400 mg group. Vomiting occurred with similar incidence in the aripiprazole IM depot 400 mg and 300 mg groups. The incidence of URTI was similar in all three treatment groups.

Approximately 40% of the TEAEs that occurred during the trial (46/102; 45.1%) were reported in the initial period during co-administration of aripiprazole IM depot and oral aripiprazole. The incidence of TEAEs during co-administration of aripiprazole IM depot and oral aripiprazole was similar in the aripiprazole IM depot 400 mg (8/14 subjects; 57.1%) and 300 mg groups (9/15 subjects; 60.0%) and higher in these groups compared with the aripiprazole IM depot 200 mg group (4/10 subjects; 40.0%).

The majority of TEAEs were mild or moderate in intensity. Severe TEAEs were reported by 4 (10.3%) subjects. Three of the subjects with severe TEAEs (aripiprazole IM depot 300 mg group) are discussed below under serious AEs (SAEs). Nonserious AEs of muscle strain and sinusitis were reported as severe for one subject in the aripiprazole IM depot 400 mg group.

TEAEs with a potential relationship to aripiprazole treatment were reported by 21 (53.8%) subjects (8 [57.1%], 8 [53.3%], and 5 [50.0%] subjects in the aripiprazole IM depot 400 mg, 300 mg, and 200 mg groups, respectively). The system organ classes most frequently associated with potentially drug-related TEAEs were Nervous System Disorders (23.1%) and Psychiatric Disorders (20.5%). Injection site pain (4 subjects), tremor (3 subjects) and sedation (2 subjects) were the only potentially drug-related TEAEs reported by more than 2 subjects in a single treatment group (aripiprazole IM depot 400 mg).

No deaths occurred during the reporting period. Three (7.7%) subjects, all from the aripiprazole IM depot 300 mg group, experienced a total of four SAEs after the first injection of trial medication. None of the individual SAE preferred terms were reported by more than one subject. One subject experienced chest pain and worsening of schizophrenic symptoms that were both classified as serious. Both of these events began during the co-administration of aripiprazole IM depot and oral aripiprazole. The remaining SAEs reported by one subject each were diabetic ketoacidosis and psychotic disorder (reported as worsening of psychosis). The latter event (worsening of psychosis) also began during co-administration of aripiprazole IM depot and oral aripiprazole. All of the SAEs were classified as severe, but were considered not related to trial treatment except for psychotic disorder that was reported as possibly related.

Four (10.3%) subjects discontinued treatment due to TEAEs. Two subjects (one in the aripiprazole IM depot 300 mg group and one in the aripiprazole IM depot 200 mg group) withdrew due to psychotic disorder (worsening of psychosis), one subject (aripiprazole IM depot 300 mg group) withdrew due to worsening of schizophrenic symptoms, and one subject (aripiprazole IM depot 300 mg group) withdrew due to drug dependence (reported as a cocaine relapse). Two of these events (worsening of schizophrenic symptoms and psychotic disorder in the aripiprazole IM depot 300 mg group) were SAEs. The only TEAE leading to discontinuation with a potential relationship to trial medication was the SAE of psychotic disorder (see above). All of the TEAEs that led to treatment discontinuation began during co-administration of aripiprazole IM depot and oral aripiprazole.

Injection site reactions, as determined by review of relevant TEAEs, were mild in intensity and resolved without sequelae. One subject in the aripiprazole IM depot 400 mg group reported injection site discomfort and pain; 3 additional subjects in this group reported injection site pain. None of the subjects in the aripiprazole IM depot 300 mg or 200 mg groups experienced injection site reactions.

Clinical Laboratory Results: No clinically relevant mean changes from baseline were observed for hematology, clinical chemistry, or urinalysis laboratory parameters. Three subjects had serum chemistry values that exceeded the criteria for potential clinical significance (all for elevated creatine phosphokinase) and none of these abnormalities were associated with TEAEs. No hematology values of potential clinical significance were identified.

Mean change from baseline to the last visit in prolactin did not reveal any clinically meaningful changes. One subject experienced a prolactin elevation of potential clinical significance, but this abnormality was not reported as a TEAE.

Vital Sign Results: No clinically relevant mean changes from baseline were observed in heart rate and blood pressure and the incidence of abnormalities of potential clinical significance was low. Of the 35 subjects for whom paired data were available, 6 (17.1%) experienced a weight gain of ≥ 7% from baseline during the trial (3 in the aripiprazole IM depot 400 mg group, 2 in the aripiprazole IM depot 300 mg group, and 1 in the aripiprazole IM depot 200 mg group). Two (5.7%) subjects experienced clinically significant weight loss (1 in the aripiprazole IM depot 400 mg group and 1 in the aripiprazole IM depot 300 mg group).

Electrocardiogram Results: No clinically relevant mean changes from baseline were observed for ECG parameters. At the last visit, the change from baseline in QTc ranged from −3.5 to 1.7 msec for aripiprazole IM depot 400 mg, from 6.9 to 14.4 msec for aripiprazole IM depot 300 mg, and from 0.9 to 1.5 msec for aripiprazole IM depot 200 mg, depending on the calculation method. A total of 4 (28.6%) subjects in the aripiprazole IM depot 400 mg group, 3 (20.0%) in the aripiprazole IM depot 300 mg group, and 1 (10.0%) in the aripiprazole IM depot 200 mg group experienced occurrences of QTc > 450 msec during the trial (by any calculation method). However, only 1 of these subjects (aripiprazole IM depot 300 mg) experienced a potentially clinically significant QTc prolongation (ie, > 450 msec) that was also reported as an unrelated, ongoing AE of mild intensity.

Other Safety Variables:
The severity of EPS was assessed by evaluating the SAS Total Score, BARS Global Score, and AIMS Movement Rating Score. The minimal overall mean changes seen in these scales were not considered to be clinically meaningful (see table below).

Change From Baseline in EPS Rating Scale Scores (LOCF)

Scale Time point	Aripiprazole IM Depot 400 mg (N = 14)			Aripiprazole IM Depot 300 mg (N = 15)			Aripiprazole IM Depot 200 mg (N = 10)		
	n	Mean Score	Mean Change (SD)	n	Mean Score	Mean Change (SD)	n	Mean Score	Mean Change (SD)
SAS (1970 Version) Total Score									
Baseline	4	0.3	-	10	0	-	3	1.3	-
Week 12	4	0.3	0 (0)	10	0.3	0.3 (0.7)	3	0.7	−0.7 (1.2)
Week 24	4	0	−0.3 (0.5)	10	0.5	0.5 (1.1)	3	0.7	−0.7 (1.2)
SAS (1997 Version) Total Score									
Baseline	10	10.3	-	4	10.3	-	7	10.1	-
Week 12	10	10.1	−0.2 (0.8)	4	10.5	0.3 (0.5)	7	10.1	0 (0.6)
Week 24	10	10.3	0 (0.5)	4	10.3	0 (0)	7	10.1	0 (0.6)

Change From Baseline in EPS Rating Scale Scores (LOCF)									
	Aripiprazole IM Depot 400 mg (N = 14)			Aripiprazole IM Depot 300 mg (N = 15)			Aripiprazole IM Depot 200 mg (N = 10)		
Scale Time point	n	Mean Score	Mean Change (SD)	n	Mean Score	Mean Change (SD)	n	Mean Score	Mean Change (SD)
BARS Global Score									
Baseline	14	0	-	14	0.1	-	10	0.1	-
Week 12	14	0.1	0.1 (0.3)	14	0.2	0.1 (0.7)	10	0.3	0.2 (0.8)
Week 24	14	0.1	0.1 (0.5)	14	0.1	0.1 (0.6)	10	0	−0.1 (0.3)
AIMS Movement Rating Score									
Baseline	14	0.4	-	14	0.2	-	10	0.2	-
Week 12	14	0.1	−0.2 (0.4)	14	0.1	−0.1 (0.8)	10	0.3	0.1 (0.3)
Week 24	14	0	−0.4 (0.8)	14	0.6	0.4 (1.8)	10	0.2	0 (0)

Note: A decrease in score indicates improvement/reduction of EPS.

Conclusions:

- Maximum aripiprazole concentrations were reached within 5.0 to 7.1 days after monthly IM depot injections.
- The mean aripiprazole terminal elimination half-lives were 29.9 days and 46.5 days for aripiprazole IM depot 300 mg and 400 mg, respectively. Aripiprazole terminal elimination half-life after the 200 mg dose could not be reported due to limited data.
- No meaningful accumulation was observed based on predose aripiprazole and dehydro-aripiprazole concentrations during the last 3 injections.
- Based on predose aripiprazole and dehydro-aripiprazole concentrations, it appeared that steady state was reached by the fifth monthly injection.
- Dose-proportional increases in aripiprazole and dehydro-aripiprazole $C_{ss,max}$, AUC_{τ}, and $C_{ss,min}$ PK parameters were observed after the 300 mg and 400 mg doses of aripiprazole IM depot. No conclusion could be made for the dose-proportionality of aripiprazole and dehydro-aripiprazole PK parameters after IM depot 300 mg group) reported a total of 4 SAEs and 4 (10.3%) subjects discontinued treatment due to TEAEs (3 in the aripiprazole IM depot 300 mg group and 1 in the aripiprazole IM depot 200 mg group). Mild injection site pain and the 200 mg dose of aripiprazole IM depot due to limited data.
- Aripiprazole mean trough plasma concentrations after the 300 mg and 400 mg IM depot injections were comparable to those of 10 mg to 30 mg oral aripiprazole administered daily to schizophrenic subjects.
- Aripiprazole IM depot was generally well tolerated by subjects with schizophrenia who received monthly doses of 400 mg, 300 mg, or 200 mg for up to 5 months. The majority of TEAEs were reported as mild or moderate. The most common TEAEs (overall incidence) were vomiting (4 subjects), injection site pain (4 subjects), URTI (4 subjects), and tremor (4 subjects). Three (7.7%) subjects (all from the aripiprazole

discomfort were reported (400 mg IM depot dose only), indicating that administration of the IM depot formulation was well tolerated by subjects.

- Aripiprazole IM depot, with co-administration of oral aripiprazole for the first 2 weeks of treatment, effectively maintained the degree of clinical stability established prior to randomization during the 14- to 28-day oral stabilization period.
- The analysis of the SAS, AIMS, and BARS scales did not suggest any increase in the severity of EPS during the trial.
- A weight gain of ≥ 7% from baseline occurred during the trial for 6 (17.1%) subjects overall (3, 2, and 1 in the aripiprazole IM depot 400 mg, 300 mg, and 200 mg groups, respectively). Two (5.7%) subjects experienced a weight loss of ≥ 7% from baseline (1 in the aripiprazole IM depot 400 mg group and 1 in the aripiprazole IM depot 300 mg group).
- Treatment with aripiprazole IM depot (up to 5 monthly injections of 400 mg, 300 mg, or 200 mg, including co-administration of oral aripiprazole for the first 2 weeks of the treatment period) did not result in any clinically meaningful changes in clinical laboratory tests, vital signs, or ECG parameters in this population of subjects with schizophrenia.
- The PK profile, coupled with the clinical data, indicates that aripiprazole IM depot 400 mg and 300 mg appear to be the most suitable doses for further investigation in the treatment of schizophrenia.

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