Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product

Aripiprazole (OPC-14597, Lu AF41155)

REVISED CLINICAL PROTOCOL

A Phase 1b, Open-label, Multiple-dose, Randomized, Parallel-arm, Safety, Tolerability, and Pharmacokinetic Trial of Aripiprazole Intramuscular Depot Administered in the Gluteal Muscle in Adult Subjects With Schizophrenia or Bipolar I Disorder

Protocol No. 031-201-00181
IND No. 134612

CONFIDENTIAL - PROPRIETARY INFORMATION

Drug Development Phase:	1b
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Protocol 031-201-00181

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: Aripiprazole (OPC-14597)	Protocol No.: 031-201-00181 IND No.: 134612
Protocol Title:	A Phase 1b, Open-label, Multiple-dose, Randomized, Parallel-arm, Safety, Tolerability, and Pharmacokinetic Trial of Aripiprazole Intramuscular Depot Administered in the Gluteal Muscle in Adult Subjects With Schizophrenia or Bipolar I Disorder
Clinical Phase:	Phase 1b
Treatment Indication:	Schizophrenia and bipolar I disorder
Objectives:	**Primary:** • To determine the safety and tolerability of multiple-dose administrations of aripiprazole in adult subjects with schizophrenia or bipolar I disorder. • To establish the similarity of aripiprazole concentrations on the last day of the dosing interval following the final administration of aripiprazole into the gluteal muscle site in adult subjects with schizophrenia or bipolar I disorder. • To establish the similarity of aripiprazole exposure over the dosing interval following the administration of aripiprazole into the gluteal muscle site in adult subjects with schizophrenia or bipolar I disorder. **Secondary:** • To determine the pharmacokinetics (PK) of aripiprazole. • To determine aripiprazole concentrations 7 days (C_7) and 14 days (C_{14}) after the first dose of aripiprazole for subjects enrolled to the robust sampling schedule. • To obtain information on the efficacy of aripiprazole over the course of 32 weeks.
Trial Design:	This is a phase 1b, open-label, multiple-dose, randomized, parallel-arm, multicenter trial. After a screening period of up to 30 days, eligible subjects will be randomized (1:1) to receive multiple doses of either aripiprazole 2 month (2M) long-acting injectable (LAI) 960 mg (4 injections) or aripiprazole IM depot 400 mg (8 injections) over the course of 32 weeks. Aripiprazole 2M LAI 960 mg will be administered at 56-day (± 2 days)

	intervals and aripiprazole IM depot 400 mg will be administered at 28-day (± 2 days) intervals. A final visit will occur 56 (± 2) days after the last dose of aripiprazole 2M LAI 960 mg or 28 (± 2) days after the last dose of aripiprazole IM depot 400 mg. Randomization to the 2 trial treatments will be stratified by the PK sampling schedule (robust or sparse) and disease type (schizophrenia or bipolar I disorder). Four to 6 trial sites will be designated as Robust Sampling Trial Sites; all other trial sites will be designated as Sparse Sampling Trial Sites. Up to 76 subjects (38 per treatment group) will be enrolled to the robust sampling schedule and 182 subjects (91 per treatment group) will be enrolled to the sparse sampling schedule. If enrollment of the number of subjects required for the robust sampling schedule is completed, the Robust Sampling Trial Sites may enroll additional subjects to the sparse sampling schedule with approval from the sponsor. Blood samples for PK analyses will be drawn from subjects at both Robust and Sparse Sampling Trial Sites after the first (Day 1) and fourth (Day 169) doses of investigational medicinal product (IMP) for subjects randomized to aripiprazole 2M LAI 960 mg, and after the first (Day 1), seventh (Day 169), and eighth (Day 197) doses of IMP for subjects randomized to aripiprazole IM depot 400 mg. Subjects enrolled to the robust sampling schedule who are randomized to aripiprazole 2M LAI 960 mg must be housed in the unit for 21 days after the first and fourth doses of IMP and will be outpatients for the rest of the trial. Subjects randomized to aripiprazole IM depot 400 mg will stay in the unit for 21 days after administration of the first, seventh, and eighth doses of IMP. Subjects who are not able to accommodate the scheduled stays in the unit may be permitted to have some visits as outpatients with approval from the medical monitor. For any outpatient visit, an unscheduled C-SSRS will be performed. Subjects enrolled to the sparse sampling schedule will be outpatients for administration of all doses of IMP; however, they may be housed in the unit for up to 21 days after administration of the first dose of IMP at the discretion of the investigator. Subjects who do not have a history of tolerating aripiprazole will receive 3 single 10-mg doses of oral aripiprazole on 3 consecutive days (total of 30 mg) in addition to their current oral antipsychotic, mood stabilizer, and if applicable, antidepressant for at least 14 days prior to the first administration of IMP to establish tolerability. Subjects may be housed in the

	unit during these 3 days at the investigator's discretion. At the time of administration of the first dose of IMP, subjects will begin a 7- to 14-day period (oral overlap) where they will transition from their current oral antipsychotic to include injections of IMP. Subjects currently stabilized on a non-aripiprazole oral antipsychotic who are enrolled to a sparse sampling schedule will continue on their medication and subjects who are enrolled to a robust sampling schedule will switch to 10 to 20 mg oral aripiprazole (dose determined by the investigator). During oral overlap, subjects will take their oral antipsychotic medications concurrently with IMP for 7 days after the first administration of aripiprazole 2M LAI 960 mg or 14 days after the first administration of aripiprazole IM depot 400 mg. Subjects stabilized on oral aripiprazole as their current antipsychotic medication will continue treatment concurrently with IMP at an adjusted dose for either 7 or 14 days. The oral antipsychotic will be discontinued after 7 days of administration of aripiprazole 2M LAI 960 mg and after 14 days of administration of aripiprazole IM depot 400 mg. There will be no oral overlap for subjects who are taking Abilify Maintena® as their current antipsychotic medication. Subjects will not be permitted entry to the trial if taking an LAI other than Abilify Maintena. Subjects with a diagnosis of bipolar I disorder who are taking a mood stabilizer (lithium, valproate, lamotrigine) will be permitted to stay on their mood stabilizer over the course of the trial, and if applicable, to continue treatment with their antidepressant unless the medication is prohibited during the trial (fluoxetine, fluoxetine/olanzapine). Subjects may resume treatment on their previous oral non-aripiprazole antipsychotic after Day 28 if there is evidence of clinical deterioration based on the judgment of the investigator. If a decision is made that a subject may resume previous oral non-aripiprazole antipsychotic medication, the investigator will continue to monitor the subject for safety and clinical stability.
Subject Population:	The trial population will include male and female subjects between the ages of 18 to 64 years of age, inclusive, with a current diagnosis of schizophrenia or bipolar I disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. Approximately 258 subjects (129 per treatment group) will be enrolled into the trial with the expectation that approximately 170 subjects (85 per treatment group) will complete the trial. An interim analysis may be

	conducted to ensure adequate power of the trial. Based on the possible sample size re-estimation in the proposed interim analysis, fewer subjects may be enrolled.

Inclusion/ Exclusion Criteria:	**Key inclusion criteria:**
	• Body mass index of 18 to 35 kg/m^2.
	• Prior history of tolerating aripiprazole and/or Abilify Maintena per the investigator's judgment. If the subject has not established tolerability, then assessment of oral aripiprazole tolerability will be completed within the screening period at least 14 days prior to the first administration of IMP (oral aripiprazole 10 mg/day for 3 consecutive days prior to Day −15).
	• Subjects must be clinically stable (based on investigator judgment, subject/caregiver report, and/or documentation) for at least 2 months prior to screening, AND
	  • On a stable dose of 1 of the following oral atypical antipsychotic medications for at least 2 months prior to screening: aripiprazole (sparse only), brexpiprazole, risperidone, olanzapine, quetiapine, paliperidone, cariprazine, lurasidone, ziprasidone, or asenapine; or Abilify Maintena (sparse only). Additionally, subjects with bipolar I disorder who are stabilized on their current medications for at least 2 months prior to screening may continue their mood stabilizer (lithium, valproic acid, lamotrigine) and antidepressant (citalopram, escitalopram, sertraline).
	  • Other oral non-aripiprazole, antipsychotic medications may be allowed if approved by the medical monitor and sponsor; however, clozapine will not be allowed. (Subjects intended to enroll to the robust sites may not be taking oral aripiprazole or Abilify Maintena as their current atypical antipsychotic.)

	Key exclusion criteria: • Use of any cytochrome P450 (CYP) 2D6 and CYP3A4 inhibitors, or CYP3A4 inducers, within 14 days (fluoxetine or fluoxetine/olanzapine within 28 days) prior to dosing, for the duration of the trial, and 30 days after the last dose of IMP. • Subjects may not receive varenicline beyond screening. If a subject is receiving varenicline at screening, attempts should be made to discontinue the medication, if clinically feasible, to allow potential subjects to enter the trial. • Subjects who participated in any clinical trial involving an oral psychotropic medication within 1 month prior to the

	administration of IMP, as well as subjects who participated in a clinical trial with an aripiprazole depot-containing formulation of a psychotropic medication within the last 1 year or a non-aripiprazole depot formulation within the last 6 months. • Subjects enrolled to the robust sampling schedule must not have taken oral aripiprazole for 30 days, or Abilify Maintena for 1 year, prior to screening. • Subjects currently in an acute relapse of schizophrenia. • Subjects with a current DSM-5 diagnosis other than schizophrenia or bipolar I disorder, including schizoaffective disorder, major depressive disorder, delirium, dementia, amnestic, or other cognitive disorders. Also, subjects with borderline, paranoid, histrionic, or antisocial personality disorder. • Subjects who are considered treatment-resistant to antipsychotic medication (subjects need to have shown a previous response to an antipsychotic medication other than clozapine). • History of any significant drug allergy or known or suspected hypersensitivity, in particular to aripiprazole or other quinolinones.
Trial Site(s):	Approximately 20 trial sites in the United States. Of the 20 trial sites, 4 to 6 will be designated as Robust Sampling Trial Sites.
Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:	Subjects will be randomized (1:1) to receive multiple doses of: • Aripiprazole 2M LAI 960 mg (test) - 2-month injection (total of 4 injections), administered every 56 days (± 2 days), over the course of 32 weeks. • Aripiprazole IM depot 400 mg (reference) - 1-month injection (total of 8 injections), administered every 28 days (± 2 days), over the course of 32 weeks. Aripiprazole 2M LAI will be supplied as aripiprazole IM depot 300 mg/mL ready-to-use single-dose vials and aripiprazole IM depot 400 mg will be supplied as single-dose lyophilized vials. Aripiprazole tablets for oral overlap will be provided from a commercial supply.
Trial Assessments:	Safety: Adverse events (AEs), vital signs, electrocardiograms (ECGs), clinical laboratory monitoring (serum chemistry, hematology, and urinalysis), physical examinations, extrapyramidal symptoms (EPS) (The Simpson-Angus Neurologic Rating Scale [SAS], Abnormal Involuntary Movement Scale [AIMS], and Barnes Akathisia Rating Scale

	[BARS]), Visual Analog Scale (VAS) scores for pain perception, Investigator's Assessment of Most Recent Injection Site, and suicidality via the Columbia-Suicide Severity Rating Scale (C-SSRS). Pharmacokinetics: Plasma concentrations of aripiprazole and its major metabolite, dehydro-aripiprazole, after administration of aripiprazole 2M LAI 960 mg or aripiprazole IM depot 400 mg over the course of 32 weeks, and after 7 days or 14 days of oral overlap of 10 to 20 mg aripiprazole administered with aripiprazole 2M LAI 960 mg or aripiprazole IM depot 400 mg, respectively, starting on Day 1 (first day of dosing). Efficacy: Positive and Negative Syndrome Scale (PANSS; schizophrenia subjects only), Clinical Global Impression - Severity (CGI-S), Clinical Global Impression - Improvement (CGI-I), Subjective Well-being under Neuroleptic Treatment-Short Form (SWN-S), Montgomery-Asberg Depression Rating Scale (MADRS; bipolar subjects only), Young Mania Rating Scale (YMRS; bipolar subjects only), and Clinical Global Impression - Bipolar Version (CGI-BP; bipolar subjects only).
	Screening/Other: Demography; documentation of medical and psychiatric history, birth control methods, and prior/concomitant medications; serum hepatitis and human immunodeficiency virus screen; urine drug and urine or breath alcohol screen; urine pregnancy test; follicle stimulating hormone test; prolactin assessment; measurements of height and weight, and calculation of body mass index; and blood sampling for pharmacogenomics testing and future biospecimen research.
Criteria for Evaluation:	**Primary endpoints:** • Safety and tolerability will be based on reported AEs, vital signs, ECGs, clinical laboratory monitoring (serum chemistry, hematology, and urinalysis), physical examinations, EPS (SAS, AIMS, and BARS), VAS scores for pain perception, Investigator's Assessment of Most Recent Injection Site, and the C-SSRS. • Plasma concentration of aripiprazole 56 days postdose (C_{56}) for aripiprazole 2M LAI 960 mg after the fourth dose or plasma concentration of aripiprazole 28 days postdose (C_{28}) for aripiprazole IM depot 400 mg after the eighth dose over the course of 32 weeks. • The area under the concentration-time curve of aripiprazole from time zero to 56 days postdose (AUC_{0-56}) for aripiprazole 2M LAI 960 mg after the fourth dose or the area

	under the concentration-time curve of aripiprazole from time zero to 28 days postdose (AUC_{0-28}) for aripiprazole IM depot 400 mg after the seventh and eighth doses over the course of 32 weeks, based on the PK data from subjects enrolled to the robust sampling schedule.
	Secondary endpoints: The following PK parameters will be estimated for aripiprazole after the administration of aripiprazole 2M LAI 960 mg and aripiprazole IM depot 400 mg: • Maximum (peak) plasma concentration of the drug (C_{max}), and time to maximum (peak) plasma concentration (t_{max}) after the first and fourth doses of aripiprazole 2M LAI 960 mg. • AUC_{0-56} and C_{56} after the first dose of aripiprazole 2M LAI 960 mg. • AUC_{0-28} and C_{29-56} after the fourth dose of aripiprazole 2M LAI 960 mg. • Peak-to-trough percent fluctuation (PTF%) after the fourth dose of aripiprazole 2M LAI 960 mg. • C_{max}, and t_{max} after the first, seventh, and eighth doses of aripiprazole IM depot 400 mg. • AUC_{0-28} and C_{28} after the first dose of aripiprazole IM depot 400 mg. • PTF% after the eighth dose of aripiprazole IM depot 400 mg. Note: C_{max}, t_{max}, AUC, and PTF% will be determined only from subjects enrolled to the robust sampling schedule; C_{56} and C_{28} will be determined from subjects enrolled to the sparse and robust sampling schedules. After the first dose of IMP, the following PK parameters will be estimated for aripiprazole after aripiprazole 2M LAI 960 mg + 10 to 20 mg oral aripiprazole for 7 days and aripiprazole IM depot 400 mg + 10 to 20 mg oral aripiprazole for 14 days (this endpoint is only for subjects enrolled to the robust sampling schedule): • Plasma concentration of aripiprazole 7 days postdose (C_7) • Plasma concentration of aripiprazole 14 days postdose (C_{14}) The efficacy of aripiprazole IM depot administration in the gluteal muscle will be assessed by the PANSS (schizophrenia subjects only), CGI-S, CGI-I, SWN-S, MADRS (bipolar subjects only), YMRS (bipolar subjects only), and CGI-BP (bipolar

	subjects only).
Statistical Methods:	**Determination of sample size:** To establish the similarity in primary PK variables, the lower bound of the 90% confidence interval (CI) of the geometric means ratio (GMR) of C_{56} and AUC_{0-56} after the fourth dose of aripiprazole 2M LAI 960 mg to C_{28} after the eighth dose and the sum of AUC_{0-28} values after the seventh and eighth doses of aripiprazole IM depot 400 mg should be greater than 80%, respectively. It is estimated that a total of at least 100 subjects (ie, 50 per group) completing the trial will have at least 80% power to ensure that the lower limit of the 90% CI of the GMR of C_{56} after the fourth dose of aripiprazole 2M LAI 960 mg (test) to C_{28} after the eighth dose of aripiprazole IM depot 400 mg (reference) is greater than 0.80, assuming the actual GMR of concentrations is 1.0 and the coefficient of variation (CV) is 46%. Among these 100 subjects, 30 completers enrolled to the robust sampling schedule will provide at least 80% power to ensure that the lower limit of the 90% CI of the GMR of AUC_{0-56} of aripiprazole 2M LAI 960 mg (test) to the sum of AUC_{0-28} values of aripiprazole IM depot 400 mg (reference) after the seventh and eighth doses is greater than 0.80, assuming the actual GMR of concentrations is 1.15 and the CV is 40%. To ensure adequate power of the trial, an interim analysis may be conducted by the Interim Analysis Review Committee (IARC). The final sample size could be increased as per recommendation of the IARC. Assuming a dropout rate of 34%, approximately 152 to 258 subjects will be enrolled to have 100 to 170 completers based on the recommendation of the proposed interim analysis.
	Primary endpoint analyses: Safety assessments including AEs, vital signs, ECGs, clinical laboratory monitoring (serum chemistry, hematology, and urinalysis), physical examinations, EPS (SAS, AIMS, and BARS), VAS scores for pain perception, Investigator's Assessment of Most Recent Injection Site, and suicidality via the C-SSRS will be summarized for the safety sample by treatment group. The mean change from baseline will be provided for vital

	signs, ECGs, clinical laboratory, and EPS assessments by visit, treatment group, and disease type. The incidence of clinically relevant abnormalities in vital sign, ECGs, and clinical laboratory results will be summarized descriptively by visit, treatment group, and disease type. Plasma concentrations of aripiprazole will be analyzed using noncompartmental methods. The following PK parameters will be estimated and summarized descriptively for aripiprazole: C_{56} and AUC_{0-56} of aripiprazole 2M LAI 960 mg after the fourth dose, C_{28} of aripiprazole IM depot 400 mg after the eighth dose, and AUC_{0-28} values of aripiprazole IM depot 400 mg after the seventh and eighth doses over the course of 32 weeks. The 90% CI of GMR of C_{56} of aripiprazole after the fourth injection of aripiprazole 2M LAI 960 mg (test) to C_{28} after the eighth injection of aripiprazole IM depot 400 mg (reference) will be provided. An analysis of variance will be performed on the natural-log transformed PK parameters using the MIXED procedure in the Statistical Analysis System (SAS). The mixed-effects linear model will include treatment group, disease type (if applicable), and PK sampling schedule as fixed effects and subject as a random effect. The least squares means for the 2 treatment groups, their difference, and the 90% CI for their difference will be derived. The antilog of the confidence limits will provide the 90% CI for the GMR of the 2 treatments. For subjects enrolled to the robust sampling schedule, the values of AUC_{0-28} after the seventh and eighth dose of aripiprazole IM depot 400 mg (reference) will be summed up before analyzing by the same method together with AUC_{0-56} after the fourth injection of aripiprazole 2M LAI 960 mg (test). Only subjects who receive a fourth dose of aripiprazole 2M LAI 960 mg or a seventh and/or eighth dose of aripiprazole IM depot 400 mg and have C_{56}, C_{28}, and AUC_{0-28} values, and AUC_{0-56} values determined for the respective treatments will be included in the analysis.

	Secondary endpoint analyses: The secondary PK endpoints will be summarized descriptively. The C_{max}, area under the concentration-time curve (AUC), t_{max}, and PTF% will be summarized based on samples from subjects enrolled to the robust sampling schedule; whereas C_{28} and C_{56} after the first injection will be summarized based on samples from subjects enrolled to the robust and sparse sampling schedules. Efficacy assessments including the PANSS (schizophrenia subjects only), CGI-S, CGI-I, SWN-S, MADRS (bipolar subjects only), YMRS (bipolar subjects only), and CGI-BP (bipolar subjects only) will be summarized for the efficacy sample at each visit by treatment group and disease type, if applicable. These analyses will be performed for both the last observation carried forward and observed case data. In addition, the linear mixed-effects model will be used to explore the effect of the treatment and change from baseline over time, as applicable.
Trial Duration:	The trial will consist of a screening period of up to 30 days and a treatment period of 169 (± 2) days with a follow-up period of 56 (± 2) days after administration of the final dose for the aripiprazole 2M LAI 960 mg treatment group, or a treatment period of 197 days with a follow-up period of 28 (± 2) days after administration of the final dose for the aripiprazole IM depot 400 mg treatment group. Individual participation for both treatment groups will be approximately 255 (± 2) days.

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
2M	2 month
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
anti-HCV	Hepatitis C antibodies
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{∞}	Area under the concentration-time curve from time zero to infinity
AUC_{0-28}	Area under the concentration-time curve of aripiprazole from time zero to 28 days postdose
AUC_{0-56}	Area under the concentration-time curve of aripiprazole from time zero to 56 days postdose
AUC_{0-84}	Area under the concentration-time curve from time zero to 84 days postdose
AUC_t	Area under the concentration-time curve from time zero to time t
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
CGI-BP	Clinical Global Impression - Bipolar Version
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
C_7	Plasma concentration of aripiprazole 7 days postdose
C_{14}	Plasma concentration of aripiprazole 14 days postdose
C_{28}	Plasma concentration of aripiprazole 28 days postdose
C_{56}	Plasma concentration of aripiprazole 56 days postdose
CI	Confidence interval
C_{max}	Maximum (peak) plasma concentration of the drug
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Score
CV	Coefficient of variation
CYP	Cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
D_x	Dopamine receptor where x is the receptor type number
ECG	Electrocardiogram
eCRF	Electronic case report form
EPS	Extrapyramidal symptoms
ET	Early termination
[redacted]	[redacted]
FDA	(United States) Food and Drug Administration
FOCBP	Females of childbearing potential
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMR	Geometric mean ratio

Abbreviation	Definition
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
5-HT_{xx}	5-hydroxytryptamine receptor where xx denotes the receptor type number
IARC	Interim Analysis Review Committee
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IM	Intramuscular
IMP	Investigational medicinal product
IND	Investigational new drug
IRB	Institutional review board
IRE	Immediately reportable event
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
LAI	Long-acting injection
LOCF	Last observation carried forward
MADRS	Montgomery-Asberg Depression Rating Scale
NDA	New Drug Application
OC	Observed case
OPC	Otsuka Pharmaceutical Co.
PANSS	Positive and Negative Syndrome Scale
PK	Pharmacokinetic
PQC	Product quality complaint
PTF%	Peak-to-trough percent fluctuation
QTcF	Corrected QT interval using Fridericia's formula
RTU	Ready-to-use
SAE	Serious adverse event
SAS	The Simpson-Angus Neurologic Rating Scale; Statistical Analysis System
SD	Standard deviation
SWN-S	Subject Well-being under Neuroleptic Treatment-Short Form
$t_{1/2}$	Terminal phase elimination half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum (peak) plasma concentration
ULN	Upper limit of normal
US	United States
VAS	Visual Analog Scale
YMRS	Young Mania Rating Scale

1 Introduction

Aripiprazole (OPC-14597, Lu AF41155) is a dopamine serotonin system stabilizer, for which efficacy is thought to be mediated through a combination of partial agonism at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonism at serotonin 5-HT_{2A} receptors.

Abilify Maintena®, an extended-release suspension for once monthly intramuscular (IM) injection, is indicated for the treatment of schizophrenia at a dose of 400 mg once monthly (deltoid or gluteal IM administration).[1] In addition, Abilify Maintena was approved by the United States (US) Food and Drug Administration (FDA) on 27 Jul 2017 for the maintenance monotherapy treatment of bipolar I disorder in adults (Supplemental New Drug Application [NDA] 202971 S-010 submitted 28 Sep 2016).

This trial will examine the safety, tolerability, and pharmacokinetics (PK) of multiple doses of aripiprazole 2 month (2M) long-acting injectable (LAI) 960 mg injected in the gluteal muscle in adult subjects with schizophrenia or bipolar I disorder over the course of 32 weeks. The aripiprazole 2M LAI 960 mg formulation is an extended-release presentation intended for dosing every 2 months. The extension of the dosing interval for aripiprazole 2M LAI 960 mg is primarily through an increase in the dose while maintaining minimum aripiprazole concentrations that are comparable to aripiprazole IM depot 400 mg after multiple doses.

Please refer to the Investigator's Brochure (IB) for more detailed information on nonclinical data and clinical data for aripiprazole.[1] A brief summary is included below.

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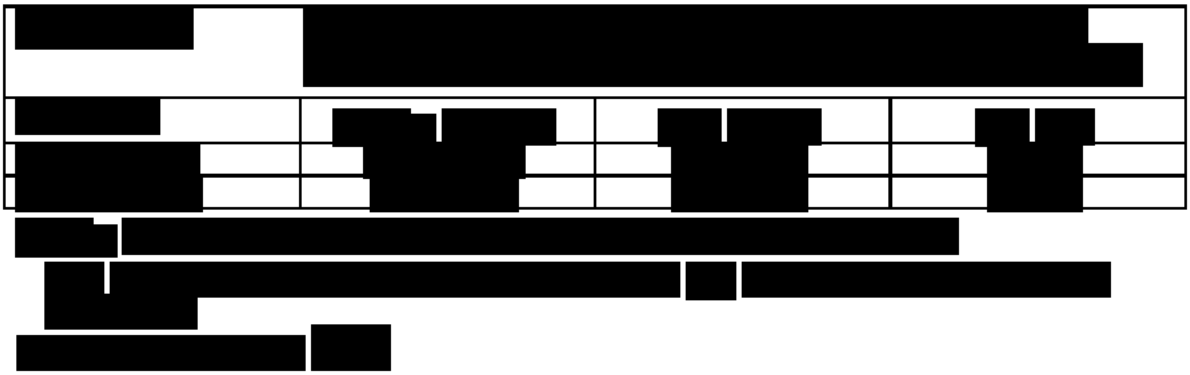

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1.2 Clinical Data

As of 01 Jun 2018, approximately 3591 adult subjects have been exposed to Abilify Maintena in all clinical trials and the safety has been well established. The Abilify Maintena safety profile is similar to that of the Abilify oral tablets, with the exception of injection site reactions, which is an IM depot-specific adverse event (AE); however, the injection site pain does not represent a particular safety concern.[1]

The efficacy of Abilify Maintena for the treatment of schizophrenia was established in:

- A phase 3, short-term (12-week), randomized, double-blind, placebo-controlled trial in acutely relapsed adult subjects with schizophrenia (Trial 31-12-291)
- A phase 3, long-term (52-week), double-blind, placebo-controlled, randomized-withdrawal trial in adult subjects with schizophrenia (Trial 31-07-246)
- A phase 3, long-term (38-week), randomized, double-blind, active-controlled trial in adult subjects with schizophrenia (Trial 31-07-247)

In Trial 31-12-291, the primary endpoint was the change from baseline in Positive and Negative Syndrome Scale (PANSS) total score to Week 10. The key secondary endpoint was the change from baseline in Clinical Global Impression - Severity (CGI-S) assessment scale to Week 10. Abilify Maintena was superior to placebo in improving the PANSS total score at the end of Week 10 (least squares mean change from baseline = −26.8 for Abilify Maintena [400 to 300 mg] and least squares mean change from baseline = −11.7 for placebo). Abilify Maintena also showed improvement in symptoms represented by the CGI-S score mean change from baseline to Week 10.

For Trial 31-07-246, in addition to the PANSS and CGI-S, clinical ratings during this trial included the Clinical Global Impression-Improvement scale and CGI-S of Suicide scale. The primary efficacy endpoint was time from randomization to relapse. The trial was terminated early because maintenance of efficacy was demonstrated at a preplanned interim analysis. The final analysis demonstrated a statistically significantly longer time to relapse in subjects randomized to the Abilify Maintena group compared to placebo-treated subjects. In the placebo group 39.6% of the subjects had progressed to impending relapse, while in the Abilify Maintena group impending relapse occurred in 10% of the subjects. The key secondary efficacy endpoint, percentage of subjects meeting the relapse criteria, was statistically significantly lower in subjects randomized to the Abilify Maintena group (10%) than in the placebo group (40%).

In addition to the above, efficacy was demonstrated in Trial 31-07-247 for registration of Abilify Maintena in the European Union. The results of analysis of the primary efficacy endpoint, the estimated proportion of subjects experiencing impending relapse by the end of Week 26 showed that Abilify Maintena 400 mg/300 mg is noninferior to Abilify oral tablets 10 to 30 mg. The estimated relapse rate by the end of Week 26 was 7.12% for Abilify Maintena and 7.76% for Abilify oral tablets 10 to 30 mg. Further, the noninferiority of Abilify Maintena compared to Abilify oral tablets 10 to 30 mg was supported by the results of the analysis of the PANSS.

The efficacy and safety of Abilify Maintena for the treatment of bipolar I disorder was established in a phase 3, 52-week, randomized, double-blind, placebo-controlled trial (Trial 31-08-250). The primary efficacy endpoint was the time to recurrence of any mood episode, as measured in subjects with bipolar I disorder who had maintained stability on aripiprazole IM depot for at least 8 weeks. The time to recurrence of any mood episode was statistically significantly delayed with aripiprazole IM depot treatment compared with placebo treatment (log-rank test $p < 0.0001$). Aripiprazole IM depot treatment significantly reduced the risk of recurrence of any mood episode over 1 year compared with placebo treatment by approximately half (hazard ratio = 0.451 [Cox proportional hazard model]; 95% confidence interval [CI], 0.299 - 0.678). The proportion of subjects who met the criteria for recurrence of any mood episode was significantly lower with aripiprazole IM depot treatment compared with placebo treatment (26.5% versus 51.1%, Cochran-Mantel-Haenszel test $p < 0.0001$).

1.3 Pharmacokinetics

Abilify Maintena activity is presumably primarily due to the parent drug, aripiprazole, and to a lesser extent, to its major metabolite, dehydro-aripiprazole, which has been

shown to have affinities for D_2 receptors similar to the parent drug and represents about 29% of the parent drug exposure in plasma.

The plasma aripiprazole concentrations after single- and multiple-dose administration of Abilify Maintena are well established. The aripiprazole 2-month RTU formulation at the 960 mg dose is expected to provide plasma concentrations of aripiprazole within the concentration range of Abilify Maintena.

Aripiprazole absorption into the systemic circulation is slow and prolonged following Abilify Maintena administration due to low solubility of aripiprazole particles. The average absorption half-life of aripiprazole from Abilify Maintena is 28 days. The absorption of aripiprazole from Abilify Maintena was complete relative to the IM standard (immediate-release) formulation. The dose-adjusted C_{max} values for the depot formulation were approximately 5% of C_{max} from the IM standard formulation. Following a single-dose administration of Abilify Maintena in the deltoid and gluteal muscle, the extent of absorption (area under the concentration-time curve [AUC]) was similar for both injection sites, but the rate of absorption (C_{max}) was higher following administration to the deltoid muscle.

Based on results from trials with oral administration of aripiprazole, aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 l/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and dehydro-aripiprazole are greater than 99% bound to serum proteins, binding primarily to albumin.

Elimination of aripiprazole is mainly through hepatic metabolism involving 2 cytochrome P450 (CYP) isozymes, CYP2D6 and CYP3A4. Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation.

Following a single oral dose of [^{14}C]-labeled aripiprazole, approximately 27% of the administered radioactivity was recovered in the urine and approximately 60% in the feces. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% was recovered unchanged in the feces.

Based on a population PK evaluation of Abilify Maintena, the total body clearance of aripiprazole was 3.71 L/h in extensive metabolizers of CYP2D6 and approximately 1.88 L/h (approximately 50% lower) in poor metabolizers of CYP2D6.[1]

In the recently completed [redacted] single-dose administration of 780 mg or 1200 mg aripiprazole LAI to the gluteal muscle resulted in, respectively, a roughly 2-and

3-fold increase in aripiprazole C_{max} and exposure (area under the concentration-time curve from time zero to infinity [AUC_∞] and area under the concentration-time curve from time zero to time t [AUC_t]) than previously observed following single-dose administration of 400 mg Abilify Maintena to the gluteal muscle. The ratio of dehydro-aripiprazole to aripiprazole for mean AUC_∞ after administration of 780 mg or 1200 mg aripiprazole LAI (0.34 and 0.31, respectively) was similar to that observed following administration of 400 mg Abilify Maintena (0.28). Administration of 780 mg or 1200 mg aripiprazole LAI resulted in a slightly less than proportional increase in aripiprazole and dehydro-aripiprazole C_{max} and a slightly more than dose proportional increase in exposure (AUC_t and AUC_∞) based on mean values corrected for dose. Administration of 780 mg aripiprazole LAI resulted in shorter median t_{max} values for aripiprazole (25.1 days versus 41.0 days) and dehydro-aripiprazole (29.6 days versus 55.0 days) when compared to the 1200 mg dose. Following administration of 780 mg or 1200 mg aripiprazole 2M LAI, the mean terminal phase elimination half-life ($t_{1/2}$) values for aripiprazole (22.1 days and 20.0 days, respectively) and dehydro-aripiprazole (25.5 days and 22.9 days, respectively) were comparable, and similar to the median $t_{1/2}$ following administration of 400 mg Abilify Maintena (24.0 days). A consistent increase in aripiprazole concentrations followed by a decline and a secondary peak in concentrations were observed following administration of 780 mg or 1200 mg aripiprazole LAI to the gluteal muscle based on examination of mean, median, and individual concentration-time profiles.

1.4 Risks and Benefits

Abilify Maintena is marketed worldwide and is approved for schizophrenia and bipolar I disorder. To date, no unexpected safety concerns have been reported. The most frequently observed adverse reactions for approved indications are weight increased and akathisia.

Based on a 12-week, double-blind, placebo-controlled trial of Abilify Maintena in adult subjects with schizophrenia, the most commonly observed adverse reactions associated with the use of Abilify Maintena (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) were increased weight (16.8% versus 7.0%), akathisia (11.4% versus 3.5%), injection site pain (5.4% versus 0.6%), and sedation (5.4% versus 1.2%).

Based on a double-blind, placebo-controlled, randomized withdrawal (maintenance) trial, the most commonly observed adverse drug reactions that were associated with the use of

Abilify Maintena (incidence of 5% or greater and aripiprazole incidence greater than placebo) were weight increased (22.7%) and akathisia (20.5%).

Other commonly reported adverse reactions (reported in 2% or more of Abilify Maintena-treated subjects and at a greater proportion than in the placebo group) during the trials included the following:

- Eye disorders: vision blurred
- Gastrointestinal disorders: constipation, dry mouth, diarrhea, vomiting, and abdominal discomfort
- Infections and infestations: upper respiratory tract infection
- Investigations: decreased weight, blood creatine phosphokinase increased
- Metabolism and nutrition disorders: increased appetite
- Musculoskeletal and connective tissue disorders: arthralgia, back pain, myalgia, and musculoskeletal pain
- Nervous system disorders: dizziness somnolence, sedation, bradykinesis, and tremor
- Psychiatric disorder: anxiety and depression
- Respiratory, thoracic, and mediastinal: nasal congestion
- Reproductive system and breast disorders: erectile dysfunction

In addition to the above, the list of adverse reactions associated with the use of Abilify Maintena or other antipsychotic/atypical antipsychotic drugs includes the following:

- Neuroleptic malignant syndrome
- Tardive dyskinesia
- Metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain
- Orthostatic hypotension
- Falls
- Sleep apnea
- Leukopenia, neutropenia, and agranulocytosis
- Impairment of judgment, thinking, or motor skills
- Disruption of the body's ability to reduce core body temperature
- Esophageal dysmotility and aspiration
- Hypersensitivity reactions
- Pathological gambling
- Hypersexuality
- Impulse control disorders

Abilify Maintena should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.

Additional detailed information on the risks of aripiprazole can be found in the IB; the trial sites will receive updated versions of the IB on an ongoing basis and should refer to the most recent version of the IB as needed.[1]

2 Trial Rationale and Objectives

2.1 Trial Rationale

The efficacy and safety of Abilify Maintena (aripiprazole IM depot) has been evaluated in adult subjects and is currently approved in the US, Canada, European Union, and Japan. The current approved recommended maintenance dose is 400 mg injected IM once monthly (deltoid or gluteal administration).[1]

This trial will assess the PK of aripiprazole at a higher dose of 960 mg IM injections given at 2-month intervals along with assessments of safety and tolerability to evaluate the feasibility of extension of the dosing interval. Over the 32 weeks of this trial, aripiprazole 2M LAI 960 mg will be administered in 4 injections at 56-day intervals for comparison with aripiprazole IM depot 400 mg administered in 8 injections at 28-day intervals.

2.2 Dosing Rationale

The extension of the dosing interval for the aripiprazole 2M LAI formulation is primarily through an increase in dose (ie, 960 mg). A recently completed single-dose trial evaluated administration of 780 mg or 1200 mg of aripiprazole to the gluteal muscle [redacted] Single-dose administration of 780 mg or 1200 mg aripiprazole LAI to the gluteal muscle resulted in, respectively, roughly a 200% and 300% higher aripiprazole C_{max} and exposure (AUC_{∞} and AUC_t) than previously observed following single-dose administration of 400 mg Abilify Maintena to the gluteal muscle (clinical study report [CSR] 31-11-290, Table 11.5.2.3.2.1-1). The mean $t_{1/2}$ for aripiprazole following administration of 780 mg or 1200 mg aripiprazole 2M LAI to the gluteal muscle (22.1 days and 20.0 days, respectively) was comparable to the $t_{1/2}$ following single-dose administration of 400 mg Abilify Maintena to the gluteal muscle. An interim model was fitted to observed PK data from [redacted] Based on simulations from the interim model, aripiprazole exposure is expected to be comparable or slightly higher after multiple-dose administration of aripiprazole 2M LAI 960 mg compared with 400 mg Abilify Maintena. Based on the simulations, the plasma steady-state of

aripiprazole is predicted to be reached by the fourth administration of aripiprazole 2M LAI 960 mg. Therefore, 4 administrations of aripiprazole 2M LAI 960 mg in the gluteal site were chosen for this trial. A total of 8 administrations of Abilify Maintena (aripiprazole IM depot 400 mg) were chosen to match the treatment duration of subjects receiving aripiprazole 2M LAI 960 mg.

2.3 Trial Objectives

2.3.1 Primary Objectives

The primary objectives of this trial are:

- To determine the safety and tolerability of multiple-dose administrations of aripiprazole in adult subjects with schizophrenia or bipolar I disorder.
- To establish the similarity of aripiprazole concentrations on the last day of the dosing interval following the final administration of aripiprazole into the gluteal muscle site in adult subjects with schizophrenia or bipolar I disorder.
- To establish the similarity of aripiprazole exposure over the dosing interval following the administration of aripiprazole into the gluteal muscle site in adult subjects with schizophrenia or bipolar I disorder.

2.3.2 Secondary Objectives

The secondary objectives of this trial are:

- To determine the PK of aripiprazole.
- To determine aripiprazole concentrations 7 days (C_7) and 14 days (C_{14}) after the first dose of aripiprazole for subjects enrolled to the robust sampling schedule.
- To obtain information on the efficacy of aripiprazole over the course of 32 weeks.

3 Trial Design

3.1 Type/Design of Trial

This is a phase 1b, open-label, multiple-dose, randomized, parallel-arm, multicenter (approximately 20 trial sites) trial in adult subjects with schizophrenia or bipolar I disorder. After a screening period of up to 30 days, eligible subjects will be randomized (1:1) to receive multiple doses of either aripiprazole 2M LAI 960 mg (4 injections) or aripiprazole IM depot 400 mg (8 injections) over the course of 32 weeks. Aripiprazole 2M LAI 960 mg will be administered at 56-day (± 2 days) intervals and aripiprazole IM depot 400 mg will be administered at 28-day (± 2 days) intervals. A final visit will occur 56 (± 2) days after the last dose of aripiprazole 2M LAI 960 mg or 28 (± 2) days

after the last dose of aripiprazole IM depot 400 mg. A schematic of the trial design is provided in Figure 3.1-1.

Randomization to the 2 trial treatments will be stratified by the PK sampling schedule (robust or sparse) and disease type (schizophrenia or bipolar I disorder). Four to 6 trial sites will be designated as Robust Sampling Trial Sites; all other trial sites will be designated as Sparse Sampling Trial Sites. Up to 76 subjects (38 per treatment group) will be enrolled to the robust sampling schedule and 182 subjects (91 per treatment group) will be enrolled to the sparse sampling schedule. If enrollment of the number of subjects required for the robust sampling schedule is completed, the Robust Sampling Trial Sites may enroll additional subjects to the sparse sampling schedule with approval from the sponsor. An interim analysis may be conducted to ensure adequate power of the trial Section 7.1.1. Based on the possible sample size re-estimation in the proposed interim analysis, fewer subjects may be enrolled.

Blood samples for PK analyses will be drawn from subjects at both Robust and Sparse Sampling Trial Sites after the first dose (Day 1) and fourth (final) dose (Day 169) of investigational medicinal product (IMP) for subjects randomized to aripiprazole 2M LAI 960 mg, and after the first dose (Day 1), seventh dose (Day 169), and eighth (final) dose (Day 197) of IMP for subjects randomized to aripiprazole IM depot 400 mg.

Subjects enrolled to the robust sampling schedule who are randomized to aripiprazole 2M LAI 960 mg must be housed in the unit for 21 days after the first and fourth doses of IMP, and will be outpatients for the rest of the trial. Subjects randomized to aripiprazole IM depot 400 mg will stay in the unit for 21 days after administration of the first, seventh, and eighth doses of IMP. Subjects who are not able to accommodate the scheduled stays in the unit may be permitted to have some visits as outpatients with approval from the medical monitor. For any outpatient visit, an unscheduled C-SSRS will be performed.

Subjects enrolled to the sparse sampling schedule will be outpatients for administration of all doses of IMP; however, they may be housed in the unit for up to 21 days after administration of the first dose of IMP at the discretion of the investigator.

Subjects who do not have a history of tolerating aripiprazole will undergo testing to determine tolerability prior to enrollment. Details of tolerability testing are provided in Section 3.2.2.

At the time of administration of the first dose of IMP, subjects will begin a 7- to 14- day period (oral overlap) where they will transition from their current oral antipsychotic to include injections of IMP. Details of the oral overlap period are provided in Section 3.2.3.

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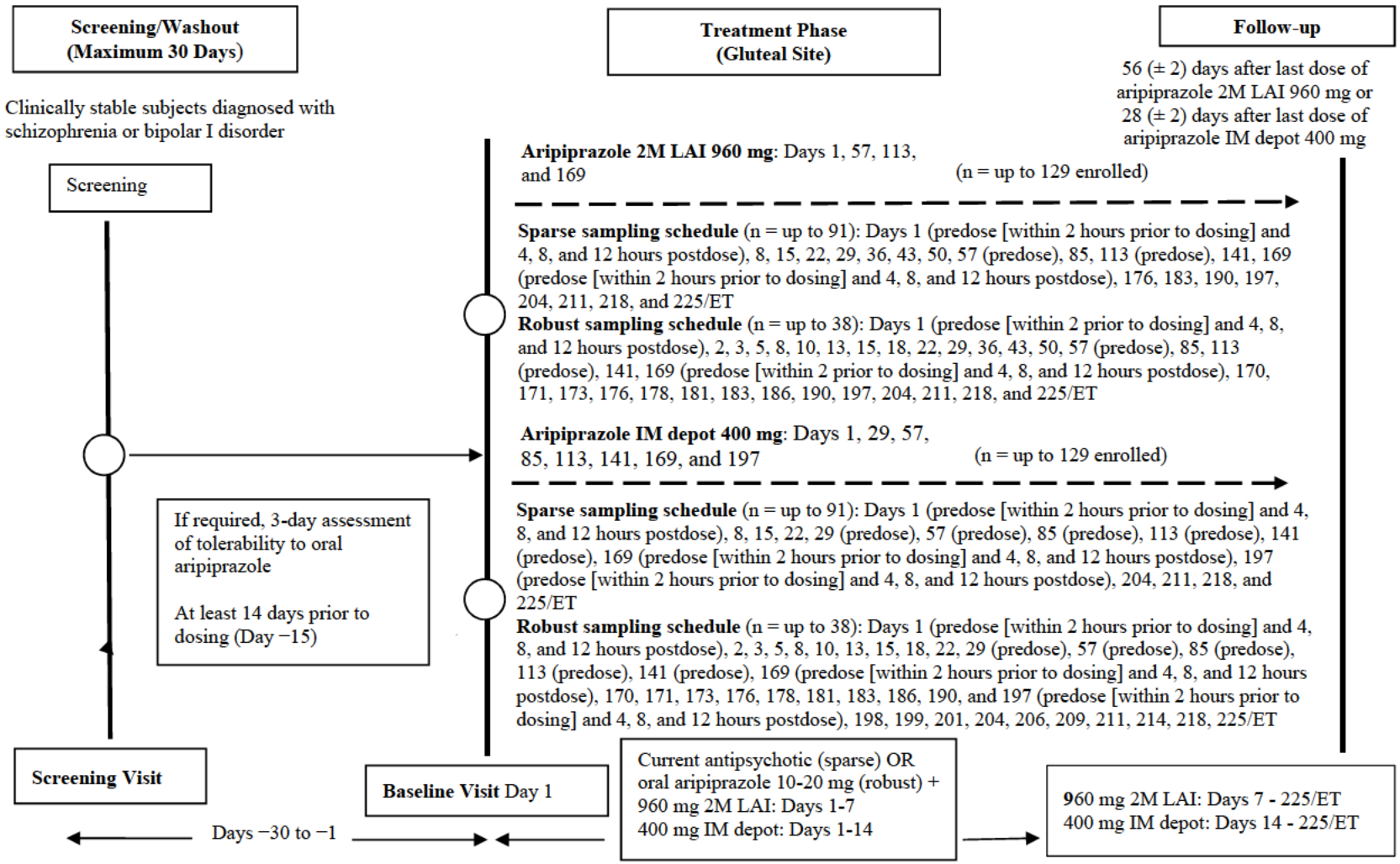

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

3.2.1 Investigational Medicinal Product

The test IMP (aripiprazole 2M LAI) administered in this trial will be supplied as aripiprazole IM depot 300 mg/mL RTU single-dose vials. The reference IMP will be aripiprazole IM depot 400 mg single-dose lyophilized vials. [redacted]

Subjects will be randomized (1:1) to receive multiple doses of:

- Aripiprazole 2M LAI 960 mg (test) - 2-month injection (total of 4 injections), administered every 56 days (± 2 days) over the course of 32 weeks.
- Aripiprazole IM depot 400 mg (reference) - 1-month injection (total of 8 injections), administered every 28 days (± 2 days) over the course of 32 weeks.

The IMP will be administered as a single injection in the gluteal muscle for a total of 4 (960 mg/injection) or 8 (400 mg/injection) injections. Due to possible safety and tolerability issues, a one-time dose reduction is allowed as outlined below:

- Aripiprazole 2M LAI 960 mg: a dose decrease to 660 mg. If the subject has had a decrease to 660 mg, a one-time increase back to 960 mg is then allowed.
- Aripiprazole IM depot 400 mg: a dose decrease to 300 mg. If the subject has had a decrease to 300 mg, a one-time increase back to 400 mg is then allowed.

Syringes and needles will be provided for the injection of IMP. Needles are selected based on the subject's body weight recorded on Day 1 and on each subsequent visit, as specified in Table 3.2.1-1. Care must be taken to avoid inadvertent injection into a blood vessel, as per administration instructions. Detailed instructions on dose preparation and administration will be included in the site manual.

Table 3.2.1-1 Needle Size for IM Depot Injection

Day 1 Body Weight	Needle Type
< 200 lb	22 gauge, 1.5 inch
≥ 200 lb	21 gauge, 2.0 inch

3.2.2 Tolerability Testing

Subjects who do not have a history of tolerating aripiprazole will receive 3 single 10-mg doses of oral aripiprazole on 3 consecutive days (total of 30 mg) in addition to their current oral antipsychotic, mood stabilizer, and if applicable, antidepressant for at least 14 days prior to the first administration of IMP to establish tolerability. Subjects may be housed in the unit during these 3 days at the investigator's discretion.

3.2.3 Oral Overlap

At the time of administration of the first dose of IMP, subjects will begin a 7- to 14-day period (oral overlap) where they will transition from their current oral antipsychotic to include injections of IMP, according to the scenarios described in Table 3.2.3-1.

Subjects currently stabilized on a non-aripiprazole oral antipsychotic who are enrolled to a sparse sampling schedule will continue on their medication and subjects who are enrolled to a robust sampling schedule will switch to 10 to 20 mg oral aripiprazole (dose determined by the investigator). Subjects will take their oral antipsychotic medications concurrently with IMP for 7 days after the first administration of aripiprazole 2M LAI 960 mg or 14 days after the first administration of aripiprazole IM depot 400 mg. The oral antipsychotic will be discontinued after 7 days of administration of aripiprazole 2M LAI 960 mg and after 14 days of administration of aripiprazole IM depot 400 mg.

For subjects currently stabilized on oral aripiprazole, the recommended supplemental oral aripiprazole dose will be reduced to 10 mg/day with the first dose of IMP for subjects with a previous dose of 10 to 20 mg/day or to 15 mg/day for subjects with a previous dose of > 20 to 30 mg/day (Table 3.2.3-2).

There will be no oral overlap for subjects who are taking Abilify Maintena® as their current antipsychotic medication. Subjects who are on Abilify Maintena as their current antipsychotic cannot be enrolled until their next scheduled dose is required as specified in the label, and they cannot receive IMP any earlier than 26 days after the last Abilify Maintena injection. In this scenario, the investigator should carefully consider the screening period and the timing of randomization in relation to the first dose of IMP and previous dose of Abilify Maintena.

Given the addition of a second antipsychotic, investigators should consider reducing the dose of the current oral antipsychotic, mood stabilizer, or antidepressant medications to the mid to lower range of the recommended dose range described in the labeling.

Aripiprazole tablets for oral overlap will be provided from a commercial supply.

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Table 3.2.3-1 Scenarios for Initiation of Oral Aripiprazole Overlap During the First 2 Weeks After the Initiation of IMP

Treatment	PK Sampling Schedule	Current Antipsychotic Medication[a]		
		Abilify Maintena[b] 300 or 400 mg	Oral Aripiprazole[c]	Non-aripiprazole Oral Antipyschotic
Aripiprazole 2M LAI 960 mg	Sparse	No oral overlap	7-day oral overlap with adjusted dose	Continue current antipsychotic for 7 days
	Robust[d]	Not applicable	Not applicable	(Switch to) Oral aripiprazole 10 to 20 mg: 7-day oral overlap
Aripiprazole IM depot 400 mg	Sparse	No oral overlap	14-day oral overlap with adjusted dose	Continue current antipsychotic for 14 days
	Robust[d]	Not applicable	Not applicable	(Switch to) Oral aripiprazole 10 to 20 mg: 14-day oral overlap

[a]Subjects with bipolar I disorder who are taking a mood stabilizer will be permitted to stay on their mood stabilizer over the course of the trial, and if taking an antidepressant, to continue treatment with their antidepressant unless it is unless the medication is prohibited during the trial (eg, fluoxetine, fluoxetine/olanzapine; Table 4.1-1).

[b]Subjects on an LAI other than Abilify Maintena are excluded from the trial. Subjects on Abilify Maintena as their current antipsychotic medication cannot enroll to the robust sampling schedule.

[c]For subjects who are taking oral aripiprazole 10 to 20 mg as their current antipsychotic, the dose will be reduced for the overlap period (Table 3.2.3-2).

[d]In order to be enrolled to the robust sampling schedule, subjects must have demonstrated prior tolerability to aripiprazole, must be stabilized on an existing non-aripiprazole antipsychotic, and must switch to oral aripiprazole on Day 1 for 7 or 14 days depending on the assigned IMP treatment.

Table 3.2.3-2 Dose Adjustment for Initiation of Oral Overlap for Subjects Currently Stabilized on Oral Aripiprazole

Current Dose of Oral Aripiprazole	Adjusted Dose of Oral Aripiprazole
10 - 20 mg	10 mg
> 20 - 30 mg	15 mg

3.2.4 Concurrent Antipsychotic Treatment

During the trial, concurrent antipsychotic treatment will be managed as follows:

- Subjects with a diagnosis of bipolar I disorder who are taking a mood stabilizer (lithium, valproate, lamotrigine) will be permitted to stay on their mood stabilizer over the course of the trial, and if applicable, to continue treatment with their antidepressant (citalopram, escitalopram, sertraline) unless the medication is prohibited during the trial (eg, (fluoxetine, fluoxetine/olanzapine; Table 4.1-1).
- Subjects may resume treatment on their previous oral non-aripiprazole antipsychotic medication after Day 28 if there is evidence of clinical deterioration based on the

judgment of the investigator. If a decision is made that a subject may resume previous oral non-aripiprazole antipsychotic medication, the investigator will continue to monitor the subject for safety and clinical stability.

3.3 Trial Population

The trial population will include male and female subjects between the ages of 18 to 64 years of age, inclusive, with a current diagnosis of schizophrenia or bipolar I disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. Approximately 258 subjects (129 per treatment group) will be enrolled into the trial with the expectation that approximately 170 subjects (85 per treatment group) will complete the trial. An interim analysis may be conducted to ensure adequate power of the trial. Based on the possible sample size re-estimation in the proposed interim analysis, fewer subjects may be enrolled.

Subjects entering the trial must have demonstrated prior tolerability to aripiprazole. In addition, subjects must be clinically stable (based on investigator judgment, subject/caregiver report, and/or documentation) for at least 2 months prior to screening AND must be on a stable dose of 1 of the following oral atypical antipsychotic medications for at least 2 months prior to screening: aripiprazole, brexpiprazole, risperidone, olanzapine, quetiapine, paliperidone, cariprazine, lurasidone, ziprasidone, or asenapine. Other oral non-aripiprazole, antipsychotic medications may be allowed if approved by the medical monitor and sponsor; however, clozapine will not be allowed. Additionally, subjects with bipolar I disorder, who are stabilized on their current medications for at least 2 months prior to screening may continue their mood stabilizer (lithium, valproic acid, lamotrigine) and antidepressant (citalopram, escitalopram, sertraline).

Subjects who are on Abilify Maintena as their current antipsychotic cannot be enrolled until their next scheduled dose is required as specified in the label, and they cannot receive IMP any earlier than 26 days after the last Abilify Maintena injection. In this scenario, the investigator should carefully consider the screening period and the timing of randomization in relation to the first dose of IMP and previous dose of Abilify Maintena.

Subjects taking oral aripiprazole or Abilify Maintena as their current antipsychotic medication cannot be enrolled to the robust sampling schedule (ie, subjects at these trial sites will not enter the screening period if they are taking oral aripiprazole or Abilify Maintena).

At screening, subjects will be assigned a unique identification (ID) number (subject identifier) upon signing the informed consent form (ICF). Subjects who meet the

inclusion criteria and do not fulfill any of the exclusion criteria will be eligible for the trial and will be enrolled as needed.

The trial sites will maintain a list identifying all subjects by their ID number and initials.

Recruitment of replacement subjects for noncompleters will be at the discretion of the sponsor. Noncompleters are defined as subjects who do not attend their last scheduled visit for PK sampling (Section 3.10).

3.4 Eligibility Criteria

Exceptions for eligibility criteria will not be permitted during the trial, either by the investigator or by the medical monitor.

3.4.1 Informed Consent

Informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws) and documented using an electronic informed consent system. The ICF will be approved by the same institutional review board (IRB) that approves this protocol.

Each ICF will comply with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[6] and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any site-specific ICF used in the trial before submission to the IRB.

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s).

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Prospective trial participants will be provided with controlled access to the electronic ICF application by trial site staff. When the trial site staff and the participant agree that the participant has enough information to make an informed decision to participate, the participant will electronically sign in the electronic ICF application and an electronic date and timestamp will be applied to the signature. The subject will be given a printed, signed copy of the ICF. Any other parties required by the IRB (trial site staff, witnesses, or legally authorized representative) are also required to sign electronically and these signatures will be stored with the electronic ICF in accordance with the ICH GCP

Guideline and local regulatory requirements/guidelines. These signatures cannot be altered, removed, or copied.

Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol results in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on trial participation.

As part of the main ICF, subjects will also provide informed consent for phamacogenomic sampling. [redacted]

3.4.2 Inclusion Criteria

Subjects are required to meet the inclusion criteria in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria

1.	Male and female subjects between 18 and 64 years, inclusive.
2.	A current diagnosis of schizophrenia or bipolar I disorder, as defined by DSM-5 criteria.
3.	Body mass index of 18 to 35 kg/m^2.
4.	Good physical health as determined by no clinically significant deviation from normal, in the opinion of the investigator, in medical history, clinical laboratory determination, ECGs, or physical examinations.
5.	Ability to provide written informed consent and/or consent obtained from a legally acceptable representative (as required by the IRB), prior to the initiation of any protocol-required procedures.
6.	Prior history of tolerating aripiprazole and/or Abilify Maintena per the investigator's judgment. If the subject has not established tolerability, then assessment of oral aripiprazole tolerability will be completed within the screening period at least 14 days prior to the first administration of IMP (oral aripiprazole 10 mg/day for 3 consecutive days prior to Day −15).
7.	Subjects must be clinically stable (based on investigator judgment, subject/caregiver report, and/or documentation) for at least 2 months prior to screening AND • On a stable dose of 1 of the following oral atypical antipsychotic medication for at least 2 months prior to screening: aripiprazole (sparse only), brexpiprazole, risperidone, olanzapine, quetiapine, paliperidone, cariprazine, lurasidone, ziprasidone, or asenapine; or Abilify Maintena (sparse only). Additionally, subjects with bipolar I disorder who are stabilized on their current medications for at least 2 months prior to screening may continue their mood stabilizer (lithium, valproic acid, lamotrigine) and antidepressant (citalopram, escitalopram, sertraline). • Other oral non-aripiprazole, antipsychotic medications may be allowed if approved by the medical monitor and sponsor; however, clozapine will not be allowed. (Subjects intended to enroll to the robust sites may not be taking oral aripiprazole or Abilify Maintena as their current atypical antipsychotic.)
8.	Able to understand the nature of trial and follow protocol requirements and procedures.

AEs = adverse events; ECG = electrocardiogram.

3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1.

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Table 3.4.3-1 Exclusion Criteria	
1.	Sexually active males who will not commit to utilizing 2 of the approved birth control methods or who will not remain abstinent during the trial and for 180 days following the last dose of IMP, or have not had an orchiectomy, or sexually active FOCBP who will not commit to utilizing 2 of the approved birth control methods or who will not remain abstinent during the trial and for 150 days following the last dose of IMP. Abstinence will be permitted if it is confirmed and documented at every trial visit. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control depot injections, implant, condom or sponge with spermicide. Note: FOCBP are defined as all women unless they have had an oophorectomy or hysterectomy or have been postmenopausal for 12 consecutive months.
2.	Subjects who have: • Met DSM-5 criteria for substance use disorder within the past 180 days. • A positive drug screen for drugs of abuse (excluding nicotine, alcohol, and marijuana). See note below for exceptions. Note: For those who test positive for alcohol and/or marijuana, and for those who test positive for a drug of abuse for which they have a prescription, the investigator must provide sufficient written rationale and discuss with the medical monitor before attaining clearance to proceed with enrollment. This rationale must include the following: 1) rationale/indication for use, 2) review of patterns of use and frequency of use, and 3) justification to support compliance with the protocol for the intended duration of treatment (eg, based on investigator conversation with the subject).
3.	Use of any CYP2D6 and CYP3A4 inhibitors, or CYP3A4 inducers, within 14 days (fluoxetine or fluoxetine/olanzapine within 28 days) prior to dosing, for the duration of the trial, and 30 days after the last dose of IMP.
4.	Subjects may not receive varenicline beyond screening. If a subject is receiving varenicline at screening, attempts should be made to discontinue the medication, if clinically feasible, to allow potential subjects to enter the trial.
5.	Subjects enrolled to the robust sampling schedule must not have taken oral aripiprazole for 30 days or Abilify Maintena for 1 year, prior to screening.
6.	Females who are pregnant, breast-feeding, lactating, and/or have a positive pregnancy test result prior to receiving IMP. A negative serum pregnancy test must be confirmed prior to the first dose of IMP for all female subjects.
7.	Subjects who participated in any clinical trial involving an oral psychotropic medication within 1 month prior to the administration of IMP, as well as subjects who participated in a clinical trial with an aripiprazole depot-containing formulation of a psychotropic medication within the last 1 year or a non-aripiprazole depot formulation within the last 6 months.
8.	Any major surgery within 30 days prior to enrollment or scheduled/elective surgery during the trial.
9.	Evidence of organ dysfunction or any clinically significant deviation from normal in the physical, electrocardiographic, or clinical laboratory examinations.
10.	Subjects who have a significant risk of committing suicide based on history, routine psychiatric status examination, investigator's judgment, or who have an answer of "yes" on questions 4 or 5 (current or over the last 6 months) on the baseline version of the C-SSRS.
11.	Subjects currently in an acute relapse of schizophrenia.
12.	Subjects with a current DSM-5 diagnosis other than schizophrenia or bipolar I disorder, including schizoaffective disorder, major depressive disorder, delirium, dementia, amnestic, or other cognitive disorders. Also, subjects with borderline, paranoid, histrionic, or antisocial personality disorder.
13.	Subjects who are considered treatment-resistant to an atypical antipsychotic medication (subjects need to have shown a previous response to an antipsychotic medication other than clozapine).
14.	Subjects with a history of neuroleptic malignant syndrome or clinically significant tardive dyskinesia as assessed by the investigator.
15.	Any other sound medical reason as determined by the clinical investigator.

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Table 3.4.3-1 Exclusion Criteria	
16.	History of any significant drug allergy or known or suspected hypersensitivity, in particular to aripiprazole or other quinolinones.
17.	History of or current hepatitis or acquired immunodeficiency syndrome or carriers of HBsAg or anti-HCV, and/or HIV antibodies.
18.	Subjects deemed intolerant of receiving injections.
19.	Subjects who have had electroconvulsive therapy within 2 months of administration of IMP.
20.	The following laboratory test, vital sign, and ECG results are exclusionary: 1) Platelets ≤ 75,000/mm^3 2) Hemoglobin ≤ 9 g/dL 3) Neutrophils, absolute ≤ 1000/mm^3 4) AST > 3x upper limit of normal 5) ALT > 3x upper limit of normal 6) Creatinine ≥ 2 mg/dL 7) Diastolic blood pressure > 105 mmHg 8) QTcF ≥ 450 msec in males or ≥ 470 msec in females, on 2 of 3 time points of triplicate ECGs performed

anti-HCV = hepatitis C antibodies; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C-SSRS = Columbia-Suicide Severity Rating Scale; FOCBP = females of childbearing potential; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; QTcF = corrected QT interval using Fridericia's formula; ULN = upper limit of normal.

Subjects excluded for a positive drug screen for drugs of abuse are not eligible to be rescreened for participation in the trial. For those who test positive for alcohol and/or marijuana, and for those who test positive for a drug of abuse for which they have a prescription, the investigator must provide sufficient written rationale and discuss with the medical monitor before attaining clearance to proceed with enrollment. This rationale must include the following: 1) rationale/indication for use, 2) review of patterns of use and frequency of use, and 3) justification to support compliance with the protocol for the intended duration of treatment (eg, based on investigator conversation with the subject).

Subjects excluded for other reasons may be rescreened at any time if the exclusion characteristic has changed. In the event that the subject is rescreened, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated. Rescreening of subjects is described in Section 3.9.

Electrocardiogram or laboratory outcomes that emerge over the course of the trial that would have been deemed exclusionary during the screening period should be reviewed and discussed with the medical monitor. For this discussion, the investigator is asked to provide an assessment of risk associated with continuation in the trial, and a recommendation for follow-up.

3.5 Endpoints

3.5.1 Primary Endpoints

3.5.1.1 Safety

Safety and tolerability will be based on reported AEs, vital signs, electrocardiograms (ECGs), clinical laboratory monitoring (serum chemistry, hematology, and urinalysis), physical examinations, extrapyramidal symptoms (EPS) (the Simpson-Angus Neurologic Rating Scale [SAS], Abnormal Involuntary Movement Scale [AIMS], and Barnes Akathisia Rating Scale [BARS]), Visual Analog Scale (VAS) scores for pain perception, Investigator's Assessment of Most Recent Injection Site, and suicidality via the Columbia-Suicide Severity Rating Scale (C-SSRS).

3.5.1.2 Pharmacokinetic

The primary PK parameters to be estimated for aripiprazole are as follows:

- Plasma concentration of aripiprazole 56 days postdose (C_{56}) of aripiprazole 2M LAI 960 mg after the fourth dose and plasma concentration of aripiprazole 28 days postdose (C_{28}) of aripiprazole IM depot 400 mg after the eighth dose over the course of 32 weeks.
- AUC_{0-56} for aripiprazole 2M LAI 960 mg after the fourth dose or AUC_{0-28} for aripiprazole IM depot 400 mg after the seventh and eighth doses over the course of 32 weeks, based on the PK data from subjects enrolled to the robust sampling schedule.

3.5.2 Secondary Endpoints

3.5.2.1 Pharmacokinetic

The following PK parameters will be estimated for aripiprazole after the administration of aripiprazole 2M LAI 960 mg and aripiprazole IM depot 400 mg:

- C_{max} and t_{max} after the first and fourth doses of aripiprazole 2M LAI 960 mg.
- AUC_{0-56} and C_{56} after the first dose of aripiprazole 2M LAI 960 mg.
- AUC_{0-28} and AUC_{29-56} after the fourth dose of aripiprazole 2M LAI 960 mg.
- Peak-to-trough percent fluctuation (PTF%) after the fourth dose of aripiprazole 2M LAI 960 mg.
- C_{max} and t_{max} after the first, seventh, and eighth doses of aripiprazole IM depot 400 mg.
- AUC_{0-28} and C_{28} after the first dose of aripiprazole IM depot 400 mg.
- PTF% after the eighth dose of aripiprazole IM depot 400 mg.

Note: C_{max}, t_{max}, AUC, and PTF% will be determined only from subjects enrolled to the robust sampling schedule; C_{56} and C_{28} will be determined from subjects enrolled to the sparse and robust sampling schedule.

After the first dose of IMP, the following PK parameters will be estimated for aripiprazole after administration of aripiprazole 2M LAI 960 mg + oral aripiprazole 10 to 20 mg for 7 days and aripiprazole IM depot 400 mg + oral aripiprazole 10 to 20 mg for 14 days (this endpoint is only for subjects enrolled to the robust sampling schedule):

- Plasma concentration of aripiprazole 7 days postdose (C_7)
- Plasma concentration of aripiprazole 14 days postdose (C_{14})

3.5.2.2 Efficacy

The efficacy of aripiprazole IM depot administration in the gluteal muscle will be assessed by the PANSS (schizophrenia subjects only), CGI-S, Clinical Global Impression - Improvement (CGI-I), Subjective Well-being under Neuroleptic Treatment-Short Form (SWN-S), Montgomery-Asberg Depression Rating Scale (MADRS; bipolar subjects only), Young Mania Rating Scale (YMRS; bipolar subjects only), and Clinical Global Impression - Bipolar Version (CGI-BP; bipolar subjects only).

3.6 Measures to Minimize/Avoid Bias

3.6.1 Randomization

Randomization avoids systematic differences between groups with respect to known or unknown baseline variables that could affect outcome. After a screening period of up to 30 days, eligible subjects will be randomized (1:1) to receive multiple doses of either aripiprazole 2M LAI 960 mg (4 injections) or aripiprazole IM depot 400 mg (8 injections) over the course of 32 weeks. Aripiprazole 2M LAI 960 mg will be administered at 56-day (± 2 days) intervals and aripiprazole IM depot 400 mg will be administered at 28-day (± 2 days) intervals.

Randomization to the 2 trial treatments will be stratified by the PK sampling schedule (robust or sparse) and disease type (schizophrenia or bipolar I disorder).

3.6.2 Blinding

Not applicable; this is an open-label trial.

3.7 Trial Procedures

The trial will consist of a screening period of up to 30 days and a treatment period of 169 (± 2) days with a follow-up period of 56 (± 2) days after administration of the final

dose for the aripiprazole 2M LAI 960 mg treatment group, or a treatment period of 197 (± 2) days with a follow-up period of 28 (± 2) days after administration of the final dose for the aripiprazole IM depot 400 mg treatment group. Individual participation for both treatment groups will be approximately 255 (± 2) days.

Subjects will provide signed informed consent prior to performing any trial procedures. Screening procedures will be performed Day −30 to −1 to determine eligibility to participate in the trial.

Subjects who meet the inclusion criteria and do not fulfill any of the exclusion criteria will return to the trial site for check-in on Day −1 or Day 1. Predose assessments and administration of IMP will be performed on Day 1. After the predose assessments, subjects will be randomized (1:1) to receive multiple doses of either aripiprazole 2M LAI 960 mg (4 injections) or aripiprazole IM depot 400 mg (8 injections) over the course of 32 weeks. Aripiprazole 2M LAI 960 mg will be administered in 56-day (± 2 days) intervals and aripiprazole IM depot 400 mg injections will be administered in 28-day (± 2 days) intervals.

All visits may occur within ± 2 days of the target visit date for subjects enrolled to the sparse sampling schedule and for subjects enrolled to the robust sampling schedule after discharge from the clinical unit. All subjects must return to the clinical trial site for scheduled doses, assessments, and PK sample collections. A final visit will occur 56 (± 2) days after the last dose of aripiprazole 2M LAI 960 mg or 28 (± 2) days after the last dose of aripiprazole IM depot 400 mg.

Trial assessments are summarized by visit in Table 3.7-1 for subjects enrolled to the sparse sampling schedule and in Table 3.7-2 for subjects enrolled to the robust sampling schedule.

Table 3.7-1 Schedule of Assessments: Sparse Sampling

	Screening	Check-in[a]	Days ± 2											
	Day −30 to −1	Day 1	8 15 22	29	36[b] 43[b] 50[b]	57	85	113	141	169	176[b] 183[b] 190[b]	197	204 211 218	225/ ET
Informed consent	X													
Confirmation of current diagnosis of schizophrenia or bipolar I disorder by DSM-5	X													
Inclusion/exclusion criteria	X	X												
Demographic information	X													
Medical and psychiatric history	X	X												
Discontinue prohibited medication/taper off restricted medication	X													
Document birth control methods	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer IMP tolerability dose	X													
Admit to trial site clinic	X[a,c]	X[d]												
Discharge from trial site clinic	X[c]		X[d]											
Outpatient visits to trial site clinic	X			X	X	X	X	X	X	X		X	X	X
Serum hepatitis and HIV screen	X													
Urine drug screen and urine or breath alcohol screen	X	X												
Urine pregnancy test[e]	X	X		X		X	X	X	X	X		X		X
FSH[f]	X													
Hematology, clinical chemistry, and urinalysis	X	X		X										X
Serum prolactin assessment	X	X		X										
Physical examination	X	X	X Day 15	X				X						X
Weight	X	X		X		X	X	X	X	X		X		X

Table 3.7-1 Schedule of Assessments: Sparse Sampling

	Screening	Check-in[a]	Days ± 2											
	Day −30 to −1	Day 1	8 15 22	29	36[b] 43[b] 50[b]	57	85	113	141	169	176[b] 183[b] 190[b]	197	204 211 218	225/ ET
Height and BMI	X													
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X	X Day 15	X		X		X						X
C-SSRS[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EPS assessments (SAS, AIMS, and BARS)	X	X	X	X		X	X	X	X	X		X		X
PANSS (schizophrenia subjects only), CGI-S, and SWN-S[j]	X	X		X		X		X		X		X		X
CGI-I						X								X
MADRS, YMRS, and CGI-BP (all 3 are in bipolar subjects only)[j]	X	X		X		X		X		X		X		X
Randomization		X												
Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy		X	X	X	X	X	X	X	X	X	X	X	X	X
VAS (perceived pain at injection site)[k]		X		X[i]		X	X[i]	X	X[i]	X		X[i]		
Investigator's assessment of injection site[k]		X		X[i]		X	X[i]	X	X[i]	X		X[i]		
Administer IMP: aripiprazole 2M LAI 960 mg		X				X		X		X				
Administer IMP: aripiprazole IM depot 400 mg		X		X		X	X	X	X	X		X		
PK blood draw		X[l,m]	X[n]	X[b,n] X[i,l,m]	X[n]	X[l,m]	X[b,n] X[i,l,m]	X[l,m]	X[b,n] X[i,l,m]	X[l,m]	X[n]	X[b,n] X[i,l,m]	X[n]	X[n]
CYP2D6 pharmacogenomics blood draw		X												

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Table 3.7-1 Schedule of Assessments: Sparse Sampling

	Screening	Check-in[a]	Days ± 2											
	Day −30 to −1	Day 1	8 15 22	29	36[b] 43[b] 50[b]	57	85	113	141	169	176[b] 183[b] 190[b]	197	204 211 218	225/ ET
[redacted]														
Assess and record AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BMI = body mass index; ET = early termination; FSH = follicle stimulating hormone.

Note: This table presents the trial assessment time points and should be used in conjunction with Table 3.7.3-1 (screening assessments and activities) and Table 3.7.3-2 (assessments and activities by trial period/trial day).

Note: Trial visits that are 2 days apart should be done in relation to the last dosing (ie, the ± 2 day window does not apply).

Note: Activities designated with superscript b are those performed in subjects randomized to aripiprazole 2M LAI 960 mg; activities designated with superscript i are those performed in subjects randomized to aripiprazole IM depot 400 mg. Activities without subscripts are performed in all subjects.

[a]Subjects can be admitted to the clinic on Day −1, but tests and assessments are to be done on Day 1.

[b]Subjects who receive aripiprazole 2M LAI 960 mg.

[c]If tolerability to aripiprazole must be established, there will be a 3-day assessment of oral aripiprazole tolerability during the screening period. At the discretion of the investigator, subjects **may be** housed in the unit for the assessment. Subjects having tolerability assessed as outpatients **must be** contacted by the site each day during the assessment period.

[d]Subjects may be housed in the clinical unit for up to 21 days following administration of the first dose of IMP, but **only** at the discretion of the investigator. Subjects who are outpatients during the 7- to 14-day oral overlap period **must be** contacted by the site every day during this period.

[e]Female subjects of childbearing potential only. If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test which may be performed by a local laboratory.

[f]Perimenopausal and postmenopausal female subjects only.

[g]Vital signs will include systolic and diastolic blood pressure, heart rate, and body temperature. Vital signs will be obtained prior to PK blood draws and ECGs at the nominal time points, where applicable. At each time point, blood pressure (systolic and diastolic) and heart rate will be taken after subjects have been in the supine position for at least 5 minutes and again after subjects have been standing for 2 minutes, but not more than 3 minutes. Body temperature will be taken with the subject in the supine position (ie, only once).

[h]The Baseline/Screening version of the C-SSRS will be administered at the screening visit and the Since Last Visit version of the C-SSRS will be administered at all other time points.

[i]Subjects who receive aripiprazole IM depot 400 mg.

[j]All efficacy assessments will be performed prior to PK blood draws and dosing, where applicable.

[k]Completed approximately 30 minutes prior to injection and 1 hour (± 15 minutes) postdose.

[l]Predose samples are collected up to 2 hours prior to dosing.

[m]Postdose samples are collected at 4, 8, and 12 hours after dosing.

[n]PK samples on non-dosing days should be obtained between 8 AM and 2 PM on the specified trial day. For outpatients, the non-dosing day must be within ± 2 days of the specified day.

Table 3.7-2 Schedule of Assessments: Robust Sampling

	Screening	**Check-in[a]**	**Days (Clinical Unit)**					**Days ± 2 (Outpatient)**							**Days (Clinical Unit) Days ± 2 (Outpatient)**					**Day ± 2**
	Day −30 to −1	**Day 1**	**2 3 5**	**8**	**10 13**	**15**	**18**	**22**	**29**	**36[b] 43[b] 50[b]**	**57**	**85**	**113**	**141**	**169**	**170 171 173 176 178 181 183 186 190**	**197**	**198[c] 199[c] 201[c] 206[c] 209[c] 214[c]**	**204 211 218**	**225/ ET**
Informed consent	X																			
Confirmation of current diagnosis of schizophrenia or bipolar I disorder by DSM-5	X																			
Inclusion/exclusion criteria	X	X																		
Demographic information	X																			
Medical and psychiatric history	X	X																		
Discontinue prohibited medication/taper off restricted medication	X																			
Document birth control methods	X	X						X	X	X	X	X	X	X	X	X Day 190	X	X	X	X
Administer IMP tolerability dose	X																			
Admit to trial site clinic	X[a,d]	X													X		X[c]			
Discharge from trial site clinic	X[d]							X								X Day 190			X[c] Day 218	
Outpatient visits to trial site clinic	X								X	X	X	X	X	X			X[b]		X[b]	X

Table 3.7-2 Schedule of Assessments: Robust Sampling

	Screening	Check-in[a]	Days (Clinical Unit)					Days ± 2 (Outpatient)							Days (Clinical Unit) Days ± 2 (Outpatient)					Day ± 2
	Day −30 to −1	Day 1	2 3 5	8	10 13	15	18	22	29	36[b] 43[b] 50[b]	57	85	113	141	169	170 171 173 176 178 181 183 186 190	197	198[c] 199[c] 201[c] 206[c] 209[c] 214[c]	204 211 218	225/ ET
Serum hepatitis and HIV screen	X																			
Urine drug screen and urine or breath alcohol screen	X	X																		
Urine pregnancy test[e]	X	X							X		X	X	X	X	X		X			X
FSH[f]	X																			
Hematology, clinical chemistry, and urinalysis	X	X							X											X
Serum prolactin assessment	X	X							X											
Physical examination	X	X				X			X				X							X
Weight	X	X							X		X	X	X	X	X		X			X
Height and BMI	X																			
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X				X			X		X		X							X
C-SSRS[h]	X	X						X	X	X	X	X	X	X	X	X[b] Day 190	X		X Days 204[b], 211[b], 218[b,c]	X

Table 3.7-2 Schedule of Assessments: Robust Sampling

	Screening	Check-in[a]	Days (Clinical Unit)					Days ± 2 (Outpatient)							Days (Clinical Unit) Days ± 2 (Outpatient)					Day ± 2
	Day −30 to −1	Day 1	2 3 5	8	10 13	15	18	22	29	36[b] 43[b] 50[b]	57	85	113	141	169	170 171 173 176 178 181 183 186 190	197	198[c] 199[c] 201[c] 206[c] 209[c] 214[c]	204 211 218	225/ ET
EPS assessments (SAS, AIMS, and BARS)	X	X		X		X		X	X		X	X	X	X	X		X			X
PANSS (schizophrenia subjects only), CGI-S, and SWN-S[i]	X	X							X		X		X		X		X			X
CGI-I											X									X
MADRS, YMRS, and CGI-BP (bipolar subjects only)[i]	X	X							X		X		X		X		X			X
Randomization		X																		
Record adjusted current oral antipsychotic, mood stabilizer, or antidepressant therapy		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VAS (perceived pain at injection site)[j]		X							X[c]		X	X[c]	X	X[c]	X		X[c]			
Investigator's assessment of injection site[j]		X							X[c]		X	X[c]	X	X[c]	X		X[c]			
Administer IMP: aripiprazole 2M LAI 960 mg		X									X		X		X					

Table 3.7-2 Schedule of Assessments: Robust Sampling

	Screening	Check-in[a]	Days (Clinical Unit)					Days ± 2 (Outpatient)							Days (Clinical Unit) Days ± 2 (Outpatient)					Day ± 2
	Day −30 to −1	Day 1	2 3 5	8	10 13	15	18	22	29	36[b] 43[b] 50[b]	57	85	113	141	169	170 171 173 176 178 181 183 186 190	197	198[c] 199[c] 201[c] 206[c] 209[c] 214[c]	204 211 218	225/ ET
Administer IMP: aripiprazole IM depot 400 mg		X							X		X	X	X	X	X		X			
PK blood draw		X[k,l]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[b,m] X[c,k]	X[b,m]	X[k]	X[b,m] X[c,k]	X[k]	X[b,m] X[c,k]	X[k,l]	X[m]	X[b,m] X[c,k,l]	X[c,m]	X[m]	X[m]
CYP2D6 pharmacogenomics blood draw		X																		
[redacted]		[redacted]																		
Assess and record AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Record prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Note: This table presents the trial assessment time points and should be used in conjunction with Table 3.7.3-1 (screening assessments and activities) and Table 3.7.3-3 (assessments and activities by trial period/trial day).

Note: Trial visits that are 2 days apart should be done in relation to the last dosing (ie, the ± 2-day window does not apply).

Note: Activities designated with superscript b are those performed in subjects randomized to aripiprazole 2M LAI 960 mg; activities designated with superscript c are those performed in subjects randomized to aripiprazole IM depot 400 mg. Activities without subscripts are performed in all subjects.

[a]Subjects can be admitted to the clinic on Day −1, but tests and assessments are to be done on Day 1.

[b]Subjects who receive aripiprazole 2M LAI 960 mg. These subjects must be housed in the unit for 21 days after administration of the first (Day 1) and fourth doses of IMP, and will be outpatients for the rest of the trial. Subjects who are not able to accommodate the scheduled stays in the unit may be permitted to have some visits as outpatients with approval from the medical monitor. For any outpatient visit, an unscheduled C-SSRS will be performed.

[c]Subjects who receive aripiprazole IM depot 400 mg. These subjects will stay in the unit for 21 days after administration of the first (Day 1), seventh (Day 169), and eighth (Day 197) doses of IMP. Subjects who are not able to accommodate the scheduled stays in the unit may be permitted to have some visits as outpatients with approval from the medical monitor. For any outpatient visit, an unscheduled C-SSRS will be performed.

[d]If tolerability to aripiprazole must be established, there will be a 3-day assessment of oral aripiprazole tolerability during the screening period. At the discretion of the investigator, subjects **may be** housed in the unit for the assessment. Subjects having tolerability assessed as outpatients **must be** contacted by the site each day during the assessment period.

[e]Female subjects of childbearing potential only. If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.

[f]Perimenopausal and postmenopausal female subjects only.

[g]Vital signs will include systolic and diastolic blood pressure, heart rate, and body temperature. Vital signs will be obtained prior to PK blood draws and ECGs at the nominal time points, where applicable. At each time point, blood pressure (systolic and diastolic) and heart rate will be taken after subjects have been in the supine position for at least 5 minutes and again after subjects have been standing for 2 minutes, but not more than 3 minutes. Body temperature will be taken with the subject in the supine position (ie, only once).

[h]The Baseline/Screening version of the C-SSRS will be administered at the screening visit and the Since Last Visit version of the C-SSRS will be administered at all other time points.

[i]All efficacy assessments will be performed prior to PK blood draws and dosing, where applicable.

[j]Completed approximately 30 minutes prior to injection and 1 hour (± 15 minutes) postdose.

[k]Predose samples are collected up to 2 hours prior to dosing.

[l]Postdose samples are collected at 4, 8, and 12 hours after dosing.

[m]PK samples on non-dosing days should be obtained between 8 AM and 2 PM on the specified trial day. For outpatients, the non-dosing day must be within ± 2 days of the specified day.

3.7.1 General Inpatient Procedures

Subjects enrolled to the robust sampling schedule who receive aripiprazole 2M LAI 960 mg must be housed in the clinical unit for 21 days after the first (Day 1) and last administration of investigational medicinal product (IMP), and will be outpatients for the rest of the trial. Subjects who receive aripiprazole IM depot 400 mg will stay in the unit for 21 days after administration of the first (Day 1), seventh (Day 169), and eighth (Day 197) doses of IMP. Subjects who are not able to accommodate the scheduled stays in the unit may be permitted to have some visits as outpatients with approval of the medical monitor. For any outpatient visit, an unscheduled C-SSRS will be performed.

Subjects enrolled to the sparse sampling schedule will be outpatients for all administrations of IMP but, at the discretion of the investigator, may be housed in the unit for up to 21 days after the first administration of IMP (Section 3.1). Subjects staying in the clinical unit may check in to the clinical unit on Day −1; however, all predose assessments will be performed on Day 1 prior to the administration of IMP.

While housed in the clinical unit, standard meals consisting of breakfast, lunch, dinner, and an evening snack will be provided at times that do not interfere with trial activities and assessments. There are no restrictions on food or water intake prior to administration of aripiprazole IM depot. Food and water will be permitted ad libitum according to the clinical unit's standard operating procedures.

Subjects will be required to present to the clinical trial site for efficacy and safety assessments and collection of PK samples on the days specified in Table 3.7-1 for subjects enrolled to the sparse sampling schedule and in Table 3.7-2 for subjects enrolled to the robust sampling schedule.

3.7.2 Dietary Requirements

With the exception of alcohol consumption, which is prohibited (Section 4), there are no other dietary restrictions in this trial.

3.7.3 Schedule of Assessments

Subjects are to continue their current oral antipsychotic, mood stabilizer, or antidepressant medications as specified in Section 3.1.

At each time point for vital signs, blood pressure (systolic and diastolic) and heart rate will be taken after subjects have been in the supine position for at least 5 minutes and again after subjects have been standing for 2 minutes, but not more than 3 minutes. Body temperature will be taken with the subject in the supine position (ie, only once). The ECG will be recorded after the subject has been supine and at rest for ≥ 10 minutes prior to the

first ECG and subjects will remain supine through the final ECG. Vital signs will be obtained prior to PK blood draws and ECGs at the nominal time points, where applicable, and ECGs will be collected prior to PK blood draws at the nominal time points, where applicable. If a PK blood sample cannot be drawn at the designated postdose times, a window of ± 15 minutes for each blood draw is acceptable, with the exact time recorded. All efficacy assessments will be performed prior to PK blood draws and dosing, where applicable.

After predose assessments on Day 1, subjects will be randomized 1:1 to receive multiple doses of aripiprazole 2M LAI 960 mg or aripiprazole IM depot 400 mg over the course of 32 weeks.

Whenever a serious adverse event (SAE) occurs, blood samples should be collected as early as is feasible to measure the plasma concentrations of aripiprazole.

Assessments performed at the screening visit are summarized in Table 3.7.3-1.

Assessments are summarized by trial day in Table 3.7.3-2 for subjects enrolled to the sparse sampling schedule and in Table 3.7.3-3 for subjects enrolled to the robust sampling schedule. Trial visits that are 2 days apart should be done in relation to the last dosing (ie, the ± 2-day window does not apply).

Table 3.7.3-1 Screening Assessments and Procedures

Days −30 to −1
Subjects will be screened within the 30-day period prior to Day 1. Screening procedures will consist of the following: • Review trial procedures and information regarding the nature of the trial and obtain informed consent prior to any trial-related procedures. • Confirm that subject is stable on current oral antipsychotic, mood stabilizer, or antidepressant medications as deemed by the investigator. • Confirm current diagnosis of schizophrenia or bipolar I disorder, as defined by DSM-5 criteria. • Review inclusion and exclusion criteria. • Collect demographic information. • Document medical and psychiatric history. • Document birth control methods. • Record current oral antipsychotic, mood stabilizer, or antidepressant medications (or Abilify Maintena, if applicable). • Discontinue prohibited medications or taper off restricted medications as per Section 4 (if applicable). • Record concomitant medications and review for prohibited or restricted medications. All medications taken within 30 days prior to starting IMP will be recorded. • Record AEs. • Perform a physical examination. • Measure height and weight and calculate BMI. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer a 12-lead safety ECG in triplicate (5 minutes apart). • Collect samples for serum hepatitis and HIV screen. • Perform a urine drug screen and a urine or breath alcohol screen. • Perform a urine pregnancy test (FOCBP only). • Collect a sample for FSH testing (perimenopausal and postmenopausal female subjects only). • Collect clinical laboratory samples for hematology, clinical chemistry, prolactin assessment, and urinalysis. • Administer the Baseline/Screening version of the C-SSRS (predose). • Assess EPS (SAS, AIMS, and BARS). • Administer the PANSS (schizophrenia subjects only). • Administer CGI-S scale and SWN-S (all subjects). • Administer the MADRS, YMRS, and CGI-BP (bipolar subjects only). **For subjects who do not have a history of tolerating aripiprazole:** • Administer 3 single 10-mg doses of oral aripiprazole on 3 consecutive days (total of 30 mg) at least 14 days prior to the administration of IMP. Subjects may be housed in the unit during these 3 days at the investigator's discretion. Subjects having tolerability assessed as outpatients **must be** contacted by the site each day during the assessment period. Subjects will continue to take their current oral antipsychotic, mood stabilizer, or antidepressant therapy

Table 3.7.3-1 Screening Assessments and Procedures
during this period. The subjects' antipsychotic, mood stabilizer, or antidepressant treatment should **not** be discontinued but dose adjustments are allowed as determined by the investigator.

Table 3.7.3-2 Sparse Sampling Schedule Trial Days and Activities
Day 1 ± 2 days (outpatient, all subjects)
Predose: • Admit subjects to the trial site clinic (if the subject has not been admitted on Day −1). Subjects may be housed in the clinical unit for up to 21 days following the first administration of IMP, if the investigator deems it necessary. Subjects will be discharged on Day 22. • Confirm that the subject is stable on current oral antipsychotic, mood stabilizer, or antidepressant medications, as deemed by the investigator. • Review inclusion and exclusion criteria. • Update medical and psychiatric history (if applicable). • Document birth control methods. • Record current oral antipsychotic, mood stabilizer, or antidepressant medications (or Abilify Maintena, if applicable). • Record prior and concomitant medications and review for prohibited or restricted medications. • Assess and record AEs. • Adjust current oral antipsychotic, mood stabilizer, or antidepressant medications. • Subjects will continue their current oral antipsychotic, mood stabilizer, or antidepressant medications for the first 7 days following aripiprazole 2M LAI 960 mg and the first 14 days following aripiprazole IM depot 400 mg. For this reason, investigators should consider reducing the dose of the oral antipsychotic, mood stabilizer, or antidepressant medications to the mid to lower range of the recommended dose range described in the labeling. Subjects who are outpatients during the 7- to 14-day oral overlap period **must be** contacted by the site every day during this period. • Perform a urine drug screen and a urine or breath alcohol screen. • Perform a urine pregnancy test (FOCBP only). • Perform a physical examination. • Measure weight (choice of needle size for IM dosing will be based upon this weight). • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer a 12-lead safety ECG in triplicate (5 minutes apart). • Collect clinical laboratory samples for hematology, clinical chemistry, prolactin assessment, and urinalysis. • Administer the Since Last Visit version of the C-SSRS. • Assess EPS (SAS, AIMS, and BARS). • Administer the PANSS (schizophrenia subjects only). • Administer CGI-S scale and SWN-S (all subjects). • Administer the MADRS, YMRS, and CGI-BP (bipolar subjects only).

Table 3.7.3-2 Sparse Sampling Schedule Trial Days and Activities

[redacted] • Draw blood for CYP2D6 pharmacogenomics. • Randomize to aripiprazole 2M LAI 960 mg or aripiprazole IM depot 400 mg. • Draw a PK blood sample within 2 hours prior to dosing. • Assessment and confirmation by the investigator that the injection site is appropriate 30 minutes prior to IMP injection. • Have subjects complete a VAS of the level of perceived pain at the injection site approximately 30 minutes prior to IMP injection. • Administer IMP (aripiprazole IM depot 400 mg or aripiprazole 2M LAI 960 mg). .**Postdose**: • Have subjects complete a VAS of the level of perceived pain at the injection site 1 hour (± 15 minutes) postdose. • Assessment of the injection site by the investigator completed approximately 1 hour (± 15 minutes) postdose. • Draw a PK blood sample at 4, 8, and 12 hours postdose.
Day 8 ± 2 days (outpatient, all subjects)
• Document birth control methods. • Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs. • Subjects assigned to aripiprazole 2M LAI 960 mg will **discontinue** taking 10 to 20 mg oral aripiprazole and/or current oral antipsychotic (as applicable) until the end of the trial. Subjects may resume treatment on their previous oral non-aripiprazole antipsychotic after Day 28, if there is evidence of clinical deterioration based on the judgment of the investigator. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer the Since Last Visit version of the C-SSRS. • Assess EPS (SAS, AIMS, and BARS). • Draw a PK blood sample between 8 AM and 2 PM.
Days 15 and 22 ± 2 days (outpatient, all subjects)
• Document birth control methods. • Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs. • Perform a physical examination (Day 15 only). • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer the Since Last Visit version of the C-SSRS. • Administer a 12-lead safety ECG in triplicate (5 minutes apart; Day 15 only).

Table 3.7.3-2 Sparse Sampling Schedule Trial Days and Activities

- Assess EPS (SAS, AIMS, and BARS).
- Draw a PK blood sample between 8 AM and 2 PM.
- Discharge subjects housed in the clinical unit for an optional stay after completing all activities (Day 22).

Day 29 ± 2 days (outpatient, all subjects)

- Document birth control methods.
- Record concomitant medications and review for prohibited or restricted medications.
- Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy.
- Assess and record AEs.
- Perform a urine pregnancy test (FOCBP only).
- Perform a physical examination.
- Measure weight.
- Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature).
- Administer a 12-lead safety ECG in triplicate (5 minutes apart).
- Collect clinical laboratory samples for hematology, clinical chemistry, prolactin assessment, and urinalysis.
- Administer the Since Last Visit version of the C-SSRS (predose).
- Assess EPS (SAS, AIMS, and BARS) (predose).
- Administer the PANSS (schizophrenia subjects only).
- Administer CGI-S scale and SWN-S (all subjects).
- Administer the MADRS, YMRS, and CGI-BP (bipolar subjects only).

For subjects who receive aripiprazole 2M LAI 960 mg:

- Draw a PK blood sample between 8 AM and 2 PM.

For subjects who receive aripiprazole IM depot 400 mg:

Predose:

- Draw a PK blood sample within 2 hours prior to dosing.
- Assessment and confirmation by the investigator that the injection site is appropriate 30 minutes prior to IMP injection.
- Have subjects complete a VAS of the level of perceived pain at the injection site approximately 30 minutes prior to IMP injection.
- Administer IMP.

Postdose:

- Have subjects complete a VAS of the level of perceived pain at the injection site approximately 1 hour (± 15 minutes) postdose.
- Assessment of the injection site by the investigator completed approximately 1 hour (± 15 minutes) postdose.

Table 3.7.3-2 Sparse Sampling Schedule Trial Days and Activities
Days 36, 43, and 50 ± 2 days (outpatient, subjects receiving aripiprazole 2M LAI 960 mg)
• Document birth control methods. • Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer the Since Last Visit version of the C-SSRS. • Draw a PK blood sample between 8 AM and 2 PM.
Day 57 ± 2 days (outpatient, all subjects)
Predose: • Document birth control methods. • Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs. • Perform a urine pregnancy test (FOCBP only). • Measure weight. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer a 12-lead safety ECG in triplicate (5 minutes apart). • Administer the Since Last Visit version of the C-SSRS. • Assess EPS (SAS, AIMS, and BARS). • Administer the PANSS (schizophrenia subjects only). • Administer CGI-S scale, CGI-I scale, and SWN-S (all subjects). • Administer the MADRS, YMRS, and CGI-BP (bipolar subjects only). • Draw a PK blood sample (within 2 hours prior to dosing). • Assessment and confirmation by the investigator that the injection site is appropriate 30 minutes prior to IMP injection. • Have subjects complete a VAS of the level of perceived pain at the injection site completed approximately 30 minutes prior to IMP injection. • Administer IMP. **Postdose**: • Have subjects complete a VAS of the level of perceived pain at the injection site approximately 1 hour (± 15 minutes) postdose. • Assessment of the injection site by the investigator completed approximately 1 hour (± 15 minutes) postdose.
Day 85 ± 2 days (outpatient, all subjects)
• Document birth control methods.

Table 3.7.3-2 Sparse Sampling Schedule Trial Days and Activities

- Record concomitant medications and review for prohibited or restricted medications.
- Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy.
- Assess and record AEs.
- Perform a urine pregnancy test (FOCBP only).
- Measure weight.Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature).
- Administer the Since Last Visit version of the C-SSRS (predose).
- Assess EPS (SAS, AIMS, and BARS) (predose).

For subjects who receive aripiprazole 2M LAI 960 mg:

- Draw a PK blood sample between 8 AM and 2 PM.

For subjects who receive aripiprazole IM depot 400 mg:

Predose:

- Draw a PK blood sample (within 2 hours prior to dosing).
- Assessment and confirmation by the investigator that the injection site is appropriate 30 minutes prior to IMP injection.
- Have subjects complete a VAS of the level of perceived pain at the injection site approximately 30 minutes prior to IMP injection.
- Administer IMP.

Postdose:

- Have subjects complete a VAS of the level of perceived pain at the injection site approximately 1 hour (± 15 minutes) postdose.
- Assessment of the injection site by the investigator completed approximately 1 hour (± 15 minutes) postdose.

Day 113 ± 2 days (outpatient, all subjects)

Predose:

- Document birth control methods.
- Record concomitant medications and review for prohibited or restricted medications.
- Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy.
- Assess and record AEs.
- Perform a urine pregnancy test (FOCBP only).
- Perform a physical examination.
- Measure weight.
- Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature).
- Administer a 12-lead safety ECG in triplicate (5 minutes apart).
- Administer the Since Last Visit version of the C-SSRS.

Table 3.7.3-2 Sparse Sampling Schedule Trial Days and Activities
• Assess EPS (SAS, AIMS, and BARS). • Administer the PANSS (schizophrenia subjects only). • Administer CGI-S scale and SWN-S (all subjects). • Administer the MADRS, YMRS, and CGI-BP (bipolar subjects only).Draw a PK blood sample within 2 hours prior to dosing. • Assessment and confirmation by the investigator that the injection site is appropriate 30 minutes prior to IMP injection. • Have subjects complete a VAS of the level of perceived pain at the injection site approximately 30 minutes prior to IMP injection. • Administer IMP (aripiprazole IM depot 400 mg or aripiprazole 2M LAI 960 mg). **Postdose**: • Have subjects complete a VAS of the level of perceived pain at the injection site 1 hour (± 15 minutes) postdose. • Assessment of the injection site by the investigator completed approximately 1 hour (± 15 minutes) postdose.
Day 141 ± 2 days (outpatient, all subjects)
• Document birth control methods. • Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs. • Perform a urine pregnancy test (FOCBP only). • Measure weight. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer the Since Last Visit version of the C-SSRS (predose). • Assess EPS (SAS, AIMS, and BARS) (predose). **For subjects who receive aripiprazole 2M LAI 960 mg:** • Draw a PK blood sample between 8 AM and 2 PM. **For subjects who receive aripiprazole IM depot 400 mg:** **Predose**: • Draw a PK blood sample (within 2 hours prior to dosing). • Assessment and confirmation by the investigator that the injection site is appropriate 30 minutes prior to IMP injection. • Have subjects complete a VAS of the level of perceived pain at the injection site approximately 30 minutes prior to IMP injection. • Administer IMP.

Table 3.7.3-2 Sparse Sampling Schedule Trial Days and Activities
Postdose: • Have subjects complete a VAS of the level of perceived pain at the injection site approximately 1 hour (± 15 minutes) postdose. • Assessment of the injection site by the investigator completed approximately 1 hour (± 15 minutes) postdose.
Day 169 ± 2 days (outpatient, all subjects)
Predose: • Document birth control methods. • Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs. • Perform a urine pregnancy test (FOCBP only). • Measure weight. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer the Since Last Visit version of the C-SSRS. • Assess EPS (SAS, AIMS, and BARS). • Administer the PANSS (schizophrenia subjects only). • Administer CGI-S scale and SWN-S (all subjects). • Administer the MADRS, YMRS, and CGI-BP (bipolar subjects only). • Draw a PK blood sample within 2 hours prior to dosing. • Assessment and confirmation by the investigator that the injection site is appropriate 30 minutes prior to IMP injection. • Have subjects complete a VAS of the level of perceived pain at the injection site approximately 30 minutes prior to IMP injection. • Administer IMP (aripiprazole IM depot 400 mg or aripiprazole 2M LAI 960 mg). **Postdose**: • Have subjects complete a VAS of the level of perceived pain at the injection site 1 hour (± 15 minutes) postdose. • Assessment of the injection site by the investigator completed approximately 1 hour (± 15 minutes) postdose. • Draw a PK blood sample at 4, 8, and 12 hours postdose.
Days 176, 183, and 190 ± 2 days (outpatient, subjects receiving aripiprazole 2M LAI 960 mg)
• Document birth control methods. • Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer the Since Last Visit version of the C-SSRS.

Table 3.7.3-2 Sparse Sampling Schedule Trial Days and Activities

- Draw a PK blood sample between 8 AM and 2 PM.

Day 197 ± 2 days (outpatient, all subjects)

- Document birth control methods.
- Record concomitant medications and review for prohibited or restricted medications.
- Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy.
- Assess and record AEs.
- Perform a urine pregnancy test (FOCBP only).
- Measure weight and calculate BMI.
- Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature).
- Administer the Since Last Visit version of the C-SSRS.
- Assess EPS (SAS, AIMS, and BARS).
- Administer the PANSS (schizophrenia subjects only).
- Administer CGI-S scale and SWN-S (all subjects).
- Administer the MADRS, YMRS, and CGI-BP (bipolar subjects only).

Subjects who receive aripiprazole 2M LAI 960 mg only:

- Draw a PK blood sample between 8 AM and 2 PM.

Subjects who receive aripiprazole IM depot 400 mg only:

Predose:

- Assessment and confirmation by the investigator that the injection site is appropriate 30 minutes prior to IMP injection.
- Have subjects complete a VAS of the level of perceived pain at the injection site approximately 30 minutes prior to IMP injection.
- Draw a PK blood sample within 2 hours prior to dosing.
- Administer IMP.

Postdose:

- Have subjects complete a VAS of the level of perceived pain at the injection site 1 hour (± 15 minutes) postdose.
- Assessment of the injection site by the investigator completed approximately 1-hour (± 15 minutes) postdose.
- Draw a PK blood sample 4, 8, and 12 hours postdose.

Days 204, 211, and 218 ± 2 days (outpatient, all subjects)

- Document birth control methods.
- Record prior and concomitant medications and review for prohibited or restricted medications.
- Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy.

Table 3.7.3-2 Sparse Sampling Schedule Trial Days and Activities
• Assess and record AEs. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer the Since Last Visit version of the C-SSRS. • Draw a PK blood sample between 8 AM and 2 PM.
Day 225/Early Termination ± 2 days (outpatient, all subjects)
• Document birth control methods. • Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs. • Perform a urine pregnancy test (FOCBP only). • Perform a physical examination. • Measure weight. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer a 12-lead safety ECG in triplicate (5 minutes apart). • Collect hematology, clinical chemistry, and urinalysis clinical laboratory samples. • Administer the Since Last Visit version of the C-SSRS. • Assess EPS (SAS, AIMS, and BARS). • Administer the PANSS (schizophrenia subjects only). • Administer CGI-S scale and SWN-S (all subjects). • Administer the MADRS, YMRS, and CGI-BP (bipolar subjects only). • Draw a PK blood sample between 8 AM and 2 PM.

Table 3.7.3-3 Robust Sampling Schedule Trial Days and Activities

Day 1
Predose:
• Admit subjects to the trial site clinic (if the subject has not been admitted on Day −1). Subjects must be housed in the clinical unit for 21 days following the first administration of aripiprazole 2M LAI 960 mg or aripiprazole IM depot 400 mg (Section 3.1).
• Confirm that the subject is stable on current oral antipsychotic, mood stabilizer or antidepressant medications, as deemed by the investigator.
• Review inclusion and exclusion criteria.
• Update medical and psychiatric history (if applicable).
• Subjects will switch from their current oral antipsychotic to 10 to 20 mg of oral aripiprazole (dose determined by the investigator) for 7 days after the first administration of aripiprazole 2M LAI 960 mg and for 14 days after the first administration of aripiprazole IM depot 400 mg. Subjects who are outpatients during the 7- to 14-day oral overlap period **must be** contacted by the site every day during this period.
• Document birth control methods.
• Record prior and concomitant medications and review for prohibited or restricted medications.
• Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant medications.
• Assess and record AEs.
• Perform a urine drug screen and a urine or breath alcohol screen.
• Perform a urine pregnancy test (FOCBP only).
• Perform a physical examination.
• Measure height and weight (choice of needle size for IM dosing will be based upon this weight); calculate BMI.
• Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature) prior to dosing.
• Administer a 12-lead safety ECG in triplicate (5 minutes apart).
• Collect clinical laboratory samples for hematology, clinical chemistry, prolactin assessment, and urinalysis.
• Administer the Since Last Visit version of the C-SSRS (predose).
• Assess EPS (SAS, AIMS, and BARS).
• Administer the PANSS (schizophrenia subjects only).
• Administer CGI-S scale and SWN-S (all subjects).
• Administer the MADRS, YMRS, and CGI-BP (bipolar subjects only).
• Randomize subjects to aripiprazole 2M LAI 960 mg or aripiprazole IM depot 400 mg.
• Draw a PK blood sample within 2 hours prior to dosing.
• Collect pharmacogenomics blood sample to determine the CYP2D6 metabolizer status.
[redacted]
• Assessment and confirmation by the investigator that the injection site is appropriate 30 minutes prior to IMP injection.
• Have subjects complete a VAS of the level of perceived pain at the injection site approximately 30 minutes prior to IMP injection.
• Administer IMP (subjects randomized to aripiprazole IM depot 400 mg and subjects randomized to aripiprazole 2M LAI 960 mg).

Table 3.7.3-3 Robust Sampling Schedule Trial Days and Activities
Postdose:
• Have subjects complete a VAS of the level of perceived pain at the injection site 1 hour (± 15 minutes) postdose.
• Assessment of the injection site by the investigator completed approximately 1 hour (± 15 minutes) postdose.
• Draw a PK blood sample 4, 8, and 12 hours postdose.
Days 2, 3, and 5 (inpatient, all subjects)
• Record concomitant medications and review for prohibited or restricted medications.
• Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy.
• Assess and record AEs.
• Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature).
• Draw a PK blood sample between 8 AM and 2 PM.
Day 8 (inpatient, all subjects)
• Subjects assigned to aripiprazole 2M LAI 960 mg will **discontinue** taking 10 to 20 mg oral aripiprazole and/or current oral antipsychotic (as applicable) until the end of the trial. Subjects may resume treatment on their previous oral non-aripiprazole antipsychotic after Day 28, if there is evidence of clinical deterioration based on the judgment of the investigator.
• Record concomitant medications and review for prohibited or restricted medications.
• Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy.
• Assess and record AEs.
• Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature).
• Assess EPS (SAS, AIMS, and BARS).
• Draw a PK blood sample between 8 AM and 2 PM.
Days 10 and 13 (inpatient, all subjects)
• Record concomitant medications and review for prohibited or restricted medications.
• Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy.
• Assess and record AEs.
• Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature).
• Draw a PK blood sample between 8 AM and 2 PM.
Days 15, 18, and 22 (inpatient, all subjects)
• Subjects assigned to aripiprazole IM depot 400 mg will **discontinue** taking 10 to 20 mg oral aripiprazole and/or current oral antipsychotic (as applicable) from Day 15 until the end of the trial. Subjects may resume treatment on their previous oral non-aripiprazole antipsychotic after Day 28, if there is evidence of clinical deterioration based on the judgment of the investigator.
• Document birth control methods (Day 22 only).
• Record concomitant medications and review for prohibited or restricted medications.
• Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy.

Table 3.7.3-3 Robust Sampling Schedule Trial Days and Activities
• Assess and record AEs. • Perform a physical examination (Day 15 only). • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer a 12-lead safety ECG in triplicate (5 minutes apart; Day 15 only). • Administer the Since Last Visit version of the C-SSRS (Day 22 only; predose). • Assess EPS (SAS, AIMS, and BARS) (Days 15 and 22 only). • Draw a PK blood sample between 8 AM and 2 PM. • Discharge subjects from clinical unit after completing all activities (Day 22).
Day 29 ± 2 days (outpatient, all subjects)
• Document birth control methods. • Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs • Perform a urine pregnancy test (FOCBP only). • Perform a physical examination. • Measure weight. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer a 12-lead safety ECG in triplicate (5 minutes apart). • Collect clinical laboratory samples for hematology, clinical chemistry, prolactin assessment, and urinalysis. • Administer the Since Last Visit version of the C-SSRS (predose). • Assess EPS (SAS, AIMS, and BARS) (predose). • Administer the PANSS (schizophrenia subjects only). • Administer CGI-S scale and SWN-S (all subjects). • Administer the MADRS, YMRS, and CGI-BP (bipolar subjects only). **For subjects who receive aripiprazole 2M LAI 960 mg:** • Draw a PK blood sample between 8 AM and 2 PM. **For subjects who receive aripiprazole IM depot 400 mg:** **Predose**: • Draw a PK blood sample within 2 hours prior to dosing. • Assessment and confirmation by the investigator that the injection site is appropriate 30 minutes prior to IMP injection.

Table 3.7.3-3 Robust Sampling Schedule Trial Days and Activities
• Have subjects complete a VAS of the level of perceived pain at the injection site approximately 30 minutes prior to IMP injection. • Administer IMP. **Postdose**: • Have subjects complete a VAS of the level of perceived pain at the injection site approximately 1 hour (± 15 minutes) postdose. • Assessment of the injection site by the investigator completed approximately 1 hour (± 15 minutes) postdose.
Days 36, 43, and 50 ± 2 days (outpatient, subjects receiving aripiprazole 2M LAI 960 mg)
• Document birth control methods. • Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer the Since Last Visit version of the C-SSRS. • Draw a PK blood sample between 8 AM and 2 PM.
Day 57 ± 2 days (outpatient, all subjects)
Predose: • Document birth control methods. • Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs. • Perform a urine pregnancy test (FOCBP only). • Measure weight. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer a 12-lead safety ECG in triplicate (5 minutes apart). • Administer the Since Last Visit version of the C-SSRS (predose). • Assess EPS (SAS, AIMS, and BARS). • Administer the PANSS (schizophrenia subjects only). • Administer CGI-S scale and SWN-S (all subjects). • Administer the MADRS, YMRS, and CGI-BP (bipolar subjects only). • Draw a PK blood sample (within 2 hours prior to dosing). • Assessment and confirmation by the investigator that the injection site is appropriate 30 minutes prior to IMP injection.

Table 3.7.3-3 Robust Sampling Schedule Trial Days and Activities
• Have subjects complete a VAS of the level of perceived pain at the injection site approximately 30 minutes prior to IMP injection. • Administer IMP. **Postdose**: • Have subjects complete a VAS of the level of perceived pain at the injection site 1 hour (± 15 minutes) postdose. • Assessment of the injection site by the investigator completed approximately 1 hour (± 15 minutes) postdose.
Day 85 ± 2 days (outpatient, all subjects)
• Document birth control methods. • Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs. • Perform a urine pregnancy test (FOCBP only). • Measure weight. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer the Since Last Visit version of the C-SSRS (predose). • Assess EPS (SAS, AIMS, and BARS) (predose). **For subjects who receive aripiprazole 2M LAI 960 mg:** • Draw a PK blood sample between 8 AM and 2 PM. **For subjects who receive aripiprazole IM depot 400 mg:** **Predose**: • Draw a PK blood sample within 2 hours prior to dosing. • Assessment and confirmation that the injection site is appropriate by the investigator 30 minutes prior to IMP injection. • Have subjects complete a VAS of the level of perceived pain at the injection site approximately 30 minutes prior to IMP injection. • Administer IMP. **Postdose**: • Have subjects complete a VAS of the level of perceived pain at the injection site approximately 1 hour (± 15 minutes) postdose. • Assessment of the injection site by the investigator completed approximately 1 hour (± 15 minutes) postdose.
Day 113 ± 2 days (outpatient, all subjects)
Predose: • Document birth control methods.

Table 3.7.3-3 Robust Sampling Schedule Trial Days and Activities
• Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs. Perform a urine pregnancy test (FOCBP only). • Perform a physical examination. • Measure weight. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer a 12-lead safety ECG in triplicate (5 minutes apart). • Administer the Since Last Visit version of the C-SSRS (predose). • Assess EPS (SAS, AIMS, and BARS). • Administer the PANSS (schizophrenia subjects only). • Administer CGI-S scale and SWN-S (all subjects). • Administer the MADRS, YMRS, and CGI-BP (bipolar subjects only). • Draw a PK blood sample (within 2 hours prior to dosing). • Assessment and confirmation by the investigator that the injection site is appropriate 30 minutes prior to IMP injection. • Have subjects complete a VAS of the level of perceived pain at the injection site approximately 30 minutes prior to IMP injection. • Administer IMP (subjects randomized to aripiprazole IM repot 400 mg and subjects randomized to aripiprazole 2M LAI 960 mg). **Postdose:** • Have subjects complete a VAS of the level of perceived pain at the injection site 1 hour (±15 minutes) postdose. • Assessment of the injection site by the investigator completed approximately 1 hour (± 15 minutes) postdose.
Day 141 ± 2 days (outpatient, all subjects)
• Document birth control methods. • Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs. • Perform a urine pregnancy test (FOCBP only). • Measure weight. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer the Since Last Visit version of the C-SSRS (predose). • Assess EPS (SAS, AIMS, and BARS) (predose).

Table 3.7.3-3 Robust Sampling Schedule Trial Days and Activities
For subjects who receive aripiprazole 2M LAI 960 mg: • Draw a PK blood sample between 8 AM and 2 PM. **For subjects who receive aripiprazole IM depot 400 mg:** **Predose**: • Draw a PK blood sample within 2 hours prior to dosing. • Assessment and confirmation by the investigator that the injection site is appropriate 30 minutes prior to IMP injection. • Have subjects complete a VAS of the level of perceived pain at the injection site approximately 30 minutes prior to IMP injection. • Administer IMP. **Postdose**: • Have subjects complete a VAS of the level of perceived pain at the injection site approximately 1 hour (±15 minutes) postdose. Assessment of the injection site by the investigator completed approximately 1 hour (±15 minutes) postdose.
Day 169 (inpatient, all subjects)
Predose: • Admit subjects to the trial site clinic. Subjects must be housed in the clinical unit for 21 days following administration of aripiprazole 2M LAI 960 mg or aripiprazole IM depot 400 mg (Section 3.1). Subjects will be discharged on Day 190. • Document birth control methods. • Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs. • Perform a urine pregnancy test (FOCBP only). • Measure weight. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer the Since Last Visit version of the C-SSRS prior to dosing. • Assess EPS (SAS, AIMS, and BARS). • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer the Since Last Visit version of the C-SSRS prior to dosing. • Assess EPS (SAS, AIMS, and BARS). • Administer the PANSS (schizophrenia subjects only). • Administer CGI-S scale and SWN-S (all subjects).

Table 3.7.3-3 Robust Sampling Schedule Trial Days and Activities
• Administer the MADRS, YMRS, and CGI-BP (bipolar subjects only). • Draw a PK blood sample (within 2 hours prior to dosing). • Assessment and confirmation by the investigator that the injection site is appropriate 30 minutes prior to IMP injection. • Have subjects complete a VAS of the level of perceived pain at the injection site approximately 30 minutes prior to IMP injection. • Administer IMP (subjects randomized to aripiprazole IM repot 400 mg and subjects randomized to aripiprazole 2M LAI 960 mg). **Postdose**: • Have subjects complete a VAS of the level of perceived pain at the injection site 1 hour (± 15 minutes) postdose. • Assessment of the injection site by the investigator completed approximately 1 hour (± 15 minutes) postdose. • Draw a PK blood sample at 4, 8, and 12 hours postdose.
Days 170, 171, 173, 176, 178, 181, 183, 186, and 190 (inpatient, all subjects)
• Document birth control methods (Day 190 only). • Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer the Since Last Visit version of the C-SSRS for subjects randomized to aripiprazole 2M LAI 960 mg only (Day 190). • Draw a PK blood sample between 8 AM and 2 PM. • Discharge subjects from clinical unit after completing all activities (Day 190).
Day 197 (inpatient, subjects receiving aripiprazole IM depot 400 mg) **Day 197 ± 2 days (outpatient, subjects receiving aripiprazole 2M LAI 960 mg)**
Subjects receiving aripiprazole IM depot 400 mg: • Admit subjects to the trial site clinic. Subjects must be housed in the clinical unit for 21 days following the administration of aripiprazole IM depot 400 mg (Section 3.1). Subjects will be discharged from the unit on Day 218. **All subjects:** • Document birth control methods. • Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs. • Perform a urine pregnancy test (FOCBP only). • Measure weight. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature).

Table 3.7.3-3 Robust Sampling Schedule Trial Days and Activities
• Administer the Since Last Visit version of the C-SSRS (predose). • Administer the PANSS (schizophrenia subjects only). • Administer CGI-S scale and SWN-S (all subjects). • Administer the MADRS, YMRS, and CGI-BP (bipolar subjects only). **Subjects who receive aripiprazole 2M LAI 960 mg only:** • Draw a PK blood sample between 8 AM and 2 PM. **Subjects who receive aripiprazole IM depot 400 mg only:** **Predose:** • Assessment and confirmation by the investigator that the injection site is appropriate 30 minutes prior to IMP injection. • Have subjects complete a VAS of the level of perceived pain at the injection site approximately 30 minutes prior to IMP injection. • Draw a PK blood sample within 2 hours prior to dosing. • Administer IMP. **Postdose**: • Have subjects complete a VAS of the level of perceived pain at the injection site 1 hour (± 15 minutes) postdose. • Assessment of the injection site by the investigator completed approximately 1-hour (± 15 minutes) postdose. • Draw a PK blood sample at 4, 8, and 12 hours postdose.
Days 198, 199, 201, 206, 209, 214 (inpatient, subjects receiving aripiprazole IM depot 400 mg) **No visits for subjects receiving aripiprazole 2M LAI 960 mg**
• Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Draw a PK blood sample between 8 AM and 2 PM.
Days 204, 211, and 218 (inpatient, subjects receiving aripiprazole IM depot 400 mg) **± 2 days (outpatient, subjects receiving aripiprazole 2M LAI 960 mg)**
• Document birth control methods (outpatients: all days; inpatients: Day 218 only). • Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant therapy. • Assess and record AEs. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature).

Table 3.7.3-3 Robust Sampling Schedule Trial Days and Activities
• Administer the Since Last Visit version of the C-SSRS to subjects randomized to aripiprazole IM Depot 400 mg only on Day 218. • Administer the Since Last Visit version of the C-SSRS to subjects randomized to aripiprazole 2M LAI 960 mg on each outpatient Days 204, 211, and 218. • Draw a PK blood sample between 8 AM and 2 PM. • Discharge subjects randomized to aripiprazole IM Depot 400 mg from the clinical unit after completing all activities (Day 218).
Day 225/Early Termination ± 2 days (outpatient, all subjects)
• Document birth control methods. • Record concomitant medications and review for prohibited or restricted medications. • Record adjustment of current oral antipsychotic, mood stabilizer, or antidepressant medications. • Assess and record AEs. • Perform a urine pregnancy test (FOCBP only). • Perform a physical examination. • Measure weight. • Take vital signs (systolic and diastolic blood pressure, heart rate, and body temperature). • Administer a 12-lead safety ECG in triplicate (5 minutes apart). • Collect hematology, clinical chemistry, and urinalysis clinical laboratory samples. • Administer the Since Last Visit version of the C-SSRS. • Assess EPS (SAS, AIMS, and BARS). • Administer the PANSS (schizophrenia subjects only). • Administer CGI-S scale and SWN-S (all subjects). • Administer the MADRS, YMRS, and CGI-BP (bipolar subjects only). • Draw a PK blood sample between 8 AM and 2 PM.

3.7.4 Prior and Concomitant Medications

The investigator will record all medications and therapies taken by the subject from 30 days prior to signing of informed consent through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and/or secondary objectives) on the electronic case report form (eCRF). The investigator will record all medications and therapies taken by the subject for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) on the eCRF.

3.7.5 Efficacy Assessments

The efficacy assessments including PANSS (schizophrenia subjects only), CGI-S, CGI-I, SWN-S, MADRS (bipolar subjects only), YMRS (bipolar subjects only), and CGI-BP (bipolar subjects only) will be administered by trained trial site staff at the time points presented in the schedule of assessments (Table 3.7-1 for sparse sampling and Table 3.7-2 for robust sampling). All efficacy assessments will be performed prior to PK blood draws and dosing, where applicable.

3.7.5.1 Positive and Negative Syndrome Scale Rating Criteria

The PANSS consists of 3 subscales containing a total of 30 symptom constructs.[7] For each symptom construct, severity is rated on a 7-point scale, with a score of 1 indicating the absence of symptoms and a score of 7 indicating extremely severe symptoms. The symptom constructs for each subscale are as follows:

1) Positive Subscale (7 positive symptom constructs: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility),
2) Negative Subscale (7 negative symptom constructs: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking), and
3) General Psychopathology Subscale (16 symptom constructs: somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance).

The PANSS will be administered using the Structured Clinical Interview (SCI) PANSS.[8] Instructions for administering this instrument will be provided to the trial site. A copy of the PANSS assessment with complete rating criteria is required as source documentation.

Direct entry of the PANSS item scores on the eCRF without verifiable source documentation is not acceptable.

3.7.5.2 Clinical Global Impression - Severity

The severity of illness for each subject will be rated using the CGI-S scale.[9] To assess CGI-S, the rater or investigator will answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" Response choices include: 0 = not assessed; 1 = normal, not ill at all; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill subjects.

3.7.5.3 Clinical Global Impression - Improvement Scale

The improvement of illness for each subject will be rated using the CGI-I scale.[9] To assess CGI-I, the rater or investigator will rate the subject's total improvement whether or not it is due entirely to drug treatment. All responses will be compared with the subject's condition at baseline. Response choices include: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. Direct entry of the CGI-I score on the eCRF without verifiable source documentation is not acceptable.

3.7.5.4 Subjective Well-being under Neuroleptic Treatment-Short Form

The subject's feeling of their own well-being will be assessed using the 20-question SWN-S.[8] The SWN- S is a validated self-report instrument to evaluate the subject's perception of well-being while receiving antipsychotic medication. Subjects will complete the questionnaire without discussing any of the items with others to avoid suggestive external manipulation. The questionnaire consists of 20 items and 5 subscales (mental functioning, social integration, emotional regulation, physical functioning, and self-control) whose items follow in random order. For items marked with a '+', response choices and scoring are as follows: not at all = 1, hardly at all = 2, a little = 3, somewhat = 4, much = 5, very much = 6. For items marked with a '-', the scoring is reversed; response choices and scoring are as follows: not at all = 6, hardly at all = 5, a little = 4, somewhat = 3, much = 2, very much = 1.

3.7.5.5 Montgomery-Asberg Depression Rating Scale

The MADRS[10] will be utilized as the primary assessment of a subject's level of depressive symptoms and must be administered using a structured interview guide. Detailed instructions for administration of the structured interview guide will be provided. This scale consists of 10 items, each with 7 defined grades of severity.

3.7.5.6 Young Mania Rating Scale

The YMRS[11] consists of 11 items assessing the core symptoms of mania and is based on the subject's subjective report of his or her clinical condition. Additional information is based upon clinical observations made during the course of the clinical interview. Each item has 5 defined categories of severity with 4 items graded on a 0 to 8 scale (irritability, speech, content, and disruptive-aggressive behavior) and 7 items graded on a 0 to 4 scale.

3.7.5.7 Clinical Global Impression - Bipolar Version

The CGI-BP scale refers to the global impression of the subject with respect to bipolar I disorder.[12] The scale rates the subject's severity of illness (CGI-BP-Severity: mania, depression, and overall bipolar illness) and change from preceding phase (CGI-BP change from preceding phase: mania, depression, and overall bipolar illness) based on a 7-point scale. Severity of illness (CGI-BP-Severity) should be rated at visits as indicated in the schedule of assessments (Table 3.7-1 for sparse sampling and Table 3.7-2 for robust sampling). At each visit other than Day 1 (baseline), the change from preceding phase (CGI-BP change from preceding phase) will be judged with respect to the subject's condition at baseline for that phase (ie, the last visit from the preceding phase).

3.7.6 Safety Assessments

3.7.6.1 Adverse Events

Refer to Section 5 for the methods and timing for assessing, recording, and analyzing AEs.

3.7.6.2 Clinical Laboratory Assessments

The tests listed in Table 3.7.6.2-1 will be collected at the time points presented in the schedule of assessments (Table 3.7-1 for sparse sampling and Table 3.7-2 for robust sampling) and processed in accordance with directions from the clinical chemistry laboratory.

Table 3.7.6.2-1 Clinical Laboratory Assessments

Hematology:	Serum Chemistry:
Hematocrit Hemoglobin Platelet count Red blood cell count White blood cell count with differential 	Albumin Alkaline phosphatase ALT (or SGPT) AST (or SGOT) Bilirubin, total Blood urea nitrogen Calcium Chloride Cholesterol (total, low-density lipoprotein and high-density lipoprotein) Creatine kinase Creatinine Gamma glutamyl transferase Glucose Lactate dehydrogenase Magnesium Phosphorus Potassium Protein, total Sodium Triglycerides Uric acid
Urinalysis: Appearance Bilirubin Color Glucose Ketones Leukocytes Nitrites Occult blood pH Protein Specific gravity Urobilinogen Microscopic analysis performed only if any part of the urinalysis is not negative	Drug Screen (all items in urine except where noted): Alcohol (urine or breath) Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine Marijuana Methadone Opiates Phencyclidine Propoxyphene

[a]Perimenopausal and postmenopausal female subjects only.

A pregnancy test will be conducted in females of childbearing potential (FOCBP) prior to trial intervention; results must be available prior to the administration of the IMP. Additional pregnancy tests will be conducted throughout the trial at the time points presented in the schedule of assessments (Table 3.7-1 for sparse sampling and Table 3.7-2 for robust sampling).

A urine drug screen will be performed at screening and at check-in; however, additional urine drug screens can be performed at any time during the trial at the investigator's discretion (positive results are to be discussed with the medical monitor). A urine drug screen should also be performed if a subject experiences an SAE during the trial and the

urine drug screen will coincide with PK sampling following the occurrence of the SAE. The PK blood samples should be collected as early as is feasible to measure the plasma concentrations of aripiprazole.

Any value outside the normal range will be flagged for the attention of the investigator, who must indicate whether or not a flagged value is of clinical significance. If one or more values are questionable, the test(s) may be repeated. If the result of any test (or repeat test, if done) is indicated as clinically significant during the screening period, the subject will NOT be enrolled into the trial without the permission of the medical monitor. In addition, follow-up unscheduled labs should be performed on clinically significant abnormalities during the course of the trial. Unscheduled laboratory tests may be repeated at any time at the discretion of the investigator for appropriate medical care.

3.7.6.3 Physical Examination and Vital Sign Assessments

Complete physical examinations will be performed at the time points presented in the schedule of assessments (Table 3.7-1 for sparse sampling and Table 3.7-2 for robust sampling). The principal investigators or designees are primarily responsible for performing the physical examination. Whenever possible, the same individual should perform all physical examinations for any individual subject. If the appointed designee is to perform the physical examination, he/she must be permitted by local regulations and his/her name must be included on the FDA Form 1572 as principal investigator or sub-investigator and must be listed on the trial site delegation of authority form as performing this function. Any clinically significant condition present at a post-treatment physical examination that was not present at the baseline physical examination should be documented as an AE and followed to a satisfactory conclusion.

Body height and weight will also be measured during screening for calculation of body mass index (BMI) and weight will be measured as part of all subsequent physical examinations. For the measurement of height, the measurement will be made without shoes. For the measurement of weight, all efforts will be made to use the same scale for all measurements throughout the trial.

Vital signs will be taken at the time points presented in the schedule of assessments (Table 3.7-1 for sparse sampling and Table 3.7-2 for robust sampling). Vital signs will be obtained prior to PK blood draws and ECGs at the nominal time points, where applicable. Vital signs will include systolic and diastolic blood pressure, heart rate, and body temperature. At each time point for vital signs, blood pressure (systolic and diastolic) and heart rate will be taken after subjects have been in the supine position for at least 5 minutes and again after subjects have been standing for 2 minutes, but not more than

3 minutes. Body temperature will be taken with the subject in the supine position (ie, only once).

3.7.6.4 Electrocardiogram Assessments

Standard 12-lead ECGs will be collected in triplicate (5 minutes apart) at the time points presented in the schedule of assessments (Table 3.7-1 for sparse sampling and Table 3.7-2 for robust sampling). Additional 12-lead ECGs may be obtained at the investigator's discretion and should always be obtained in the event of an early termination (ET) of any cause. The ECGs will be collected prior to PK blood draws and after vital signs at the nominal time points, where applicable.

Standard 12-lead ECGs will be recorded after the subject has been supine and at rest for ≥ 10 minutes prior to the first ECG and subjects will remain supine through the final ECG. Heart rate, ventricular rate, RR interval, PR interval, QRS duration, and QT intervals will be recorded. The corrected QT interval using Fridericia's formula (QTcF) will be calculated. The 12-lead ECGs will be evaluated at the trial sites to determine the subject's eligibility and to monitor safety during the trial. The principal investigators or designees (licensed physician) will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. The ECG will be repeated if any results are considered to be clinically significant. The reviewers must be listed on FDA Form 1572 and the trial site delegation of responsibility form. Electrocardiogram data will be recorded electronically (ie, eCRFs) by the central ECG laboratory and by the trial site. Eligibility for the trial will be based on the central ECG report at the screening visit and the trial site's local ECG reading at Day 1 predose.

3.7.6.5 Columbia-Suicide Severity Rating Scale

Suicidality will be monitored during the trial using the C-SSRS. The Baseline/Screening version and the Since Last Visit version of the C-SSRS will be completed by trained trial site staff at the time points presented in the schedule of assessments (Table 3.7-1 for sparse sampling and Table 3.7-2 for robust sampling). This scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicide events and suicidal ideation and a postbaseline evaluation that focuses on suicidality since the last assessment.

3.7.6.6 Other Safety Assessments

3.7.6.6.1 Extrapyramidal Symptoms

Extrapyramidal symptoms will be assessed by trained trial site staff using the SAS, AIMS, and BARS at the time points presented in the schedule of assessments (Table 3.7-1 for sparse sampling and Table 3.7-2 for robust sampling).

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3.7.6.6.1.1 Simpson-Angus Scale

The SAS[13] consists of a list of 10 symptoms of Parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item will be rated on a 5-point scale, with a score of 1 representing absence of symptoms and a score of 5 representing a severe condition. The SAS Total Score is the sum of the scores for all 10 items.

3.7.6.6.1.2 Abnormal Involuntary Movement Scale

The AIMS[9] assessment consists of 10 items describing symptoms of dyskinesia. Facial and oral movements (items 1 through 4), extremity movements (items 5 and 6), and trunk movements (item 7) will be observed unobtrusively while the subject is at rest (eg, in the waiting room), and the investigators will also make global judgments on the subject's dyskinesias (items 8 through 10). Each item will be rated on a 5-point scale, with a score of 0 representing absence of symptoms (for item 10, no awareness), and a score of 4 indicating a severe condition (for item 10, aware/severe distress). For this scale, the subject is to be sitting on a hard, firm chair. In addition, the AIMS includes 2 yes/no questions that address the subject's dental status.

The AIMS Movement Rating Score is defined as the sum of items 1 through 7 (ie, items 1 through 4, facial and oral movements; items 5 through 6, extremity movements; and item 7, trunk movements).

3.7.6.6.1.3 Barnes Akathisia Rating Scale

The BARS[14] consists of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the subject, subject distress due to akathisia, and global evaluation of akathisia. The first 3 items will be rated on a 4-point scale, with a score of 0 representing absence of symptoms and a score of 3 representing a severe condition. The global clinical evaluation will be made on a 6-point scale, with 0 representing absence of symptoms and a score of 5 representing severe akathisia. To complete this scale, subjects will be observed while they are seated and then standing for a minimum of 2 minutes in each position. Symptoms observed in other situations (eg, while engaged in neutral conversation or engaged in activity on the ward) may also be rated. Subjective phenomena are to be elicited by direct questioning.

The BARS Global Score is from the global clinical assessment of akathisia from the panel BARS in the eCRF.

3.7.6.6.2 Pain Perception - Visual Analog Scale

Subjects will assess the pain associated with the injection of IMP using the VAS. The VAS will be completed at the time points presented in the schedule of assessments (Table 3.7-1 for sparse sampling and Table 3.7-2 for robust sampling).

3.7.6.6.3 Investigator's Assessment of Injection Site

The investigators or designees will assess the injection site at the time points presented in the schedule of assessments (Table 3.7-1 for sparse sampling and Table 3.7-2 for robust sampling).

Whenever possible, the same individual should perform all assessments of the injection site for any individual subject.

3.7.7 Pharmacokinetic Assessments

3.7.7.1 Pharmacokinetic Assessments

3.7.7.1.1 Pharmacokinetic Blood Plasma Samples

To obtain a good distribution of PK sampling times, the trial sites will be divided into either sparse (majority of the sites) or robust (extensive) PK sampling trial sites.

Blood will be collected for concentrations of aripiprazole and its major metabolite, dehydro-aripiprazole, for the subjects who will receive aripiprazole 2M LAI 960 mg:

- Sparse sampling schedule: Day 1 (predose [within 2 hours prior to dosing] and 4, 8, and 12 hours postdose), Day 8, Day 15, Day 22, Day 29, Day 36, Day 43, Day 50, Day 57 (predose), Day 85, Day 113 (predose), Day 141, Day 169 (predose [within 2 hours prior to dosing] and 4, 8, and 12 hours postdose), Day 176, Day 183, Day 190, Day 197, Day 204, Day 211, Day 218, and Day 225/ET.
- Robust sampling schedule: Day 1 (predose [within 2 hours prior to dosing] and 4, 8, and 12 hours postdose), Day 2, Day 3, Day 5, Day 8, Day 10, Day 13, Day 15, Day 18, Day 22, Day 29, Day 36, Day 43, Day 50, Day 57 (predose), Day 85, Day 113 (predose), Day 141, Day 169 (predose [within 2 hours prior to dosing] and 4, 8, and 12 hours postdose), Day 170, Day 171, Day 173, Day 176, Day 178, Day 181, Day 183, Day 186, Day 190, Day 197, Day 204, Day 211, Day 218, and Day 225/ET.

Blood will be collected for concentrations of aripiprazole and its major metabolite, dehydro-aripiprazole, for the subjects who will receive aripiprazole IM depot 400 mg:

- Sparse sampling schedule: Day 1 (predose [within 2 hours prior to dosing] and 4, 8, and 12 hours postdose), Day 8, Day 15, Day 22, Day 29 (predose), Day 57 (predose), Day 85 (predose), Day 113 (predose), Day 141 (predose), Day 169 (predose [within 2 hours prior to dosing] and 4, 8, and 12 hours postdose), Day 197 (predose [within 2 hours prior to dosing] and 4, 8, and 12 hours postdose), 204, 211, 218, and 225/ET.

- Robust sampling schedule: Day 1 (predose [within 2 hours prior to dosing] and 4, 8, and 12 hours postdose), Day 2, Day 3, Day 5, Day 8, Day 10, Day 13, Day 15, Day 18, Day 22, Day 29 (predose), Day 57 (predose), Day 85 (predose), Day 113 (predose), Day 141 (predose), Day 169 (predose [within 2 hours prior to dosing] and 4, 8, and 12 hours postdose), Day 170, Day 171, Day 173, Day 176, Day 178, Day 181, Day 183, Day 186, Day 190, Day 197 (predose [within 2 hours prior to dosing] and 4, 8, and 12 hours postdose), 198, 199, 201, 204, 206, 209, 211, 214, 218, and 225/ET.

While predose samples must be collected on the specified day prior to dosing, other PK samples should be collected at any time between 8 AM and 2 PM on the specified days.

An additional PK sample will be collected from subjects who experience an SAE immediately (at the earliest possible time point available) after the occurrence of the SAE.

All tubes must be labeled such that the protocol number, subject ID number, date of collection, and nominal sample postdose collection time can be verified. The labels must be approved by the bioanalytical scientist prior to use. It is important to note the exact time of the blood collection in the eCRF, not the scheduled PK collection time. The exact time of dosing will also be noted.

3.7.8 Genetic Assessments

3.7.8.1 Deoxyribonucleic Acid Blood Samples for Pharmacogenomic Testing

A pharmacogenomics sample will be collected on Day 1 prior to dosing.

The pharmacogenomics blood sample will be taken in order to collect deoxyribonucleic acid (DNA) for the determination of genotypes related to CYP2D6 drug metabolizing enzymes.

[redacted]

3.7.10 End of Trial

The end of trial date is defined as the last date of contact or the date of the final contact attempt from the post-treatment follow-up eCRF page for the last subject completing or withdrawing from the trial.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial or Treatment Arm(s)

In the event of sponsor termination or suspension of the trial for any reason, prompt notification will be given to investigators, IRBs, and regulatory authorities in accordance with regulatory requirements.

3.8.2 Individual Site

The sponsor, investigator, or the IRB has the right to terminate the participation of a particular trial site, if necessary, due to lack of subject enrollment, noncompliance with the protocol, or if judged to be necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP. The sponsor is to be notified promptly if the trial was terminated by the investigator or the IRB at the trial site.

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Discontinuation

After the first dose of IMP, a subject may discontinue from the trial for a variety of reasons. Treatment discontinuations may be initiated by a subject or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other reasons, as determined by the investigator. If a subject discontinues treatment, their participation in the trial will be discontinued. Discontinued subjects should be encouraged to complete all ET and follow-up assessments with ET assessments conducted as soon as possible after the subject is withdrawn.

3.8.3.2 Documenting Reasons for Discontinuation

All subjects have the right to withdraw and the investigator can discontinue a subject's participation in the trial at any time if medically necessary. In addition, subjects meeting the following criteria must be withdrawn from the trial (only one reason for discontinuation [the main reason] can be recorded in the eCRF):

- Death

- Disease relapse or disease progression
- Failure to meet randomization criteria
- Lost to follow-up
- Non-compliance with IMP (if confirmed not related to an AE)
- Physician decision (other than AE)
- Pregnancy (see Section 5.5)
- Site terminated by sponsor
- Trial terminated by sponsor
- Withdrawal of consent by parent/guardian (if confirmed not related to an AE)
- Withdrawal of consent by subject (if confirmed not related to an AE)

If the subject discontinues IMP due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow-up procedures in Section 3.8.3.1 must be followed. Subjects may be replaced, if discontinuations/withdrawals occur, as described in Section 3.3.

3.8.3.3 Withdrawal of Consent

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent for use of data already collected as part of the trial, but only for future participation.

Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be understood, documented, and managed to protect the rights of the subject and the integrity of the trial.

At any time, a subject may withdraw from the substudy [redacted] and may request that the sponsor destroy their sample(s) by contacting the trial site. Should the subject choose to withdraw their consent to the storage and use of their sample(s), such sample(s) will not be used from that point on and will be promptly destroyed. Subjects will not lose any benefits, medical treatment, or legal rights which they are allowed if they request their sample(s) to be destroyed. Leaving the main trial does not mean that their sample(s) used for this substudy will automatically be destroyed. Subjects will have to make a request for their sample(s) to be destroyed after they leave the trial.

Subjects who withdraw should be encouraged to complete all ET and follow-up assessments with ET assessments conducted as soon as possible after the subject is withdrawn.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who is not randomized or assigned trial treatment. In the case where a subject had a positive screen for stimulants or marijuana and was therefore excluded, the medical monitor should be contacted to determine if rescreening is an option. However, subjects excluded for any other reasons may be rescreened at any time if the exclusion characteristic has changed. In the event that the subject is rescreened, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated. After 2 screening attempts, the medical monitor should be consulted to confirm whether or not the subject can be enrolled.

3.10 Definition of Completed Subjects

The evaluation period is defined as the time period during which subjects are evaluated for primary and secondary objectives of the trial irrespective of whether the subject is administered IMP. Subjects who are evaluated at the last scheduled visit (Day 225 for aripiprazole 2M LAI 960 mg and Day 197 for aripiprazole IM depot 400 mg) during the treatment phase will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before Day 225, or later, and who do not have a known reason for discontinuation (eg, withdrew consent or AE, etc.), except those who have completed the trial as defined in Section 3.10, will be classified as “lost to follow-up” as the reason for discontinuation.

The trial site will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site will attempt to contact the subject via certified mail or an alternative similar method where appropriate, before assigning a “lost to follow-up” status.

3.12 Subject Compliance

The actual time and dose of IMP administration will be recorded on the eCRF. Information regarding any inappropriately administered dose will also be documented on the eCRF.

3.13 Protocol Deviations

In the event of a major deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or

concomitant medication criteria), the investigator or designee will contact the sponsor at the earliest possible time by telephone. The investigator, or designee, and sponsor will come to a joint decision as quickly as possible regarding the subject's continuation in the trial. If the decision reached is to allow the subject to continue in the trial, this must be documented by the investigator and the sponsor, and approved or disapproved by the medical monitor.

4 Restrictions

4.1 Prohibited Medications

With the exception of the subject's current atypical antipsychotic medication (and/or mood stabilizer or antidepressant for subjects with bipolar I disorder), any other psychotropics must be discontinued at least 14 days prior (with the exception of fluoxetine or fluoxetine/olanzapine, which need to be discontinued at least 28 days prior) to administration of IMP, and will not be allowed during the course of the trial (see Inclusion Criterion 7 in Table 3.4.2-1). Subjects on any LAI other than Abilify Maintena will be excluded from the trial. Other oral non-aripiprazole antipsychotic medications may be allowed if approved by the medical monitor and sponsor; however, clozapine and monoamine oxidase inhibitors (MAOIs) will not be allowed. Subjects may not receive varenicline beyond screening. If a subject is receiving varenicline at enrollment, attempts should be made to discontinue the medication if clinically feasible, to allow potential subjects to enter the trial.

Subjects must stop all other prohibited concomitant medications prior to dosing and for the duration of the trial. Subjects must wash out from antipsychotics that are known to cause corrected QT interval (QTc) prolongation, such as haloperidol, within 14 days prior to administration of IMP. Use of quetiapine or ziprasidone is permitted.

Inhibitors and inducers of CYP3A4 and inhibitors of CYP2D6 isozymes are not allowed within 14 days prior to dosing and for the duration of the trial, since these are the pathways in which aripiprazole is metabolized. An example list of CYP3A4 and CYP2D6 inhibitors and CYP3A4 inducers that are prohibited during the trial are listed in Table 4.1-1.

Table 4.1-1 Example List of CYP3A4 and CYP2D6 Inhibitors and CYP3A4 Inducers Prohibited During the Trial

CYP3A4 Inhibitors	
Amiodarone	Fluvoxamine
Amprenavir	Indinavir
Aprepitant	Itraconazole
Chloramphenicol	Ketoconazole
Cimetidine	Nefazodone
Clarithromycin	Nelfinavir
Clotrimazole (if used orally)	Quinupristin/Dalfopristin
Delavirdine	Ritonavir
Diltiazem	Saquinavir
Erythromycin	Troleandomycin
Fluconazole	Verapamil
CYP2D6 Inhibitors	
Bupropion	Hydroxyzine
Celecoxib	Methadone
Chloroquine	Moclobemide
Chlorpheniramine	Paroxetine
Clemastine	Pyrilamine
Clomipramine	Quinidine
Diphenhydramine	Terbinafine
Fluoxetine	Tripelennamine
Halofantrine	
CYP3A4 Inducers	
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Efavirenz	Rifampin
Nevirapine	St. John's wort
Phenobarbital	Troglitazone

Note: The above is not an exhaustive list and there may be additional CYP3A4 and CYP2D6 inhibitors and CYP3A4 inducers that are prohibited during the trial.

4.2 Restricted Medications

Benzodiazepine use is allowed up to a maximum of 6 mg/day lorazepam or equivalent, but not within 8 hours of any rating scales during the trial. The use of IM lorazepam is also permitted for emergent agitation, but only if deemed absolutely necessary by the investigator. The following guide should be used to determine approximate lorazepam equivalents: 1 mg lorazepam = 5 mg diazepam = 15 mg oxazepam = 15 mg clorazepate. Subjects must not be on more than one benzodiazepine beyond the screening visit.

If a subject is receiving 2 benzodiazepines at the screening visit (eg, lorazepam and oxazepam), attempts should be made to discontinue one of the benzodiazepines, if clinically warranted, to allow potential subjects to enter the trial. The second benzodiazepine should be tapered off over an appropriate amount of time within the

30-day screening period to prevent side effects, and the subject should be maintained on the remaining benzodiazepine for at least 14 days prior to the administration of IMP. Benzodiazepine and non-benzodiazepine use is allowed during the trial as needed to manage AEs such as agitation, anxiety, sleep disturbance, and insomnia. Combined use of both drug classes (ie, benzodiazepines and non-benzodiazepine sleep aids) as treatment for insomnia is not allowed. Benzodiazepine use should be discontinued as soon as the AE for which it was initiated subsides, as per the investigator's discretion, to avoid any withdrawal effects.

Medications that are restricted during the trial are listed in Table 4.2-1.

Table 4.2-1 Medications Restricted During the Trial

Medication	Screening	Treatment Period
Anticholinergics[a]	≤ 4 mg/day benztropine or equivalent	≤ 4 mg/day benztropine or equivalent
Propranolol (for akathisia or tremor)[b, c]	Maximum 60 mg propranolol per day	Maximum 60 mg propranolol per day
Benzodiazepines[b]	-	No more than one benzodiazepine and **not** in combination with other sleep aid medication

[a]Anticholinergics are not allowed within 12 hours of any rating scales during any phase of the trial.

[b]Propranolol is not allowed within 8 hours of any rating scales during any phase of the trial.

[c]Subjects receiving propranolol for heart disease may remain on stable, pretrial doses, as needed, throughout the trial, so long as the total dose does not exceed 60 mg/day.

4.3 Nontherapy Precautions and Restrictions

Subjects will be instructed to refrain from drinking alcoholic beverages or using illicit drugs during participation in the trial.

Electroconvulsive therapy must not be conducted within 2 months prior to administration of the IMP and is not allowed during the course of the trial.

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Adverse events would not include information recorded as medical history at screening for preplanned procedures for which the underlying condition was known and no worsening occurred.

An adverse reaction is any untoward and unintended response to an IMP related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE. For the purpose of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the IMP and the AE. "Suspected adverse reaction" implies a lesser degree of certainty about causality than "adverse reaction".

An SAE includes any event that results in any of the following outcomes:

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient hospitalization or prolongs hospitalization
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered SAEs.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above, eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious AEs are all AEs that do not meet the criteria for a "serious" AE.

Immediately Reportable Event (IRE):

- Any SAE
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 5.4).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented on the AE eCRF if there is a complication or abnormality in the newborn.

Clinical Laboratory Assessment Value Changes: It is the investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if this is an abnormal (ie, clinically relevant) change from baseline for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered clinically relevant by the investigator (eg, subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated on the eCRF. The intensity of an AE is defined as follows:

1 = Mild: Discomfort noticed, but no disruption to daily activity.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: Inability to work or perform normal daily activity.

IMP Causality: Assessment of causal relationship of an AE to the use of IMP:

Related: There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.

Not Related: There is no temporal or reasonable relationship between the IMP and the AE.

5.2 Eliciting and Reporting Adverse Events

The investigator will assess subjects for the occurrence of AEs from the time the ICF is signed until the end of the trial. For this trial, information on AEs will be followed for up to 28 days after the last dose of aripiprazole IM depot 400 mg has been administered and 56 days after the last of aripiprazole 2M LAI 960 mg has been administered. To avoid bias in eliciting AEs, subjects should be asked the following nonleading question: "How are you feeling?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and eCRFs provided by the sponsor. Serious AE collection is to begin after a subject has signed the ICF.

Use medical terminology in AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms. Exacerbation or disease progression should be reported as

AEs only if there are unusual or severe clinical features that were not present, not experienced earlier, or not expected based on the course of the condition.

In addition, the sponsor must be notified immediately by telephone, fax, or e-mail of any IREs according to the procedure outlined below in Section 5.3. Special attention should be paid to recording hospitalization and concomitant medications.

5.3 Immediately Reportable Events

The investigator must report any SAE, any AE related to occupational exposure, potential serious hepatotoxicity, or confirmed pregnancy immediately after either the investigator or trial site personnel become aware of the event. An IRE form should be completed and sent by fax, e-mail, or overnight courier, using the contact information on the title page of this protocol. (Please note that the IRE form is a specific form and is NOT the AE eCRF).

Subjects experiencing SAEs should be followed clinically as described in Section 5.7.2. It is expected that the investigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor.

5.4 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) that is ≥ 3 times the upper limit of normal (ULN), a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, complete an IRE form with all values listed and also report as an AE on the eCRF.

5.5 Pregnancy

Females of childbearing potential are women whose menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months).

For men and FOCBP, who are sexually active, there must be a documented agreement that the subject and their partner will take effective measures (ie, 2 different approved methods of birth control or remains abstinent) to prevent pregnancy during the course of the trial and for 150 after the last dose of IMP for a female subjects or 180 days after the last dose of IMP for a male subjects. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy, have had a hysterectomy, or have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchiectomy) or remains abstinent during the trial and for 150 days after the last dose of IMP for a female subject or 180 days after the last dose of IMP for a male subject, 2 of the following approved methods of birth control must be used: vasectomy, tubal ligation, intrauterine device, birth control pills, birth control implant, birth control depot injection, condom with

spermicide, sponge with spermicide, or occlusive cap (vaginal diaphragm or cervical/vault cap) with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented in the eCRF. Male subjects must also agree not to donate sperm from trial screening through 180 days after the last dose of IMP.

Before enrolling men and women in this clinical trial, investigators must review the below information about trial participation as part of the ICF process. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Follow-up of a reported pregnancy

Before trial enrollment, men and FOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Subjects must sign the ICF confirming that the above-mentioned risk factors and the consequences were discussed.

A urine or serum pregnancy test for human chorionic gonadotropin will be performed on all FOCBP at screening and throughout the trial at the time points presented in the schedule of assessments (Table 3.7-1 for sparse sampling and Table 3.7-2 for robust sampling). If a urine test is performed and is positive, the investigator will follow-up with a confirmatory serum test.

During the trial, all FOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle). Male subjects should also be instructed to contact the investigator immediately, during the trial, if their partners suspect that they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial. Exceptions to trial

discontinuation may be considered for life-threatening conditions only after consultations with the sponsor (see the title page of this protocol for contact information).

The investigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for at least 150 days after the last dose of IMP for a female subject or 180 days after the last dose of IMP for a male subject, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward the Pregnancy Surveillance Form(s) to the investigator for monitoring the outcome of the pregnancy.

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the sponsor, on the Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

5.6 Procedure for Breaking the Blind

Not applicable; this is an open-label trial.

5.7 Follow-up of Adverse Events

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eCRF with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing on the eCRF. For any AE having been identified throughout the trial, during data analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation). Subjects should be given appropriate medical treatment until the resolution of any AE.

5.7.2 Follow-up of Serious Adverse Events and Immediately Reportable Events

This trial requires that subjects be actively monitored for SAEs and IREs up to 28 days after the last dose of aripiprazole IM depot 400 mg is administered and 56 days after the last dose of aripiprazole 2M LAI 960 mg is administered.

Serious AEs and nonserious IREs that are identified or ongoing at the last scheduled contact must be recorded as such on the AE eCRF page. If updated information (eg, resolved status) on SAE or IRE status becomes available after a subject's last scheduled contact (up to last in clinic visit for the entire trial), this must be reported to the sponsor and recorded on the AE eCRF page, according to the appropriate reporting procedures. The investigator will follow SAEs until the events are resolved or stabilized, or the subject is lost to follow-up or has died. Resolution means the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up or has died.

5.7.3 Follow-up and Reporting of Serious Adverse Events and Immediately Reportable Events Occurring After Last Scheduled Contact

Any new SAEs or IREs reported to the investigator which occur after the last scheduled contact and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported to the sponsor. This may include SAEs or IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period. The investigator should follow SAEs or IREs identified after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

6 Pharmacokinetic/Pharmacodynamic/Pharmacogenomic Analysis

6.1 Pharmacokinetic Methods

Plasma concentrations of aripiprazole and its major metabolite, dehydro-aripiprazole, will be analyzed using noncompartmental methods.

Pharmacokinetic data will be summarized using descriptive statistics (median, mean, standard deviation [SD], percent coefficient of variation [CV], minimum, and maximum) for each cohort. Pharmacokinetic data will also be presented in listings.

6.2 Pharmacodynamic Methods

No pharmacodynamic endpoints are to be evaluated.

6.3 Pharmacokinetic/Pharmacodynamic Methods

No PK/pharmacodynamic analysis is planned.

6.4 Pharmacogenomic Methods

No pharmacogenomic analysis is planned.

7 Statistical Analysis

7.1 Determination of Sample Size

To establish the similarity in primary PK variables, the lower bound of the 90% CI of the geometric means ratio (GMR) of C_{56} and AUC_{0-56} after the fourth dose of aripiprazole 2M LAI 960 mg to C_{28} after the eighth dose and the sum of AUC_{0-28} values after the seventh and eighth doses of aripiprazole IM depot 400 mg should be greater than 80%, respectively.

It is estimated that a total of at least 100 subjects (ie, 50 per group) completing the trial will have at least 80% power to ensure that the lower limit of the 90% CI of the GMR of C_{56} after the fourth dose of aripiprazole 2M LAI 960 mg (test) to C_{28} after the eighth dose of aripiprazole IM depot 400 mg (reference) is greater than 0.80, assuming that the actual GMR of concentrations is 1.0 and the CV is 46%.

Among these 100 subjects, at least 30 completers enrolled to the robust sampling schedule will provide at least 80% power to ensure that the lower limit of the 90% CI of the GMR of AUC_{0-56} of aripiprazole 2M LAI 960 mg (test) to the sum of AUC_{0-28} values of aripiprazole IM depot 400 mg (reference) after the seventh and eighth doses is greater than 0.80, assuming the actual GMR of concentrations is 1.15 and the CV is 40%.

The assumption of CV used in the sample calculation is based on the PK data in the previous multiple-dose aripiprazole IM depot PK Trial 31-11-298.

To ensure adequate power of the trial, an interim analysis may be conducted by the Interim Analysis Review Committee (IARC). The final sample size could be increased as per recommendation of the IARC and as further described in Section 7.1.1.

Assuming a dropout rate of 34%, approximately 152 to 258 subjects will be enrolled to have 100 to 170 completers based on the recommendation of the proposed interim analysis.

7.1.1 Interim Analysis/Sample Size Re-estimation

An interim analysis of the PK data is planned during the trial and may be performed by an IARC on approximately 50 subjects (25 subjects per treatment group) completing the trial. In this case, completers will be defined as subjects who receive a final dose of IMP (both treatment groups) at the maximum dose. Out of the 50 subjects, approximately

14 subjects (7 subjects per treatment group) will have been enrolled to the robust sampling schedule. Subjects will continue to be enrolled into the trial until either the interim analysis is complete and recommends no sample size increase or there are enough subjects enrolled to ensure 170 completers.

If the trial is stopped due to futility (as described by the interim analysis), randomized subjects will be terminated; however, if the interim analysis stops the trial for having enough conditional power, then all randomized subjects will continue until the last observation. Subjects in screening will be discontinued and no further randomization will occur.

An alpha level of 0.001 (1-sided) is allocated to estimate the sample size during this interim analysis. The corresponding final significance level is 0.049 (1-sided).

The sample size will be re-estimated only based on the conditional power determined at the interim analysis. The adaptive designs methodology published by Chen, DeMets, and Lan (2004)[15] will be used to increase the sample size based on an interim estimate of the treatment effect size, possibly combined with other external information, without inflating the Type I error.

All the detailed calculations and re-estimation methods will be prespecified and included in the statistical analysis plan and interim analysis plan.

Table 7.1.1-1 Sample Size Re-estimation

Endpoints	Conditional Power	Interim Analysis Recommendation	Outcome
AUC_{0-56} versus sum of AUC_{0-28} values	≥ 80%	No adaption to the planned sample size	30 completers (15 per group)
	< 80%	Increase sample size to up to 50 completers	Up to 50 completers (25 per group)
C_{56} versus C_{28} after the last scheduled injection	≥ 80%	No adaption to the planned sample size	100 completers (50 per group)
	≥ 30% and < 80%	Increase sample size to up to 170 completers	Up to 170 completers (85 per group)
	< 30%	Stop the trial	

7.2 Datasets for Analysis

The following datasets will be analyzed:

- The randomized sample will include all subjects who are randomized.
- The PK sample will consist of all dosed subjects who have evaluable aripiprazole PK parameters. For analysis of the primary PK endpoint, only the completers with available values of the primary endpoints after the last scheduled injection will be included.

- The safety sample will include all randomized subjects who receive at least one dose of aripiprazole injection, regardless of any protocol violation.
- The efficacy sample will include all randomized subjects who receive at least one dose of aripiprazole injection and have at least one efficacy assessment.

7.3 Handling of Missing Data

No data imputation will be done for missing data in the PK analysis. The last observation carried forward (LOCF) method is used to impute missing data of the safety EPS assessment scales and efficacy assessment scales at postbaseline visits. The observed case (OC) dataset corresponding to a visit consists of data from all subjects who are evaluated at that visit. In the LOCF dataset, missing data at a postbaseline visit are imputed with the value obtained at the nearest preceding visit, except that baseline values are not carried forward to impute missing values at a postbaseline visit.

In addition, for the safety endpoints other than the EPS assessment scales, the LOCF method is also applicable for the values from the last visit for laboratory tests, vital sign parameters, ECG parameters, C-SSRS suicidality-related parameters, VAS for Subject-reported Rating of Pain at Most Recent Injection Site, and Investigator's Assessment of Most Recent Injection Site.

7.4 Primary and Secondary Endpoint Analyses

7.4.1 Primary Endpoint Analyses

Safety assessments including AEs, vital signs, ECGs, clinical laboratory monitoring (serum chemistry, hematology, and urinalysis), physical examinations, EPS (SAS, AIMS, and BARS), VAS scores for pain perception, Investigator's Assessment of Most Recent Injection Site, and suicidality via the C-SSRS will be summarized for the safety sample by treatment group. The mean change from baseline will be provided for vital signs, ECGs, clinical laboratory, and EPS assessments by visit, treatment group, and disease type. The incidence of clinically relevant abnormalities in vital signs, ECGs, and clinical laboratory results will be summarized descriptively by visit, treatment group, and disease type.

Plasma concentrations of aripiprazole will be analyzed using noncompartmental methods. The following PK parameters will be estimated and summarized descriptively for aripiprazole: C_{56} and $AUC_{0\text{-}56}$ of aripiprazole 2M LAI 960 mg after the fourth dose, C_{28} of aripiprazole IM depot 400 mg after the eighth dose, and $AUC_{0\text{-}28}$ of aripiprazole IM depot 400 mg after the seventh and eighth doses over the course of 32 weeks. The 90%

CI of GMR of C_{56} of aripiprazole after the fourth injection of aripiprazole 2M LAI 960 mg (test) to C_{28} after the eighth injection of aripiprazole IM depot 400 mg (reference) will be provided. An analysis of variance will be performed on the natural-log transformed PK parameters using the MIXED procedure in the Statistical Analysis System (SAS). The mixed-effects linear model will include treatment group, disease type (if applicable), and PK sampling schedule as fixed effects and subject as a random effect. The least squares means for the 2 treatment groups, their difference, and the 90% CI for their difference will be derived. The antilog of the confidence limits will provide the 90% CI for the GMR of the 2 treatments. For subjects enrolled to the robust sampling schedule, the values of AUC_{0-28} after seventh and eighth doses of aripiprazole IM depot 400 mg (reference) will be summed up before analyzing by the same method together with AUC_{0-56} after the fourth injection of aripiprazole 2M LAI 960 mg (test). Only subjects who receive a fourth dose of aripiprazole 2M LAI 960 mg or a seventh and/or eighth dose of aripiprazole IM depot 400 mg and have C_{56}, C_{28}, AUC_{0-28}, and AUC_{0-56} values determined for the respective treatments will be included in the analysis.

7.4.2 Secondary Endpoint Analyses

Individual and summary tables, using descriptive statistics (N, median, mean, SD, CV, minimum, maximum) will be provided for the following aripiprazole PK endpoints:

- C_{max} and t_{max} after the first and fourth doses of aripiprazole 2M LAI 960 mg
- AUC_{0-56} and C_{56} after the first dose of aripiprazole 2M LAI 960 mg
- AUC_{0-28} and AUC_{29-56} after the fourth dose of aripiprazole 2M LAI 960 mg
- PTF% after the fourth dose of aripiprazole 2M LAI 960 mg (for aripiprazole only)
- C_{max} and t_{max} after the first, seventh, and eighth doses of aripiprazole IM depot 400 mg
- AUC_{0-28} and C_{28} after the first dose of aripiprazole IM depot 400 mg
- PTF% after the eighth dose of aripiprazole IM depot 400 mg (for aripiprazole only)
- C_7 and C_{14} after the first injection of aripiprazole 2M LAI 960 mg and aripiprazole IM depot 400 mg from subjects enrolled to the robust sampling schedule.

Values for C_{max}, AUC, t_{max}, and PTF% will be summarized based on samples from subjects enrolled to the robust sampling schedule; whereas C_{28} and C_{56} after the first injection will be summarized based on samples from subjects enrolled to the robust and sparse sampling schedules.

Efficacy assessments including the PANSS (schizophrenia subjects only), CGI-S, CGI-I, SWN-S, MADRS (bipolar subjects only), YMRS (bipolar subjects only), and CGI-BP (bipolar subjects only) will be summarized for the efficacy sample at each visit by treatment group and disease type, if applicable. These analyses will be performed for both LOCF and OC data. In addition, the linear mixed-effects model will be used to explore the effect of the treatment and change from baseline over time, as applicable.

7.5 Analysis of Demographic and Baseline Characteristics

The randomized sample will be used for demographic and baseline characteristic analyses. Demographic characteristics (including age, weight, height, BMI, sex, race, and ethnicity) will be summarized using descriptive statistics (frequency, mean, median, standard deviation, maximum, minimum, and percentage when applicable) and reported by treatment group, by robust/sparse sampling schedule, and by disease type.

Disease characteristics at baseline and psychiatric history (age of first diagnosis for schizophrenia or bipolar I disorder and treatment given for previous episodes) will be presented using descriptive statistics and reported for the randomized sample by treatment group, by robust/sparse sampling schedule, and by disease type.

7.6 Safety Analysis

7.6.1 Adverse Events

All AEs will be coded by system organ class and the Medical Dictionary for Regulatory Activities preferred term. A treatment-emergent adverse event (TEAE) is defined as an AE which starts after the first dose of IMP or an AE that continues from baseline and is serious, IMP-related, or results in death, discontinuation, interruption or reduction of IMP. The incidence of the following events will be summarized by treatment group and by disease type**:**

- TEAEs
- TEAEs by severity
- TEAEs potentially causally related to the IMP
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

7.6.2 Clinical Laboratory Data

The potentially clinically relevant laboratory test abnormalities will be listed by subject and by test for the safety sample. The incidences of potentially clinically relevant laboratory tests abnormalities based on the observation from the scheduled and the unscheduled postbaseline visits will be tabulated by treatment group. Summary statistics (frequency, mean, standard deviation, minimum, and maximum) for the clinical laboratory measurements and changes from baseline will be presented by visit, treatment group, and disease type.

7.6.3 Physical Examination and Vital Signs Data

Physical examination data will be listed by subject.

The potential clinically relevant vital sign abnormalities will be listed by subject. Incidences of clinically relevant vital signs abnormalities based on the observation from the scheduled visits and unscheduled postbaseline visits will be tabulated by treatment group. In addition, vital sign parameters and changes from baseline at each visit and the last visit will be summarized by treatment group and disease type.

7.6.4 Electrocardiogram Data

The potentially clinically relevant ECG abnormalities will be listed by subject. The incidences of abnormal ECGs of potentially clinical relevance based on the observation at the scheduled and the unscheduled post-baseline visits will be tabulated by treatment group. Descriptive statistics of change from baseline in ECG intervals of PR, QRS, RR, QT, and QTcF will be presented by visit, treatment group, and disease type.

7.6.5 Other Safety Data

7.6.5.1 Columbia-Suicide Severity Rating Scale

Suicidality data collected from the C-SSRS assessments will be summarized by treatment group and disease type in incidence of suicidality, suicidal behavior only, emergence of suicidal behavior, suicidal ideation only, emergence of suicidal ideation, emergence of serious suicidal ideation, and worsening of suicidal ideation at each visit and last visit in addition to the overall during the treatment phase.

Descriptive statistics of the incidence of suicidality and incidence of suicidality by type (suicidal behavior and suicidal ideation), as well as the mean changes of Suicidal Ideation Intensity total scores for the most severe ideation from baseline will be reported by visit, treatment group, and disease type.

7.6.5.2 Extrapyramidal Symptoms Rating Scales

Descriptive statistics of the EPS rating scales for both LOCF and OC data and the mean changes of the scales from baseline will be reported by visit, treatment group, and disease type.

7.6.5.3 Visual Analog Scale Scores for Pain Perception

Descriptive statistics for VAS scores will be tabulated by treatment group and disease type at each injection.

7.6.5.4 Investigator's Assessment of the Injection Site

The Investigator's Assessment of Most Recent Injection Site including pain, swelling, redness, and induration will be reported in 4-point categorical scale (absent, mild, moderate, and severe) by treatment group and disease type at each injection.

7.7 Pharmacodynamic Analysis

No pharmacodynamic analysis is planned.

8 Management of Investigational Medicinal Product

8.1 Packaging and Labeling

The IMP will be provided to the investigator(s) and the persons designated by the investigator(s) or institutions(s) by the sponsor or designated agent. Aripiprazole 2M LAI will be supplied as aripiprazole IM depot 300 mg/mL RTU single-dose vials and aripiprazole IM depot 400 mg will be supplied as single-dose lyophilized vials. Aripiprazole tablets for oral overlap will be provided from a commercial supply. Detailed preparation and administration instructions will be provided in the site manual.

Each vial and carton used during the dosing period will be labeled according to Title 21 of the FDA Code of Federal Regulations.

8.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to the investigators and their designees. Neither the investigators nor any designees may provide IMP to any subject not participating in this protocol.

The IMP will be stored according to the storage conditions indicated on the clinical label(s).

The clinical trial site staff will maintain a temperature log in the drug storage area recording the temperature at least once each working day.

8.3 Accountability

The investigator, or designee, must maintain an inventory record of IMP received, dispensed, administered, destroyed, or returned.

8.4 Returns and Destruction

The IMP will be destroyed by the clinical trial site. The IMP may only be destroyed by the trial sites, if approved by the sponsor and if the IMP destruction meets all local regulations. The IMP accountability must be completed and verified by the assigned trial monitor prior to destruction. The trial sites may utilize qualified third party vendors for IMP destruction.

8.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate, or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness, or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blisters)
- Bottle (eg, under/over-fill, no safety seal)
- Vial defects
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record all PQCs identified through any means from the receipt of the IMP from sponsor, or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the sponsor (or sponsor's designee) by e-mail or telephone immediately after of becoming aware of the PQC according to the procedure outlined below.

Identification of a PQC by the subject should be reported to the site investigator, who should then follow one of the reporting mechanisms below.

- E-mail - Send information required for reporting purposes (listed in Section 8.5.2) to OAPI-EQCProductComplaints@Otsuka-us.com
- Phone - Rocky Mountain Call Center at 1-800-438-6055

8.5.2 Information Required for Reporting Product Quality Complaints

The following information is required for reporting purposes:

- Description of complaint
- Reporter ID (eg, subject, investigator, site information, etc)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, kit number, or bottle number)
- Clinical protocol reference (number and trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Availability for return

8.5.3 Return Process for Product Quality Complaints

Indicate during the report of the PQC if the complaint sample is available for return. If the complaint sample is available for return, the sponsor will provide instructions for complaint sample return, when applicable.

It must be documented in the site accountability record that a complaint sample for a dispensed kit has been forwarded to the sponsor for complaint investigation.

8.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor.

8.6 Investigational Medicinal Product Reserve Sample Requirements

In order to comply with FDA regulations 21CRF320.38 and 320.63, the trial sites must maintain sufficient reserve samples of the IMP (test and reference listed drug) to conduct full analytical testing 5 times (5 X). This reserve sample requirement is applicable to each shipment of IMP received at the trial sites. Each shipment of IMP sent to the trial sites will contain IMP to be used for conduct of the trial, as well as 5 X reserve samples. The trial sites will randomly select the IMP containers to be used in the trial, and will designate the remaining containers as reserve samples. Procedures for selecting IMP for

clinical trial use and for storing reserve samples are provided in the Study Operations Manual.

The trial sites must store the reserve samples per the clinical label storage condition requirements for a period of at least 5 years after marketing approval, or, if marketing approval is not obtained, at least 5 years following the date of completion of the bioequivalence trial unless FDA representatives collect the reserve samples for testing. Sites maybe elect to store samples at an off-site facility over the duration of storage requirements; in this case, the site continues to maintain responsibility for the reserve samples.

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

9.2 Data Collection

During each subject's visit to the clinic, a clinician participating in the trial will record progress notes to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding visit or day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;

- The signature (or initials) and date of all clinicians (or designee) who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Source documents and source data will be captured electronically in this trial, and will meet the same fundamental elements of data quality (eg, attributable, legible, contemporaneous, original, and accurate) as paper records. These data will be collected into a system (eSource) that is fully validated. Changes to the data will be captured by an automatic audit trail.

The trial site will be given a tablet to directly record subject data and clinical observations on electronic forms. Designated trial site staff will not be given access to the system until they have been appropriately trained. Information to be originally captured and reviewed electronically shall include details of the subject visit and the protocol required assessments performed as a part of these visits, medical history, AEs, and concomitant medications. Because this trial is using an electronic source record as the original point of data capture, there is no additional data entry step for the trial site for data collected directly into the application - rather, the electronic source record directly populates the trial database.

Some data may be captured via paper and then entered into the eSource system. These and any other data treated in this manner will be source data verified by the trial clinical research associate, and the location of the source data (ie, eSource, paper, or a local electronic system) will be documented before the trial start. Any changes to information in paper source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

Another exception will be safety laboratory or central ECG data, where the official source documentation will be considered the report issued by the analyzing laboratory.

Remote monitoring of the original electronic source records will take place; however, on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to

ensure protocol adherence, to assess trial site operational capabilities, and to perform other monitoring activities that cannot be performed remotely.

At the end of the trial, the investigator must certify that the data entered into the eSource application are complete and accurate. After database lock, the investigator will receive an electronic copy of the subject data.

9.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline E6 and as required by applicable local regulations. The trial site file will include all source documentation as well as completed eCRF data for all subjects screened or enrolled at the trial site. The investigator/institution will take measures to ensure confidentiality and prevent accidental or premature destruction of these documents.

9.4 Record Retention at the Trial Site

Federal FDA regulations require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- A period of at least 2 years following the date on which a NDA is approved by the FDA;
- A period of 2 years after the sponsor has notified the FDA that investigation with this drug is discontinued.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) providing an opportunity for the sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial, including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial or withdraws during the record retention period (eg, due to relocation or retirement or trial site closure), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, ICH E6 GCP: Consolidated Guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's (or sponsor designee's) monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and trial site clinical personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.2 Auditing

The sponsor's (or designee's) Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to participate with audits.

Regulatory authorities may inspect the trial site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

10.3 Protocol Deviations

Due to the complexity of clinical trial protocols and despite training and preventive efforts, deviations from the written protocol may occur and potentially result in harm to subjects, biased or inaccurate results, and possible rejection of all or part of the trial data. Per the ICH E3 guidance on the structure and content of clinical study reports, Section 10.2, protocol deviations should be summarized by site and grouped into different categories such as:

- Major IMP dosing errors that may compromise subject safety or efficacy assessments.
- Administration of an excluded concomitant medication during the course of the trial.

The FDA defines a protocol deviation/violation as an unplanned excursion from the protocol that is not implemented or intended as a systematic change.

Otsuka categorizes clinical protocol deviations as major versus minor. A major deviation is an intentional or accidental action or omission in a trial conduct that could potentially have a negative impact on the integrity of the trial's primary scientific objectives or has a significant potential to have a negative impact on the safety or efficacy assessments of any trial subject. Major deviations are those that might significantly affect the completeness, accuracy, or reliability of the trial data or that might significantly affect a subject's rights, safety, or well-being.

A minor deviation is an intentional or accidental action or omission during trial conduct in which the protocol is not strictly followed, but which has inconsequential impact on the integrity of the trial as a whole or the safety or efficacy analyses of an individual subject.

All protocol deviations will be categorized as major or minor according to the above definitions and only major deviations will be summarized in the CSR.

If the same protocol deviation occurs for multiple subjects, it must be recorded separately for each subject.

Investigators are expected to document potential protocol deviations as well as their medical assessment regarding continuation of the subject(s) due to the protocol deviation.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, FDA, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science guidelines, and applicable local laws and regulations. The trial sites will seek approval/favorable opinion by an IRB according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling eCRFs, the investigator, sub-investigator, and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number or subject identifier will be used to identify each subject.

Financial aspects, subject insurance, and publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

12 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, and other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject identifiers in eCRFs. If further subject ID is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

13 Amendment Policy

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB. Any permanent change to the protocol, whether an overall change or a change for specific trial sites, must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB, as required by local regulations. Except for "administrative" or "nonsubstantial" amendments, investigators will wait for IRB approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the sponsor and investigator, followed by IRB notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agency within local applicable timelines.

When the IRB, investigators, or the sponsor conclude that the protocol amendment substantially alters the trial design or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB, repeat written informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

14 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other trial participants who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial participants consent to such acknowledgement in any publications resulting from its conduct.

15 References

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Appendix 1 Names of Sponsor Personnel

Report IREs (SAEs, AEs related to occupational exposure, potential serious hepatotoxicity, and pregnancies) to:

Pharmaceutical Research Associates, Inc. (PRA Health Sciences)
Phone: PRA Safety Helpline: +1-800-772-2215
Fax: +1-888-772-6919 or +1-434-951-3482
Email: CHOSafety@prahs.com

For Medical Emergencies (use only if sponsor personnel listed above are unavailable):
301-990-0030

Senior Director, Global Clinical Development
Phone:
Fax:

Stephen R. Zukin, MD
Medical Monitor
Phone:
Fax:

Director, Clinical Management
Phone:
Fax:

Suzanne Watkin
Associate Director, Clinical Management
Phone:

[redacted]

Protocol 031-201-00181

Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Research Agreement.

I will provide copies of the protocol to all physicians, nurses and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the Investigational New Drug, aripiprazole (OPC-14597), the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the institutional review board (IRB) responsible for such matters in the clinical trial facility where aripiprazole (OPC-14597) will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on case report forms by me and my staff will be utilized by the sponsor in various ways such as for submission to governmental regulatory authorities or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await IRB approval before implementation of any protocol amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and sub-investigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol may involve a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____	_____
Principal Investigator Print Name	Signature	Date

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Appendix 4 Protocol Amendment 1

Amendment 1 Approval Date: 31 May 2019

PURPOSE:

The purpose of amending Protocol 031-201-00181, issued 14 Dec 2018, was to extend the treatment period by 8 weeks for subjects randomized to aripiprazole IM depot 400 mg to include an additional dose for comparison of PK parameters over the same duration as subjects randomized to aripiprazole 2M LAI 960 mg. Additional measurements of plasma aripiprazole concentrations and AUC were added. Clarification of eligibility requirements related to current use of antipsychotic medications at screening and guidance for management of the use of these medications during the trial were also added. Minor edits were made throughout the document for clarification.

BACKGROUND:

Changes to Protocol 031-201-00181 were made in response to a recommendation by BfArM (Germany) for an additional dose of aripiprazole IM depot 400 mg to better align the treatment duration with aripiprazole 2M LAI 960 mg, and to compare PK parameters between aripiprazole IM depot 400 mg and aripiprazole 2M LAI 960 mg over the last 8 weeks of treatment. Additional measurements of plasma aripiprazole concentrations and AUC were also requested.

MODIFICATIONS TO PROTOCOL:

General Revisions:

- Added an eighth dose (Day 197) for subjects randomized to aripiprazole IM depot 400 mg.
- Added 10 days (198, 199, 201, 204, 206, 209, 211, 214, 218, and 225) for collection of PK samples following administration of the eighth dose of aripiprazole IM depot 400 mg to subjects enrolled to the robust sampling schedule.
- Added 4 days (204, 211, 218, and 225) for collection of PK samples following administration of the eighth dose of aripiprazole IM depot 400 mg to subjects enrolled to the sparse sampling schedule.

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- Added collection of an additional 4 blood samples (predose and at 4, 8, and 12 hours postdose) for PK analysis after administration of the eighth dose (Day 197) for all subjects randomized to aripiprazole IM depot 400 mg.
- Added new PK parameters for plasma aripiprazole concentrations and AUC, which included a new secondary endpoint (AUC_{0-28} and AUC_{29-56} after the fourth dose of aripiprazole 2M LAI 960 mg).
- Specified the antipsychotic, mood stabilizer, and antidepressant medications allowed at screening to determine eligibility to enroll in the trial and described eligibility requirements specific to enrollment to the robust sampling schedule.
- Added guidelines for use of mood stabilizers and antidepressants by subjects with bipolar disorder during tolerability testing, oral overlap, and the treatment period.
- Reduced the number of visits that the C-SSRS would be administered to subjects enrolled to the robust sampling schedule to align the frequency of these assessments with subjects enrolled to the sparse sampling schedule.
- Added Section 8.6 Investigational Medicinal Product Reserve Sample Requirements.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

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Appendix 5 Protocol Amendment 2

Amendment 2 Approval Date: 31 Jul 2019

PURPOSE:

The purpose of amending Protocol 031-201-00181, issued 31 May 2019, was to add additional C-SSRS assessments on outpatient days. Minor administrative clarifications were also made throughout the document.

BACKGROUND:

Changes to Protocol 031-201-00181 were made to add additional C-SSRS assessments on outpatient days to the schedule of assessments for both trial treatment arms aripiprazole IM Depot 400 mg and aripiprazole 2M LAI 960 mg sparse and robust sampling schedules. Administrative changes were also made to clarify that unscheduled C-SSRS assessments will be performed during any outpatient visits, including those that may occur within 21 days after aripiprazole 2M LAI 960 mg dosing for subjects enrolled to the robust sampling schedule, and to clarify that the trial will take place from Day -30 to Day 225/ET for both treatment arms.

MODIFICATIONS TO PROTOCOL:

General Revisions:

- Clarified globally that subjects enrolled to the robust sampling schedule who are randomized to aripiprazole 2M LAI 960 mg and who are not able to accommodate the scheduled stay of 21 days in the clinical unit may be permitted to have some visits as outpatients with approval from the medical monitor. In addition, for any outpatient visit, an unscheduled C-SSRS will be performed.
- Clarified that the trial will take place from Day -30 to Day 225/ET for both treatment arms in Figure 3.1-1 Trial Design Schematic.
- Added C-SSRS assessments on Days 8, 15, 22, 36, 43, 50, 176, 183, 190, 204, 211, and 218 to Table 3.7-1 Schedule of Assessments: Sparse Sampling and Table 3.7.3-2 Sparse Sampling Schedule Trial Days and Activities.
- Added C-SSRS assessments on Days 36, 43, 50, 204, 211, and 218 to Table 3.7-2 Schedule of Assessments: Robust Sampling and Table 3.7.3-3 Robust Sampling Schedule Trial Days and Activities.

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ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

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SIGNATURE PAGE

Document Name: Protocol 031-201-00181 Amendment 2

Document Number: [redacted]

Document Version: 4.0

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
[redacted]	Clinical Pharmacology Approval	31-Jul-2019 21:36:47
[redacted]	Biostatistics Approval	31-Jul-2019 12:14:54
[redacted]	Clinical Approval	31-Jul-2019 21:00:56