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Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

Aripiprazole OPC-14597

REVISED CLINICAL PROTOCOL

An Open-Label, Multicenter, Rollover, Long-term Study of Aripiprazole Intramuscular Depot in Patients with Schizophrenia
Protocol No. 31-10-270
IND No. 67,380

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3
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Protocol 31-10-270

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Protocol 31-10-270

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: Aripiprazole (OPC-14597)	Protocol# 31-10-270 IND# 67,380
Protocol Title:	An Open-Label, Multicenter, Rollover, Long-term Study of Aripiprazole Intramuscular Depot in Patients with Schizophrenia
Clinical Phase/Trial Type:	3/Therapeutic use
Treatment Indication:	Schizophrenia
Objective(s):	The primary objective of this open-label study is to continue to provide aripiprazole intramuscular (IM) Depot treatment (400 mg or 300 mg) to subjects with schizophrenia completing the 52-week, open-label safety and tolerability Study 31-08-248 (hereafter referred to as Study 248). Subjects can receive this treatment until aripiprazole IM Depot is commercially available in any dosage (including generic formulation[s]) in the country that the study is being conducted or until the study end date of 31 Dec 2018 is reached. The secondary objective is to collect long-term safety data on aripiprazole IM Depot in addition to what was collected in Study 248 (52-weeks).
Trial Design:	This is an open-label, multicenter rollover non-comparative trial designed to continue to provide aripiprazole IM Depot (400 mg or 300 mg) to adult subjects with schizophrenia who completed aripiprazole IM Depot treatment in Study 248. The decision to enroll into the long-term open-label study will be a joint decision by the investigator and subject. No subjects who discontinued or did not complete Study 248 are allowed to enroll in Study 31-10-270 (hereafter referred to as Study 270). Eligible subjects will enter this study directly after completing the End of Treatment visit (Week 52) of Study 248. The End of Treatment evaluations conducted at the last study visit for Study 248 will serve as the baseline evaluations for Study 270. Subjects in this study will continue to receive aripiprazole IM Depot every month (study months are every 4 weeks which is defined as 28 [−2/+10] days) as a continuation of their previous monthly dose in Study 248. The minimum interval of 26 days and maximum interval of 38 days between injections is to ensure that therapeutic plasma concentrations of aripiprazole are maintained. The monthly dose can be modified, either reduced from 400 mg to 300 mg to address tolerability or increased from 300 mg to 400 mg to address efficacy, at the discretion of the investigator. Following the baseline visit, subjects will receive monthly injections and at the same visit, adverse events (AEs) and concomitant medications will be recorded and the Columbia Suicide Severity Rating Scale (C-SSRS) will be completed. Every 3 months, all of the monthly assessments will be completed along with a urine pregnancy test for women of childbearing potential (WOCBP). Every 6 months, all of the 3-month assessments will be completed along with the Clinical Global Impression - Severity (CGI-S) scale, vital signs, and extrapyramidal symptoms (EPS) assessments (including the Abnormal

	Involuntary Movement Scale [AIMS], Simpson-Angus Scale [SAS], and Barnes Akathisia Rating Scale [BARS]). At the 12-month visit, all of the 6-month assessments will be completed along with clinical laboratory tests and assessments of body weight, height, and waist circumference. Urine drug screening and blood alcohol testing will be obtained at baseline and can be re-obtained at the investigator's discretion at any time during the study. A Visual Analog Scale (VAS) for subject-reported rating of pain at the most recent injection site and the investigator's assessment for pain, redness, induration, and swelling of the most recent injection site will be performed at baseline and may be reassessed at the discretion of the investigator. Clinical laboratory tests, physical examination, and electrocardiogram (ECG) obtained at baseline may also be performed at the discretion of the investigator based on clinical necessity. A Study Completion visit or Early Termination visit (−2/+10 days) will include the following assessments: C-SSRS, AEs, concomitant medications, a urine pregnancy test for WOCBP, CGI-S, vital signs, EPS assessments (AIMS, BARS, SAS), clinical laboratory tests, and body height and weight. A 30-Day Post Treatment Follow-up phone call will be made 30 days (± 3 days) after it has been determined that the subject will no longer participate in this study and will include questions about any AEs that have occurred and any concomitant medications taken since the last visit. No oral antipsychotic rescue medication (including aripiprazole) is allowed in this study. If a subject experiences an exacerbation of psychotic symptoms, the investigator should assess the suitability of the subject's continuation in the study and ensure that the subject is treated appropriately. If the investigator deems that other antipsychotic therapy is warranted, the subject should be discontinued from this study. Aripiprazole IM Depot treatment in this open-label rollover study will continue until there are clinical and/or administrative reasons for discontinuation of the subject's study treatment or until the study end date of 31 Dec 2018 is reached, whichever occurs first. Clinical reasons for discontinuing study treatment include, but are not limited to: the subject voluntarily withdrawing consent; the subject becoming lost to follow-up; if a subject misses 2 consecutive injections at any time in the study or if a subject misses 3 injections in a 52-week time period; or the investigator determines that the subject is no longer receiving benefit from aripiprazole IM Depot. Administrative reasons for discontinuing study treatment include, but are not limited to: aripiprazole IM Depot becomes commercially available in any dosage (including a generic formulation) in the country where the study is being conducted, the commercial availability of aripiprazole IM Depot is terminated by the sponsor, or until the study end date of 31 Dec 2018 is reached, whichever occurs first. Once aripiprazole IM Depot becomes commercially available in any dosage (including generic formulation[s]) in the country where the subject is participating in the study or the commercial availability of aripiprazole IM Depot is terminated by the sponsor, study treatment will be discontinued within approximately 6 weeks of the subject's previous injection for clinical transition purposes. If the sponsor terminates the study prior to 31 Dec 2018 for any reason other than commercial availability, investigators in some countries where the sponsor has limited or delayed commercialization plans, or where no

	commercialization activity is anticipated, may be eligible to participate in a managed access program until aripiprazole IM Depot is commercially available in their country or until 31 Dec 2018.
Subject Population:	The subject population will be comprised of subjects who have completed Study 248 and in the investigator's judgment may benefit from continued participation in an aripiprazole IM Depot study, in countries where aripiprazole IM Depot is not commercially available. It is anticipated that approximately 500 to 800 subjects from Study 248 will enroll in this study.
Inclusion/Exclusion Criteria:	Subjects enrolling into Study 270 from Study 248 will have fulfilled the inclusion and exclusion criteria for Study 248. A complete list and description of inclusion and exclusion criteria is provided in Section 3.4. Key inclusion criteria for Study 270 include subjects with a current diagnosis of schizophrenia, (as defined by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* [DSM-IV-TR] criteria), who completed the open-label extension Study 248; subjects who, in the investigator's judgment, may benefit from continued participation in aripiprazole IM Depot study; and subjects who have an outpatient status. The baseline visit for Study 270 (which is the Week 52 visit of Study 248) and the first injection for Study 270 must occur within 4 weeks (which is defined as 28 [−2/+10] days) of the last injection in Study 248. Key exclusion criteria include subjects with a current DSM-IV-TR diagnosis other than schizophrenia, including schizoaffective disorder, major depressive disorder, bipolar disorder, delirium, dementia, amnestic or other cognitive disorders; subjects who are known to be allergic, intolerant, or unresponsive to prior treatment with aripiprazole or other quinolinones; dependence on substances of abuse; a history of violent behavior, seizures, neuroleptic malignant syndrome, clinically significant tardive dyskinesia, or other medical condition that would expose the subject to undue risk or interfere with study assessments; involuntary incarceration; electroconvulsive therapy within 180 days prior to entry; clinically significant abnormalities in laboratory test results, vital signs, or ECG results; require hospitalization; may require any other antipsychotic medication, varenicline, cytochrome P450 (CYP) 2D6 or CYP3A4 inhibitors, or CYP3A4 inducers during the study; and if aripiprazole IM Depot (including generic formulation) is commercially available in the country where the study is being conducted.
Trial Site(s):	Approximately 250 sites globally (the number of sites globally in Study 248). New sites will not be used.
Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	The investigational products will be aripiprazole IM Depot 400 mg supplied as lyophilized vials. Both doses of aripiprazole IM Depot used in this trial (400 mg and 300 mg) will be obtained from the 400-mg lyophilized vials. IM Depot will be administered every month (study months are every 4 weeks which is defined as 28 [−2/+10] days). All doses of IM Depot must be injected into the gluteal muscle, and care must be taken to avoid inadvertent injection into a blood vessel.

Trial Assessments:	**Safety:** Safety will be assessed by adverse event and concomitant medication reporting at baseline (post-IM administration) and at each subsequent monthly injection visit (study months are every 4 weeks which is defined as 28 [−2/+10] days). The C-SSRS will be used to assess suicidality at baseline and at each subsequent monthly injection visit. Extrapyramidal symptoms will be assessed using the AIMS, SAS, and BARS assessment questionnaires at baseline, every 6 months, at the discretion of the investigator at any subsequent visit, and at Study Completion or the Early Termination visit. Clinical laboratory tests will be performed at baseline, every 12 months, and at Study Completion or the Early Termination visit. Vital signs will be assessed every 6 months and at Study Completion or the Early Termination visit. Body height and weight, body mass index (BMI), and waist circumference will be assessed at baseline; body height, weight, and waist circumference will be reassessed every 12 months; and body height and weight will be assessed at Study Completion or the Early Termination visit. For WOCBP, a urine pregnancy test will be administered at baseline, every 3 months, and at Study Completion or the Early Termination visit. **Efficacy:** Efficacy will be evaluated using the CGI-S administered every 6 months.
Criteria for Evaluation:	**Safety Endpoints:** • Frequency and severity of adverse events, serious adverse events (clinical and laboratory) and discontinuations from the study due to adverse events. • Suicide risk as assessed and classified by the C-SSRS. • Extrapyramidal symptoms will be evaluated by calculating the mean change from baseline in AIMS, SAS, and BARS. • The incidence of clinically significant changes will be calculated for vital signs. Mean change from baseline and incidence of clinically significant changes will be calculated for body weight and waist circumference. **Efficacy Endpoint:** • CGI-S score will be evaluated by calculating mean change from baseline.
Statistical Methods:	Due to the open-label single-arm nature of the study, all data on safety and efficacy/outcome will be summarized by descriptive statistics (eg, mean, standard deviation, maximum, minimum, and proportions).
Trial Duration:	Subjects will continue to receive aripiprazole IM Depot in this open-label rollover study until there are clinical and/or administrative reasons for discontinuation of the subject's study treatment or until the study end date of 31 Dec 2018 is reached, whichever occurs first (see "Trial Design" section above). Once aripiprazole becomes available commercially at any dosage (including generic formulation[s]) in the country where the study is being conducted, the commercial availability of aripiprazole IM Depot is terminated by the sponsor, or until the study end date of 31 Dec 2018 is reached, treatment will be discontinued. If aripiprazole IM Depot is commercially available or if the availability of aripiprazole IM Depot is terminated by the sponsor, then the subject will discontinue treatment within approximately 6 weeks of last injection for clinical transition purposes.

Protocol 31-10-270

Table of Contents

Protocol 31-10-270

Protocol 31-10-270

Protocol 31-10-270

List of In-text Tables

Protocol 31-10-270

List of In-text Figures

Protocol 31-10-270

List of Appendices

List of Abbreviations and Definitions of Terms

AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the concentration curve
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
C_{max}	Maximum plasma concentration
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
CNS	Central nervous system
CRF	Case report form
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	Cytochrome P450
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
ECG	Electrocardiogram
EDC	Electronic data capture
EPS	Extrapyramidal symptoms
EU	European Union
FDA	Food and Drug Administration
GERD	Gastroesophageal reflux disease
GCP	Good Clinical Practice
IAQ	Investigator's Assessment Questionnaire
ICF	Informed consent form

ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IM	Intramuscular
IRB	Institutional review board
IRE	Immediately reportable event
IUD	Intrauterine device
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No-observable-adverse-effect-level
OPDC	Otsuka Pharmaceutical Development and Commercialization, Inc.
PANSS	Positive and Negative Syndrome Scale
PE	Physical examination
QTc	Corrected QT interval
QTcB	QTc (Bazett correction)
QTcF	QTc (Fredericia correction)
SAE	Serious adverse event
SAS	Simpson-Angus Scale
SmPC	Summary of Product Characteristics
US	United States
USPI	Unites States Prescribing Information
VAS	Visual Analog Scale
WOCBP	Women of childbearing potential

Protocol 31-10-270

1 Introduction

Schizophrenia is a chronic condition that requires continual treatment to maintain adequate cognitive and social functioning. Noncompliance with antipsychotic medications remains a frequent cause of relapse among patients with schizophrenia. An estimated 50% of patients do not adhere to prescribed medication regimens for a variety of reasons.[1] This lack of compliance leads to increased morbidity, decreased quality of life, and consequently, an associated increase in healthcare costs.[2] One of the patient-driven reasons for noncompliance is their inability to adhere to daily dosing on a long-term basis, particularly in those who abuse or are dependent on alcohol or illegal drugs.[3] In this respect, an intramuscular (IM) depot formulation administered every month (study months are every 4 weeks which is defined as 28 [–2/+10] days) may have a positive impact on compliance, and potentially on patient outcomes.[4,5] Limited data comparing oral and depot formulations of typical antipsychotic agents suggest that depot formulations may have an advantage over oral formulations for relapse prevention.[6] And yet, existing depot formulations, particularly for typical antipsychotics, are not ideal in that they exhibit many of the same undesirable effects that have been observed with oral administration (eg, hyperprolactinemia and extrapyramidal symptoms [EPS]).[4,7,8]

ABILIFY® (aripiprazole, OPC-14597, BMS-337039), a second generation antipsychotic, which exhibits partial agonism (agonism/antagonism) at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonism at serotonin 5-HT_2 receptors, is approved and marketed in the United States (US) for use in the following indications.[9]

In adults, aripiprazole is indicated:

- for treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder as monotherapy or adjunctive to lithium or valproate.
- for adjunctive treatment of major depressive disorder (MDD) in adults.
- as an injection for treatment of adults with agitation associated with schizophrenia or bipolar I disorder, manic or mixed episodes.
- as an IM depot formulation for treatment of schizophrenia.

In pediatrics, aripiprazole is indicated:

- for treatment of schizophrenia (ages 13 to 17 years).
- for treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy or adjunctive to lithium or valproate (ages 10 to 17 years).

- for treatment of irritability associated with autistic disorder in children and adolescents (ages 6 to 17 years).

In the European Union (EU), aripiprazole is also approved for the treatment of moderate to severe manic episodes in bipolar I disorder and for the prevention of new manic episodes in those patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment, as well as for the treatment of schizophrenia in adults and adolescents (Appendix 13). The aripiprazole immediate-release IM injection formulation is approved for the treatment of agitation associated with schizophrenia or bipolar mania in the US and EU. In addition, an oral solution formulation and orally disintegrating (dispersible) tablets have been approved and marketed in the US and EU.

The favorable side effect profile of oral aripiprazole, including its low incidence of EPS, low risk of prolactin elevation, decreased adrenergic and anticholinergic side effects, and minimal weight gain, makes it an excellent candidate for a long-acting depot formulation. Aripiprazole IM depot formulation is currently being developed for maintenance treatment of schizophrenia and bipolar I disorder, and was approved for the treatment of schizophrenia in the US in February 2013. Its efficacy was demonstrated in a pivotal phase 3 registrational trial (Study 31-07-246) designed to evaluate the efficacy, safety, and tolerability of the long-acting IM depot formulation of aripiprazole administered to adult subjects with a diagnosis of schizophrenia as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). A marketing application was submitted in September 2011 to the Food and Drug Administration (FDA) for use of the aripiprazole IM depot formulation as maintenance treatment in patients with schizophrenia, which was approved in February 2013 (Appendix 13). A marketing application was submitted in December 2012 to the European Medicines Agency.

Study 31-08-248 is included in the development plan for aripiprazole IM Depot to supplement the safety data that will be generated as part of the phase 3 program and to provide additional efficacy data for the maintenance treatment of patients with schizophrenia. The current study (31-10-270, hereafter referred to as *Study 270*), will allow subjects who completed Study 31-08-248 (hereafter referred to as *Study 248*) to continue treatment with aripiprazole IM Depot until it is commercially available in any dosage (including generic formulation[s]) in the country where the study is being conducted, the commercial availability of aripiprazole IM Depot is terminated by the

sponsor, or until the study end date of 31 Dec 2018 is reached. This study will provide additional long-term safety information.

If the sponsor terminates the study prior to 31 Dec 2018 for any reason other than commercial availability, investigators in some countries where the sponsor has limited or delayed commercialization plans, or where no commercialization activity is anticipated, may be eligible to participate in a managed access program until aripiprazole IM Depot is commercially available in their country or until 31 Dec 2018. Availability and requirements of such a program varies by jurisdiction, and would only be an option for subjects who were receiving aripiprazole IM Depot in the current study, and who in the physician's opinion, may benefit from continued treatment with aripiprazole. To gain access to aripiprazole IM Depot for eligible subjects via a managed access program, each physician will be responsible for gaining appropriate local regulatory approvals, which will be granted by authorities on a case-by-case basis. The sponsor makes no guarantee that such a program is available or approvable in all of the jurisdictions where the study is conducted.

Please refer to the Investigator's Brochure[9], ABILIFY US Prescribing Information (USPI) (Appendix 13), and EU Summary of Product Characteristics (SmPC) (Appendix 13) for detailed information on preclinical and clinical data. A brief summary is included below.

1.1 Nonclinical Data

The mechanism of action of aripiprazole differs from that of currently marketed typical and atypical antipsychotics. It has been proposed that aripiprazole's effectiveness in schizophrenia is mediated through a combination of partial agonism (agonism/antagonism) at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonism at serotonin 5-HT_2 receptors. Aripiprazole has the properties of an agonist in an animal model of dopaminergic hypoactivity and the properties of an antagonist in animal models of dopaminergic hyperactivity. Aripiprazole exhibits high affinity for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors and moderate affinity for dopamine D_4 serotonin 5-HT_{2C} and 5-HT_7, alpha$_1$-adrenergic, histamine H_1 receptors and the serotonin reuptake site. Aripiprazole also displays 5-HT_{1A} partial agonist and 5-HT_{2A} antagonist activity in nonclinical studies. The emerging literature for other antipsychotics indicates that 5-HT_{1A} and 5-HT_{2A} activity may be correlated with the clinical observation of effectiveness against negative symptoms in patients with schizophrenia. It seems likely

that the favorable safety and tolerability profile of aripiprazole is also mediated by its unique profile of interaction with central neuroreceptors.

Toxicokinetic evaluations of a prototype formulation of aripiprazole IM Depot were conducted in single-dose IM irritation and toxicity studies in rats and dogs. Systemic exposures to aripiprazole were dose-related and generally higher in females than in males. Plasma concentrations of aripiprazole were measurable at all doses up to Day 43 in rats (maximum plasma concentration [C_{max}] approximately 190 ng/mL at 1 mg/kg)[10] and Day 42 in dogs (C_{max} approximately 30 ng/mL, area under the concentration curve $[AUC]_{0\text{-}28\ days}$ approximately 300 ng-days/mL at 100 mg/dog),[11] indicating sustained absorption over these periods. Clinically relevant exposures were not readily achieved in rats or dogs due to the markedly greater metabolic clearance of aripiprazole in animals versus humans, and because release of drug from the injection site, as desired, was slow. Plasma concentrations of the pharmacologically active metabolite, BMS-337040, were generally below the lower limit of quantitation in both species, whereas plasma concentrations of BMS-337044 (dehydro-aripiprazole, another active metabolite) were measurable at most time points in dogs, but not in rats.

The IM depot formulation was well tolerated by all species; the principal gross finding at injection sites was generally dose-related, linear foci of white or tan discoloration in skeletal muscle that slowly decreased in size over time. Microscopically, the foci of white/tan discoloration were characterized as a localized and generally dose-dependent foreign-body type of granulomatous inflammation (minimal to mild in rats; minimal to moderate in rabbits and dogs) associated with deposits of drug (birefringent polymorphic crystalline material) that remained localized at the injection site. As is characteristic of a foreign-body reaction, resolution of the granulomatous inflammation at injection sites was slow, and recovery was incomplete by Day 43 and 45 postdose in dogs and rats, respectively, and by Day 57 postdose in rabbits.

Pivotal nonclinical studies to support the IM depot formulation for clinical use included single-dose IM irritation and toxicity studies in rats (0, 75, or 100 mg/kg), rabbits (0, 150, or 200 mg), and dogs (0, 150, 200, 300, or 400 mg), and repeated-dose toxicity studies in rats (0, 25, 50, and 100 mg/kg weekly for 26 weeks) and beagle dogs (0, 10, 20, and 40 mg/kg weekly for 26 weeks). All doses of this IM depot formulation were well tolerated by all species. As with the earlier IM irritation and toxicity studies, the principal injection site findings in all species were deposits of drug that remained localized at the injection site and associated foreign-body type of granulomatous inflammation, both of which resolved slowly over time. Importantly, there was no

significant muscle injury or fibroplasia/fibrosis associated with the drug deposits or the associated inflammation. Considering that the local tissue reaction (foreign-body type of granulomatous inflammation) was consistent in all species tested, it is anticipated that the depot formulation will produce a similar local reaction in humans that will resolve over time.

Repeated IM doses of the depot formulation for clinical use were also well tolerated by rats and dogs. The local tissue reactions of both repeated dose studies were comparable to those of the single dose studies. For the systemic toxicity in rats, 6 months of intermittent repeated IM injections at the maximal dose of 100 mg/kg were well tolerated, and no morphological changes were observed, except for the findings considered to be pharmacologically mediated and a consequence of the D_2 partial agonistic activity of aripiprazole. The no-observable-adverse-effect-level (NOAEL) in the rat study was considered to be 50 mg/kg/week in the males and 100 mg/kg/week in the females. For the systemic toxicity in dogs, 6 months intermittent repeated IM injections at the maximal dose of 40 mg/kg were well tolerated, and the NOAEL was considered to be 40 mg/kg/week under the conditions of the study. Thus, preclinical safety data of the IM depot formulation revealed no special hazard for clinical use based on the studies of single and repeat-dose toxicity.

Further details of results of nonclinical studies with the IM depot formulation and information on nonclinical studies following aripiprazole administration via other dose routes can be found in the Investigator's Brochure.[9]

1.2 Clinical Data

A comprehensive clinical program to evaluate the effectiveness of aripiprazole was conducted. The studies of subjects with an acute exacerbation of schizophrenia established the effectiveness of aripiprazole in the treatment of schizophrenia, including positive and negative symptoms. These studies also demonstrated its early onset of action. The long-term studies showed that aripiprazole treatment maintained stability in subjects with schizophrenia. The Investigator's Brochure provides additional safety data on studies not described below.[9]

Two phase 2, double-blind, placebo-controlled studies conducted in acutely relapsing hospitalized schizophrenic subjects gave support for the effectiveness, safety, and tolerability of aripiprazole in this population. Three phase 3 trials established the efficacy of oral doses of aripiprazole 10, 15, 20, and 30 mg/day for the treatment of acute relapse of schizophrenia or schizoaffective disorder. The two 4-week studies (31-97-201 and

31-97-202) [12,13] each included 2 fixed doses of aripiprazole (15 mg and 30 mg for 31-97-201 and 20 mg and 30 mg for 31-97-202), an active comparator (for comparison of safety profiles), and placebo. Review of the data from these trials indicated that all of the doses of aripiprazole were effective in the treatment of acute psychosis. All aripiprazole doses were statistically significant compared to placebo with regard to the primary endpoints of change from baseline in the Positive and Negative Syndrome Scale (PANSS) Total Score, PANSS positive score, and Clinical Global Impression - Severity (CGI-S) score. As expected, the active comparators (haloperidol and risperidone), demonstrated effectiveness in the treatment of psychosis as measured by these endpoints. The third double-blind, placebo-controlled, phase 3 study (CN138001)[14] was 6 weeks in duration and included aripiprazole oral doses of 10, 15, and 20 mg/day. All doses of aripiprazole demonstrated significant improvement compared with placebo for change from baseline in the PANSS Total Score and the positive and negative subscales.

Three phase 3, double-blind, controlled studies were conducted to show the long-term efficacy of aripiprazole. Study CN138047[15,16] was a 26-week study designed to document the long-term efficacy of oral aripiprazole 15 mg/day compared with placebo in stable schizophrenic subjects. The primary efficacy variable was time to relapse from randomization, as measured by Clinical Global Impression - Improvement (CGI-I) score ≥ 5, PANSS scores for hostility or uncooperativeness ≥ 5, or $\geq 20\%$ increase in PANSS Total Score. The results indicated that subjects treated with aripiprazole 15 mg daily experienced a significantly longer time to relapse over the 26-week assessment period compared with those receiving placebo. Two 52-week studies (Studies 31-98-217 and 31-98-304-01)[17,18] of aripiprazole 30 mg versus haloperidol 10 mg were conducted in acutely relapsing schizophrenic subjects with the intention of pooling the data for analysis. On the primary efficacy measure (time to failure to maintain response in responders) no difference was seen between aripiprazole and haloperidol. However, analysis of secondary efficacy measures showed that aripiprazole 30 mg was superior to haloperidol on negative symptoms, depressive symptoms, and discontinuation for any reason.

The subject-rated and investigator-rated acceptability of aripiprazole treatment has been examined in open-label studies. Subjects treated with open-label oral aripiprazole 10 to 30 mg for 8 weeks indicated a general preference for aripiprazole over the antipsychotic medication(s) taken prior to entering the study (CN138087 and CN138100). A separate open-label study (CN138152)[19,20] compared aripiprazole (oral doses of 10 to 30 mg daily) to standard of care treatment (clinician-prescribed olanzapine, risperidone, or

quetiapine) in community-treated schizophrenic subjects for whom an alteration in antipsychotic medication was clinically warranted. Aripiprazole demonstrated superior effectiveness as measured by the Investigator's Assessment Questionnaire (IAQ), which provides an overall assessment of efficacy and tolerability.[21]

Aripiprazole showed an excellent safety and tolerability profile both in acute or chronic schizophrenia, with no evidence of increased rates of somnolence, EPS-related side effects, clinically significant weight gain, hyperprolactinemia, or prolongation of corrected QT interval (QTc). The recommended starting and target oral dose for aripiprazole in the treatment of schizophrenia is 10 mg or 15 mg/day administered on a once-a-day schedule without regard to meals. Aripiprazole has been systematically evaluated and shown to be effective in an oral dose range of 10 mg to 30 mg/day; however, there is no evidence that doses higher than 15 mg per day are associated with increased efficacy.

1.3 Known and Potential Risks and Benefits

As of 01 Jun 2014, all voluntary reports of adverse events (AEs) in patients taking aripiprazole received since market introduction that were considered by the sponsor as medically relevant have been listed in the USPI and EU SmPC (Appendix 13). The USPI and EU SmPC also contain the currently available phase 2/3/4 clinical safety information (Appendix 13). Across the short-term, double-blind, placebo-controlled studies conducted in schizophrenic subjects, the AE profile of oral aripiprazole was generally comparable to that of placebo. There was little difference in the incidence of discontinuation due to AEs between aripiprazole-treated (7%) and placebo-treated (9%) subjects. Akathisia was the only commonly observed AE that occurred in ≥ 5% of aripiprazole-treated subjects and at an incidence more than twice that of placebo (8% vs. 4%, respectively). Aripiprazole was well-tolerated in the long-term studies. Changes in body weight, fasting glucose, lipid profile, and serum prolactin levels were similar between aripiprazole- and placebo-treated subjects. No clinically relevant changes in QTc were observed in either group.[16] In the pooled analysis of the two 52-week studies comparing aripiprazole with haloperidol, the incidence of EPS-related AEs was significantly higher for haloperidol (58%) compared with aripiprazole (27%). In the one 52-week study in which prolactin levels were measured, significantly fewer aripiprazole-treated subjects (3.4%) experienced prolactin elevations above the upper limit of normal compared with the haloperidol group (61%).[18]

The comparative safety profile of oral aripiprazole relative to placebo in subjects with acute bipolar mania raised no new safety concerns and was similar to that observed in

subjects with schizophrenia. Additionally, aripiprazole exhibited a more favorable safety profile than haloperidol in the 26-week active-controlled study in acute bipolar mania. The safety profile was consistent with that observed in haloperidol-controlled schizophrenia studies, as evidenced by a lower incidence of AE discontinuation; EPS-related AEs, and prolactin elevation.[22]

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia in subjects treated with aripiprazole. Although fewer subjects have been treated with aripiprazole, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in subjects with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related AEs is not completely understood. However, epidemiological studies which did not include aripiprazole suggest an increased risk of treatment-emergent hyperglycemia-related AEs in subjects treated with the atypical antipsychotics included in these studies. Because aripiprazole was not marketed at the time these studies were performed, it is not known if aripiprazole is associated with this increased risk. Precise risk estimates for hyperglycemia-related AEs in subjects treated with atypical antipsychotics are not available.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs, including aripiprazole, are at an increased risk of death compared with placebo. Over the course of three 10-week, placebo-controlled studies of aripiprazole in elderly subjects with psychosis associated with Alzheimer's disease, the rate of death in aripiprazole-treated subjects was 3.5%, compared with a rate of 1.7% in the placebo group during or within 30 days after termination from the double-blind phase of the studies. Although the causes of death were varied, most of the deaths were either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Overall, 1.3% of aripiprazole-treated subjects reported cerebrovascular AEs (eg, stroke, transient ischemic attack) compared with 0.6% of placebo-treated subjects in these trials. This difference was not statistically significant. However, in one of these trials, a fixed-dose trial, there was a significant dose-response relationship for cerebrovascular AEs in subjects treated with aripiprazole. Aripiprazole is not approved for the treatment of dementia-related psychosis. In clinical studies and postmarketing experience, accidental or intentional acute overdose of aripiprazole alone was reported in adult

patients with estimated doses up to 1260 mg with no fatalities. The potentially medically important signs and symptoms observed included lethargy, increased blood pressure, somnolence, tachycardia, and vomiting. In addition, reports of accidental overdose with aripiprazole alone (up to 195 mg) in children were received with no fatalities. The potentially medically serious signs and symptoms reported included somnolence and transient loss of consciousness. In the patients who were evaluated in hospital settings, there were no reported observations indicating clinically important adverse change in vital signs, laboratory assessments, or electrocardiograms (ECGs). Additional information can be obtained from the ABILIFY USPI and EU SmPC (Appendix 13).

2 Trial Rationale and Objectives

2.1 Trial Rationale

The efficacy, safety, and tolerability of aripiprazole IM Depot administered every month are being investigated in two phase 3 clinical trials (Studies 31-07-246 and 31-07-247). The main efficacy objective of these studies is relapse prevention with aripiprazole IM Depot relative to placebo (Study 31-07-246) and to oral aripiprazole (Study 31-07-247). Study 248 was included in the development plan for aripiprazole IM Depot to supplement the safety data that will be generated as part of the phase 3 program by allowing an additional 52 weeks of treatment with open-label aripiprazole IM Depot to qualifying subjects. Current literature suggests that remission of symptoms should be explored as a goal of ongoing longer-term schizophrenia treatment.[23,24,25,26]

The current study (31-10-270) will allow the long-term subjects who completed Study 248 to continue to receive aripiprazole IM Depot treatment until aripiprazole IM Depot is either commercially available in any dosage (including generic formulation[s]) in the country where the study is being conducted, the commercial availability of aripiprazole IM Depot is terminated by the sponsor, or until the study end date of 31 Dec 2018 is reached.

If the sponsor terminates the study prior to 31 Dec 2018 for any reason other than commercial availability, investigators in some countries where the sponsor has limited or delayed commercialization plans, or where no commercialization activity is anticipated, may be eligible to participate in a managed access program until aripiprazole IM Depot is commercially available in their country or until 31 Dec 2018. Availability and requirements of such a program varies by jurisdiction, and would only be an option for subjects who were receiving aripiprazole IM Depot in the current study, and who in the physician's opinion, may benefit from continued treatment with aripiprazole. To gain

access to aripiprazole IM Depot for eligible subjects via a managed access program, each physician will be responsible for gaining appropriate local regulatory approvals, which will be granted by authorities on a case-by-case basis. The sponsor makes no guarantee that such a program is available or approvable in all of the jurisdictions where the study is conducted.

Aripiprazole IM Depot 400 mg is the highest dose being studied in the pivotal trials and in the current study. However, investigators will have the option to decrease the dose of aripiprazole IM Depot to 300 mg, if needed for tolerability. Dose-adjustment between aripiprazole IM Depot 400 mg and 300 mg will be permitted as often as necessary to maintain stability with acceptable tolerability.

2.2 Trial Objectives

The primary objective of this open-label study is to continue to provide aripiprazole IM Depot treatment (400 mg or 300 mg) to subjects with schizophrenia who completed the 52-week, open-label safety and tolerability Study 248. Subjects can receive this therapy until aripiprazole IM Depot is commercially available in any dosage (including generic formulation[s]) in the country where the study is being conducted, the commercial availability of aripiprazole IM Depot is terminated by the sponsor, or until the study end date of 31 Dec 2018 is reached.

The secondary objective is to collect long-term safety data on aripiprazole IM Depot in addition to what was collected in Study 248 (52-weeks).

3 Trial Design

3.1 Type/Design of Trial

This is an open-label, multicenter rollover non-comparative study designed to continue to provide aripiprazole IM Depot (400 mg or 300 mg) to adult subjects with schizophrenia who completed aripiprazole IM Depot treatment in Study 248. The decision to enroll into the long-term open-label study will be a joint decision by the investigator and subject. No subjects who discontinued or did not complete Study 248 are allowed to enroll in Study 270.

Eligible subjects will enter this study directly after completing the End of Treatment visit (Week 52) of Study 248. The End of Treatment (Week 52) evaluations conducted at the last study visit for Study 248 will serve as the baseline evaluations for Study 270. The baseline visit for Study 270 (which is the Week 52 visit for Study 248) and the first

injection for Study 270 must occur within 4 weeks (which is defined as 28 [–2/+10] days) of the last injection in Study 248.

Subjects will continue to receive aripiprazole IM Depot (400 mg or 300 mg) every month (study months are every 4 weeks which is defined as 28 [–2/+10] days) as a continuation of their previous monthly dose in Study 248. The minimum interval of 26 days and maximum interval of 38 days between injections is to ensure that therapeutic plasma concentrations of aripiprazole are maintained. The monthly dose can be modified, either reduced from 400 mg to 300 mg to address tolerability or increased from 300 mg to 400 mg to address efficacy, at the discretion of the investigator.

Following the baseline visit (described in detail in Section 3.6.1.1), subjects will receive monthly injections and at the same visit, AEs and concomitant medications will be recorded and the Columbia Suicide Severity Rating Scale (C-SSRS) will be completed (Section 3.6.1.2). Every 3 months (Section 3.6.1.3), all of the monthly assessments will be completed along with a urine pregnancy test for women of childbearing potential (WOCBP) (see Section 5.4 for the definition of WOCBP). Every 6 months (Section 3.6.1.4), all of the 3-month assessments will be completed along with the CGI-S scale, vital signs, and EPS assessments (Abnormal Involuntary Movement Scale [AIMS], Simpson-Angus Scale [SAS], and Barnes Akathisia Rating Scale [BARS]). Every 12 months (Section 3.6.1.5), all of the 6-month assessments will be completed along with clinical laboratory tests and assessments of body weight, height, and waist circumference.

At the discretion of the investigator, the baseline assessments for clinical chemistry and hematology, urine drug screening, and blood alcohol testing may be repeated at any subsequent study visit. For each visit, all the assessments, except for those specified as post-injection assessments, should be performed prior to the aripiprazole IM Depot injection.

A Study Completion visit or Early Termination visit (–2/+10 days) will include the following assessments (Section 3.6.1.6): C-SSRS, AEs, concomitant medications, a urine pregnancy test for WOCBP, CGI-S, vital signs, EPS assessments (AIMS, BARS, SAS), clinical laboratory tests, and body height and weight.

A 30-Day Post Treatment Follow-up phone call will be performed 30 days (± 3 days) after it has been determined that the subject will no longer participate in this study and include the recording of AEs that have occurred and any concomitant medications taken since the last study visit.

No oral antipsychotic rescue medication (including aripiprazole) is allowed in this study. If a subject experiences an exacerbation of psychotic symptoms, the investigator should

assess the suitability of the subject's continuation in the study and ensure that the subject is treated appropriately. If the investigator deems that other antipsychotic therapy is warranted, the subject should be discontinued from this study.

Aripiprazole IM Depot treatment in this open-label rollover study will continue until there are clinical and/or administrative reasons for discontinuation of the subject's study treatment or until the study end date of 31 Dec 2018 is reached, whichever occurs first. Clinical reasons for discontinuing study treatment include, but are not limited to: the subject voluntarily withdraws consent; the subject becomes lost to follow-up; if a subject misses 2 consecutive injections at any time in the study or 3 injections in any 52-week time period; or the investigator determines that the subject is no longer receiving benefit from aripiprazole IM Depot. Administrative reasons for discontinuing study treatment include, but are not limited to: aripiprazole IM Depot is commercially available in any dosage (including a generic formulation) in the country where the study is being conducted, the commercial availability of aripiprazole IM Depot is terminated by the sponsor, or until the study end date of 31 Dec 2018 is reached, whichever occurs first.

If the sponsor terminates the study prior to 31 Dec 2018 for any reason other than commercial availability, investigators in some countries where the sponsor has limited or delayed commercialization plans, or where no commercialization activity is anticipated, may be eligible to participate in a managed access program until aripiprazole IM Depot is commercially available in their country or until 31 Dec 2018. Availability and requirements of such a program varies by jurisdiction, and would only be an option for subjects who were receiving aripiprazole IM Depot in the current study, and who in the physician's opinion, may benefit from continued treatment with aripiprazole. To gain access to aripiprazole IM Depot for eligible subjects via a managed access program, each physician will be responsible for gaining appropriate local regulatory approvals, which will be granted by authorities on a case-by-case basis. The sponsor makes no guarantee that such a program is available or approvable in all of the jurisdictions where the study is conducted.

Once aripiprazole IM Depot becomes commercially available in the country where the subject is participating in the study (including generic formulation[s]) or the commercial availability of aripiprazole IM Depot is terminated by the sponsor, study treatment will be discontinued within approximately 6 weeks of the subject's previous injection for clinical transition purposes.

The study design is presented in Figure 3.1-1.

Protocol 31-10-270

<table>
<tr><td>Study Entry
→
Study 248 Completers only</td><td colspan="2">Open-label IM Depot Treatment
→
Every month: Injection, C-SSRS, AEs, and concomitant medications
Every 3 months[a]: Urine pregnancy test for WOCBP
Every 6 months[a]: CGI-S, vital signs, and EPS assessments (AIMS, BARS, SAS)
Every 12 months[a]: Clinical laboratory tests, body weight and height, and waist circumference</td><td>Follow-up
→
One 30-day post End of Study phone call - AEs and concomitant medications</td></tr>
<tr><td>Week 52 Visit of Study 248 = Baseline for Study 270</td><td colspan="2">Injection visit window = 28 (−2/+10) days
Assessment visit window = −2/+10 days</td><td>± 3 days</td></tr>
</table>

Figure 3.1-1 Study 31-10-270 Trial Design Schema

BMI = body mass index.

[a]The 3-month, 6-month, and 12-month visits include assessments from the previous visit. For example, the 3-month visit includes all of the monthly visit assessments in addition to the 3-month visit assessments. A Study Completion or Early Termination visit will also be performed. Refer to Table 3.6-1 for a comprehensive Schedule of Assessments at each visit.

3.2 Treatments

Subjects meeting the eligibility criteria will receive aripiprazole IM Depot (400 mg or 300 mg) every month (study months are every 4 weeks which is defined as 28 [–2/+10] days) as a continuation of their previous monthly dose in Study 248. The monthly dose can be modified, either reduced from 400 mg to 300 mg to address tolerability or increased from 300 mg to 400 mg to address efficacy, at the discretion of the investigator.

Needle length for injection of aripiprazole IM Depot will be selected based on body mass index (BMI) obtained at baseline as follows: 21 gauge, 1.5 inch for BMI $\leq$ 28 kg/m^2; 21 gauge, 2 inch for BMI > 28 kg/m^2. The BMI should be calculated in kg/m^2 from the baseline height and the weight using one of the following formulas, as appropriate:

$$\text{Weight (kg)} \div [\text{Height (m)}]^2 \text{ or } \text{Weight (lb)} \div [\text{Height (in)}]^2 \times 703.$$

The BMI should be provided to the individual administering each dose of IM depot. If a noticeable fluctuation in body height and weight has occurred during the study, at the investigator's discretion, body weight can be remeasured and BMI recalculated and used for the next aripiprazole IM Depot injection. All doses of aripiprazole IM Depot must be injected into the gluteal muscle (rotate sites of injection), and care must be taken to avoid

inadvertent injection into a blood vessel, as per the administration guidance in the Operations Manual.

No oral antipsychotic rescue therapy (including aripiprazole) is allowed in this study.

If a subject experiences an exacerbation of psychotic symptoms, the investigator should assess the suitability of the subject's continuation in the study and ensure that the subject is treated appropriately. If the investigator deems that other antipsychotic therapy is warranted, the subject should be discontinued from this study.

3.3 Trial Population

The subject population will be comprised of subjects who have completed Study 248 and in the investigator's judgment, may benefit from continued participation in an aripiprazole IM Depot study, in countries where aripiprazole IM Depot is not commercially available.

It is anticipated that approximately 500 to 800 subjects from Study 248 will be enrolled from the 250 sites involved in Study 248 worldwide. New sites will not be utilized.

3.4 Eligibility Criteria

3.4.1 Informed Consent

Each investigator has both ethical and legal responsibility to ensure that subjects being considered for inclusion in this trial are given a full explanation of the protocol. This shall be documented on a written informed consent form (ICF) that shall be approved by the same institutional review board/independent ethics committee (IRB/IEC) responsible for approval of this protocol. Each ICF shall include the elements required by the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[27] and local regulatory requirements and must adhere to the ethical principles that have their origin in the Declaration of Helsinki. The investigator agrees to obtain approval from the sponsor of any written ICF used in the trial, prior to submission to the IRB/IEC.

Written informed consent will be obtained from all subjects (or their legal representative, as applicable for local laws). Any patient stipend as indicated in the ICF should be documented in the source documentation. Investigators may discuss the availability of the trial 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 this trial, including withdrawal from current medication(s). When this is done in

anticipation of, or in preparation for, the research, it is considered to be part of the research.

Once the appropriate essential information has been provided to the subject and fully explained in layman's language by the investigator (or a qualified designee) and it is felt that the subject understands the implications of participating, the IRB/IEC-approved written ICF shall be personally signed and dated by both the subject and the person obtaining consent (investigator or designee), and by any other parties required by the IRB/IEC. The subject shall be given a copy of the signed ICF; the original shall be kept on file by the investigator. All of the above mentioned activities must be completed prior to the subject's participating in the trial.

3.4.2 Inclusion Criteria

The following inclusion criteria must be met by subjects entering the open-label rollover study at the End of Treatment visit of Study 248 (Week 52):

Table 3.4.2-1	**Inclusion Criteria**
1.	Subjects with a current diagnosis of schizophrenia, as defined by DSM-IV-TR criteria, who completed the open-label extension Study 248 (completed Study 248 Study Completion visit, Week 52).
2.	Subjects who, in the investigator's judgment, may benefit from continued participation in an aripiprazole IM Depot study.
3.	The baseline visit for Study 270 (which is the Week 52 visit of Study 248) and the first injection for Study 270 must occur within 4 weeks (which is defined as 28 [−2/+10] days) of the last injection in Study 248.
4.	Subjects who are able to provide written informed consent and/or consent obtained from a legally acceptable representative (as required by IRB/IEC), prior to the initiation of any protocol-required procedures.
5.	Subjects able to understand the nature of the study and follow protocol requirements and who can read and understand the written word in order to complete patient-reported outcomes measures.
6.	Outpatient status.

3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria:

Table 3.4.3-1	**Exclusion Criteria**
Sex and Reproductive Status	
1.	Sexually active males who are not practicing double-barrier birth control or who will not remain abstinent during the study and for 180 days following the last dose of study medication, or sexually active females of childbearing potential who are not practicing double-barrier birth control or who will not remain abstinent during the study and for 150 days following the last dose of study medication. If employing birth control, two of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device (IUD), birth control pill, birth control implant, condom with spermicide, or sponge with spermicide.
2.	Females who have a positive serum pregnancy test result at study entry.

Table 3.4.3-1 Exclusion Criteria	
Target Disease	
3.	Subjects with a current DSM-IV-TR diagnosis other than schizophrenia, including schizoaffective disorder, MDD, bipolar disorder, delirium, dementia, amnestic or other cognitive disorders. Also, subjects with borderline, paranoid, histrionic, schizotypal, schizoid, or antisocial personality disorder.
Medical History and Concurrent Disease	
4.	Subjects with a significant risk of violent behavior or a significant risk of committing suicide based on the investigator's judgment.
5.	Subjects who currently meet DSM-IV-TR criteria for substance dependence; including alcohol and benzodiazepines, but excluding caffeine and nicotine.
6.	Subjects who have a history or evidence of a medical condition that would expose them to an undue risk of a significant AE or interfere with assessments of safety or efficacy during the course of the trial, including but not limited to hepatic, renal, respiratory, cardiovascular, endocrine, neurologic, hematologic, or immunologic disease as determined by the clinical judgment of the investigator.
7.	Subjects with epilepsy or a history of seizures, except for a single childhood febrile seizure, post traumatic, alcohol withdrawal, etc.
Physical and Laboratory Test Findings	
8.	Any subject with a positive drug screen for cocaine or other drugs of abuse (excluding marijuana, stimulants, and other prescribed medications).
9.	The following laboratory test, vital sign, and ECG results are exclusionary: a) Platelets $\leq 75{,}000/mm^3$ b) Hemoglobin ≤ 9 g/dL c) Neutrophils, absolute $\leq 1000/mm^3$ d) Aspartate transaminase (AST) > 3x upper limit of normal e) Alanine transaminase (ALT) > 3x upper limit of normal f) Creatinine ≥ 2 mg/dL g) Diastolic blood pressure > 105 mm Hg h) At baseline, QTc > 475 msec on either the QTcB (Bazett) or QTcF (Fridericia) corrections on 2 of 3 time points of triplicate ECGs performed (refer to NOTE below).
	NOTE: In addition, subjects should be excluded if they have any other abnormal laboratory tests, vital sign results, or ECG findings which in the investigator's judgment is medically significant and that would impact the safety of the subject or the interpretation of the study results. Criteria are provided in Appendix 3, Appendix 4, and Appendix 5 to assist investigators in their assessments of results that may be potentially medically significant, depending on the subject's medical history and clinical presentation. Abnormal results for laboratory parameters, or vital signs should be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. The ECG criteria for baseline ECG for Study 270 (which is the Week 52 visit of Study 248) will be done per Study 248 requirements. The central ECG service will provide the corrections for the three ECGs done approximately five minutes apart (each ECG result reported is derived from the average of the triplicate ECG done at each time point.) Based on the QTcB or QTcF corrections reported by the central service, a subject will be excluded if either of the corrections exceed 475 msec for 2 of the 3 time points of triplicate ECGs done. If only one triplicate ECG time point has a corrected QTc greater than 475 msec on either correction factor, and this is not reproduced at the other 2 time points, this subject can be included in the study. Subjects may enroll into the study prior to obtaining baseline results, but will be subsequently withdrawn if clinically significant results are identified.
Allergies and Adverse Drug Reactions	
10.	Subjects who are known to be allergic, intolerant, or unresponsive to prior treatment with aripiprazole or other quinolinones.
11.	Subjects with a history of neuroleptic malignant syndrome or clinically significant tardive dyskinesia at screening.

Protocol 31-10-270

Table 3.4.3-1 Exclusion Criteria	
Prohibited Therapies and/or Medications	
12.	Subjects likely to require prohibited concomitant therapy during the trial (see Table 4.1-1).
13.	Subjects who may require cytochrome P450 (CYP) 2D6 or CYP3A4 inhibitors or CYP3A4 inducers during the trial (see Table 4.1-1 and Section 4.2.1).
14.	Any subject who requires or may need any other antipsychotic medications during the course of the study.
Other Exclusion Criteria	
15.	Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for any reason must not be enrolled into this trial.
16.	Electroconvulsive therapy within 180 days prior to entry.
17.	Aripiprazole IM Depot (including generic formulation) is commercially available in the subject's country.

3.5 Primary and Secondary Endpoints

3.5.1 Safety Endpoints

Adverse events will be examined by frequency, severity, seriousness, and discontinuation due to AEs. The C-SSRS will be completed at baseline and every subsequent monthly visit to assess the risk of suicide events and to classify reported suicide events. Extrapyramidal symptoms will be evaluated by calculating mean change from baseline in AIMS, SAS, and BARS every 6 months (more frequently if warranted, see Table 3.6-1) and at Study Completion or the Early Termination visit. Clinical laboratory tests will be performed at baseline, every 12 months, and at Study Completion or the Early Termination visit. Vital signs will be assessed every 6 months and at Study Completion or the Early Termination visit. Body weight, height, and waist circumference will be assessed every 12 months; body weight and height will also be assessed at Study Completion or the Early Termination visit.

3.5.2 Efficacy Endpoint

CGI-S will be evaluated by calculating mean change from baseline every 6 months over the course of the study.

3.6 Trial Procedures

A schedule of assessments is provided in Table 3.6-1.

Protocol 31-10-270

Table 3.6-1 Schedule of Assessments (Study 31-10-270)

Assessment	Baseline (Week 52 Visit of previous Otsuka 31-08-248 study)[a]	Study Visits				Study Completion or Early Termination (−2/+10 days)	30-Day Post Treatment Follow-up Phone Call[c] (± 3 days)
		Every Month[b] (−2/+10 days)	Every 3 Months[b] (−2/+10 days)	Every 6 Months[b] (−2/+10 days)	Every 12 Months[b] (−2/+10 days)		
STANDARD							
Informed consent	X						
Inclusion/exclusion criteria	X						
Medical history	X						
STUDY ASSESSMENTS							
CGI-S	X			X	X	X	
C-SSRS	X	X	X	X	X	X	
AIMS[d]	X			X	X	X	
SAS[d]	X			X	X	X	
BARS[d]	X			X	X	X	
VAS pain at injection site[e]	X	At the discretion of the investigator					
Investigator rating of injection site[e]	X	At the discretion of the investigator					
Body height and weight[f]	X				X	X	
BMI[f]	X	At the discretion of the investigator					
Waist circumference[f]	X				X		
Adverse events[g]	X	X	X	X	X	X	X
Clinical laboratory tests (hematology, serum chemistry, and urinalysis)	X	At the discretion of the investigator			X	X	
Vital signs	X			X	X	X	
Physical exam	X	At the discretion of the investigator					
ECG	X	At the discretion of the investigator					
Urine pregnancy test[h]	X		X	X	X	X	

Protocol 31-10-270

Table 3.6-1 Schedule of Assessments (Study 31-10-270)

Assessment	Baseline (Week 52 Visit of previous Otsuka 31-08-248 study)[a]	Study Visits				Study Completion or Early Termination (−2/+10 days)	30-Day Post Treatment Follow-up Phone Call[c] (± 3 days)
		Every Month[b] (−2/+10 days)	Every 3 Months[b] (−2/+10 days)	Every 6 Months[b] (−2/+10 days)	Every 12 Months[b] (−2/+10 days)		
Urine drug screen and blood alcohol test[i]	X	At the discretion of the investigator					
Concomitant medications	X	X	X	X	X	X	X
STUDY MANAGEMENT							
Administer open-label IM Depot[j]	X	X	X	X	X		

VAS = visual analog scale.

[a]Baseline visit for Study 270 will be the End of Treatment visit for Study 248 (Week 52).

[b]Study months (study months are every 4 weeks which is defined as 28 [−2/+10] days) for assessments:

Every month: Months 1 through 104.
Every 3 months: Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99, and 102.
Every 6 months: Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, and 102.
Every 12 months: Months 12, 24, 36, 48, 60, 72, 84, and 96.

[c]The 30-Day Post Treatment Follow-up Phone Call will be conducted 30 days (± 3 days) after it has been determined that the subject will no longer participate in this open-label, rollover study, regardless of the reason.

[d]Extrapyramidal symptoms (EPS) will be assessed using AIMS, SAS, and BARS at baseline, every 6 months, at Study Completion or the Early Termination visit, and at other any study visit at the discretion of the investigator if warranted by the presence of symptoms.

[e]At baseline (Week 52 visit of the previous Otsuka 31-08-248 study), each subject will complete the pain evaluation and the investigator (or qualified designee) will assess the most recent injection site for localized pain, redness, swelling, and induration. These assessments will occur as the last evaluations prior to the IM Depot injection. Approximately 30 minutes prior to the injection, the investigator and subject will complete the injection site evaluation and VAS pain assessment, respectively, with the most recent injection site as the basis for the evaluation (ie, the site from the last injection). These assessments will be repeated at 1 hour (± 15 min) after the injection is administered with focus again on the most recent injection site. The pre- and post-injection evaluations must be completed on the same day (ie, the day the injection is administered). The 1-hour post injection follow-up is to assess the injection site and any reaction to medication. This assessment may be repeated at the discretion of the investigator.

Protocol 31-10-270

[f] Needle length for injection of aripiprazole IM Depot will be selected based on BMI (21 gauge, 1.5 inch for BMI ≤ 28 kg/m^2; 21 gauge, 2 inch for BMI > 28 kg/m^2). The BMI will be calculated in kg/m^2 from the baseline height and weight at the baseline visit using one of the following formulae, as appropriate: Weight (kg) ÷ [Height (m)]^2 or Weight (lb) ÷ [Height (in)]^2 x 703. If a noticeable fluctuation in body height and weight has occurred during the study, at the investigator's discretion, body weight can be remeasured and BMI recalculated and used for the next aripiprazole IM Depot injection. Body weight, height, and waist circumference will be reassessed annually, and body weight and height will also be assessed at Study Completion or the Early Termination visit.

[g] All ongoing AEs and clinically significant AEs from Study 248 will be recorded as Medical History of Study 270.

[h] A urine pregnancy test is required for all WOCBP at baseline, every 3 months, and at Study Completion or the Early Termination visit, but can be performed at any point during the trial if pregnancy is suspected. All positive urine pregnancy test results must be confirmed by a serum test. WOCBP is defined as ALL women unless they have had an oophorectomy and/or hysterectomy or have been menopausal for at least 12 consecutive months. This should be documented in their medical history. Subjects with positive serum test results will be excluded from the study. Treated subjects with a positive serum pregnancy test must discontinue treatment, be withdrawn from the study, and an immediately reportable event (IRE) form should be completed.

[i] Urine drug screen and blood alcohol test are required at baseline and anytime at the investigator's discretion.

[j] Aripiprazole IM Depot (400 mg or 300 mg) will be injected every month (study months are every 4 weeks which is defined as 28 [−2/+10] days).

Protocol 31-10-270

3.6.1 Schedule of Assessments

For each visit, all assessments, except for post-injection assessments, should be performed prior to the aripiprazole IM Depot injection.

3.6.1.1 Baseline

The baseline visit for Study 270 (which is the Week 52 visit of Study 248) and the first injection for Study 270 must occur within 4 weeks (which is defined as 28 [–2/+10] days) of the last injection in Study 248. At this visit, subjects will sign an Informed Consent for Study 270 and their eligibility will be confirmed.

The Study 248 Week 52 assessments will also serve as the baseline assessments for Study 270: CGI-S; C-SSRS; EPS assessments (AIMS, SAS, BARS); injection site pain assessed by the subject using VAS; investigator's injection site assessment for pain, redness, swelling, and induration; body weight and height; BMI; waist circumference; AEs; clinical laboratory tests; vital signs; physical exam; ECG; urine pregnancy test for WOCBP (see Section 5.4 for the definition of WOCBP); urine drug screen; blood alcohol test; and concomitant medications (see Table 3.6-1). All ongoing AEs and clinically significant AEs from Study 248 will be recorded as Medical History of Study 270; please refer to the Operations Manual or case report form (CRF) Completion Guidelines for additional detail.

In addition to the assessments, the baseline visit will also include the first aripiprazole IM Depot injection for Study 270.

3.6.1.2 Injection and Assessments Performed Every Month

Monthly assessments (study months are every 4 weeks which is defined as 28 [–2/+10] days) include a C-SSRS assessment and recording of AEs experienced since the last visit and concomitant medications, followed by the aripiprazole IM Depot injection. The monthly injections and assessments should be performed on Study Months 1 through 104.

3.6.1.3 Assessments Performed Every 3 Months

Every 3 months (study months are every 4 weeks which is defined as 28 [–2/+10] days), the following assessments will be performed: injection, C-SSRS, AEs, concomitant medications, and a urine pregnancy test for WOCBP. These assessments should be performed on Study Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99, and 102.

3.6.1.4 Assessments Performed Every 6 Months

Every 6 months (study months are every 4 weeks which is defined as 28 [−2/+10] days) the following assessments will be performed: injection, C-SSRS, AEs, concomitant medications, a urine pregnancy test for WOCBP, CGI-S, vital signs, and EPS assessments (AIMS, BARS, SAS). These assessments should be performed on Study Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, and 102.

3.6.1.5 Assessments Performed Every 12 Months

Every 12 months (study months are every 4 weeks which is defined as 28 [−2/+10] days) the following assessments will be performed: injection, C-SSRS, AEs, concomitant medications, a urine pregnancy test for WOCBP, CGI-S, vital signs, and EPS assessments (AIMS, BARS, SAS), clinical laboratory tests, body height and weight, and waist circumference. These assessments should be performed on Study Months 12, 24, 36, 48, 60, 72, 84, and 96.

3.6.1.6 Study Completion or Early Termination Visit

A Study Completion visit or Early Termination visit (−2/+10 days) will be performed and will include the following assessments: C-SSRS, AEs, concomitant medications, a urine pregnancy test for WOCBP, CGI-S, vital signs, and EPS assessments (AIMS, BARS, SAS), clinical laboratory tests, and body height and weight.

3.6.1.7 30-Day Post Treatment Follow-up Phone Call

A 30-Day Post Treatment Follow-up phone call will be performed 30 days (± 3 days) after it has been determined that the subject will no longer participate in this study and will include the recording of AEs that have occurred since the last visit and any concomitant medications taken since the last visit.

3.6.2 Efficacy Assessment (CGI-S)

The severity of illness for each subject will be rated using the CGI-S scale.[28] 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 patient 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 patients. A sample of the CGI-S Scale is provided in Appendix 6.

Protocol 31-10-270

3.6.3 Safety Assessments

3.6.3.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.6.3.2 Clinical Laboratory Assessments

A central laboratory designated by the sponsor will be used for all laboratory testing required. Reports from the central laboratory should be filed with the source documents for each subject. The central laboratory will provide laboratory results to the sponsor electronically.

Samples for serum chemistry, hematology, and urinalysis will be obtained at baseline, every 12 months (study months are every 4 weeks which is defined as 28 [−2/+10] days), and at Study Completion or the Early Termination visit as specified in Table 3.6-1. Urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment.

Subjects should be fasting for a minimum of 10 hours prior to any blood draws for assessment of safety, including baseline. If a nonfasting blood sample is initially obtained and the test results possibly impacted, a fasting blood sample should be drawn shortly afterwards and the affected lab test(s) repeated. The laboratory tests to be evaluated in this trial are listed in Table 3.6.3.2-1.

For Study 270, a urine pregnancy test will be performed at baseline, every 3 months, at Study Completion or the Early Termination visit, and at any time at the discretion of the investigator when pregnancy is suspected for all WOCBP (see Section 5.4 for the definition of WOCBP) to confirm that the subject is not pregnant. Any positive urine pregnancy test result will be confirmed by a serum test.

Protocol 31-10-270

Table 3.6.3.2-1 Baseline Clinical Laboratory Assessments

Hematology: White Blood Cell Count (WBC) with differential Red Blood Cell Count (RBC) Hematocrit Hemoglobin Platelet count Urinalysis Specific gravity pH Glucose Protein Ketones Blood Microscopic exam (performed only if any part of the urinalysis is not negative) Other Urine pregnancy (WOCBP)[a] Serum beta-human chorionic gonadotropin (β-hCG) (WOCBP)[a] Urine drug screen Blood alcohol	Serum Chemistry: Blood Urea Nitrogen (BUN) Creatinine Creatine Phosphokinase (CPK) Aspartate Transaminase (AST or SGOT) Alanine Transaminase (ALT or SGPT) Lactate Dehydrogenase (LDH) Alkaline Phosphatase (ALP) Total Bilirubin Triglycerides Cholesterol (total, low-density lipoprotein [LDL], and high-density lipoprotein [HDL]) Calcium Glucose Hemoglobin A1c[b] Insulin Sodium Potassium Total Protein Uric acid Gamma Glutamyl Transferase (GGT) Prolactin

NOTE: Subjects should be fasting for a minimum of 10 hours prior to any blood draws for assessment of safety. If a nonfasting blood sample is initially obtained and the test results possibly impacted, a fasting blood sample should be drawn shortly afterwards and the affected lab test(s) repeated.

[a] A urine pregnancy test will be performed at baseline for all WOCBP (see Section 5.4 for the definition of WOCBP) to assess eligibility for the study and will be repeated every 3 months throughout the trial, at Study Completion or the Early Termination visit, and at any time at the discretion of the investigator when pregnancy is suspected. All positive urine pregnancy test results must be confirmed by a serum test.

[b] At the discretion of the investigator, hemoglobin A1c will be measured if the subject's fasting glucose is ≥ 125 mg/dL and/or the urinalysis is positive for glucose. If the subject's glucose is ≥ 125 mg/dL, but the sample was not obtained with the subject in a fasted state, a fasting glucose should be performed to confirm that the value is ≥ 125 mg/dL before testing hemoglobin A1c.

Any baseline 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. Subjects may enroll into the study prior to obtaining baseline results, but will be subsequently withdrawn if clinically significant results are identified. In addition, follow-up unscheduled labs should be performed on clinically significant abnormalities. Unscheduled laboratory tests may be repeated at any time at the discretion of the investigator for appropriate medical care.

The following laboratory test 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

In addition, subjects should be excluded if they have any other abnormal laboratory test result at baseline that, in the investigator's judgment, is medically significant in that it would impact the safety of the subject or interpretation of the study results. Appendix 4 is included to assist investigators in their assessments of the results that may be potentially medically significant, depending on the subject's medical history and clinical presentation.

3.6.3.3 Physical Examination and Vital Signs

3.6.3.3.1 Physical Examination

A complete physical examination, including height, will be performed at baseline. The physical examination may be repeated at the discretion of the investigator at any subsequent visit. Height will be measured with a stadiometer, measuring stick, or tape. The principal investigator or his/her appointed designee is primarily responsible to perform the physical exam. If the appointed designee is to perform the physical exam, he/she must be permitted by local regulations and his/her name must be included on the US FDA Form 1572. Whenever possible, the same individual should perform all physical exams. Any condition present at subsequent physical exams that was not present at the baseline exam should be documented as an AE and followed to a satisfactory conclusion.

3.6.3.3.2 Vital Signs

Vital sign measurements will be performed at baseline, every 6 months (study months are every 4 weeks which is defined as 28 [−2/+10] days), and at Study Completion or the Early Termination visit, and will include body temperature, systolic and diastolic blood pressure, and heart rate. Orthostatic assessments of blood pressure and heart rate will be made after the subject has been supine for at least 5 minutes and again after the subject has been sitting for 2 minutes.

A diastolic blood pressure > 105 mm Hg is exclusionary. In addition, subjects should be excluded if they have any other vital sign measurement at screening that, in the investigator's judgment, is medically significant in that it would impact the safety of the subject or the interpretation of the study results. Appendix 3 is included to assist investigators in their assessments of results that may be potentially medically significant, depending on the subject's medical history and clinical presentation.

3.6.3.3.3 Body Height and Weight and Body Mass Index

Body height and weight will be measured at baseline prior to the first dose of aripiprazole IM Depot, every 12 months (study months are every 4 weeks which is defined as 28 [–2/+10] days), and at Study Completion or the Early Termination visit. The following guidelines will aid in the standardization of these measurements:

- The same scale should be used to weigh a given subject each time.
- Scales should be calibrated and reliable; scales should be at zero just prior to each subject's weigh-in session.
- A subject should void prior to being weighed and be minimally clothed (ie, no shoes or heavy overgarments).
- Weight should be recorded before a subject's meal and at approximately the same time at each visit.

BMI (kg/m^2) will be calculated from the baseline height and the weight using one of the following formulae, as appropriate:

$$\text{Weight (kg)} \div [\text{Height (m)}]^2 \text{ or Weight (lb)} \div [\text{Height (in)}]^2 \times 703.$$

For the IM depot injection, the BMI will be supplied to the individual administering the injection so that the appropriate needle length can be selected based on BMI (21 gauge, 1.5 inch for BMI ≤ 28 kg/m^2; 21 gauge, 2 inch for BMI > 28 kg/m^2). If a noticeable fluctuation in body weight has occurred during the study, at the investigator's discretion, body height and weight can be remeasured and BMI recalculated and used for the next aripiprazole IM Depot injection. BMI may be calculated at subsequent visits at the discretion of the investigator. Body height and weight (not BMI) will be reassessed annually and at any study visit at the discretion of the investigator.

Protocol 31-10-270

3.6.3.3.4 Waist Circumference

Waist circumference will be measured at baseline and every 12 months (study months are every 4 weeks which is defined as 28 [–2/+10] days), or at other visits at the discretion of the investigator. The following procedures will aid in the standardization of these measurements:

- The subject should be minimally clothed (ie, lightweight clothing; no heavy over garments).
- Waist circumference should be recorded before a subject's meal and at approximately the same time at each visit.
- Measurement will be accomplished by locating the upper hip bone and the top of the right iliac crest and placing the measuring tape in a horizontal plane around the abdomen at the level of the crest. Before reading the tape measure, the assessor should assure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is to be made at the end of a normal exhalation.[28]

3.6.3.4 ECG Assessments

Twelve-lead ECGs will be recorded at baseline and at the discretion of the investigator. The ECG criteria for baseline ECG for Study 270 (which is the Week 52 visit of Study 248) will be done per Study 248 requirements.

At baseline, three ECG recordings will be obtained approximately 5 minutes apart. All ECGs will be evaluated at the investigational site to determine the subject's eligibility. The principal investigator or qualified designee will review, sign, and date each ECG reading obtained, 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. As of Amendment 4, ECG results will not be obtained centrally after the baseline assessment. Any subsequent ECG assessments will be obtained locally at the discretion of the investigator.

At baseline, QTc > 475 msec on either the QTcB (Bazett) or QTcF (Fridericia) corrections on 2 of 3 time points of triplicate ECGs performed is exclusionary (see Exclusion #9 in Table 3.4.3-1). In addition, subjects should be excluded if they have any other abnormal ECG finding at baseline that, in the investigator's judgment, is medically significant in that it would impact the safety of the subject or the interpretation of the study results. However, any screening ECG with abnormal result(s) considered to be clinically significant should be repeated to confirm the finding(s) before excluding the subject from the study. Appendix 5 is provided as a guide for determining potentially clinically relevant ECG abnormalities.

Protocol 31-10-270

3.6.3.5 Extrapyramidal Symptoms

Extrapyramidal symptoms are assessed at baseline, every 6 months (study months are every 4 weeks which is defined as 28 [–2/+10] days), and at Study Completion or the Early Termination visit. The EPS symptoms may also be reassessed at the discretion of the investigator using the instruments described in Section 3.6.3.5.1, Section 3.6.3.5.2, and Section 3.6.3.5.3.

3.6.3.5.1 Abnormal Involuntary Movement Scale

The AIMS[29] assessment (Appendix 7) 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 investigator 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, awareness/severe distress). For this scale, the subject is to be sitting on a hard, firm chair. In addition, the AIMS includes two 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).

3.6.3.5.2 Simpson-Angus Scale

The SAS[30] (Appendix 8) 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.

3.6.3.5.3 Barnes Akathisia Rating Scale

The BARS[31] (Appendix 9) 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 CRF.

3.6.3.6 Suicidality

Suicidality will be monitored using the C-SSRS at baseline, every subsequent monthly visit, and at Study Completion or the Early Termination visit. The C-SSRS was developed by a team of researchers at Columbia University to address the need for standardized classification of suicide reports to assess suicide risk. This scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicide events and suicidal ideation and a post-baseline evaluation that focuses on suicidality since the last study visit. A baseline C-SSRS will be completed and a C-SSRS Since Last Visit form will be completed at all designated visits. Copies of the C-SSRS forms are provided in Appendix 10.

3.6.3.7 Injection Site Evaluation

Injection site reaction will be assessed at baseline and at the discretion of the investigator (or qualified designee) and the subject at any subsequent study visit in a manner similar to that used for the evaluation of other IM depot compounds.[5,32] Investigators (or qualified designees) at baseline will rate localized pain, redness, swelling, and induration at the most recent injection site using a 4-point categorical scale ranging from absent to severe (Appendix 12). The subject will indicate the degree of pain at the most recent injection site using a VAS (Appendix 11). Ratings will range from 0 (no pain) to 100 (unbearably painful). If required, these assessments will be completed both pre- and post-injection, after all other study assessments, and within 30 minutes prior to the IM depot injection. The subject will then receive the injection and will be followed for 1 hour post-injection to assess the injection site and any reaction to medication. The subject will complete the VAS and the investigator (or qualified designee) will re-assess localized pain, redness, swelling, and induration at the injection site at 1 hour (± 15 min) post-injection with focus on the current injection site which is now the new injection site from the latest injection. Pre- and post-injection evaluations must be completed on the same day (ie, the day the injection is administered). As of Amendment 4, VAS and injection site assessments are no longer required at any post-baseline study visits.

3.6.4 End of Trial

The End of Trial Date is defined as the last Date of Contact or the Date of Final Contact Attempt from the Post-treatment Follow-up case report form (CRF) page for the last subject completing or withdrawing from the trial.

3.7 Stopping Rules, Withdrawal Criteria, and Procedures

3.7.1 Entire Trial or Treatment Arm(s)

The sponsor should be notified promptly if the trial is terminated at your site. If the sponsor decides to terminate or suspend the trial for safety or unanticipated other reasons or if aripiprazole IM Depot becomes commercially available in the country of the study site, the sponsor will promptly notify investigators, IRBs/IECs, and regulatory authorities as required by the applicable regulatory requirements.

The sponsor will terminate the study in countries where aripiprazole IM Depot becomes commercially available (including generic formulation[s]), the commercial availability of aripiprazole IM Depot is terminated by the sponsor, or if the study end date of 31 Dec 2018 is reached.

If the sponsor terminates the study prior to 31 Dec 2018 for any reason other than commercial availability, investigators in some countries where the sponsor has limited or delayed commercialization plans, or where no commercialization activity is anticipated, may be eligible to participate in a managed access program until aripiprazole IM Depot is commercially available in their country or until 31 Dec 2018. Availability and requirements of such a program varies by jurisdiction, and would only be an option for subjects who were receiving aripiprazole IM Depot in the current study, and who in the physician's opinion, may benefit from continued treatment with aripiprazole. To gain access to aripiprazole IM Depot for eligible subjects via a managed access program, each physician will be responsible for gaining appropriate local regulatory approvals, which will be granted by authorities on a case-by-case basis. The sponsor makes no guarantee that such a program is available or approvable in all of the jurisdictions where the study is conducted.

3.7.2 Individual Center

A particular center may be terminated from the trial at the discretion of the investigator, sponsor, or IRB, eg, for non-enrolment of subjects or non-compliance with the protocol.

Protocol 31-10-270

3.7.3 Individual Subject

All subjects have the right to withdraw at any time during treatment without prejudice. 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:

1) Occurrence of any AE, intercurrent illness or abnormality in laboratory assessment results which, in the opinion of the investigator, warrants the subject's permanent withdrawal from the trial;
2) Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator;
3) Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures (see Section 3.11);
4) At the request of the subject, investigator, sponsor, or regulatory authority;
5) Subject becomes pregnant;
6) Subject is hospitalized due to exacerbation of psychotic symptoms;
7) Subject is lost to follow-up;
8) Subject misses 2 consecutive or 3 non-consecutive aripiprazole IM Depot injections in a 52-week period;
9) Aripiprazole IM Depot is commercially available (including a generic formulation) in the country where the study is being conducted or the commercial availability of aripiprazole IM Depot is terminated by the sponsor.

The sponsor should be notified promptly when a subject is withdrawn according to procedures outlined in the Operations Manual and/or in the Adverse Events Reporting Plan.

3.8 Screen Failures

There is no screening period in Study 270 as only subjects completing Study 248 and directly rolling over to Study 270 are eligible for inclusion. However a subject who does not meet baseline inclusion/exclusion criteria for Study 270 may still be considered a screening failure, which is defined as a subject from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who is not started on Study 270 open-label treatment. Subjects who meet this criterion and are listed as screen failure subjects in Study 270 are not permitted to be re-screened at a later date.

3.9 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually received all doses of the study medication. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. Subjects who have their last visit by 31 Dec 2018, because they have reached the end of the study, will be defined as completers. For purposes of this trial, subjects who discontinue due to the commercial availability of study drug in the country where the study is being conducted will be defined as completers. In addition, subjects in countries where a managed access program is available for continued treatment with aripiprazole at the time of trial closure in their respective country, regardless of whether they transition to a managed access program, will also be defined as completers. Protocol-specified post-treatment follow-up contacts will not qualify as "last scheduled" visit.

3.10 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted at any time up through the last scheduled follow-up visit and who do not have a known reason for discontinuation (eg, withdrew consent or AE, etc) will be classified as "lost to follow-up" as the reason for discontinuation. Three attempts will be made by investigative sites to reach subjects, two by phone and one via certified mail.

3.11 Subject Compliance

Visit compliance is critical to achieving and maintaining stability of psychotic symptoms and to maintaining subjects on a schedule that will lead to completion of the IM Depot treatment within an acceptable time window. The key features of compliance can be summarized as follows:

1) IM depot injections are to be administered within an interval of 28 days between injections. The minimum allowable interval between IM depot injections is 26 days and the maximum interval is 38 days. Every effort should be made to adhere to the 28-day cycle.
2) If a subject misses 2 consecutive injections at any time in the study, or if a subject misses 3 injections in a 52-week time period, then this subject is considered noncompliant and must be withdrawn from the study.

Evaluations conducted outside of the windows defined in Table 3.6-1 will be considered deviations, but will not impact the subject's ability to continue the study.

Visit windows are provided not only to allow flexibility with scheduling, but also to assure an adequate supply of study medication between injections. If a subject misses an injection, the injection should be given at the earliest opportunity. A missed dose of IM depot is defined as a lapse of > 38 days between injections. The minimum interval of 26 days and maximum interval of 38 days between injections is to ensure that therapeutic plasma concentrations of aripiprazole are maintained.

The time and date of each dose of aripiprazole IM Depot will be recorded on the CRF. If a dose was not administered as scheduled, an explanation will be provided in the CRF and supported by source documentation. The accountability of IM depot vials will be maintained at the vial level. Subjects who, in the investigator's judgment, are noncompliant with the IM depot injection schedule should be counseled on the importance of adhering to the treatment schedule. Reasons for noncompliance should be determined, if possible. Investigators should use their judgment to assess the feasibility of continuing subjects in the study who are significantly noncompliant.

3.12 Protocol Deviations

This trial is intended to be conducted as described in this protocol. In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, study drug dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of significant eligibility criteria or concomitant medication criteria), the investigator or designee must contact the sponsor's designee (Medical Monitor) at the earliest possible time according to the Approval for Study Continuation process which is outlined in the Operations Manual. This will allow an early joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the designated Medical Monitor, and reviewed by the study monitor.

4 Restrictions

4.1 Prohibited Medications

Medications that are prohibited or restricted prior to screening and/or during the trial are listed by phase in Table 4.1-1. No prohibited or restricted medications should be used within the visit windows when transitioning from Study 248 to Study 270. The prohibited and restricted medications also apply to any clinical transition period within allowed visit windows from Study 248 into Study 270.

Protocol 31-10-270

Table 4.1-1 List of Medications Prohibited or Restricted in Study 270	
Psychotropic Medications	
Antipsychotics	Not allowed
Antidepressants (including MAOIs)	Allowed, except for CYP2D6 or CYP3A4 inhibitors or CYP3A4 inducers
Benzodiazepine[a]	Allowed
Mood stabilizers	Allowed
Non-benzodiazepine sleep aids[a]	Allowed
Other Medications	
Anticholinergics	Allowed
Propranolol (for akathisia, tremor, or if taking for cardiac reasons)[b]	Allowed
Varenicline	Not allowed
Nutritional supplements and non-prescription herbal preparations with CNS effects (eg, St. John's Wort, omega-3 fatty acids, kava extracts, GABA supplements, etc.)	Allowed, but use caution
CYP3A4 or CYP2D6 inhibitors or CYP3A4 inducers (see Section 4.2.1)	Not allowed

CNS = central nervous system; GABA = gamma-aminobutyric acid.

Note: No prohibited or restricted medications should be used within the visit windows when transitioning from Study 248 to Study 270. The prohibited and restricted medications also apply to any clinical transition period within allowed visit windows from Study 248 into Study 270.

[a]Benzodiazepine use is allowed during the study to manage treatment emergent AEs such as agitation, anxiety, and insomnia; however, non-benzodiazepine sleep aids are recommended for 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.

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

4.2 Other Restrictions

4.2.1 Restricted Therapies and Precautions

No prohibited or restricted medications should be used within the visit windows when transitioning from Study 248 to Study 270. The prohibited and restricted medications also apply to any clinical transition period within allowed visit windows from Study 248 into Study 270.

The subject's best medical interests should guide the investigator in the management of conditions that are pre-existing or that develop during the study (intercurrent illness or AEs). All study personnel should be familiar with the content of the Investigator's Brochure for aripiprazole[9] in order to manage the subject's condition adequately and select appropriate concomitant medications, if needed. The investigator should carefully

assess the potential for interaction with aripiprazole before prescribing any concomitant medications.

The use of CYP3A4 or CYP2D6 inhibitors and CYP3A4 inducers is not permitted during the study, as they may affect the pharmacokinetics of aripiprazole. Examples of inhibitors include, but are not limited to, amiodarone, celecoxib, chlorpheniramine, cimetidine, clarithromycin, clemastine, diltiazem, erythromycin, itraconazole, ketoconazole, methadone, nafazodone, pyrilamine, quinidine, rifampin, terbinafine, tripelennamine, verapamil, and human immunodeficiency virus protease inhibitors (eg, amprenavir, indinavir, nelfinavir, ritonavir, and saquinavir). Examples of inducers include, but are not limited to, carbamazepine, dexamethasone, phenobarbital, phenytoin, and non-nucleoside reverse transcriptase inhibitors (eg, efavirenz and nevirapine). The Medical Monitor should be consulted for any questions regarding the potential for pharmacokinetic interactions with concomitant medications used by subjects during the trial.

Other guidelines for use of concomitant medications during the trial include:

- Treatment of allergy symptoms: Non-sedating antihistamines are permitted.
- Treatment of cold/flu symptoms: Medications containing ingredients that have central nervous system (CNS) effects should be limited to short-term use and discontinued as soon as the symptom(s) resolve.
- Treatment of gastroesophageal reflux disease (GERD): The use of cimetidine is prohibited. All other medications for the treatment of GERD are permitted.
- Treatment of hypertension: Medications that are CYP3A4 or CYP2D6 inducers or inhibitors (eg, verapamil) are prohibited.
- Treatment of diabetes: No additional guidelines.
- Treatment of infection: No additional guidelines.

4.2.2 Non-therapy Precautions and Restrictions

Subjects will be instructed to refrain from drinking alcoholic beverages or using illicit drugs during participation in the trial. The investigator should consult with the Medical Monitor in the event that a false-positive drug screen result is suspected (eg, drug screen testing in subjects taking medications that have phenylpropanolamine or pseudoephedrine may produce a false-positive result for amphetamine). The investigator may request a blood or urine drug screen at any time during the study if there is a suspicion of illicit drug use.

5 Reporting of Adverse Events

The following describes the methods and timing for assessing, recording, and analyzing safety parameters, as well as the procedures for eliciting reports of and recording and reporting AEs and intercurrent illnesses and the type and duration of the follow-up of subjects after AEs.

5.1 Definitions

An adverse event (AE) is defined as any new medical problem, or exacerbation of an existing problem, experienced by a subject while enrolled in the study, whether or not it is considered drug-related by the investigator.

A serious AE (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 disability/incapacity.
- Requires in-patient hospitalization or prolongs hospitalization.
- 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.

Non-serious adverse events are all AEs that do not meet the criteria for a "serious" adverse event.

Immediately Reportable Event (IRE):

- Any serious adverse event.
- Any AE that necessitates discontinuation of study drug.
- Potential Hy's Law cases (Any increase of AST or ALT ≥ three times the upper normal limit with ≥ two times increase in total bilirubin).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an adverse event, it will mandate drug discontinuation and must be reported on an IRE form to Otsuka Pharmaceutical Development and Commercialization, Inc. (OPDC). Pregnancy will only be documented on the AE-CRF if there is an abnormality or complication.

Clinical Laboratory 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 significant) 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 determined by the investigator to be an abnormal change from baseline for that subject, this is considered an AE.

Severity: AEs will be graded on a 3-point scale and reported as indicated on the CRF.

The intensity of an adverse experience 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.

The causal relationship of the study drug to an AE is assessed as related or unrelated, as follows:

Related:

Definite: There is a reasonable causal relationship between the study drug and the AE or the event responds to withdrawal of the study drug (dechallenge) and the Investigator's assessment of the event is deemed "Definitely Related" based on the sum of available clinical information gathered.

Probable: There is a reasonable causal relationship between the study drug and the AE. The event may respond to dechallenge or the Investigator's assessment of the event is deemed "Probably Related" based on the sum of available clinical information gathered.

Possible: There is a reasonable causal relationship between the study drug and the AE. Dechallenge is lacking or unclear and the Investigator's assessment of the event is deemed "Possibly Related" based on the sum of clinical information gathered.

Unrelated:

Not Likely: There is a temporal relationship to study drug administration, but based on the available clinical information the Investigator deems that there is no reasonable causal relationship between the study drug and the event.

Not Related: Based on the available clinical information the Investigator deems that there is no temporal or causal relationship to study drug administration.

5.2 Eliciting and Reporting Adverse Events

The investigator will periodically assess subjects for the occurrence of AEs. In order to avoid bias in eliciting AEs, subjects should be asked the following nonleading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and CRFs provided by the sponsor or designee.

Note: Normal pregnancy is not an AE and should not be recorded on the AE form of the CRF; guidelines outlined in Section 5.4 should be followed for pregnancy reporting.

In addition, OPDC or their designee (see Appendix 2) must be notified immediately by telephone or fax of any immediately reportable events according to the procedure outlined below (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, potential Hy's law case or confirmed pregnancy, by telephone [(888) 724-4908] or by fax [(888) 887-8097] to OPDC or their designee immediately after the investigator becomes aware of the event. An Immediately Reportable Event (IRE) form should be completed and sent by fax or overnight courier to the sponsor or their designee up to and including 24 hours of knowledge of the event by the site. (Please note that the IRE form is NOT the adverse event case report form.)

Non-serious events that require discontinuation of study drug (including laboratory abnormalities) should be reported to OPDC or their designee up to and including 3 working days. The IRE form should be completed and sent by fax or overnight courier to OPDC or their designee.

Subjects experiencing serious adverse events should be followed clinically until their health has returned to baseline status or until all parameters have returned to normal, or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate supportive care for the subject.

5.4 Pregnancy

WOCBP is defined as ALL women unless they have had an oophorectomy and/or hysterectomy or have been menopausal for at least 12 consecutive months. This should be documented in their medical history. Subjects with positive serum test results will be excluded from the study.

WOCBP who are sexually active must use an effective method of birth control during the course of the trial so risk of failure is minimized. Unless the subject and his/her partner(s) are sterile (ie, women who have had an oophorectomy and/or hysterectomy or have been postmenopausal for at least 12 consecutive months; or men who have had orchidectomy) or remain abstinent, two of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, IUD, birth control pills, birth control implant, condom with spermicide, or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy.

Before enrolling WOCBP in this clinical trial, investigators must review guidelines about trial participation for WOCBP. The topics should include:

- General information
- Informed Consent Form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Prior to trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Males should also be instructed not to impregnate their partners while on study drug. The subject must sign an ICF stating that the above-mentioned risk factors and the consequences were discussed.

During the trial, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle).

If a subject or investigator suspects that the subject may be pregnant prior to administration of the study drug, administration must be withheld until the results of blood serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the study drug or be enrolled in the trial. If pregnancy is suspected while the subject is receiving treatment, the study drug 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 study drug 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 Drug Safety Services (see Appendix 2).]

The investigator must immediately notify Drug Safety Services of any pregnancy associated with exposure to aripiprazole IM Depot. For subjects who received at least one dose of IM depot, the reporting period includes 150 days after last injection for female subjects and 180 days after the last injection for female partners of male subjects. For all pregnancy reports, the investigator will record the event on the IRE form and forward it to the Drug Safety Services department of the sponsor's designee. Drug Safety Services will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy. Pregnancy will only be documented on the AE CRF if there is an abnormality or complication to be reported.

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 (or sponsor's designee) on appropriate 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.

5.5 Follow-up of Adverse Events

5.5.1 Follow-up of Non-serious Adverse Events

Non-serious AEs that are identified on the last scheduled contact must be recorded on the AE CRF with the current status noted. All non-serious events that are ongoing at this time will be recorded as ongoing on the CRF. Site personnel will make a follow-up call to the subject 30 days (± 3 days) after the last study visit to inquire about any AEs that were ongoing at the time of the last visit and any new AEs and to assess if any new SAEs have occurred.

5.5.2 Follow-up of Serious Adverse Events

SAEs that are **identified on the last scheduled contact** must be recorded on the AE CRF page and reported to the sponsor's designee according to the reporting procedures outlined in Section 5.3. This may include **unresolved previously reported SAEs**, or

new SAEs. The investigator should follow these SAEs until the events are resolved, or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the subject's condition. The investigator should continue to report any significant follow-up information to the sponsor's designee up to the point the event has been resolved.

This trial requires that withdrawn subjects be actively monitored for SAEs up to 30 days (± 3 days) after discharge from the trial. Any new SAEs reported by the subject to the investigator that occur after the last scheduled contact, and are determined by the investigator to be reasonably associated with the use of the study drug, should be reported to the sponsor's designee. This may include SAEs that are captured on follow-up personal or telephone contact or at any other time point after the defined trial period (ie, up to last scheduled contact). The investigator should follow serious related AEs identified after the last scheduled contact until the events are resolved, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to the sponsor's designee up to the point the event has been resolved.

6 Pharmacokinetic or Pharmacodynamic Analysis

No pharmacokinetic or pharmacodynamic assessments will be conducted.

7 Statistical Analysis

The safety and tolerability evaluated will be based on safety parameters, eg, AEs, vital signs, ECGs, laboratory assessments, and injection pain assessments by the subject and investigator. Additionally, the risk of suicide will be evaluated using the C-SSRS. Efficacy will be evaluated using the CGI-S.

Due to the open-label single-arm nature of the study, all data on safety and efficacy/outcome will be summarized using descriptive statistics (eg, mean, standard deviation, maximum, minimum, and proportions).

Withdrawn subjects will not be replaced.

7.1 Dataset for Analysis

Since subjects in this study will be rolling over from another open-label study of aripiprazole IM Depot and will already be exposed to aripiprazole, all enrolled subjects will constitute the core data set for analysis. All safety analyses will be based on this core dataset. The dataset for efficacy outcome analyses will be derived from the core

dataset. In particular, for a change from baseline analysis, only subjects having a baseline and a post-baseline value on the efficacy outcome measure will be included.

7.2 Baseline Values

Since subjects will be rolling over in the study from Study 248, evaluations at the Week 52 visit of Study 248 will be used as baseline for this study.

7.3 Primary Outcome Measures

In this safety and tolerability study, the primary measures are (1) frequency and severity of adverse events, (2) frequency and severity of serious adverse events (including adverse events related to laboratory abnormalities), and (3) rates of discontinuation from study due to adverse events.

Safety and tolerability data will be summarized as follows: Incidence of adverse events and serious adverse events (with severity grades) will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) terms; similarly, incidence of discontinuations due to AE will be tabulated by MedDRA terms.

7.4 Secondary Outcome Measures

Mean change from baseline of vital signs parameters, laboratory tests, and ECG parameters will be provided by visit. Incidence of clinically significant abnormalities in vital signs parameters, laboratory tests, and ECG parameters will be tabulated. Percentage of subjects showing significant weight gain or loss from enrollment to endpoint (significant weight change is defined as a $\geq$ 7% increase or decrease in weight) will be provided. Injection site reactions will be summarized by visit using the mean of VAS subject-reported rating scores and investigator's rating of local pain, swelling, redness and induration at the injection site. Data collected on the C-SSRS will be summarized by visit also.

Mean and mean change from baseline in the efficacy endpoint CGI-S score will be summarized by visit. Descriptive statistics of EPS will be provided by calculating mean change from baseline in AIMS, SAS, and BARS. Results will be summarized by visit.

7.5 Sample Size

In this open-label, single arm rollover study, no formal sample computations were employed. The anticipated number of subjects from Study 248 that is predicted to enroll in this study is approximately 500 to 800 subjects.

Protocol 31-10-270

8 Management of Investigational Medicinal Product

8.1 Packaging and Labeling

The study drug will be provided to the investigator(s) by the sponsor or designated agent. The aripiprazole IM Depot formulation will be supplied as aripiprazole 400 mg lyophilized vials packaged in supply cartons labeled similarly to the oral study medication. Prior to injection, vials of aripiprazole IM Depot 400 mg will be reconstituted with a designated quantity of Sterile Water for Injection. A volume corresponding to the dose to be administered (ie, aripiprazole 400 mg or aripiprazole 300 mg) will be withdrawn from the proper vial using an appropriate size syringe.

The reconstituted drug product must be prepared using aseptic technique and administered intramuscularly. The dose must be administered to the subject within the required timeframe of preparation. Needle length for injection of aripiprazole IM Depot will be selected based on BMI (21 gauge, 1.5 inch for BMI $\leq$ 28 kg/m^2; 21 gauge, 2 inch for BMI > 28 kg/m^2). All doses of aripiprazole IM Depot must be injected into the gluteal muscle, and care must be taken to avoid inadvertent injection into a blood vessel. Specific directions for the reconstitution and administration of IM depot injections will be provided in the Operations Manual.

8.2 Storage

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

Lyophilized vials of aripiprazole IM Depot should be stored in a refrigerator at 2 to 8°C (36 to 46°F) and protected from light. The clinical 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 the study drug received, dispensed, administered, and returned to assure regulatory authorities and the sponsor that the study drug will not be dispensed to any person who is not a subject under the terms and conditions set forth in this protocol.

8.4 Returns and Destruction

Upon completion or termination of the trial, all unused and/or partially used study drug must be returned to the sponsor or a designated agent.

All study drug returned to the sponsor must be accompanied by the appropriate documentation and be clearly identified by protocol number and trial site number on the outermost shipping container. Returned supplies should be in the original containers (eg, subject kits). The assigned trial monitor should facilitate the return of unused and/or partially used study drug.

If the study drug is authorized to be destroyed at the site by the sponsor, it is the investigator's responsibility to ensure that arrangements have been made for the disposal. Written authorization should be issued by the sponsor, procedures for proper disposal should be established according to applicable regulations, guidelines and procedures, and appropriate records of the disposal should be documented and forwarded to the sponsor.

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 as defined in the ICF.

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;
- 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 study drug 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 each clinician (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. Any changes to information in the trial progress notes and other source

documents will be initialed and dated on the day the change is made by a 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.

Information from the trial progress notes and other source documents will be data entered by investigative site personnel directly onto electronic CRFs in the electronic data capture (EDC) system provided by the sponsor (or sponsor's designee).

9.3 File Management at the Trial Site

It is the responsibility of the investigator to ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline and as required by applicable local regulations. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

9.4 Records Retention at the Trial Site

Regulatory requirements for the archiving of records for this trial necessitate that participating investigators maintain detailed clinical data for the longest of the following three periods:

- A period of at least 3 years following the date on which approval to manufacture the drug is obtained (or, if development of the study drug is discontinued, the date on which development is discontinued); OR
- A period of at least 3 years after the date on which the trial is completed or terminated.
- In addition, longer, region-specific storage requirements may apply as described in the Operations Manual for this trial.

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 shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial, including the CRF data on the CD-ROM received from the sponsor (or designee). Such documentation is subject to inspection by the sponsor, sponsor's designee, and relevant regulatory authorities. If the investigator withdraws from the trial (eg, relocation, retirement), 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, prior to the action taking place.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial carefully in a detailed and orderly manner in accordance with established research principles, the ICH GCP Guideline, 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 monitors (or designees) will visit the site during the trial in addition to maintaining frequent telephone and written communication.

10.2 Auditing

The sponsor's Quality Management Unit (or representative) may conduct audits at the trial site(s). Audits will include, but are not limited to, drug supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents. The investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may inspect the investigator site during or after the trial. The investigator should contact the sponsor immediately if this occurs, and must fully cooperate with the inspections conducted at a reasonable time in a reasonable manner.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, the ICH GCP Guideline, and applicable local laws and regulatory requirements.

12 Confidentiality

All information generated in this trial must be considered highly confidential and must not be disclosed to any persons not directly concerned with the trial without written prior permission from the sponsor. Subject confidentiality requirements of the region(s) where the trial is conducted must be met. However, authorized regulatory officials and sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. All study drugs, subject bodily fluids, and/or 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 initials and unique subject numbers in CRFs. Their full names may, however, be made known to a regulatory agency or other authorized officials if necessary.

13 Amendment Policy

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval by the IRB/IEC. Any permanent change to the protocol, whether it is an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB/IEC. Except for "non-substantial (ie, administrative)" amendments, investigators will wait for IRB/IEC approval of the amended protocol before implementing the change(s). Non-substantial amendments are defined to have no effect on the safety or physical or mental integrity of subjects, the conduct or management of the trial, the scientific value of the trial, or the quality or safety of the study drug(s) used in the trial. However, a protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, followed by IRB/IEC notification within 5 working days. The sponsor will submit protocol amendments to the FDA or other regulatory agencies.

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

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Protocol 31-10-270

Appendix 1 Names of Sponsor Personnel

PPD

Otsuka Pharmaceutical Development & Commercialization, Inc.
508 Carnegie Center
Princeton, NJ 08540
Phone: PPD
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Appendix 2 Institutions Concerned With the Trial

Clinical Research Organization
Covance Inc,
210 Carnegie Center
Princeton, NJ 08540
Phone: PPD

Safety Reporting
Please report SAEs, AEs requiring discontinuation of the study drug, and pregnancies to:

Covance Drug Safety Services
PPD
Phone: PPD
Fax: PPD

Clinical Lab – ECG Central Reader
eResearch Technology
30 South 17th St.
Philadelphia, PA 19103
Phone: PPD

Central Laboratory
Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214
Phone: PPD
Toll free: PPD
Fax: PPD

Protocol 31-10-270

Appendix 3 Criteria for Identifying Vital Signs of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart rate[b]	> 120 bpm < 50 bpm	≥ 15 bpm increase ≥ 15 bpm decrease
Systolic Blood Pressure[b]	> 180 mm Hg < 90 mm Hg	≥ 20 mm Hg increase ≥ 20 mm Hg decrease
Diastolic Blood Pressure[b]	> 105 mm Hg < 50 mm Hg	≥ 15 mmHg increase ≥ 15 mmHg decrease
Orthostatic Hypotension	≥ 20 mmHg decrease in systolic blood and a ≥ 25 bpm increase in heart rate from supine to sitting/standing	Not applicable (baseline status not considered)
Weight	-	≥ 7% increase ≥ 7% decrease

[a] In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

[b] As defined in "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87).

Protocol 31-10-270

Appendix 4 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry[a]	
AST (SGOT)	≥ 3 x upper limit of normal (ULN)
ALT (SGPT)	≥ 3 x ULN
Alkaline phosphatase	≥ 3 x ULN
LDH	≥ 3 x ULN
BUN	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Uric Acid	
Men	≥ 10.5 mg/dL
Women	≥ 8.5 mg/dL
Bilirubin (total)	≥ 2.0 mg/dL
CPK	≥ 3 x ULN
Prolactin	> ULN
Hematology[a]	
Hematocrit	
Men	≤ 37 % and decrease of ≥ 3 percentage points from baseline
Women	≤ 32 % and decrease of ≥ 3 percentage points from baseline
Hemoglobin	
Men	≤ 11.5 g/dL
Women	≤ 9.5 g/dL
White blood count	≤ 2,800 mm^3 or ≥ 16,000 mm^3
Eosinophils	≥ 10%
Neutrophils	≤ 15%
Platelet count	≤ 75,000/ mm^3 or ≥ 700,000/ mm^3
Urinalysis[a]	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Casts	Increase of ≥ 2 units
Additional Criteria	
Chloride	≤ 90 mEq/L or ≥ 118 mEq/L
Potassium	≤ 2.5 mEq/L or ≥ 6.5 mEq/L
Sodium	≤ 126 mEq/L or ≥ 156 mEq/L
Calcium	≤ 8.2 mg/dL or ≥ 12 mg/dL
Glucose	
Fasting	≥ 115 mg/dL
Non-Fasting	≥ 200 mg/dL
Total Cholesterol, Fasting	≥ 240 mg/dL
LDL Cholesterol, Fasting	≥ 160 mg/dL
HDL Cholesterol, Fasting	≤ 30 mg/dL
Triglycerides, Fasting	
Men	≥ 160 mg/dL
Women	≥ 120 mg/dL

[a] As defined in "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87).

Appendix 5 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Rate		
Tachycardia	≥ 120 bpm	increase of ≥ 15 bpm
Bradycardia	≤ 50 bpm	decrease of ≥ 15 bpm
Rhythm		
Sinus tachycardia[b]	≥ 120 bpm	increase of ≥ 15 bpm
Sinus bradycardia[c]	≤ 50 bpm	decrease of ≥ 15 bpm
Supraventricular premature beat	all	not present → present
Ventricular premature beat	all	not present → present
Supraventricular tachycardia	all	not present → present
Ventricular tachycardia	all	not present → present
Atrial fibrillation	all	not present → present
Atrial flutter	all	not present → present
Conduction		
1° atrioventricular block	PR ≥ 0.20 second	increase of ≥ 0.05 second
2° atrioventricular block	all	not present → present
3° atrioventricular block	all	not present → present
Left bundle-branch block	all	not present → present
Right bundle-branch block	all	not present → present
Pre-excitation syndrome	all	not present → present
Other intraventricular conduction block[d]	QRS ≥ 0.12 second	increase of ≥ 0.02 second
Infarction		
Acute or subacute	all	not present → present
Old	all	not present → present ≥ 12 weeks post study entry
ST/T Morphological		
Myocardial Ischemia	all	not present → present
Symmetrical T-wave inversion	all	not present → present
Increase in QTc	QTc ≥ 450 msec	≥ 10% increase

[a] In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

[b] No current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.

[c] No current diagnosis of atrial fibrillation, atrial flutter, or other rhythm abnormality.

[d] No current diagnosis of left bundle branch block or right bundle branch block.

Protocol 31-10-270

Appendix 6 Clinical Global Impression Severity (CGI-S) Scale

Circle the appropriate number for item below.

SEVERITY OF ILLNESS

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

0 = Not assessed	4 = Moderately ill
1 = Normal, not at all ill	5 = Markedly ill
2 = Borderline mentally ill	6 = Severely ill
3 = Mildly ill	7 = Among the most extremely ill patients

Adapted from Guy W. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976.

Protocol 31-10-270

Appendix 7 Abnormal Involuntary Movement Scale (AIMS)

This scale consists of 10 items, each to be rated on a 4-point scale of severity, and two questions to be answered by yes or no. To complete the scale, observe the patient unobtrusively at rest (eg, in waiting room). The chair to be used for this examination should be a hard, firm one without arms.

For each item, please mark in the right column, the rating which best describes the patient's present condition.

Instructions for Rating Items 1 to 9: 0 = none, 1 = minimum, 2 = mild, 3 = moderate, 4 = severe Instructions for Rating Item 10: 0 = no awareness; 1 = aware, no distress ; 2 = aware, mild distress ; 3 = aware, moderate distress ; 4 = aware, severe distress		
SYMPTOMS	**DESCRIPTION OF SYMPTOMS**	**RATING**
FACIAL AND ORAL MOVEMENTS	1. Muscles of facial expression - eg, movements of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing	
	2. Lips and perioral area - eg, puckering, pouting, smacking.	
	3. Jaw - eg biting, clenching, chewing, mouth opening, lateral movement.	
	4. Tongue - Rate only increase in movement both in and out of mouth, NOT inability to sustain movement.	
EXTREMITY MOVEMENTS	5. Upper (arms, wrists, hands, fingers) - Include choreic movements (eg: rapid, objectively purposeless, irregular, spontaneous); athetoid movements (eg, slow, irregular, complex, serpentine). DO NOT include tremor (eg, repetitive, regular, rhythmic).	
	6. Lower (legs, knees, ankles, toes) - eg, lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and of foot	
TRUNK MOVEMENTS	7. Neck, shoulders, hips - eg, rocking, twisting, squirming, pelvic gyrations	
GLOBAL JUDGEMENTS	8. Severity of abnormal movements.	
	9. Incapacitation due to abnormal movements	
	10. Patient's awareness of abnormal movements	
DENTAL STATUS	Current problems with teeth and/or dentures 0 = no ; 1 = yes	
	Does patient usually wear dentures ? 0 = no ; 1 = yes	

Adapted from Guy W. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976.

Protocol 31-10-270

Appendix 8 The Simpson-Angus Neurologic Rating Scale (SAS)

This scale consists of a list of 10 symptoms, each to be rated on a 5-point scale of severity. For each symptom, please mark the rating which best describes the patient's present condition.

1. GAIT - The patient is examined as he walks into the examining room - his gait, the swing of his arms, his general posture, all form the basis for an overall score for this item.

1 = Normal
2 = Mild diminution in swing while the patient is walking
3 = Obvious diminution in swing suggesting shoulder rigidity
4 = Stiff gait with little or no arm swing noticeable
5 = Rigid gait with arms slightly pronated; or stooped-shuffling gait with propulsion and retropulsion
9 = Not ratable

2. ARM DROPPING - The patient and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal patient, a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome, the arms fall very slowly:

1 = Normal, free fall with loud slap and rebound
2 = Fall slowed slightly with less audible contact and little rebound
3 = Fall slowed, no rebound
4 = Marked slowing, no slap at all
5 = Arms fall as though against resistance; as though through glue
9 = Not ratable

3. SHOULDER SHAKING - The patient's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grasps one hand and also clasps the other around the patient's elbow. The patient's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as detailed. The procedure is repeated with one hand palpating the shoulder cuff while rotation takes place.

1 = Normal
2 = Slight stiffness and resistance
3 = Moderate stiffness and resistance
4 = Marked rigidity with difficulty in passive movement
5 = Extreme stiffness and rigidity with almost a frozen joint
9 = Not ratable

Protocol 31-10-270

4. ELBOW RIGIDITY - The elbow joints are separately bent at right angles and passively extended and flexed, with the patient's biceps observed and simultaneously palpated. The resistance to this procedure is rated.

1 = Normal
2 = Slight stiffness and resistance
3 = Moderate stiffness and resistance
4 = Marked rigidity with difficulty in passive movement
5 = Extreme stiffness and rigidity with almost a frozen joint
9 = Not ratable

5. WRIST RIGIDITY - The wrist is held in one hand and the fingers held by the examiner's other hand, with the wrist moved to extension, flexion, and ulnar and radial deviation or the extended wrist is allowed to fall under its own weight, or the arm can be grasped above the wrist and shaken to and fro. A "1" score would be a hand that extends easily, falls loosely, or flaps easily upwards and downwards.

1 = Normal
2 = Slight stiffness and resistance
3 = Moderate stiffness and resistance
4 = Marked rigidity with difficulty in passive movement
5 = Extreme stiffness and rigidity with almost a frozen wrist
9 = Not ratable

6. HEAD ROTATION - The patient sits or stands and is told that you are going to move his head from side to side, that it will not hurt and that he should try and relax. (Questions about pain in the cervical area or difficulty in moving his head should be obtained to avoid causing any pain). Clasp the patient's head between the two hands with the fingers on the back of the neck. Gently rotate the head in a circular motion 3 times and evaluate the muscular resistance to this movement.

1 = Loose, no resistance
2 = Slight resistance to movement although the time to rotate may be normal
3 = Resistance is apparent and the time of rotation is shortened
4 = Resistance is obvious and rotation is slowed
5 = Head appears stiff and rotation is difficult to carry out
9 = Not ratable

7. GLABELLA TAP - Patient is told to open his eyes wide and not to blink. The glabella region is tapped at a steady, rapid speed. Note number of times patient blinks in succession. Take care to stand behind the patient so that he does not observe the movement of the tapping finger. A full blink need not be observed; there may be a contraction of the infraorbital muscle producing a twitch each time a stimulus is delivered. Vary speed of tapping to assure that muscle contraction is related to the tap.

1 = 0 to 5 blinks
2 = 6 to 10 blinks
3 = 11 to 15 blinks
4 = 16 to 20 blinks
5 = 21 and more blinks
9 = Not ratable

8. TREMOR - Patient is observed walking into examining room and then is re-examined for this item with arms extended at right angles to the body and the fingers spread out as far as possible.

1 = Normal
2 = Mild finger tremor, obvious to sight and touch
3 = Tremor of hand or arm occurring spasmodically
4 = Persistent tremor of one or more limbs
5 = Whole body tremor
9 = Not ratable

9. SALIVATION - Patient is observed while talking and then asked to open his mouth and elevate his tongue.

1 = Normal
2 = Excess salivation so that drooling takes place if mouth is opened and tongue raised
3 = Excess salivation is present and might occasionally result in difficulty in speaking
4 = Speaking with difficulty because of excess salivation
5 = Frank drooling
9 = Not ratable

10. AKATHISIA - Patient is observed for restlessness. If restlessness is noted, ask: "Do you feel restless or jittery inside; is it difficult to sit still?" Subjective response is not necessary for scoring but patient report can help make the assessment.

1 = No restlessness reported or observed
2 = Mild restlessness observed, eg, occasional jiggling of the foot occurs when patient is seated
3 = Moderate restlessness observed, eg, on several occasions, jiggles foot, crosses and uncrosses legs or twists a part of the body
4 = Restlessness is frequently observed, eg, the foot or legs moving most of the time
5 = Restlessness persistently observed, eg, patient cannot sit still, may get up and walk
9 = Not ratable

Adapted from Simpson GM and Angus JWS. Acta Psychiatr Scand. 1970;212:S11-S19.

Protocol 31-10-270

Appendix 9 Barnes Akathisia Rating Scale (BARS)

Patients should be observed while they are seated and then standing (for a minimum of two minutes in each position). Symptoms observed in other situations (eg, while engaged in neutral conversation, engaged in activity on the ward) may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

1. OBJECTIVE

0 = Normal, occasional fidgety movements of the limbs
1 = Presence of characteristic restless movements: Shuffling or tramping movements of the legs/feet, or swinging one leg while sitting, and/or rocking from foot to foot or "walking-on-the-spot" when standing, but movement present for less than half the time observed
2 = Observed phenomena as described in (1) above, which are present for at least half the observation period
3 = The patient is constantly engaged in characteristic restless movements, and/or has the inability to remain seated or standing without walking or pacing, during the time observed

2. SUBJECTIVE - AWARENESS OF RESTLESSNESS

0 = Absence of inner restlessness
1 = Non-specific sense of inner restlessness
2 = The patient is aware of inability to keep the legs still, or a desire to move legs and/or complains of inner restlessness associated specifically by being required to stand still
3 = Awareness of an inner compulsion to move most of the time and/or reports a strong desire to walk or pace most of the time

3. SUBJECTIVE - DISTRESS RELATED TO RESTLESSNESS

0 = No distress
1 = Mild
2 = Moderate
3 = Severe

Protocol 31-10-270

4. GLOBAL CLINICAL ASSESSMENT OF AKATHISIA

0 = Absent - No evidence of awareness of restlessness. Observation of characteristic movement of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia

1 = Questionable - Non specific inner tension and fidgety movements

2 = Mild akathisia - Awareness of restlessness in the legs and/or inner restlessness worse when required to stand still. Fidgety movement present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress.

3 = Moderate akathisia - Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements; finds the condition distressing

4 = Marked akathisia - Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. Constant restlessness which is associated with intense distress and insomnia

5 = Severe akathisia - The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia.

Adapted from Barnes TR. Br J Psychiatry. 1989;154:672-6.

Protocol 31-10-270

Appendix 10 Suicide Severity Rating Scale (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact PPD New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact PPD

Protocol 31-10-270

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Lifetime: Time He/She Felt Most Suicidal
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

Protocol 31-10-270

INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (0) Does not apply.	____

Protocol 31-10-270

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Lifetime
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted ___
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐

Protocol 31-10-270

Answer for Actual Attempts Only	**Most Recent Attempt** Date:	**Most Lethal Attempt** Date:	**Initial/First Attempt** Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Protocol 31-10-270

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

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Protocol 31-10-270

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

Protocol 31-10-270

INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Protocol 31-10-270

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted ____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐
Completed Suicide:	**Yes** **No** ☐ ☐

Protocol 31-10-270

Answer for Actual Attempts Only		**Most Lethal Attempt**
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	**Date**	
	Enter #	
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	**Date**	
	Enter #	

Protocol 31-10-270

Appendix 11 Visual Analog Scale (VAS) for Subject-reported Rating of Pain at Most Recent Injection Site

Date: _____ Time of Assessment: _____

Patient evaluation of pain at the most recent injection site via visual analog scale:

No pain |——————————————————————| Unbearably painful

Note: VAS is 100 mm line; current sample is not to scale

Adapted from Kane et al. Am J Psychiatry. 2003;160:1125-32.

Protocol 31-10-270

Appendix 12 Investigator's Assessment of Most Recent Injection Site

Date: _____ Time of Assessment: _____

The subject and most recent injection site should be observed and evaluated by the investigator on a 4-point categorical scale (absent, mild, moderate, severe) for the presence or absence of any of the following symptoms.

ITEM	Absent	Mild	Moderate	Severe
PAIN	0 ☐	1 ☐	2 ☐	3 ☐
SWELLING	0 ☐	1 ☐	2 ☐	3 ☐
REDNESS	0 ☐	1 ☐	2 ☐	3 ☐
INDURATION	0 ☐	1 ☐	2 ☐	3 ☐

Adapted from Kane et al. Am J Psychiatry. 2003;160:1125-32 and Lindenmayer JP et al. Int Clin Psychopharmacol. 2005;20:213-21.

Protocol 31-10-270

Appendix 13 Product Labels

ABILIFY (aripiprazole) US Prescribing Information (USPI)

Please see current US Prescribing Information in the Investigator Site File (ISF) and/or the Trial Master File (TMF).

ABILIFY (aripiprazole) EU Summary of Product Characteristics (SmPC)

Please see current SmPC in the Investigator Site File (ISF) and/or the Trial Master File (TMF).

Protocol 31-10-270

Appendix 14 Protocol Amendment(s)/Administrative Change(s)

Amendment Number: Amendment 4

Issue Date: 08 Jul 2015

PURPOSE:

In this protocol amendment, the number and types of assessments obtained during the trial have been reduced to decrease the burden on study subjects. Subjects being treated with aripiprazole IM Depot in Trial 31-10-270 may continue treatment until the trial ends as described in the protocol.

If the sponsor terminates the study prior to 31 Dec 2018 for any reason other than commercial availability, investigators in some countries where the sponsor has limited or delayed commercialization plans, or where no commercialization activity is anticipated, may be eligible to participate in a managed access program until aripiprazole IM Depot is commercially available in their country or until 31 Dec 2018. Availability and requirements of such a program varies by jurisdiction, and would only be an option for subjects who were receiving aripiprazole IM Depot in the current study, and who in the physician's opinion, may benefit from continued treatment with aripiprazole. To gain access to aripiprazole IM Depot for eligible subjects via a managed access program, each physician will be responsible for gaining appropriate local regulatory approvals, which will be granted by authorities on a case-by-case basis. The sponsor makes no guarantee that such a program is available or approvable in all of the jurisdictions where the study is conducted.

BACKGROUND:

The well-established safety profile of both oral aripiprazole and aripiprazole IM Depot across the completed double-blind and long-term Phase 3 trials allows this reduction in required study assessments for subjects enrolled under Amendment 4, while maintaining appropriate safety monitoring.

Protocol 31-10-270

MODIFICATIONS TO PROTOCOL:

- The frequency has been reduced for these assessments: CGI-S, EPS assessments (AIMS, BARS, SAS), vital signs, BMI, physical exam, ECGs, urine drug screen and blood alcohol tests, and assessments by the investigator and subject of injection site reactions. Although these assessments are not required at specific time points, any of these assessments may be obtained at any study visit at the discretion of the investigator. Details are provided in Table 3.6-1.
- Added information about a managed access program.
- Updated the Introduction.
- Updated titles for specific sponsor representatives and updated the sponsor's mailing address.
- Fixed typographical errors and made minor changes to reflect current styles (not displayed in the table below).

Sectional Revisions:

Details of the by-section changes that were updated are shown in the table that follows.

Protocol 31-10-270

Location	Old Text	Updated Text
Title Page	PPD PPD	PPD PPD
Title Page	(New Text)	Date of Amendment 4: 08 Jul 2015
Synopsis/ Trial Design	... Subjects will continue to receive aripiprazole IM Depot every month (study months are every 4 weeks which is defined as 28 [-2/+10] days) as a continuation of their previous monthly dose in Study 248. ... ... Following the Baseline visit, the Columbia Suicide Severity Rating Scale (C-SSRS), adverse events and concomitant medications will be assessed at the monthly injection study visit. The Clinical Global Impression - Severity (CGI-S) scale, vital signs, and urine pregnancy test (for women of childbearing potential [WOCBP] only; see Section 5.4 for definition of WOCBP) will be assessed every 3 months. Urine drug screening and blood alcohol testing, at the investigator's discretion, can be performed every 3 months. Visual Analog Scale (VAS) for subject-reported rating of pain at the most recent injection site and the investigator's assessment for pain, redness, induration, and swelling of most recent injection site will be performed every 6 months. The following scales will be used to assess extrapyramidal symptoms (EPS) every 6 months (more frequently if warranted, see Table 3.6-1): Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Scale (SAS), and Barnes Akathisia Rating Scale (BARS). These EPS scales can be administered at any visit at the discretion of the investigator if warranted by the presence of symptoms. Clinical laboratory tests, physical examination, and electrocardiogram (ECG) will be performed annually. For each visit, all assessments, except for post-injection assessments, should be performed prior to the aripiprazole IM Depot injection.	... Subjects in this study will continue to receive aripiprazole IM Depot every month (study months are every 4 weeks which is defined as 28 [−2/+10] days) as a continuation of their previous monthly dose in Study 248. ... ... Following the baseline visit, subjects will receive monthly injections and at the same visit, adverse events (AEs) and concomitant medications will be recorded and the Columbia Suicide Severity Rating Scale (C-SSRS) will be completed. Every 3 months, all of the monthly assessment will be completed along with a urine pregnancy test for women of childbearing potential (WOCBP). Every 6 months, all of the 3-month assessments will be completed along with the Clinical Global Impression - Severity (CGI-S) scale, vital signs, and extrapyramidal symptoms (EPS) assessments (including the Abnormal Involuntary Movement Scale [AIMS], Simpson-Angus Scale [SAS], and Barnes Akathisia Rating Scale [BARS]). At the 12-month visit, all of the 6-month assessments will be completed along with clinical laboratory tests and assessments of body weight, height, and waist circumference. Urine drug screening and blood alcohol testing will be obtained at baseline and can be re-obtained at the investigator's discretion at any time during the study. A Visual Analog Scale (VAS) for subject-reported rating of pain at the most recent injection site and the investigator's assessment for pain, redness, induration, and swelling of the most recent injection site will be performed at baseline and may be reassessed at the discretion of the investigator.

Protocol 31-10-270

Location	Old Text	Updated Text
	A Study Completion Visit or Early Termination Visit (-2/+10 days) will be performed and include the following assessments: CGI-S; C-SSRS; injection site assessment by the subject using VAS and by the investigator for pain, redness, induration, and swelling; AEs; EPS (AIMS, SAS, and BARS); clinical laboratory tests; vital signs, body height and weight; BMI; physical examination; ECG; urine pregnancy test for WOCBP; and concomitant medications. A 30-Day Post Treatment Follow-up phone call will be performed 30 days (± 3 days) after it has been determined that the subject will no longer participate in this study and include the recording of AEs that have occurred and any concomitant medications taken since the last visit. ... Aripiprazole IM Depot treatment in this open-label rollover study will continue until there are clinical and/or administrative reasons for discontinuation of the subject's study treatment or through the end of study date of 31 Dec 2018 is reached. ... Administrative reasons for discontinuing study treatment include, but are not limited to: aripiprazole IM Depot is commercially available in any dosage (including a generic formulation) in the country where the study is being conducted, the commercial availability of aripiprazole IM Depot is terminated by the sponsor, or until the study end date of 31 Dec 2018 is reached, which ever occurs first. Once aripiprazole IM Depot becomes commercially available in any dosage (including generic formulations) in the country where the subject is participating in the study or the commercial availability of aripiprazole IM Depot is terminated by the sponsor, study treatment will be discontinued within 6 weeks of the subject's previous injection for clinical transition purposes.	Clinical laboratory tests, physical examination, and electrocardiogram (ECG) obtained at baseline may also be performed at the discretion of the investigator based on clinical necessity. A Study Completion visit or Early Termination visit (−2/+10 days) will include the following assessments: C-SSRS, AEs, concomitant medications, a urine pregnancy test for WOCBP, CGI-S, vital signs, EPS assessments (AIMS, BARS, SAS), clinical laboratory tests, and body height and weight. A 30-Day Post Treatment Follow-up phone call will be made 30 days (± 3 days) after it has been determined that the subject will no longer participate in this study and will include questions about any AEs that have occurred and any concomitant medications taken since the last visit. ... Aripiprazole IM Depot treatment in this open-label rollover study will continue until there are clinical and/or administrative reasons for discontinuation of the subject's study treatment or until the study end date of 31 Dec 2018 is reached, whichever occurs first. ... Administrative reasons for discontinuing study treatment include, but are not limited to: aripiprazole IM Depot becomes commercially available in any dosage (including a generic formulation) in the country where the study is being conducted, the commercial availability of aripiprazole IM Depot is terminated by the sponsor, or until the study end date of 31 Dec 2018 is reached, whichever occurs first. Once aripiprazole IM Depot becomes commercially available in any dosage (including generic formulation[s]) in the country where the subject is participating in the study or

Location	Old Text	Updated Text
		the commercial availability of aripiprazole IM Depot is terminated by the sponsor, study treatment will be discontinued within approximately 6 weeks of the subject's previous injection for clinical transition purposes. If the sponsor terminates the study prior to 31 Dec 2018 for any reason other than commercial availability, investigators in some countries where the sponsor has limited or delayed commercialization plans, or where no commercialization activity is anticipated, may be eligible to participate in a managed access program until aripiprazole IM Depot is commercially available in their country or until 31 Dec 2018.
Synopsis/ Trial Assessments	**Safety**: Safety will be assessed by adverse event reporting, every month (study months are every 4 weeks which is defined as 28 [-2/+10] days). The C SSRS will be used to assess suicidality every month. VAS for subject-reported rating of pain at the most recent injection site and the investigator's assessment for pain, redness, induration, and swelling of the most recent injection site will be performed every 6 months. Extrapyramidal symptoms will be assessed every 6 months using the AIMS, SAS, and BARS assessments. Vital signs will be assessed every 3 months and clinical laboratory tests, ECG, physical examinations, body height and weight, BMI, and waist circumference will be assessed every 12 months. **Efficacy**: Efficacy will be evaluated using the CGI-S and administered every 3 months.	**Safety:** Safety will be assessed by adverse event and concomitant medication reporting at baseline (post-IM administration) and at each subsequent monthly injection visit (study months are every 4 weeks which is defined as 28 [−2/+10] days). The C-SSRS will be used to assess suicidality at baseline and at each subsequent monthly injection visit. Extrapyramidal symptoms will be assessed using the AIMS, SAS, and BARS assessment questionnaires at baseline, every 6 months, at the discretion of the investigator at any subsequent visit, and at Study Completion or the Early Termination visit. Clinical laboratory tests will be performed at baseline, every 12 months, and at Study Completion or the Early Termination visit. Vital signs will be assessed every 6 months and at Study Completion or the Early Termination visit. Body height and weight, body mass index (BMI), and waist circumference will be assessed at baseline; body height, weight, and waist circumference will be reassessed every 12 months; and body height and weight will be assessed at Study Completion or the Early Termination visit. For WOCBP, a urine pregnancy test will be administered at baseline, every 3 months, and at Study Completion or the Early Termination visit.

Protocol 31-10-270

Location	Old Text	Updated Text
		Efficacy: Efficacy will be evaluated using the CGI-S administered every 6 months.
Synopsis/ Criteria for Evaluation	**Safety Endpoints:** ... • The incidence of clinically significant changes will be calculated for vital signs and routine laboratory tests. Mean change from baseline and incidence of clinically significant changes will be calculated for ECG parameters and body weight. By-patient listings of physical findings will be reviewed as a further assessment of safety.	**Safety Endpoints:** ... • The incidence of clinically significant changes will be calculated for vital signs. Mean change from baseline and incidence of clinically significant changes will be calculated for body weight and waist circumference.
Synopsis/ Trial Duration	Subjects will continue to receive aripiprazole IM Depot in this open-label rollover study until there are clinical and/or administrative reasons for discontinuation of the subject's study treatment or the end of study date of 31 Dec 2018 is reached (see "Trial Design" section above). Once aripiprazole becomes available commercially at any dosage [including generic formulation(s)] in the country where the study is being conducted, the commercial availability of aripiprazole IM Depot is terminated by the sponsor, or until the study end date of 31 Dec 2018 is reached, treatment will be discontinued. If aripiprazole IM Depot is commercially available or if the availability of aripiprazole IM Depot is terminated by the sponsor, then the subject will discontinue treatment within 6 weeks of last injection for clinical transition purposes.	Subjects will continue to receive aripiprazole IM Depot in this open-label rollover study until there are clinical and/or administrative reasons for discontinuation of the subject's study treatment or until the study end date of 31 Dec 2018 is reached, whichever occurs first (see "Trial Design" section above). Once aripiprazole becomes available commercially at any dosage (including generic formulation[s]) in the country where the study is being conducted, the commercial availability of aripiprazole IM Depot is terminated by the sponsor, or until the study end date of 31 Dec 2018 is reached, treatment will be discontinued. If aripiprazole IM Depot is commercially available or if the availability of aripiprazole IM Depot is terminated by the sponsor, then the subject will discontinue treatment within approximately 6 weeks of last injection for clinical transition purposes.
1 Introduction	ABILIFY® (aripiprazole) oral tablets are approved in the United States (US) for the treatment of adults and adolescents with acute schizophrenia, maintenance of stability in adults with schizophrenia, treatment of acute manic episodes associated with Bipolar I Disorder in adults and pediatric patients, maintenance of efficacy in adults with Bipolar I Disorder, and as adjunctive treatment of	ABILIFY® (aripiprazole, OPC-14597, BMS-337039), a second generation antipsychotic, which exhibits partial agonism (agonism/antagonism) at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonism at serotonin 5-HT_2 receptors, is approved and marketed in the United States (US) for use in the following indications.[9]

Protocol 31-10-270

Location	Old Text	Updated Text
	major depressive disorder (MDD). Aripiprazole is also approved for the treatment of schizophrenia in the European Union (EU), Australia, and a number of countries in Asia, Europe, and Latin America. The aripiprazole immediate-release IM formulation is approved for the treatment of agitation in patients with schizophrenia and bipolar mania in the US and EU. In addition, an oral solution formulation and orally disintegrating (dispersible) tablets have been approved and marketed in the US and EU. The favorable side effect profile of oral aripiprazole, including its low incidence of EPS, low risk of prolactin elevation, decreased adrenergic and anticholinergic side effects, and minimal weight gain, makes it an excellent candidate for a long-acting depot formulation. The efficacy, safety, and tolerability of an IM depot formulation of aripiprazole are being examined for the treatment of schizophrenia in 2 pivotal Phase 3 studies (31-07-246 and 31-07-247). Study 31-08-248 is included in the development plan for aripiprazole IM Depot to supplement the safety data that will be generated as part of the Phase 3 program and to provide additional efficacy data for the maintenance treatment of patients with schizophrenia. The current study (31-10-270, hereafter referred to as *Study 270*), will allow subjects who completed Study 31-08-248 (hereafter referred to as *Study 248*) to continue treatment with aripiprazole IM Depot until it is commercially available in any dosage [including generic formulation(s)] in the country where the study is being conducted, the commercial availability of aripiprazole IM Depot is terminated by the sponsor, or until the study end date of 31 Dec 2018 is reached. This study will provide additional long-term safety information.	In adults, aripiprazole is indicated: • for treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder as monotherapy or adjunctive to lithium or valproate. • for adjunctive treatment of major depressive disorder (MDD) in adults. • as an injection for treatment of adults with agitation associated with schizophrenia or bipolar I disorder, manic or mixed episodes. • as an IM depot formulation for treatment of schizophrenia. In pediatrics, aripiprazole is indicated: • for treatment of schizophrenia (ages 13 to 17 years). • for treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy or adjunctive to lithium or valproate (ages 10 to 17 years). • for treatment of irritability associated with autistic disorder in children and adolescents (ages 6 to 17 years). In the European Union (EU), aripiprazole is also approved for the treatment of moderate to severe manic episodes in bipolar I disorder and for the prevention of new manic episodes in those patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment, as well as for the treatment of schizophrenia in adults and adolescents (Appendix 13). The aripiprazole immediate-release IM injection formulation is approved for the treatment of agitation associated with schizophrenia or bipolar mania in the US and EU. In addition, an oral solution formulation and orally disintegrating (dispersible) tablets have been approved and marketed in the US and EU.

Protocol 31-10-270

Location	Old Text	Updated Text
		The favorable side effect profile of oral aripiprazole, including its low incidence of EPS, low risk of prolactin elevation, decreased adrenergic and anticholinergic side effects, and minimal weight gain, makes it an excellent candidate for a long-acting depot formulation. Aripiprazole IM depot formulation is currently being developed for maintenance treatment of schizophrenia and bipolar I disorder, and was approved for the treatment of schizophrenia in the US in February 2013. Its efficacy was demonstrated in a pivotal phase 3 registrational trial (Study 31-07-246) designed to evaluate the efficacy, safety, and tolerability of the long-acting IM depot formulation of aripiprazole administered to adult subjects with a diagnosis of schizophrenia as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). A marketing application was submitted in September 2011 to the Food and Drug Administration (FDA) for use of the aripiprazole IM depot formulation as maintenance treatment in patients with schizophrenia, which was approved in February 2013 (Appendix 13). A marketing application was submitted in December 2012 to the European Medicines Agency. Study 31-08-248 is included in the development plan for aripiprazole IM Depot to supplement the safety data that will be generated as part of the phase 3 program and to provide additional efficacy data for the maintenance treatment of patients with schizophrenia. The current study (31-10-270, hereafter referred to as Study 270), will allow subjects who completed Study 31-08-248 (hereafter referred to as Study 248) to continue treatment with aripiprazole IM Depot until it is commercially available in any dosage (including generic formulation[s]) in the country where the study is being conducted, the commercial availability of aripiprazole IM Depot is terminated by the sponsor, or until the study end date of 31 Dec 2018 is reached. This study will provide

Location	Old Text	Updated Text
		additional long term safety information. If the sponsor terminates the study prior to 31 Dec 2018 for any reason other than commercial availability, investigators in some countries where the sponsor has limited or delayed commercialization plans, or where no commercialization activity is anticipated, may be eligible to participate in a managed access program until aripiprazole IM Depot is commercially available in their country or until 31 Dec 2018. Availability and requirements of such a program varies by jurisdiction, and would only be an option for subjects who were receiving aripiprazole IM Depot in the current study, and who in the physician's opinion, may benefit from continued treatment with aripiprazole. To gain access to aripiprazole IM Depot for eligible subjects via a managed access program, each physician will be responsible for gaining appropriate local regulatory approvals, which will be granted by authorities on a case-by-case basis. The sponsor makes no guarantee that such a program is available or approvable in all of the jurisdictions where the study is conducted.
1.2 Clinical Data	A comprehensive clinical program to evaluate the effectiveness of aripiprazole was conducted. The studies of subjects with an acute exacerbation of schizophrenia established the effectiveness of aripiprazole in the treatment of schizophrenia, including positive and negative symptoms. These studies also demonstrated its early onset of action. The long-term studies showed that aripiprazole treatment maintained stability in subjects with schizophrenia.	A comprehensive clinical program to evaluate the effectiveness of aripiprazole was conducted. The studies of subjects with an acute exacerbation of schizophrenia established the effectiveness of aripiprazole in the treatment of schizophrenia, including positive and negative symptoms. These studies also demonstrated its early onset of action. The long-term studies showed that aripiprazole treatment maintained stability in subjects with schizophrenia. The Investigator's Brochure provides additional safety data on studies not described below.[9]
1.3 Known and Potential Risks and Benefits	As of 16 Apr 2007, 14,632 patients had been treated with aripiprazole oral-tablet formulation in Phase 2/3/4 studies (representing 8102 patient-exposure years). Of these, 3774 (25.8%) patients were treated with aripiprazole for 180 days or longer; 2063 (14.1%) patients received aripiprazole for at	As of 01 Jun 2014, all voluntary reports of adverse events (AEs) in patients taking aripiprazole received since market introduction that were considered by the sponsor as medically relevant have been listed in the USPI and EU SmPC (Appendix 13). The USPI and EU SmPC also contain

Location	Old Text	Updated Text
	least 360 days, with 908 (6.2%) patients continuing aripiprazole treatment for at least 720 days.[9]	the currently available phase 2/3/4 clinical safety information (Appendix 13).
2.1 Trial Rationale	The current study (31-10-270) will allow the long-term patients who completed Study 248 to continue to receive aripiprazole IM Depot treatment until aripiprazole IM Depot is either commercially available in any dosage [including generic formulation(s)] in the country where the study is being conducted, the commercial availability of aripiprazole IM Depot is terminated by the sponsor, or until the study end date of 31 Dec 2018 is reached.	The current study (31-10-270) will allow the long-term subjects who completed Study 248 to continue to receive aripiprazole IM Depot treatment until aripiprazole IM Depot is either commercially available in any dosage (including generic formulation[s]) in the country where the study is being conducted, the commercial availability of aripiprazole IM Depot is terminated by the sponsor, or until the study end date of 31 Dec 2018 is reached. If the sponsor terminates the study prior to 31 Dec 2018 for any reason other than commercial availability, investigators in some countries where the sponsor has limited or delayed commercialization plans, or where no commercialization activity is anticipated, may be eligible to participate in a managed access program until aripiprazole IM Depot is commercially available in their country or until 31 Dec 2018. Availability and requirements of such a program varies by jurisdiction and would only be an option for subjects who were receiving aripiprazole IM Depot in the current study, and who in the physician's opinion, may benefit from continued treatment with aripiprazole. To gain access to aripiprazole IM Depot for eligible subjects via a managed access program, each physician will be responsible for gaining appropriate local regulatory approvals, which will be granted by authorities on a case-by-case basis. The sponsor makes no guarantee that such a program is available or approvable in all of the jurisdictions where the study is conducted.
3.1 Type/ Design of Trial	... Following the Baseline visit, the Columbia Suicide Severity Rating Scale (C-SSRS), adverse events and concomitant medications will be assessed at the monthly injection study visit. The CGI-S scale, vital signs, and urine pregnancy test (for women of child-bearing potential [WOCBP] only; see	... Following the baseline visit (described in detail in Section 3.6.1.1), subjects will receive monthly injections and at the same visit, AEs and concomitant medications will be recorded and the Columbia Suicide Severity Rating Scale (C-SSRS) will be completed (Section 3.6.1.2). Every

Protocol 31-10-270

Location	Old Text	Updated Text
	Section 5.4 for definition of WOCBP) will be assessed every 3 months. Urine drug screening and blood alcohol testing, at the investigator's discretion, can be performed every 3 months. Visual Analog Scale (VAS) for subject-reported rating of pain at the most recent injection site and the investigator's assessment for pain, redness, induration, and swelling of most recent injection site will be performed every 6 months. The following scales will be used to assess EPS every 6 months (more frequently if warranted, see Table 3.6-1): Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Scale (SAS), and Barnes Akathisia Rating Scale (BARS). These EPS scales can be administered at any visit at the discretion of the investigator if warranted by the presence of symptoms. Clinical laboratory tests, a physical examination, an ECG, body height and weight, BMI, and waist circumference will be performed annually. For each visit, all the assessments, except for post-injection assessments, should be performed prior to the aripiprazole IM Depot injection. A Study Completion Visit or Early Termination Visit (-2/+10 days) will be performed and include the following assessments: CGI-S; C-SSRS; injection site assessment by the subject using VAS and by the investigator for pain, redness, induration, and swelling; AEs; EPS (AIMS, SAS, and BARS); clinical laboratory tests; vital signs, body height and weight; BMI; physical examination; ECG; urine pregnancy test for WOCBP; and concomitant medications. ... Aripiprazole IM Depot treatment in this open-label rollover study will continue until there are clinical and/or administrative reasons for discontinuation of the subject's study treatment or the end of study date of 31 Dec 2018 is reached. ... Once aripiprazole IM Depot becomes commercially	3 months (Section 3.6.1.3), all of the monthly assessments will be completed along with a urine pregnancy test for women of childbearing potential (WOCBP) (see Section 5.4 for the definition of WOCBP). Every 6 months (Section 3.6.1.4), all of the 3-month assessments will be completed along with the CGI-S scale, vital signs, and EPS assessments (Abnormal Involuntary Movement Scale [AIMS], Simpson-Angus Scale [SAS], and Barnes Akathisia Rating Scale [BARS]). Every 12 months (Section 3.6.1.5), all of the 6-month assessments will be completed along with clinical laboratory tests and assessments of body height, weight, and waist circumference. At the discretion of the investigator, the baseline assessments for clinical chemistry and hematology, urine drug screening, and blood alcohol testing may be repeated at any subsequent study visit. For each visit, all the assessments, except for those specified as post-injection assessments, should be performed prior to the aripiprazole IM Depot injection. A Study Completion visit or Early Termination visit (−2/+10 days) will include the following assessments (Section 3.6.1.6): C-SSRS, AEs, concomitant medications, a urine pregnancy test for WOCBP, CGI-S, vital signs, EPS assessments (AIMS, BARS, SAS), clinical laboratory tests, and body height and weight. ... Aripiprazole IM Depot treatment in this open-label rollover study will continue until there are clinical and/or administrative reasons for discontinuation of the subject's study treatment or until the study end date of 31 Dec 2018 is reached, whichever occurs first. ... If the sponsor terminates the study prior to 31 Dec 2018 for any reason other than commercial availability, investigators in some countries where the sponsor has limited or delayed

Protocol 31-10-270

Location	Old Text	Updated Text
	available in the country where the subject is participating in the study [including generic formulation(s)] or the commercial availability of aripiprazole IM Depot is terminated by the sponsor, study treatment will be discontinued within 6 weeks of the subject's previous injection for clinical transition purposes.	commercialization plans, or where no commercialization activity is anticipated, may be eligible to participate in a managed access program until aripiprazole IM Depot is commercially available in their country or until 31 Dec 2018. Availability and requirements for such a program varies by jurisdiction, and would only be an option for subjects who were receiving aripiprazole IM Depot in the current study, and who in the physician's opinion, may benefit from continued treatment with aripiprazole. To gain access to aripiprazole IM Depot for eligible subjects via a managed access program, each physician will be responsible for gaining appropriate local regulatory approvals, which will be granted by authorities on a case-by-case basis. The sponsor makes no guarantee that such a program is available or approvable in all of the jurisdictions where the study is conducted. Once aripiprazole IM Depot becomes commercially available in the country where the subject is participating in the study (including generic formulation[s]) or the commercial availability of aripiprazole IM Depot is terminated by the sponsor, study treatment will be discontinued within approximately 6 weeks of the subject's previous injection for clinical transition purposes.
Figure 3.1-1 Study 31-10-270 Trial Design Schema	Both Figures are displayed below	

Protocol 31-10-270

Amendment 3

Study Entry	Open Label IM Depot Treatment	Follow-up
→	→	→
Study 248 Completers only	Every Month: Injection visits, C -SSRS, AEs, & concomitant medications Every 3 months: CGI-S, vital signs, urine pregnancy test, optional drug and alcohol testing Every 6 months: Injection site assessments and EPS (AIMS, SAS, & BARS) Every 12 months: Clinical laboratory tests, PE, ECG, body height & weight, BMI, and waist circumference	One 30-day post End of Study
Week 52 Visit of Study 248 = Baseline for Study 270	*Injection visit window = 28 (-2/+10) days* *Assessment visit windows = -2/+10 days*	*±3 days*

Figure 3.1-1 Study 31-10-270 Trial Design Schema

AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BMI = body mass index; CGI-S = Clinical Global Impression – Severity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EPS = extrapyramidal symptoms; IM = intramuscular; PE = physical examination; SAS = Simpson-Angus Scale.

Protocol 31-10-270

Amendment 4

Study Entry	Open-label IM Depot Treatment		Follow-up
Study 248 Completers only	Every month: Every 3 months[a]: Every 6 months[a]: Every 12 months[a]:	Injection, C-SSRS, AEs, and concomitant medications Urine pregnancy test for WOCBP CGI-S, vital signs, and EPS assessments (AIMS, BARS, SAS) Clinical laboratory tests, body weight and height, and waist circumference	One 30-day post End of Study phone call - AEs and concomitant medications
Week 52 Visit of Study 248 = Baseline for Study 270	Injection visit window = 28 (−2/+10) days Assessment visit window = −2/+10 days		± 3 days

Figure 3.1-1 Study 31-10-270 Trial Design Schema

BMI = body mass index.

[a]The 3-month, 6-month, and 12-month visits include assessments from the previous visit. For example, the 3-month visit includes all of the monthly visit assessments in addition to the 3-month visit assessments. A Study Completion or Early Termination visit will also be performed. Refer to Table 3.6-1 for a comprehensive Schedule of Assessments at each visit.

Protocol 31-10-270

Location	Old Text	Updated Text
3.2 Treatments	Needle length for injection of aripiprazole IM Depot will be selected based on body mass index (BMI) as follows: 21 gauge, 1.5 inch for BMI ≤ 28 kg/m^2; 21 gauge, 2 inch for BMI > 28 kg/m^2.	Needle length for injection of aripiprazole IM Depot will be selected based on body mass index (BMI) obtained at baseline as follows: 21 gauge, 1.5 inch for BMI ≤ 28 kg/m^2; 21 gauge, 2 inch for BMI > 28 kg/m^2.
Table 3.4.3-1 Exclusion Criteria	... If employing birth control, two of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device (IUD), birth control pill, birth control implant, condom, or sponge with spermicide.	... If employing birth control, two of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device (IUD), birth control pill, birth control implant, condom with spermicide, or sponge with spermicide.
3.5.1 Safety Endpoints	AEs will be examined by frequency, severity, seriousness, and discontinuation due to AEs. The Columbia Suicide Severity Rating Scale (C-SSRS) will be completed at baseline and every month to assess the risk of suicide events and to classify reported suicide events. Injection site pain will be evaluated by mean VAS scores as reported by the subject once every 6 months before and after injection. Extrapyramidal symptoms will be evaluated by calculating mean change from baseline in AIMS, SAS, and BARS every 6 months (more frequently if warranted, see Table 3.6.-1). The investigator rating of localized pain, redness, induration, and swelling at the injection site will also be tabulated every 6 months. Vital signs will be assessed every 3 months and clinical laboratory tests, ECG, and physical examinations will be assessed every 12 months.	Adverse events will be examined by frequency, severity, seriousness, and discontinuation due to AEs. The C-SSRS will be completed at baseline and every subsequent monthly visit to assess the risk of suicide events and to classify reported suicide events. Extrapyramidal symptoms will be evaluated by calculating mean change from baseline in AIMS, SAS, and BARS every 6 months (more frequently if warranted, see Table 3.6.-1) and at Study Completion or the Early Termination visit. Clinical laboratory tests will be performed at baseline, every 12 months, and at Study Completion or the Early Termination visit. Vital signs will be assessed every 6 months and at Study Completion or the Early Termination visit. Body weight, height, and waist circumference will be assessed every 12 months; body weight and height will also be assessed at Study Completion or the Early Termination visit.
3.5.2 Efficacy Endpoint	CGI-S will be evaluated by calculating mean change from baseline every 3 months over the course of the study.	CGI-S will be evaluated by calculating mean change from baseline every 6 months over the course of the study.
Table 3.6-1 Schedule of Assessments (Study 31-10-270)	Both Tables are presented below	

Protocol 31-10-270

Amendment 3

Table 3.6-1 Schedule of Assessments (Study 31-10-270)

Assessment	Baseline (Week 52 Visit of previous Otsuka 31 08-248 study)[a]	Study Visits				Study Completion or Early Termination (-2/+10 days)	30-Day Post Treatment Follow-up Phone Call[c] (± 3 days)
		Every Month[b] (-2/+10 days)	Every 3 Months[b] (-2/+10 days)	Every 6 Months[b] (-2/+10 days)	Every 12 Months[b] (-2/+10 days)		
STANDARD							
Informed consent	X						
Inclusion/exclusion criteria	X						
Medical history	X						
STUDY ASSESSMENTS							
CGI-S	X		X	X	X	X	
C-SSRS	X	X	X	X	X	X	
AIMS[d]	X	<----------	---------->	X	X	X	
SAS[d]	X	<----------	---------->	X	X	X	
BARS[d]	X	<----------	---------->	X	X	X	
VAS pain at injection site[e]	X			X	X	X	
Investigator rating of injection site[e]	X			X	X	X	
Body height and weight	X				X	X	
BMI[f]	X				X	X	
Waist circumference	X				X		
Adverse events[g]	X	X	X	X	X	X	X
Clinical laboratory tests (hematology, serum chemistry, and urinalysis)	X				X	X	
Vital signs	X		X	X	X	X	
Physical exam	X				X	X	
ECG	X				X	X	
Urine pregnancy test (WOCBP only)[h]	X		X	X	X	X	

Protocol 31-10-270

Table 3.6-1 Schedule of Assessments (Study 31-10-270)

Assessment	Baseline (Week 52 Visit of previous Otsuka 31 08-248 study)[a]	Study Visits				Study Completion or Early Termination (-2/+10 days)	30-Day Post Treatment Follow-up Phone Call[c] (± 3 days)
		Every Month[b] (-2/+10 days)	Every 3 Months[b] (-2/+10 days)	Every 6 Months[b] (-2/+10 days)	Every 12 Months[b] (-2/+10 days)		
Urine drug screen and blood alcohol test[i]	X		X	X	X		
Concomitant medications	X	X	X	X	X	X	X
STUDY MANAGEMENT							
Administer open-label IM Depot[j]	X	X	X	X	X		

Protocol 31-10-270

Amendment 4

Table 3.6-1 Schedule of Assessments (Study 31-10-270)

Assessment	Baseline (Week 52 Visit of previous Otsuka 31-08-248 study)[a]	Study Visits				Study Completion or Early Termination (−2/+10 days)	30-Day Post Treatment Follow-up Phone Call[c] (± 3 days)
		Every Month[b] (−2/+10 days)	Every 3 Months[b] (−2/+10 days)	Every 6 Months[b] (−2/+10 days)	Every 12 Months[b] (−2/+10 days)		
STANDARD							
Informed consent	X						
Inclusion/exclusion criteria	X						
Medical history	X						
STUDY ASSESSMENTS							
CGI-S	X			X	X	X	
C-SSRS	X	X	X	X	X	X	
AIMS[d]	X			X	X	X	
SAS[d]	X			X	X	X	
BARS[d]	X			X	X	X	
VAS pain at injection site[e]	X	At the discretion of the investigator					
Investigator rating of injection site[e]	X	At the discretion of the investigator					
Body height and weight[f]	X				X	X	
BMI[f]	X	At the discretion of the investigator					
Waist circumference[f]	X				X		
Adverse events[g]	X	X	X	X	X	X	X
Clinical laboratory tests (hematology, serum chemistry, and urinalysis)	X	At the discretion of the investigator			X	X	
Vital signs	X			X	X	X	
Physical exam	X	At the discretion of the investigator					

Protocol 31-10-270

Table 3.6-1 Schedule of Assessments (Study 31-10-270)

Assessment	Baseline (Week 52 Visit of previous Otsuka 31-08-248 study)[a]	Study Visits				Study Completion or Early Termination (−2/+10 days)	30-Day Post Treatment Follow-up Phone Call[c] (± 3 days)
		Every Month[b] (−2/+10 days)	Every 3 Months[b] (−2/+10 days)	Every 6 Months[b] (−2/+10 days)	Every 12 Months[b] (−2/+10 days)		
ECG	X	At the discretion of the investigator					
Urine pregnancy test[h]	X		X	X	X	X	
Urine drug screen and blood alcohol test[i]	X	At the discretion of the investigator					
Concomitant medications	X	X	X	X	X	X	X
STUDY MANAGEMENT							
Administer open-label IM Depot[j]	X	X	X	X	X		

Protocol 31-10-270

Location	Old Text	Updated Text
Table 3.6-1 Schedule of Assessments (Study 31-10-270), Footnotes	... d Extrapyrimidal symptoms (EPS) will be assessed using AIMS, SAS, and BARS at least every 6 months, but these EPS scales can be administered at any visit at the discretion of the investigator if warranted by the presence of symptoms. e The subject will complete the pain evaluation and the investigator (or qualified designee) will assess the most recent injection site for localized pain, redness, swelling, and induration. These assessments will occur as the last evaluations prior to the IM Depot injection. Approximately 30 minutes prior to the injection, the investigator and subject will complete the injection site evaluation and VAS pain assessment, respectively, with the most recent injection site as the basis for the evaluation (ie, the site from the last injection). These assessments will be repeated at 1 hour (± 15 min) after the injection is administered with focus again on the most recent injection site, which is now the new injection site from the latest injection. The pre- and post-injection evaluations must be completed on the same day (ie, the day the injection is administered). The 1-hour post injection follow-up is to assess the injection site and any reaction to medication. f Needle length for injection of aripiprazole IM Depot will be selected based on BMI (21 gauge, 1.5 inch for BMI ≤28 kg/m^2; 21 gauge, 2 inch for BMI > 28 kg/m^2). The BMI, which will be calculated in kg/m^2 from the baseline height and weight at the baseline visit using one of the following formulae, as appropriate: Weight (kg) ÷ [Height (m)]^2 or Weight (lb) ÷ [Height (in)]2 x 703. If a noticeable fluctuation in body height and weight has occurred during the study, at the investigator's discretion, body weight can	... d Extrapyramidal symptoms (EPS) will be assessed using AIMS, SAS, and BARS at baseline, every 6 months, at Study Completion or the Early Termination visit, and at any other study visit at the discretion of the investigator if warranted by the presence of symptoms. e At baseline (Week 52 visit of the previous Otsuka 31-08-248 study), each subject will complete the pain evaluation and the investigator (or qualified designee) will assess the most recent injection site for localized pain, redness, swelling, and induration. These assessments will occur as the last evaluations prior to the IM Depot injection. Approximately 30 minutes prior to the injection, the investigator and subject will complete the injection site evaluation and VAS pain assessment, respectively, with the most recent injection site as the basis for the evaluation (ie, the site from the last injection). These assessments will be repeated at 1 hour (± 15 min) after the injection is administered with focus again on the most recent injection site. The pre- and post-injection evaluations must be completed on the same day (ie, the day the injection is administered). The 1-hour post injection follow-up is to assess the injection site and any reaction to medication. This assessment may be repeated at the discretion of the investigator. f Needle length for injection of aripiprazole IM Depot will be selected based on BMI (21 gauge, 1.5 inch for BMI ≤ 28 kg/m^2; 21 gauge, 2 inch for BMI > 28 kg/m^2). The BMI will be calculated in kg/m^2 from the baseline height and weight at the baseline visit using one of the following formulae, as appropriate: Weight (kg) ÷ [Height (m)]^2 or Weight (lb) ÷ [Height (in)]2 x 703. If a noticeable

Protocol 31-10-270

Location	Old Text	Updated Text
	be remeasured and BMI recalculated and used for the next aripiprazole IM Depot injection. ... h A urine pregnancy test is required for all women of childbearing potential (WOCBP) at the designated times, but can be performed at any point during the trial if pregnancy is suspected. All positive urine pregnancy test results must be confirmed by a serum test. WOCBP is defined as ALL women unless they have had an oophorectomy and/or hysterectomy or have been menopausal for at least 12 consecutive months. This should be documented in their medical history. Subjects with positive serum test results will be excluded from the study. Treated subjects with a positive serum pregnancy test must discontinue treatment, be withdrawn from the study, and an IRE form should be completed. i Urine drug screen and blood alcohol test are required at Baseline and optional every 3 months afterwards, at the investigator's discretion.	fluctuation in body height and weight has occurred during the study, at the investigator's discretion, body weight can be remeasured and BMI recalculated and used for the next aripiprazole IM Depot injection. Body weight, height, and waist circumference will be reassessed annually, and body weight and height will also be assessed at Study Completion or the Early Termination visit. ... h A urine pregnancy test is required for all WOCBP at baseline, every 3 months, and at Study Completion or the Early Termination visit, but can be performed at any point during the trial if pregnancy is suspected. All positive urine pregnancy test results must be confirmed by a serum test. WOCBP is defined as ALL women unless they have had an oophorectomy and/or hysterectomy or have been menopausal for at least 12 consecutive months. This should be documented in their medical history. Subjects with positive serum test results will be excluded from the study. Treated subjects with a positive serum pregnancy test must discontinue treatment, be withdrawn from the study, and an immediately reportable event (IRE) form should be completed. i Urine drug screen and blood alcohol test are required at baseline and anytime at the investigator's discretion.
3.6.1.1 Baseline	The baseline visit for Study 270 (which is the Week 52 visit of Study 248) and the first injection for Study 270 must occur within 4 weeks (which is defined as 28 [-2/+10] days) of the last injection in Study 248. The Week 52 assessments for Study 248 include the necessary assessments for Study 270 baseline: CGI-S; C-SSRS; AIMS; SAS; BARS; injection site pain assessed by the subject using VAS; investigator's injection site assessment for pain, redness, swelling, and induration; body weight and height; BMI; waist circumference; AEs; clinical laboratory tests; vital signs; physical exam; ECG; urine pregnancy test	The baseline visit for Study 270 (which is the Week 52 visit of Study 248) and the first injection for Study 270 must occur within 4 weeks (which is defined as 28 [−2/+10] days) of the last injection in Study 248. At this visit, subjects will sign an Informed Consent for Study 270 and their eligibility will be confirmed. The Study 248 Week 52 assessments will also serve as the baseline assessments for Study 270: CGI-S; C-SSRS; EPS assessments (AIMS, SAS, BARS); injection site pain assessed by the subject using VAS; investigator's injection

Protocol 31-10-270

Location	Old Text	Updated Text
	for WOCBP (see Section 5.4 for definition of WOCBP); urine drug screen; blood alcohol test; and concomitant medications (see Table 3.6-1). All ongoing AEs and clinically significant AEs from Study 248 will be recorded as Medical History of Study 270; please refer to the Operations Manual or CRF Completion Guidelines for additional detail.	site assessment for pain, redness, swelling, and induration; body weight and height; BMI; waist circumference; AEs; clinical laboratory tests; vital signs; physical exam; ECG; urine pregnancy test for WOCBP (see Section 5.4 for the definition of WOCBP); urine drug screen; blood alcohol test; and concomitant medications (see Table 3.6-1). All ongoing AEs and clinically significant AEs from Study 248 will be recorded as Medical History of Study 270; please refer to the Operations Manual or case report form (CRF) Completion Guidelines for additional detail.
3.6.1.2 Injection and Assessments Performed Every Month		–
3.6.1.3 Assessments Performed Every 3 Months	In addition to the monthly assessments, every 3 months (study months are every 4 weeks which is defined as 28 [-2/+10] days) CGI-S, vital signs, and urine pregnancy test for WOCBP will also be performed or assessed. In addition to these assessments, urine drug screening and blood alcohol testing, at the investigator's discretion, can be performed every 3 months.	Every 3 months (study months are every 4 weeks which is defined as 28 [−2/+10] days), the following assessments will be performed: injection, C-SSRS, AEs, concomitant medications, and a urine pregnancy test for WOCBP.
3.6.1.4 Assessments Performed Every 6 Months	In addition to the monthly and 3-month assessments, every 6 months (study months are every 4 weeks which is defined as 28 [2/+10] days) injection pain will be assessed by the subject using VAS, and the investigator injection site assessment for pain, redness, induration, and swelling at the most recent injection site will also be performed. Extrapyramidal symptoms will be assessed every 6 months (more frequently if warranted, see Table 3.6-1) using the AIMS, SAS, and BARS assessments.	Every 6 months (study months are every 4 weeks which is defined as 28 [−2/+10] days) the following assessments will be performed: injection, C-SSRS, AEs, concomitant medications, a urine pregnancy test for WOCBP, CGI-S, vital signs, and EPS assessments (AIMS, BARS, SAS).
3.6.1.5 Assessments Performed Every 12 Months	In addition to the monthly, 3-month, and 6-month assessments, every 12 months (study months are every 4 weeks which is defined as 28 [-2/+10] days) clinical laboratory tests, a physical examination, and an ECG will also be performed. Every 12 months, body height and weight and waist circumference will be measured and BMI calculated.	Every 12 months (study months are every 4 weeks which is defined as 28 [−2/+10] days) the following assessments will be performed: injection, C-SSRS, AEs, concomitant medications, a urine pregnancy test for WOCBP, CGI-S, vital signs, and EPS assessments (AIMS, BARS, SAS), clinical laboratory tests, body height and weight, and waist circumference.
3.6.1.6 Study Completion or Early	A Study Completion Visit or Early Termination Visit	A Study Completion visit or Early Termination visit

Protocol 31-10-270

Location	Old Text	Updated Text
Termination Visit	(-2/+10 days) will be performed and include the following assessments: CGI-S; C -SSRS; EPS (AIMS, SAS, and BARS), injection site assessment by the subject using VAS and by the investigator for pain, redness, induration, and swelling; AEs, clinical laboratory tests, vital signs, body height and weight, BMI, ECG, physical examination, urine pregnancy test for WOCBP, and concomitant medications.	(−2/+10 days) will be performed and will include the following assessments: C-SSRS, AEs, concomitant medications, a urine pregnancy test for WOCBP, CGI-S, vital signs, and EPS assessments (AIMS, BARS, SAS), clinical laboratory tests, and body height and weight.
3.6.1.7 30-Day Post Treatment Follow-up Phone Call	A 30-Day Post Treatment Follow-up phone call will be performed 30 days (± 3 days) after it has been determined that the subject will no longer participate in this study and include the recording of AEs that have occurred and any concomitant medications taken since the last visit.	A 30-Day Post Treatment Follow-up phone call will be performed 30 days (± 3 days) after it has been determined that the subject will no longer participate in this study and will include the recording of AEs that have occurred since the last visit and any concomitant medications taken since the last visit.
3.6.3.2 Clinical Laboratory Assessments	A central laboratory designated by the sponsor will be used for all laboratory testing required during the study. The central laboratory should be used for all laboratory testing whenever possible (including unscheduled and follow-up labs, if needed). Reports from the central laboratory should be filed with the source documents for each subject. The central laboratory will provide laboratory results to the sponsor electronically. Samples for serum chemistry, hematology, and urinalysis will be obtained once every 12 months and at the Study Completion visit or the Early Termination visit as specified in Table 3.6-1. Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. Subjects should be fasting for a minimum of 10 hours prior to any blood draws for assessment of safety, including baseline. If a nonfasting blood sample is initially obtained and the test results possibly impacted, a fasting blood sample should be drawn shortly afterwards and the affected lab test(s) repeated. The laboratory tests to be evaluated in this trial are listed in Table 3.6.3.2-1. To better understand	A central laboratory designated by the sponsor will be used for all laboratory testing required. Reports from the central laboratory should be filed with the source documents for each subject. The central laboratory will provide laboratory results to the sponsor electronically. Samples for serum chemistry, hematology, and urinalysis will be obtained at baseline, every 12 months (study months are every 4 weeks which is defined as 28 [−2/+10] days), and at Study Completion or the Early Termination visit as specified in Table 3.6-1. Urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment. Subjects should be fasting for a minimum of 10 hours prior to any blood draws for assessment of safety, including baseline. If a nonfasting blood sample is initially obtained and the test results possibly impacted, a fasting blood sample should be drawn shortly afterwards and the affected lab test(s) repeated. The laboratory tests to be evaluated in this trial are listed in Table 3.6.3.2-1. For Study 270, a urine pregnancy test will be performed at

Protocol 31-10-270

Location	Old Text	Updated Text
	the risk of diabetes mellitus in this subject population, hemoglobin A1c will be measured only if fasting glucose is ≥ 125 mg/dL and/or the urinalysis is positive for glucose. For Study 270, a urine pregnancy test will be performed at baseline and every 3 months for all WOCBP (see Section 5.4 for the definition of WOCBP) to confirm that the subject is not pregnant. Any positive urine pregnancy test result will be confirmed by a serum test. ... 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.	baseline, every 3 months, at Study Completion or the Early Termination visit, and at any time at the discretion of the investigator when pregnancy is suspected for all WOCBP (see Section 5.4 for the definition of WOCBP) to confirm that the subject is not pregnant. Any positive urine pregnancy test result will be confirmed by a serum test. ... Any baseline 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.
Table 3.6.3.2-1 Baseline Clinical Laboratory Assessments, Footnotes	a A urine pregnancy test will be performed at baseline for all WOCBP (see Section 5.4 for the definition of WOCBP) to assess eligibility for the study and will be repeated every 3 months throughout the trial. All positive urine pregnancy test results must be confirmed by a serum test. b To better understand the risk of diabetes mellitus in this subject population, hemoglobin A1c will be measured if the subject's fasting glucose is ≥ 125 mg/dL and/or the urinalysis is positive for glucose.	a A urine pregnancy test will be performed at baseline for all WOCBP (see Section 5.4 for the definition of WOCBP) to assess eligibility for the study and will be repeated every 3 months throughout the trial, at Study Completion or the Early Termination visit, and at any time at the discretion of the investigator when pregnancy is suspected. All positive urine pregnancy test results must be confirmed by a serum test. b At the discretion of the investigator, hemoglobin A1c will be measured if the subject's fasting glucose is ≥ 125 mg/dL and/or the urinalysis is positive for glucose.
3.6.3.3.1 Physical Examination	A complete physical examination, including height, will be performed at baseline. The physical examination will be repeated once every 12 months and at the Study Completion visit or the Early Termination visit (as designated in Table 3.6-1). ... Any condition present at the post-treatment physical exam that was not present at the baseline exam should be documented as an AE and followed to a satisfactory conclusion. A full physical exam will be performed with the exception of the genitourinary (GU) body system. It will be	A complete physical examination, including height, will be performed at baseline. The physical examination may be repeated at the discretion of the investigator at any subsequent visit. ... Any condition present at subsequent physical exams that was not present at the baseline exam should be documented as an AE and followed to a satisfactory conclusion.

Protocol 31-10-270

Location	Old Text	Updated Text
	mandatory that there is a baseline GU exam, which can have been performed up to 1 calendar year prior to the date of the ICF being signed; the subject must provide a copy of the progress note/details of the exam as the source. If no records of such prior GU exam are provided, a GU exam will be done as part of the baseline physical exam by a qualified practitioner listed on the FDA Form 1572. Postbaseline, a GU exam will be required annually, by either the subject's private practitioner (provision of a copy of the documented results of the exam is mandatory) or by a qualified practitioner on the 1572. Medically relevant questions about the GU body system should be asked of the subject at all protocol-required physical exams, with answers recorded accordingly in the source documentation. Any documentation received from an exam performed by a practitioner not on the 1572 form should be reviewed by the investigator or a medically qualified subinvestigator, and a note should be written by this investigator or subinvestigator confirming the review and documenting any necessary follow-up in their opinion.	
3.6.3.3.2 Vital Signs	Vital sign measurements will be performed at baseline and every 3 months (study months are every 4 weeks which is defined as 28 [-2/+10] days) and include body temperature, systolic and diastolic blood pressure, and heart rate.	Vital sign measurements will be performed at baseline, every 6 months (study months are every 4 weeks which is defined as 28 [−2/+10] days), and at Study Completion or the Early Termination visit, and will include body temperature, systolic and diastolic blood pressure, and heart rate.
3.6.3.3.3 Body Height and Weight and Body Mass Index	Body height and weight will be measured at baseline prior to the first dose of aripiprazole IM Depot and every 12 months (study months are every 4 weeks which is defined as 28 [-2/+10] days) and at the Study Completion visit or the Early Termination visit. ... ... If a noticeable fluctuation in body weight has occurred during the study, at the investigator's discretion, body height and weight can be remeasured and BMI recalculated and used for the next aripiprazole IM Depot injection.	Body height and weight will be measured at baseline prior to the first dose of aripiprazole IM Depot, every 12 months (study months are every 4 weeks which is defined as 28 [−2/+10] days), and at Study Completion or the Early Termination visit. ... ... If a noticeable fluctuation in body weight has occurred during the study, at the investigator's discretion, body height and weight can be remeasured and BMI recalculated and used for the next aripiprazole IM Depot injection. BMI may be calculated at subsequent visits at the discretion of the

Protocol 31-10-270

Location	Old Text	Updated Text
		investigator. Body height and weight (not BMI) will be reassessed annually and at any study visit at the discretion of the investigator.
3.6.3.3.4 Waist Circumference	Waist circumference will be measured at baseline and every 12 months (study months are every 4 weeks which is defined as 28 [-2/+10] days).	Waist circumference will be measured at baseline and every 12 months (study months are every 4 weeks which is defined as 28 [−2/+10] days), or at other visits at the discretion of the investigator.
3.6.3.4 ECG Assessments	Twelve-lead ECGs will be recorded at baseline and every 12 months (study months are every 4 weeks which is defined as 28 [-2/+10] days) and at the Study Completion visit or the Early Termination visit as specified in Table 3.6-1. The ECG criteria for baseline ECG for Study 270 (which is the Week 52 visit of Study 248) will be done per Study 248 requirements. At baseline, three ECG recordings will be obtained approximately 5 minutes apart. Additional 12 lead ECGs may be obtained at the investigator's discretion and should always be obtained in the event of an early termination. ECGs will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety during the trial. The principal investigator or qualified designee 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. A central ECG service will be utilized for reading all ECGs in order to standardize interpretations for the safety analysis. ... The ECG assessments performed after baseline will be a single ECG, not done in triplicate. Additional ECGs can be done if warranted by a clinically significant finding or abnormality, an error, or as deemed necessary by the investigator.	Twelve-lead ECGs will be recorded at baseline and at the discretion of the investigator. The ECG criteria for baseline ECG for Study 270 (which is the Week 52 visit of Study 248) will be done per Study 248 requirements. At baseline, three ECG recordings will be obtained approximately 5 minutes apart. All ECGs will be evaluated at the investigational site to determine the subject's eligibility. The principal investigator or qualified designee will review, sign, and date each ECG reading obtained, 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. As of Amendment 4, ECG results will not be obtained centrally after the baseline assessment. Any subsequent ECG assessments will be obtained locally at the discretion of the investigator.
3.6.3.5 Extrapyramidal Symptoms	(All text here is new)	Extrapyramidal symptoms are assessed at baseline, every 6 months (study months are every 4 weeks which is defined as 28 [−2/+10] days), and at Study Completion or the Early Termination visit. The EPS symptoms may also be

Protocol 31-10-270

Location	Old Text	Updated Text
		reassessed at the discretion of the investigator using the instruments described in Section 3.6.3.5.1, Section 3.6.3.5.2, and Section 3.6.3.5.3.
3.6.3.6 Suicidality	Suicidality will be monitored throughout the study (from Study Month 1 through Study Completion or the Early Termination visit, if the subject discontinues the study before completion) using the C-SSRS at every visit. ... A baseline C-SSRS will be completed at baseline. The C-SSRS Since Last Visit form will be completed at all subsequent visits.	Suicidality will be monitored using the C-SSRS at baseline, every subsequent monthly visit, and at Study Completion or the Early Termination visit. ... A baseline C-SSRS will be completed and a C-SSRS Since Last Visit form will be completed at all designated visits.
3.6.3.7 Injection Site Evaluation	Injection site reaction will be assessed by the investigator (or qualified designee) and the subject in a manner similar to that used for the evaluation of other IM depot compounds.[5,32] Investigators (or qualified designees) will rate localized pain, redness, swelling, and induration at the most recent injection site using a 4-point categorical scale ranging from absent to severe (Appendix 12). The subject will indicate the degree of pain at the most recent injection site using a VAS (Appendix 11). Ratings will range from 0 (no pain) to 100 (unbearably painful). These assessments will occur at baseline, every 6 months, and at the Study Completion visit or the Early Termination visit. These assessments will be completed both pre- and post-injection. The investigator's rating of the most recent injection site (ie, the site of the last injection given) and the subject-rated VAS pertaining to this location will be completed after all other study assessments, and within 30 minutes prior to the IM depot injection	Injection site reaction will be assessed at baseline and at the discretion of the investigator (or qualified designee) and the subject at any subsequent study visit in a manner similar to that used for the evaluation of other IM depot compounds.[5,32] Investigators (or qualified designees) at baseline will rate localized pain, redness, swelling, and induration at the most recent injection site using a 4-point categorical scale ranging from absent to severe (Appendix 12). The subject will indicate the degree of pain at the most recent injection site using a VAS (Appendix 11). Ratings will range from 0 (no pain) to 100 (unbearably painful). If required, these assessments will be completed both pre- and post-injection, after all other study assessments, and within 30 minutes prior to the IM depot injection. ... As of Amendment 4, VAS and injection site assessments are no longer required at any post-baseline study visits.
3.7.1 Entire Trial of Treatment Arm(s)	The sponsor will terminate the study in countries where aripiprazole IM Depot becomes commercially available [including generic formulation(s)], the commercial availability of aripiprazole IM Depot is terminated by the sponsor, or if the study end date of 31 December 2018 is reached.	The sponsor will terminate the study in countries where aripiprazole IM Depot becomes commercially available (including generic formulation[s]), the commercial availability of aripiprazole IM Depot is terminated by the sponsor, or if the study end date of 31 Dec 2018 is reached. If the sponsor terminates the study prior to 31 Dec 2018 for any reason other than commercial availability, investigators

Location	Old Text	Updated Text
		in some countries where the sponsor has limited or delayed commercialization plans, or where no commercialization activity is anticipated, may be eligible to participate in a managed access program until aripiprazole IM Depot is commercially available in their country or until 31 Dec 2018. Availability and requirements of such a program varies by jurisdiction, and would only be an option for subjects who were receiving aripiprazole IM Depot in the current study, and who in the physician's opinion, may benefit from continued treatment with aripiprazole. To gain access to aripiprazole IM Depot for eligible subjects via a managed access program, each physician will be responsible for gaining appropriate local regulatory approvals, which will be granted by authorities on a case-by-case basis. The sponsor makes no guarantee that such a program is available or approvable in all of the jurisdictions where the study is conducted.
3.9 Definition of Completed Subjects	... For purposes of this trial, subjects who discontinue due to the commercial availability of study drug in the country where the study is being conducted will be defined as completers. Protocol-specified post-treatment follow-up contacts will not qualify as "last scheduled" visit.	... For purposes of this trial, subjects who discontinue due to the commercial availability of study drug in the country where the study is being conducted will be defined as completers. In addition, subjects in countries where a managed access program is available for continued treatment with aripiprazole at the time of trial closure in their respective country, regardless of whether they transition to a managed access program, will also be defined as completers. Protocol-specified post-treatment follow-up contacts will not qualify as "last scheduled" visit.
5.4 Pregnancy	Unless the subject and his/her partner(s) are sterile (ie, women who have had an oophorectomy and/or hysterectomy or have been postmenopausal for at least 12 consecutive months; or men who have had orchidectomy) or remain abstinent, two of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, IUD, birth control pills, birth control implant, condom, or sponge with spermicide.	Unless the subject and his/her partner(s) are sterile (ie, women who have had an oophorectomy and/or hysterectomy or have been postmenopausal for at least 12 consecutive months; or men who have had orchidectomy) or remain abstinent, two of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, IUD, birth control pills, birth control implant, condom with spermicide, or sponge with spermicide.
14 References	9 Aripiprazole Investigator Brochure, Version No. 13,	9 Aripiprazole Investigator's Brochure, edition 18.1. Otsuka

Protocol 31-10-270

Location	Old Text	Updated Text
	BMS Document Control V.15.0 No. 920002092 11.0. 04 Aug 2009. 27 International Conference on Harmonisation (ICH). E6: Good Clinical Practice: Consolidated Guideline [finalized 1996 May, corrected 1996 Jun 1996; cited 2005 Dec 6]. Available from: http://www.ich.org/cache/compo/276-254-1.html.	IB, issued 18 Nov 2014. 27 International Conference on Harmonisation (ICH). E6: Good Clinical Practice: Consolidated Guideline [finalized 01 May 1996, corrected 10 Jun 1996; cited 06 Dec 2005]. Available from: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

Protocol 31-10-270

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 Trial 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) or receive a favorable opinion by the Independent Ethics Committee (IEC) 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- or IEC-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 and/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/IEC approval before implementation of any substantial 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/IEC within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB/IEC 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 involves 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
_____	_____	_____
Sponsor Representative Print Name	Signature	Date

Otsuka Pharmaceutical Development & Commercialization, Inc.
This page is a manifestation of an electronically captured signature

OPC-14597

SIGNATURE PAGE

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