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ARIPIPRAZOLE, ABILIFY MAINTENA®
CLINICAL STUDY REPORT

An Open-label, Multi-center, Longitudinal, Within-subject Comparison Study to Evaluate the Effects of Aripiprazole Once Monthly in Subjects with Schizophrenia on 30-, 90- and 180-day Re-hospitalization Rates Following Hospital Discharge Compared with Retrospective Re-hospitalization Rates while on Oral Antipsychotic Medication

Collaborative Protocol No. 031-104-0014

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CONFIDENTIAL – PROPRIETARY INFORMATION

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2 SYNOPSIS

Name of Sponsor: JohnW. Newcomer, M.D. at Florida Atlantic University **Name of Product:** Abilify Maintena®, aripiprazole	
Protocol Title:	An Open-label, Multi-center, Longitudinal, Within-subject Comparison Study to Evaluate the Effects of Aripiprazole Once Monthly in Subjects with Schizophrenia on 30-, 90-, and 180-day Re-hospitalization Rates Following Hospital Discharge Compared with Retrospective Re-hospitalization Rates while on Oral Antipsychotic Medication
Treatment Indication:	Schizophrenia
Objective(s):	The primary objective of the study was: • To evaluate the effect of aripiprazole once monthly on 30-, 90-, and 180-day psychiatric re-hospitalization rates following discharge due to symptoms associated with schizophrenia, compared with prior 30-, 90-, and 180-day psychiatric hospitalization rates in subjects previously treated with oral antipsychotic medication. The secondary objectives of the study were: Efficacy: • To evaluate the effect of aripiprazole once monthly on: o 30-, 90-, and 180-day rates of unscheduled psychiatric emergency department (ED) visits compared with prior 30-, 90-, and 180-day unscheduled visits o Psychiatric ED visits plus hospitalizations compared with prior 30-, 90-, and 180-day psychiatric visits plus hospitalizations o Total psychiatric hospitalization days over the 180-day study period compared with the total psychiatric hospitalization days over the prior 180-day period o Change from baseline in Clinical Global Impression–Severity (CGI-S) and Clinical Global Impression–Improvement (CGI-I) scores at 30-, 90-, and 180- days • To evaluate changes from baseline for the following indicators for cardiometabolic risk (CMR): o Weight and body mass index (BMI) o Fasting glucose concentrations o Glycosylated hemoglobin (HbA1c) concentrations o Fasting plasma lipid concentrations (i.e., fasting triglycerides [primary analysis], total cholesterol, high-density lipoprotein [HDL], and low-density lipoprotein [LDL]) The exploratory objectives of the study are: Safety: • To evaluate changes from baseline to 180 days in: o Adverse events (AEs) o Clinical laboratory tests (i.e., hematology, fasting clinical chemistry, prolactin, and urinalysis) o Vital signs

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Objectives continued:	○ Personal and Social Performance Scale (PSP) ○ Injection site reactions (i.e., localized pain, redness, swelling, and induration) ○ Extrapyramidal side effects (EPS): ▪ Abnormal Involuntary Movement Scale (AIMS) ▪ Simpson-Angus Scale (SAS) ▪ Barnes Akathisia Rating Scale (BARS) ○ Columbia Suicide Severity Rating Scale (C-SSRS) for suicidality
Study Design:	This was an open-label, multi-center, longitudinal, within-subject comparison study of the effects of aripiprazole once monthly on 30-, 90-, and 180-day psychiatric re-hospitalization rates following hospital discharge in subjects with schizophrenia compared with prior psychiatric hospitalization rates while on oral antipsychotics. Prospective subjects underwent screening for eligibility for entry into the study during or immediately after hospitalization for symptoms due to schizophrenia. Prospective subjects were hospitalized for the necessary length of time as determined by the assigned treatment provider as clinically indicated, per the current standard of care. To be eligible, the anticipated duration of hospitalization was to be long enough to accommodate the screening procedures, the 3-day Oral Tolerability Phase (if applicable), and initiation of treatment with aripiprazole once monthly. During the Screening Period, subjects could be treated with any oral antipsychotic medication of the clinician's choice, with the exception of clozapine. However, oral olanzapine was permitted, during the Screening Period only, for subjects who were eligible for Phase A. Following the Screening Period, subjects who had no history of aripiprazole use were entered into Phase A, the Oral Tolerability Phase. Subjects from Phase A that demonstrated tolerability to aripiprazole were then entered into Phase B (i.e., the Treatment Phase, where all subjects were treated with long-acting injectable aripiprazole). Subjects who already had a history of tolerating at least three consecutive oral doses of aripiprazole were entered directly into Phase B. All eligible subjects would eventually enter Phase B. Subjects may also have entered the study if they were clinically started on long-acting injectable aripiprazole during the hospitalization just prior to study entry. Subjects who met the inclusion and exclusion criteria and had no history of oral aripiprazole use entered Phase A after the Screening Period while still hospitalized. Subjects in Phase A were administered oral aripiprazole, as indicated in the product labeling, to determine tolerability. Dosage was based on symptoms and the judgment of the investigator. The dose of oral aripiprazole could be titrated as needed. Prior antipsychotic medications were tapered off and discontinued during the Screening Period and Phase A as clinically appropriate.

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Study Design continued:	During Phase A, tolerability to oral aripiprazole was evaluated daily (using clinical judgment) for a minimum of 3 days with baseline safety and tolerability measures (i.e., AIMS, BARS, and SAS) either during or closely following completion of oral treatment. If the subject showed tolerability to the oral aripiprazole, the Phase B baseline/Day 1 was to occur with the first aripiprazole once monthly injection. If a subject was unable to tolerate oral aripiprazole during the tolerability assessment in Phase A, he or she was withdrawn from the study. Subjects could have their baseline assessments performed any time during or immediately after treatment with oral antipsychotic aripiprazole (unless eligible to skip Phase A in which it is any oral antipsychotic), ideally prior to starting long-acting injectable aripiprazole. Participants were allowed, with Principal Investigator approval, to enter the study after starting treatment with long-acting injectable aripirazole in the hospital and baseline assessments were performed as soon as feasible. During Phase B, the subject received the first aripiprazole once monthly intramuscular (IM) injection, in conjunction with the first of 14 doses of concomitant oral aripiprazole, as indicated in the product labeling, after the baseline data were collected. In cases where subjects were enrolled after starting long-acting injectable aripiprazole in the hospital, baseline data were collected no later than 48 hours after hospital discharge whenever possible and with Principal Investigator approval. All subjects were required to attend scheduled visits at the Baseline Visit and Weeks 2, 4, 8, 12, 16, 20, and 24, totaling 180 days. Aripiprazole once monthly injections occurred at the Baseline Visit and every 28 (-2, + 5) days at Weeks 4, 8, 12, 16, 20, and 24, totaling seven injections. After the initial injection of 400 mg, the monthly dosage could be decreased to 300 mg, based on the clinical judgment of the investigator. All aripiprazole once monthly injections were administered based on the investigator's judgment and the prescribing information. For subjects who entered the studies after starting the first dose of long-acting injectable aripiprazole in the hospital, if the initial injection was not 400 mg, the second injection should have been 400 mg, and thereafter, the monthly dose could be decreased to 300 mg, based on clinical judgment of the investigator. For subjects who were psychiatrically stabilized and discharged prior to the completion of the required 14-day course of oral aripiprazole, a pre-discharge assignment was given to a community support worker (CSW) or Study Coordinator (SC). The CSW/SC maintained regular contact with the subject until the first outpatient visit in Phase B (Week 2), when oral aripiprazole was discontinued. Regular contact was defined as no less than weekly, but could be more frequent depending on the clinical judgment of the CSW/SC and outpatient treatment team. Following the Week 2 Visit, subjects had contact with their assigned CSW/SC based on routine clinical care. Contact with the CSW/SC could be in person or by telephone, as clinically appropriate. Note: All long-acting antipsychotics were excluded from use during the study; however, aripiprazole once monthly was allowed (See Table 1 for more information about Prohibited and Restricted Medications).

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Subject Population:	**Planned:** Approximately 177 subjects were planned to be enrolled competitively between each of four designated clinical sites across the state of Missouri to reach a total of 90 completed subjects. This was to account for an expected 40% screen failure rate and an additional 40% drop-out rate. Subjects served as their own controls. Prospective subjects were to be recruited from one of four established clinical sites at four inpatient hospitals associated with outpatient community mental health centers in Missouri: Washington University in St. Louis, University of Missouri, Columbia, MO; University of Missouri, Kansas City, MO; and Burrell Behavioral Health in Springfield, MO. **Actual:** A total of 9 subjects were recruited from a total of two of three active clinical sites. Burrell Behavioral Health in Springfield, MO never joined the study and did not screen or enroll any subjects. Subjects who did not meet all of the inclusion criteria or who met any of the exclusion criteria were not eligible to receive study drug.
Study Drug, Dose, Formulation, Mode of Administration:	• Aripiprazole, administered once monthly via gluteal or deltoid IM injection, as outlined in the product labeling • Oral aripiprazole o Subjects in Phase A were administered oral aripiprazole to determine tolerability, based on the prescribing information • Aripiprazole, both oral and once monthly was administered or prescribed as outlined in the product labeling
Results:	**Efficacy:** Due to low enrollment, no analysis of the primary or secondary outcome variables were possible. **Safety:** Due to low enrollment and subject discontinuations, no analysis of safety was performed. All available safety data are provided.
Statistical Methods:	**Planned:** For the primary outcome, 30-, 90-, and 180-day re-hospitalization rates following aripiprazole once monthly IM injections were to be compared with prior 30-, 90-, and 180-day hospitalization rates in subjects previously treated with oral antipsychotic medication. Descriptive statistics were to be provided for all efficacy variables and safety variables. Continuous variables, including fasting laboratory values, were to be summarized by tabulations of mean, median, range, and standard deviation using change from baseline to 30-, 90-, and 180-day values. Tabulations of frequency distributions were provided for categorical variables. The primary and secondary outcomes were to be analyzed using repeated measures analysis of covariance models. **Actual:** No statistical analyses were performed
Study Duration:	**Planned:** An approximate 6-month duration per subject was expected. Subject recruitment was estimated at 18 months with a 180-day treatment period followed by a 30-day follow-up period. Total study duration was expected to be approximately 2.5 years, allowing an additional 6 months for data analysis and manuscript preparation. **Actual:** First patient, first visit: June 2016; Last patient last visit May 2017. Study was terminated due to slow enrollment.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
AST	aspartate transaminase
BARS	Barnes Akathisia Rating Scale
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CGI-I	Clinical Global Impression–Improvement
CGI-S	Clinical Global Impression–Severity
CFR	Code of Federal Regulations
CMR	cardiometabolic risk
CMS	Centers for Medicare and Medicaid Services
CNS	central nervous system
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
CSW	community support worker
CV	curriculum vitae
CYP	cytochrome P450
DMH	Missouri Department of Mental Health
DSM-5	Diagnostic and Statistical Manual, Fifth Edition
ECG	electrocardiogram
ED	emergency department
EEG	electroencephalogrsm
EPS	extrapyramidal side effects
EU	European Union
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
HbA1c	glycosylated hemoglobin
HDL	high-density lipoprotein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IM	intramuscular
IRB	institutional review board
ITT	intent-to-treat
LAI	long-acting injectable

LDL	low-density lipoprotein
MCHC	mean corpuscular hemoglobin concentration
LNH	low/normal/high
LOCF	last observation carried forward
MAOI	monoamine oxidase inhibitor
MCV	mean corpuscular volume
MIMH	Missouri Institute of Mental Health
MO	Missouri
OAPI	Otsuka America Pharmaceutical, Inc.
OC	observed case
OPC	Otsuka Pharmaceutical Company, Ltd.
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
PANSS	Positive and Negative Syndrome Scale
PK	pharmacokinetic
PQC	product quality complaint
PSP	Personal and Social Performance Scale
PT	preferred term
QT	interval from beginning of the QRS complex to end of the T wave in the frontal plane
QTc	corrected QT interval
RBC	red blood cell
REALM-SF	Rapid Estimate of Adult Literacy in Medicine-Short Form
SAE	serious adverse event
SC	Study Coordinator
RSRR	risk-standardized readmission rate
SAS	Simpson Angus Scale
SD	standard deviation
SOC	standard of care
TEAE	treatment-emergent adverse event
UBACC	University of California, San Diego Brief Assessment of Capacity to Consent
ULN	upper limit of normal
US	United States
WBC	white blood cell

5 ETHICS

This study was conducted in compliance with the protocol, United States (US) Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and all other applicable local laws and regulatory requirements. Each study sought approval by an institutional review board (IRB) according to regional requirements. The IRB evaluated the ethical, scientific, and medical appropriateness of the study. Further, in preparing and handling case report forms (CRFs), the investigator, sub-investigator and their staff took measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject identification code was used to identify each subject.

5.1 INFORMED CONSENT

All subjects had the purpose of the study, study interventions and evaluations, and the potential risks and benefits of participation explained to them and any questions were answered. If a subject agreed to participate in the study, the subject reviewed and signed the informed consent form (ICF).

Written informed consent was obtained from all subjects (or their guardian or legal representative, as applicable for local laws). Consent was documented on a written ICF. The ICF was approved by the same IRB that approved the protocol. Each ICF complied with the FDA regulations in Title 21 Code of Federal Regulations (CFR) Part 50 ICH, GCP, and local regulatory requirements. The investigator agreed to obtain approval from the sponsor for any written ICF used in the study, prior to submission to the IRB.

Investigators could discuss study availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must have been obtained and documented prior to initiation of any procedures that were performed solely for the purpose of determining eligibility for this study, including withdrawal from current medication(s).

Once appropriate essential information was provided and fully explained in layman's language to the subject by the investigator, or a qualified designee, the IRB-approved written ICF was signed and dated by both the subject and the person obtaining consent (i.e., investigator or designee), as well as by any other parties required by the IRB. The subject received a copy of the signed informed consent form; the original was kept on file by the investigator.

6 INVESTIGATORS AND STUDY PERSONNEL

This was a collaboratively designed, investigator-sponsored study that was conducted at four centers in the US.

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7 INTRODUCTION

The prevalence of long-acting injectable (LAI) antipsychotic agent use for the treatment of schizophrenia, especially for early-onset or first-episode patients, remains at or below 30% in most developed countries[1-3]. Remarkably, even when identified as treatment non-adherent, less than a third of schizophrenia patients are prescribed LAI antipsychotics in the US[4]. In general, antipsychotic treatment non-adherence is common in patients with schizophrenia[5,6], and is associated with costly acute psychiatric care including emergency room visits and inpatient hospitalization[7]. Non-pharmacologic efforts to improve treatment adherence include patient-provider agreements[8] and enhanced outpatient case management services, including compulsory care[9]. However, these approaches tend to be only modestly effective at improving treatment adherence. The use of LAIs in this patient population is associated with decreased rates of symptomatic relapse, better long-term symptom management and improvement in functional outcomes[10]. These clinical advantages lead to potential advantages in cost-effectiveness over oral antipsychotic treatment[11].

Efforts to promote the use of evidence-based treatments that improve clinical outcomes and contain healthcare costs, especially in chronic medical and psychiatric illnesses, have been a major focus of health care quality improvement initiatives. The Centers for Medicare and Medicaid Services (CMS) has focused interest on 30-day hospital readmission rates as an indicator of cost-effective health care delivery. In October 2012, CMS established the Accountable Care Organization[12] with a plan to assess the risk-standardized readmission rate (RSRR) of all conditions, with a specific goal of lowering RSRR scores in hospitals by increasing quality of health care and decreasing need for rehospitalization[13]. For repeated hospital readmissions within 30 days, hospitals can incur adjustment in Medicare readmission payments of up to 1% reduction in payment in 2013[14]. The Federal Register (May 2012) estimated that the Hospital Readmissions Reduction Program will result in a 0.3% decrease, or approximately $300 million reduction, in payments to hospitals in 2013[15]. Nationally, it is estimated that hospitals may lose approximately a minimum of $150,000 to a maximum of $3.9 million in 2013[16]. Medicare 2013 readmission reports for 76 hospitals in Missouri to date indicate that 72% of hospitals were required to forfeit an average of 0.47% of their total Medicare reimbursements, while only 28% of hospitals had no reported readmission penalties[17].

In patients with severe illnesses such as schizophrenia, the risk for relapse and re-hospitalization is substantially increased following hospitalizations for acute exacerbation, in part due to limited access to outpatient mental health services to assist with adherence to oral antipsychotic medication. Non-adherence to antipsychotic medication is a well-established risk factor for symptomatic relapse. LAI antipsychotics can improve treatment adherence, but there has been no study to our knowledge of the effect of LAI antipsychotics on the policy- and cost-relevant endpoint of 30-day hospital readmission rates.

Abilify Maintena®, approved by FDA for the treatment of schizophrenia on 28 February 2013, is now available to prescribers. Given high interest from clinicians, policy-makers, and healthcare administrators on the effect of new medications on cost-effective health care delivery, we proposed to study the impact of this new LAI on hospital readmission rates in the high-cost population of patients with schizophrenia who use hospital services.

7.1 ABILIFY® (ARIPIPRAZOLE)

Aripiprazole (ABILIFY®) is a dopamine partial agonist discovered by Otsuka Pharmaceutical Company, Ltd. (OPC) and co-developed by Bristol-Myers Squibb and OPC. OPC and H. Lundbeck A/S are jointly developing the intramuscular (IM) injection formulation of aripiprazole. Aripiprazole oral tablets are approved in the 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 major depressive disorder. 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 injection formulation is approved for agitation in schizophrenia and bipolar mania in the US and EU. In addition, an oral solution formulation and orally disintegrating (i.e., 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 extrapyramidal side effects (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 injection formulation. The aripiprazole once monthly formulation was recently approved for treatment of schizophrenia in the US.

A brief summary of nonclinical and clinical data is included below.

7.2 RELEVANT NONCLINICAL STUDIES

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 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 D3 and 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, and 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 subjects with schizophrenia. It seems likely that the favorable safety and tolerability profile of aripiprazole, including its low incidence of EPS, lack of prolactin elevation, decreased adrenergic and anticholinergic side effects, and decreased weight gain, is also mediated by its unique profile of interaction with central neuroreceptors. Please refer to the Investigator's Brochure (IB)[18] for information regarding nonclinical toxicity and pharmacokinetic (PK) studies conducted using aripiprazole in animals.

7.3 RELEVANT CLINICAL STUDIES

7.3.1 Schizophrenia Studies with Oral Aripiprazole

A comprehensive clinical program to evaluate the effectiveness of oral aripiprazole monotherapy 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.

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 studies established the efficacy of aripiprazole 10, 15, 20, and 30 mg for the treatment of acute relapse of schizophrenia or schizoaffective disorder. The two 4-week studies (31-97-201 and 31-97-202)[19,20] each included two 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 studies indicated that all of the doses of aripiprazole were effective in the treatment of acute psychosis. All aripiprazole doses were statistically significant compared with 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)[21] was 6 weeks in duration and included aripiprazole doses of 10, 15, and 20 mg. All doses of aripiprazole demonstrated significant improvement compared with placebo for mean change from baseline to endpoint 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[22,23] was a 26-week study designed to document the long-term efficacy of aripiprazole 15 mg 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)[24,25] 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 (i.e., 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 for negative symptoms, depressive symptoms, and discontinuation for any reason.

The subject-rated and investigator-rated acceptability of aripiprazole treatment was examined in open-label studies. Subjects treated with open-label 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)[26]. A separate open-label study (CN138152)[27,28] compared aripiprazole 10 to 30 mg daily with standard of care (SOC) treatment with

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, which provides an overall assessment of efficacy and tolerability[29].

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 (QT_C). The recommended starting and target 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 a 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. Additional details of results of clinical studies with aripiprazole in other indications are provided in the IB[18].

7.3.2 Agitation Studies with Injectable Aripiprazole

The efficacy of immediate-release IM aripiprazole for the treatment of agitation was established in three short-term (i.e., 24-hour) placebo-controlled studies[30]. Two studies in agitated inpatients with schizophrenia, schizoaffective disorder, or schizophreniform disorder showed that aripiprazole at doses of 5.25, 9.75, and 15 mg/day was significantly more effective than placebo for controlling agitation, as measured by change from baseline in PANSS Excited Component at 2 hours post-IM injection. A similar result was observed in agitated inpatients with bipolar disorder who received aripiprazole 9.75 mg/day.

7.3.3 Clinical Studies in Schizophrenia with Aripiprazole Once Monthly

Protocol CN138020, a clinical study conducted by Bristol-Myers Squibb, assessed the safety, tolerability, and PK of single doses of the aripiprazole once monthly formulation. This was an open-label, two-phase, nonrandomized, ascending dose, sequential panel study in subjects with a confirmed diagnosis of chronic schizophrenia or schizoaffective disorder. Subjects received a single 5 mg dose of the standard IM formulation followed by safety and PK monitoring. After a minimum 28-day washout, subjects who qualified based on no significant adverse events (AEs) or clinical laboratory abnormalities received a single dose of 15, 50, 100, 200, 300, or 400 mg of aripiprazole once monthly formulation, followed by safety and PK monitoring. The IM formulation appeared to be well tolerated. Peak plasma concentrations in most subjects were observed after approximately 100 hours. Most AEs were mild (43%) to moderate (33%) in severity. The most commonly reported treatment emergent AEs were headache (4 subjects, 19%) and anxiety (3 subjects, 14.3%). All other AEs occurred in ≤ 2 subjects. There were no discontinuations due to AEs and none of the AEs appeared to be dose-related. There were two serious adverse events (SAEs), attempted suicide and exacerbation of schizophrenia, which were considered to be unrelated to study drug.

Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) conducted a Phase 1B study (i.e., Protocol 31-05-244) to assess the safety, tolerability, and PK of multiple doses of the aripiprazole once monthly formulation in subjects with schizophrenia. The results showed that once monthly administration of the 400-mg and 300-mg IM injections resulted in mean

aripiprazole trough and average plasma concentrations that were comparable to the therapeutic concentrations of 10-mg to 30-mg oral aripiprazole administered daily to schizophrenic subjects. All three doses of aripiprazole once monthly (i.e., 200, 300, and 400 mg) demonstrated acceptable safety, tolerability, and potential effectiveness[31].

A Phase 3 study (i.e., Protocol 31-07-246) was conducted to evaluate the efficacy and safety of aripiprazole once monthly compared with placebo in schizophrenic subjects who had maintained stability on aripiprazole once monthly for at least 12 weeks. Aripiprazole once monthly 400- or 300-mg administered as monthly gluteal injections was effective for the maintenance treatment of schizophrenia in adults as demonstrated by a statistically significant difference, compared with placebo, in the primary efficacy endpoint of time to impending relapse. The percentage of subjects who met the criteria for impending relapse was significantly lower in the aripiprazole once monthly group than in the placebo group. The maintenance of stability was also demonstrated by statistically significant differences favoring aripiprazole once monthly in PANSS and CGI scores that remained significant throughout the double-blind, placebo-controlled phase. In addition, the Personal and Social Performance (PSP) Scale total score, cognitive function assessments, and Investigator's Assessment Questionnaire score were supportive of the efficacy of aripiprazole once monthly treatment. Aripiprazole once monthly was well tolerated by adult subjects with schizophrenia as demonstrated by an AE profile similar to placebo. Most treatment-emergent adverse events (TEAEs) were either mild or moderate in severity. The only TEAE reported by ≥ 5% of subjects receiving aripiprazole once monthly and at least twice the incidence of placebo was tremor. The increased rate of tremor over placebo treatment was consistent in studies with oral aripiprazole, as also reported in the aripiprazole product labeling. Generally, AEs of tremor were mild in severity and occurred with a low frequency throughout the study. No report of tremor was classified as a SAE or was associated with discontinuation of treatment. There were no clinically relevant findings with regard to laboratory values, vital signs, weight, electrocardiogram (ECG) findings, EPS, suicidality, or injection site.

7.3.4 Known and Potential Risks and Benefits

As of 10 Jun 2010, 15,088 adult subjects were treated with aripiprazole oral tablet formulation in Phase 2, 3, and 4 studies, representing 8,577 subject-exposure years. Of these, 3,901 (25.9%) subjects were treated with aripiprazole for 180 days or longer; 2,259 (15.0%) subjects received aripiprazole for at least 360 days, with 933 (6.2%) subjects continuing aripiprazole treatment for at least 720 days.

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[23].

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 (ULN) compared with the haloperidol group (61%)[25].

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[32].

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical neuroleptics. 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 neuroleptic 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 neuroleptic 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 neuroleptics 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 neuroleptics are not available.

Elderly patients with dementia-related psychosis treated with atypical neuroleptic 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 (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Overall, 1.3% of aripiprazole-treated subjects reported cerebrovascular AEs (e.g., stroke, transient ischemic attack) compared with 0.6% of placebo-treated subjects in these studies. This difference was not statistically significant. However, in one of these studies, a fixed-dose study, there was a significant dose-response relationship for cerebrovascular AEs in patients 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 changes in vital signs, laboratory assessments, or ECGs. Additional information can be obtained from the ABILIFY US package insert.

7.4 STUDY RATIONALE

Non-adherence to antipsychotic medication is a well-established risk factor for symptomatic relapse. LAI antipsychotics can improve treatment adherence, but at the time of this study there were, to our knowledge, no study on the effect of LAI antipsychotics on the policy- and cost-relevant endpoint of 30-day hospital readmission rates.

The primary hypothesis was that treatment with aripiprazole once monthly would result in lower hospitalization rates for psychiatric symptom recurrence than patients experienced prior to treatment with aripiprazole once monthly.

The secondary hypotheses were that treatment with aripiprazole once monthly would result in fewer unscheduled psychiatric emergency department (ED) visits, ED visits associated with psychiatric hospitalization, and fewer total psychiatric hospitalization days than patients experienced prior to treatment with aripiprazole once monthly. In addition, we hypothesize that clinical functioning, measured by CGI-S and CGI-I scores, and change from baseline in measures of cardiometabolic risk (CMR) such as weight, body mass index (BMI), fasting glucose, and glycosylated hemoglobin (HbA1c) would improve from baseline in patients treated with aripiprazole once monthly that were previously treated with oral antipsychotics.

The study design, following well-characterized subjects for 180 days after starting aripiprazole once monthly treatment, and retrospectively reviewing data regarding prior hospitalizations, psychiatric ED visits, and prior total psychiatric hospitalization days, will allow the proposed hypotheses to be tested.

8 STUDY OBJECTIVES

8.1 PRIMARY OBJECTIVE(S)

The primary objective of the study was:

- To evaluate the effect of aripiprazole once monthly on 30-, 90-, and 180-day psychiatric re-hospitalization rates following discharge due to symptoms associated with schizophrenia, compared with prior 30-, 90-, and 180-day psychiatric hospitalization rates in subjects previously treated with oral antipsychotic medication.

8.2 SECONDARY OBJECTIVE(S)

The secondary objectives of the study were:

Efficacy:

- To evaluate the effect of aripiprazole once monthly on:
  - 30-, 90-, and 180-day rates of unscheduled psychiatric ED visits compared with prior 30-, 90-, and 180-day unscheduled visits
  - Psychiatric ED visits plus hospitalizations compared with prior 30-, 90-, and 180-day psychiatric visits plus hospitalizations
  - Total psychiatric hospitalization days over the 180-day study period compared with the total psychiatric hospitalization days over the prior 180-day period
  - Change from baseline in CGI-S and CGI-I scores at 30-, 90-, and 180-days
- To evaluate changes from baseline for the following indicators for CMR:
  - Weight and BMI
  - Fasting glucose concentrations
  - HbA1c concentrations
  - Fasting plasma lipid concentrations (i.e., fasting triglyceride [primary analysis], total cholesterol, high-density lipoprotein [HDL], and low-density lipoprotein [LDL])

8.3 EXPLORATORY OBJECTIVES

The exploratory objectives of the study were:

Safety:

- To evaluate changes from baseline to 180 days in:
  - AEs
  - Clinical laboratory tests (i.e., hematology, fasting clinical chemistry, prolactin, and urinalysis)

- Vital signs
- PSP
- Injection site reactions (i.e., localized pain, redness, swelling, and induration)
- EPS:
  - Abnormal Involuntary Movement Scale (AIMS)
  - Simpson-Angus Scale (SAS)
  - Barnes Akathisia Rating Scale (BARS)
- Columbia Suicide Severity Rating Scale (C-SSRS) for suicidality

9 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN

This was an open-label, multi-center, longitudinal, within-subject comparison study of the effects of aripiprazole once monthly on 30-, 90-, and 180-day psychiatric re-hospitalization rates following hospital discharge in subjects with schizophrenia compared with prior psychiatric hospitalization rates while on oral antipsychotics.

Prospective subjects underwent screening for eligibility for entry into the study during or immediately after hospitalization for symptoms due to schizophrenia.

An overview of the planned study design is provided in Figure 1.

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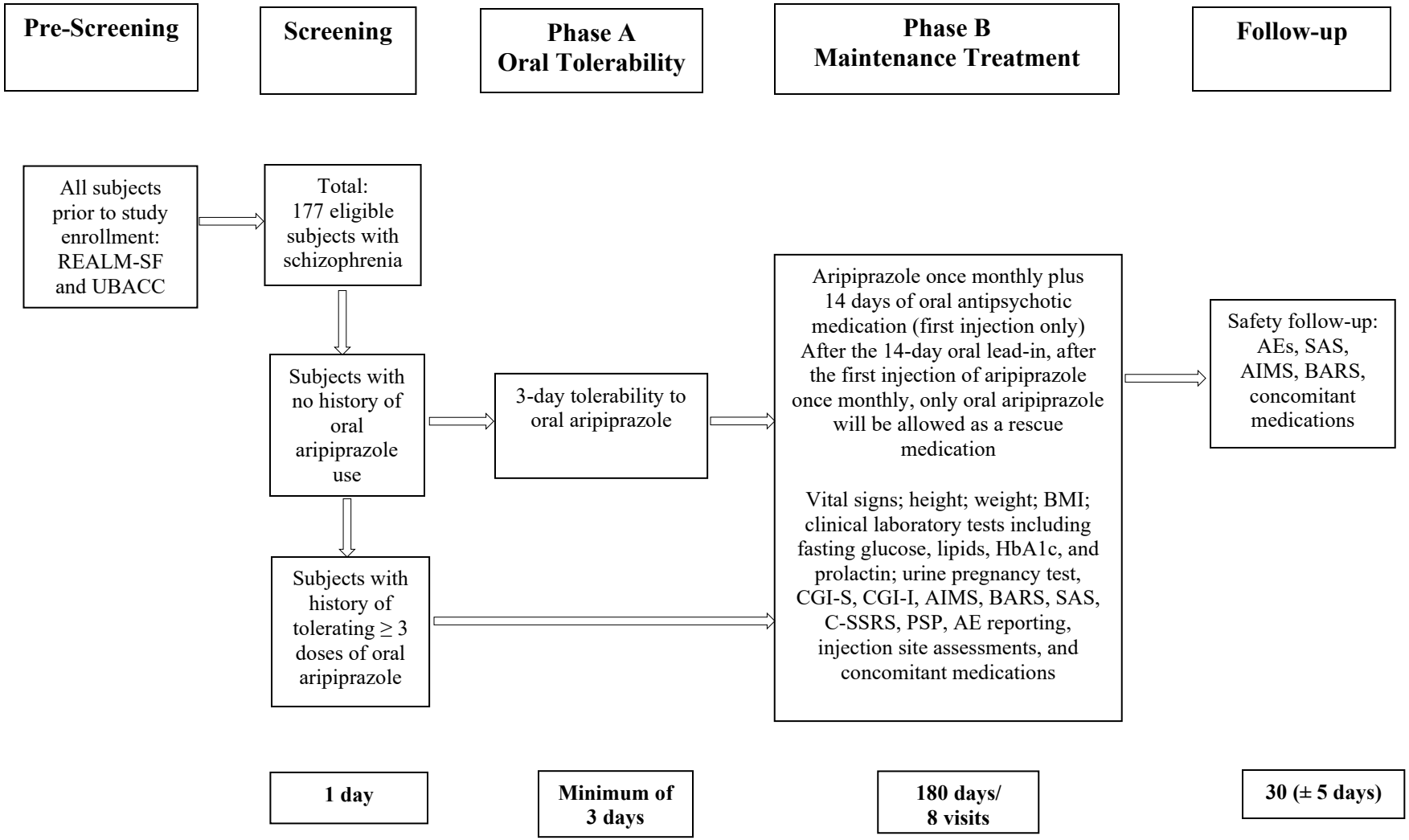

Figure 1 Study Schematic

AE = adverse event, AIMS = Abnormal Involuntary Movement Scale, BARS = Barnes Akathisia Rating Scale, BMI = body mass index, CGI-I = Clinical Global Impression–Improvement, CGI-S = Clinical Global Impression–Severity, C-SSRS = Columbia Suicide Severity Rating Scale, HbA1c = glycosylated hemoglobin, PSP = Personal and Social Performance Scale, REALM-SF = Rapid Estimate of Adult Literacy in Medicine–Short Form, SAS = Simpson Angus Scale, UBACC = University of California, San Diego Brief Assessment of Capacity to Consent

9.1.1 Pre-Screening Assessments

Pre-Screening assessments were conducted to help investigators identify any subjects with literacy or capacity to consent issues prior to study enrollment.

These assessments occurred before the subject entered the Screening Period and gave their written consent via the ICF. Pre-Screening assessments were conducted via the following:

- Rapid Estimate of Adult Literacy in Medicine–Short Form (REALM-SF)
- University of California, San Diego Brief Assessment of Capacity to Consent (UBACC)

9.1.2 Screening Period

All recruitment methods conformed to the guidelines of the IRB at the clinical site. The subjects participating in this study had to be capable of understanding the nature of the study. The ICF contained a full description of the procedures and their associated risks. Subjects were given both verbal and written descriptions of the procedures, discomforts, risks, and potential benefits by study personnel. After briefing subjects on the reasons for the research, their rights as a subject, and the risks involved, they were given the opportunity to ask questions. Subjects were asked to paraphrase the ICF. When ready, subjects were asked to give written consent to participate in the study. After the ICF was signed by both the subject and the investigator, each subject was given a copy of the signed ICF. The investigator had full responsibility for all issues pertaining to assent and informed consent. Procedures to be followed when obtaining informed consent are detailed in Section 5.1.

During the Screening Period, subjects could be treated with any oral antipsychotic medication of the clinician's choice, with the exception of clozapine. However, oral olanzapine was permitted during the Screening Period only for subjects who were eligible for Phase A.

Eligibility for the study was determined during the screening period, which could occur at any time, beginning with the first day of hospitalization. Eligibility for the study was assessed via the following:

- Confirmation of a current diagnosis of schizophrenia according to Diagnostic and Statistical Manual, Fifth Edition (DSM-5) criteria
- Review of inclusion and exclusion criteria
- Complete medical history, including demographics, complete psychiatric history including all psychiatric and non-psychiatric hospitalizations and medical interventions occurring within the 6 months prior to the date of signing the ICF:
    - Data regarding psychiatric and non-psychiatric hospitalizations, including treatment records relevant to determination of study eligibility and identified outcome variables related to ED, outpatient and inpatient treatment episodes as described in the inclusion and exclusion criteria (Section 9.3.1 and Section 9.3.2, respectively) occurring within the 6 months prior to the date of signing the ICF were obtained by searching MO

HealthNet (Medicaid) and Missouri Department of Mental Health (DMH) data via collaboration with the Missouri Institute of Mental Health (MIMH) or confirmed through all available medical records and reliable data from caregivers. Availability of Medicaid data or documentation of at least one inpatient hospitalization, ED visit, or equivalent (i.e., urgent care center) visit within the previous 6 months of screening was required for eligibility (see inclusion and exclusion criteria, Section 9.3).

- Admission vital signs (e.g., blood pressure, heart rate, respiratory rate, and temperature)
- Admission height, weight, and calculation of BMI
- Admission ECG
- Admission HbA1c, if available
- Admission safety clinical laboratory tests (Section 9.5.1.4.1)
- Admission clinical laboratory results were assessed to rule out exclusionary values (Section 9.3)
- Urine pregnancy test for women of childbearing age
- Previous medications taken within 30 days prior to starting study drug were recorded. Concomitant medications including details (e.g., drug name, dose, and frequency) of all current medication(s) and any antipsychotic medications taken within 6 months of screening were recorded.
- The nature of acute hospitalization in this population could indicate prior discontinuation of antipsychotic medications due to noncompliance. Appropriate review of all medications for psychiatric illness, including newly prescribed antipsychotic medication was conducted during screening. Discontinuation or tapering of any psychotropic medication, if deemed clinically appropriate or necessary for those subjects entering Phase A (i.e., Oral Tolerability Phase), started at screening and continued during Phase A.
- Additional clinical laboratory tests (fasting or non-fasting as needed) which were not obtained at admission, were deemed necessary by the PI and/or were required to verify inclusion and exclusion criteria

Fasting or non-fasting clinical laboratory tests that were required to establish eligibility could be performed at any time during the Screening Period. Study specific clinical laboratory tests that required fasting (i.e., fasting lipid profile and fasting glucose) were performed during the Baseline Visit.

Prospective subjects were hospitalized for the necessary length of time as determined by the assigned treatment provider as clinically indicated, per the current SOC. To be eligible, the anticipated duration of hospitalization was to be long enough to accommodate the screening procedures, the 3-day Oral Tolerability Phase (if applicable), and initiation of treatment with

aripiprazole once monthly. However, some subjects could also enter the study if they were clinically started on long-acting injectable aripiprazole during the hospitalization just prior to study entry.

Following the Screening Period, subjects who had no history of aripiprazole use were entered into Phase A, the Oral Tolerability Phase. Subjects from Phase A that demonstrated tolerability to aripiprazole were then entered into Phase B, the Treatment Phase, where all subjects were treated with long-acting injectable aripiprazole. Subjects who already had a history of tolerating at least three consecutive oral doses of aripiprazole were entered directly into Phase B. All eligible subjects eventually entered Phase B.

9.1.3 Phase A – Oral Tolerability Phase

The Oral Tolerability Phase lasted for a minimum of 3 days. Subjects with a history of tolerating aripiprazole (e.g., a history of at least 3 days of oral exposure) were not entered into Phase A; these subjects were entered directly into Phase B following the Screening Phase.

Subjects who met the inclusion and exclusion criteria and had no history of oral aripiprazole use entered Phase A after the Screening Period while still hospitalized. Subjects in Phase A were administered oral aripiprazole, as indicated in the product labeling, to determine tolerability. Dosage was based on symptoms and the judgment of the investigator. The dose of oral aripiprazole could be titrated as needed. Prior antipsychotic medications were tapered off and discontinued during the Screening Period and Phase A as clinically appropriate.

During Phase A, tolerability to oral aripiprazole was evaluated daily for a minimum of 3 days using baseline safety and tolerability measures (i.e., AIMS, BARS, and SAS) either during or closely following completion of oral treatment, in conjunction with clinical judgment. If a subject was unable to tolerate oral aripiprazole, he or she was withdrawn from the study. If the subject showed tolerability to the oral aripiprazole, Phase B baseline/Day 1 occurred with the first aripiprazole once monthly injection given immediately after the Phase B baseline/Day 1 assessments.

Prior antipsychotic medications could be continued or tapered to discontinuation at the investigators discretion based on his or her clinical judgment. Reporting and recording of AEs was completed.

9.1.4 Phase B (Treatment Phase)

9.1.4.1 Baseline

Baseline was considered Day 1, or first day of long-acting injectable treatment, of Phase B. However, some subjects could have had their baseline assessments (including any remaining clinical laboratory tests required for screening) performed any time during or immediately after treatment with oral antipsychotic aripiprazole (unless eligible to skip Phase A in which it is any oral antipsychotic), ideally prior to starting long-acting injectable aripiprazole. Participants were allowed, with Principal Investigator approval, to enter the study after starting treatment with long-acting injectable aripiprazole in the hospital and baseline assessments were performed as soon as feasible within 48 hours of hospital discharge.

Subjects who completed the baseline assessments and met the criteria for inclusion and not for exclusion (Section 9.3.1 and Section 9.3.2) began the Treatment Phase (Phase B).

Baseline assessments were:

- Contact from the community support worker (CSW) or study coordinator (SC) via telephone or in-person
- Routine vital signs (e.g., blood pressure, heart rate, respiratory rate, and temperature)
- Height, weight, and calculation of BMI
- Fasting lipid profile (e.g., fasting triglycerides, cholesterol [total, HDL, LDL])
- HbA1c
- Prolactin concentration
- CGI-I
- C-SSRS (Since Last Visit) for suicidality
- AIMS, BARS, and SAS to assess EPS
- PSP
- Injection site reaction assessment (i.e., localized pain, redness, swelling, and induration), if applicable
- AEs and concomitant medications
- Aripiprazole once monthly IM injection plus Day 1 of 14 days of oral aripiprazole, (last baseline procedure), unless subject received injection while hospitalized prior to study entry.

9.1.4.2 Treatment Phase

Eligible subjects who had a history of tolerating oral aripiprazole or were currently taking oral aripiprazole entered Phase B directly from the Screening Period. All other subjects entered Phase B following successful completion of Phase A. After the baseline assessments were completed, the subject received the first aripiprazole once monthly IM injection, in conjunction with the first of 14 doses of concomitant oral antipsychotic medication (see Figure 1). Use of concomitant oral aripiprazole during this lead-in was per the investigator's judgment based on the prescribing instructions.

All subjects must have attended scheduled visits at the Baseline Visit and Weeks 2, 4, 8, 12, 16, 20, and 24, totaling 180 days. Aripiprazole once monthly injections occurred at the Baseline Visit and every 28 (-2, +5) days at Weeks 4, 8, 12, 16, 20, and 24, totaling seven injections. After the

initial injection of 400 mg, the monthly dosage could be decreased to 300 mg, based on the clinical judgment of the investigator. All aripiprazole once monthly injections were administered based on the investigator's judgment and the prescribing information. For subjects who entered the studies after starting the first dose of long-acting injectable aripiprazole in the hospital, if the initial injection was not 400 mg, the second injection should have been 400 mg, and thereafter, the monthly dose could be decreased to 300 mg, based on clinical judgment of the investigator.

For subjects who were psychiatrically stabilized and discharged prior to the completion of the required 14-day course of oral antipsychotic medication, a pre-discharge assignment was given to a CSW/SC. The CSW/SC maintained regular contact with the subject until the first outpatient visit in Phase B (Week 2), when oral aripiprazole was discontinued. Regular contact was defined as no less than weekly, but could have been more frequent depending on the clinical judgment of the CSW/SC and outpatient treatment team. Following the Week 2 Visit, subjects were to have contact with their assigned CSW/SC based on routine clinical care. Contact with the CSW/SC could be in person or by telephone, as clinically appropriate.

The treating clinician performed a clinical interview and mental status examination based on current clinical standards of care at all outpatient visits, whether scheduled or unscheduled. All episodes of clinical care (i.e., psychiatric and non-psychiatric) were recorded in the source documentation. In addition, the following clinical evaluations were performed as outlined in Table 3:

- Routine vital signs (e.g., blood pressure, heart rate, respiratory rate, and temperature) at each visit
- Height, weight and calculation of BMI at each visit
- Fasting lipid tests [e.g., fasting triglycerides, cholesterol (total, HDL, LDL)]
- HbA1c
- Additional clinical laboratory testing (e.g., hematology, fasting clinical chemistry, prolactin, urinalysis and urine pregnancy test) as described in Table 3 and clinically indicated and determined by treatment team
- AEs and concomitant medications
- CGI-I
- PSP
- C-SSRS (Since Last Visit) for suicidality
- AIMS, BARS, and SAS to assess EPS
- Injection site reaction (i.e., localized pain, redness, swelling, and induration)

9.1.4.3 Early Termination

All subjects who completed or withdrew from the study received a telephone call for safety follow-up at 30 (± 5) days after the last study visit unless they withdrew their consent for participation in the study. This telephone contact was made to assess if there were any AEs experienced since the last visit. In addition, the subject was asked about any new medications or changes in existing medications and the information was documented in the source documentation. The study site registered the contact in the interactive voice response system or interactive web response system.

The end of the study was the date of the last study visit for the last subject.

9.2 DISCUSSION OF STUDY DESIGN

The study design, following well-characterized patients for 180 days after starting aripiprazole once monthly treatment, and retrospectively reviewing data regarding prior hospitalizations, psychiatric ED visits, and prior total psychiatric hospitalization days, was planned to allow the proposed hypotheses to be tested adequately.

By utilizing retrospective review of hospitalizations, each subject served as his or her own control. The 30-, 90-, and 180-day analyses allowed for relatively equivalent comparison of the previous 6-month data.

This was an open-label study with one treatment arm, therefore, no active or placebo control or randomization was used. Treatment bias was eliminated via the objective assessments employed.

9.3 SELECTION OF STUDY POPULATION

Approximately 177 subjects were planned to be enrolled competitively between each of four designated clinical sites across the state of Missouri to reach a total of 90 completed subjects. This was to account for an expected 40% screen failure rate and an additional 40% drop-out rate. Subjects served as their own controls.

Prospective subjects were planned to be recruited from two of three established clinical sites at inpatient hospitals associated with outpatient community mental health centers in Missouri: Washington University in St. Louis, University of Missouri, Columbia, MO; and University of Missouri, Kansas City, MO.

Subjects who did not meet all of the inclusion criteria or who met any of the exclusion criteria were not eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must have met all of the following criteria to be included in this study:

1. Were able to provide written informed consent.

2. Were male and female subjects 18 to 65 years of age, inclusive, at time of informed consent

3. Had a current and confirmed diagnosis of schizophrenia as defined by DSM-5 criteria and a history of the illness for at least 6 months prior to screening from a reliable source (e.g., subject, family member, friend, caregiver, healthcare provider, or medical records)

4. Present at one of the selected inpatient units with acute psychotic symptoms for hospitalization at study entry

5. Had a clinically indicated need for a change in current antipsychotic therapy

6. Were on Medicaid with searchable claims data or were Medicaid-eligible

7. Had at least one inpatient psychiatric hospitalization or psychiatric ED visit within the 6 months prior to screening as confirmed through Medicaid or all available medical records and reliable data from caregivers

8. Had been previously prescribed oral antipsychotic treatment for at least a substantial portion of the 6 consecutive months prior to screening, with estimated duration of prescribed treatment within the 6 months prior to screening as determined by Principal Investigator discretion and confirmed through Medicaid or all available medical records and reliable data from caregivers

9. Had a history of response to antipsychotic treatment, with no history of clozapine treatment

10. Were able to understand the nature of the study and follow protocol requirements, including the prescribed dosage regimens, tablet ingestion, aripiprazole once monthly injection, and discontinuation of prohibited concomitant medications

11. Were able to read and understand the written word with a passing score of 4 to 6 (i.e., equivalent to seventh to eighth grade reading level for REALM-SF literacy assessment) in order to complete subject-reported outcomes measures

12. Were willing to accept a monthly injection

13. Were male and female subjects who were surgically sterile (i.e., have undergone orchiectomy or hysterectomy, respectively); female subjects who were postmenopausal for at least 12 consecutive months; or male and female subjects who agreed to use an approved form of birth control during study participation

9.3.2 Exclusion Criteria

Subjects who met any of the following criteria were excluded from this study:

1. Had current psychotic symptoms that could be explained by a diagnosis other than schizophrenia, including schizophreniform disorder, schizoaffective disorder, major depressive disorder, bipolar disorder, delirium, dementia, amnestic or other cognitive disorders. Also excluded were subjects with borderline, paranoid, histrionic, schizotypal, schizoid, or antisocial personality disorder.

2. Prisoners or subjects who were involuntarily incarcerated, or were incarcerated in the past 7 months for any reason

3. Required potent cytochrome P450 (CYP)2D or CYP3A4 inhibitors or CYP3A4 inducers

4. Were allergic, intolerant, or unresponsive to prior treatment with aripiprazole or other quinolinones or had a history of hypersensitivity to antipsychotic agents

5. Had received electroconvulsive therapy within the 6 months prior to screening

6. Had a history of neuroleptic malignant syndrome or clinically significant tardive dyskinesia as assessed by the investigator

7. Had a current diagnosis of diabetes or known fasting triglyceride levels consistent with risk for pancreatitis

8. Met DSM-5 criteria for a current substance use disorder within 3 months prior to screening:

    a. Ingestion of an identified substance alone may not have met the criteria for substance use diagnosis and therefore might not exclude the patient. Exceptions to this included the use of intravenous drugs within 3 months prior to screening.

    b. Patients with a diagnosis of a substance use disorder greater than 3 months prior to screening may or may not have been still in remission even if they have had some sporadic use. They must have met DSM-5 criteria identified for the specific substance to be out of remission.

9. Received treatment with long-acting injectable antipsychotics (e.g., haloperidol decanoate, fluphenazine decanoate, risperidone long acting injection [Risperdal Consta®], paliperidone palmitate extended release injectable suspension [Invega® Sustenna®], olanzapine for extended release injectable suspension [Zyprexa® Relprevv™]), in which the last dose was within 7 months prior to screening. Prior use of aripiprazole was allowed, but must have been discontinued prior to the current hospitalization.

10. Had a significant risk of committing suicide based on history, routine psychiatric status examination, investigator's judgment, or who had an answer of "yes" on Question 4 or Question 5 within the last 30 days on the baseline version of the C-SSRS

11. Had 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 study, including but not limited to hepatic, renal, respiratory, cardiovascular, endocrine, neurologic, hematologic, or immunologic disease as determined by the clinical judgment of the investigator

12. Had results from one or more of the following laboratory tests, vital signs, and ECG tests at screening that were exclusionary (laboratory testing and ECGs were performed locally):

    a. Platelets $\leq 75{,}000/mm^3$

b. Hemoglobin ≤ 9 g/dL

c. HbA1c > 7.0% or fasting blood glucose > 126 mg/dL

d. Neutrophils, absolute ≤ 1000/mm^3

e. Aspartate transaminase (AST) > 3x ULN

f. Alanine transaminase (ALT) > 3x ULN

g. Creatinine ≥ 2 mg/dL

h. Diastolic blood pressure > 105 mmHg

i. QTc > 475 msec on either the QTcB (Bazett) or QTcF (Fridericia) corrections on ECG, confirmed by a second tracing

j. Any other abnormal laboratory tests, vital sign results, or ECG findings that, in the judgment of the investigator, were medically significant and would affect the safety of the subject or the interpretation of the study results. Abnormal results for laboratory parameters or vital signs were to be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above.

13. Had been previously enrolled in an aripiprazole once monthly clinical study

14. Had participated in any clinical study with an investigational agent within the past 30 days

15. Were pregnant or lactating

9.3.3 Removal of Subjects from Therapy or Assessment

9.3.3.1 Entire Study

If the sponsor terminated or suspended the study for safety or unanticipated other reasons, prompt notification was to be given to Otsuka America Pharmaceutical, Inc. (OAPI), IRBs, and regulatory authorities in accordance with regulatory requirements.

9.3.3.2 Individual Center

The sponsor was to notify OAPI promptly if the study is terminated by the sponsor or the IRB at the site.

9.3.3.3 Individual Subject

If a subject discontinued from the study prematurely, the reason must have been fully evaluated and recorded appropriately in source documents and the CRF. If the subject was being withdrawn because of an AE, that AE should have been indicated as the reason for withdrawal.

An increase in suicidal ideation or homicidal ideation would result in withdrawal from the study, based on the investigators discretion.

All subjects had the right to withdraw at any point during treatment without prejudice. The investigator could discontinue a subject's participation in the study at any time if medically necessary. In addition, subjects meeting the following criteria were to be withdrawn from the study:

1. Occurrence of any AE, intercurrent illness or abnormality in a laboratory assessment which, in the opinion of the investigator, warranted the subject's permanent withdrawal from the study

2. Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of adverse events under direction of the investigator

3. Subject noncompliance, defined as refusal or inability to adhere to the study schedule or procedures per the investigator's discretion

4. At the request of the subject, investigator, OAPI or designee, or regulatory authority

5. Subject became pregnant

6. Subject was lost to follow-up

The sponsor notified OAPI promptly when a subject was withdrawn.

9.4 TREATMENTS

9.4.1 Treatments Administered

All active study drugs were provided by the manufacturer at no cost.

Aripiprazole once monthly and oral aripiprazole were prescribed and administered according to recommendations contained in their respective product labeling.

The following treatments were administered to subjects in this study:

- Aripiprazole, administered once monthly via gluteal or deltoid IM injection, as outlined in the product labeling

- Oral aripiprazole:
  - Subjects in Phase A were administered oral aripiprazole to determine tolerability, based on the prescribing information

DOSAGE ADJUSTMENTS FOR MISSED DOSES OF ARIPIPRAZOLE ONCE MONTHLY

If the second or third doses were missed:

- If > 4 weeks and < 5 weeks elapsed since the last injection, the injection as administered soon as possible

- If > 5 weeks elapsed since the last injection, concomitant oral aripiprazole was restarted and given for 14 days with the next administered injection

If the fourth or subsequent doses were missed:

- If > 4 weeks and < 6 weeks elapsed since the last injection, the injection was administered as soon as possible

- If > 6 weeks elapsed since the last injection, concomitant oral aripiprazole was restarted and given for 14 days with the next administered injection

9.4.2 Identity and Storage of Drug Under Study(s)

All study drug was securely locked in a cabinet or enclosure according to the storage instructions on the product labeling. Access was limited to the investigators and their designees. Neither investigators nor any designees were allowed to provide study drugs to any subject not participating in this protocol.

9.4.3 Method of Assigning Subjects to Treatment Groups

A total of 177 subjects were planned to be enrolled in the study. Subjects were assigned a subject ID number chronologically based on the order of enrollment into the study. The study was a single-arm, nonrandomized study.

9.4.4 Blinding

The study was not blinded.

9.4.5 Prohibited Medication

During the Screening Period, subjects could be treated with any oral antipsychotic of the clinician's choice, with the exception of clozapine and olanzapine. However, oral olanzapine was permitted during the Screening Period only for subjects who are eligible for Phase A.

Following the concomitant 14-day oral lead-in in Phase B after the first injection of aripiprazole once monthly, oral aripiprazole was the only allowed rescue medication. Subjects requiring any other antipsychotic medications except for oral aripiprazole for rescue during Phase B of the study after the first 14 days were discontinued.

A summary of medications that are prohibited or restricted prior to screening or during the study is provided in Table 1.

Table 1: Prohibited and Restricted Medications

Medication	Prohibition or Restriction
Antipsychotics	No more than one SOC antipsychotic allowed
Antidepressants including MAOIs	No new starts allowed; could continue if already taking for ≥ 2 months on a stable dose
Benzodiazepine	The use of one benzodiazepine was allowed.
Mood stabilizers	No new starts allowed – could continue if already taking for ≥ 2 months on a stable dose
Non-benzodiazepine sleep aids[a]	Allowed
Anticholinergics	≤ 4 mg/day benztropine or equivalent; not within 12 hours of any rating scales
Propranolol for akathisia or tremor	Maximum 60 mg/day; not within 8 hours of any rating scales. Subjects receiving propranolol for heart disease could remain on stable, pre-study doses, as needed as long as the dose did not exceed 60 mg/day.
Varenicline	Not allowed
Nutritional supplements and non-prescription herbal preparations with CNS effects (e.g., St. John's Wort, omega-3 fatty acids, kava extracts, GABA supplements)	Not allowed
CYP3A4 or CYP2D6 inhibitors or CYP3A4 inducers	CYP3A4 or CYP2D6 inhibitors were allowed, however, the investigator could adjust the dose of study drug per the prescribing instructions. CYP3A4 inducers were not allowed
Oral olanzapine[b] and clozapine	During Screening Period
All long-acting antipsychotics, except for aripiprazole once monthly[c]	Not allowed

CNS = central nervous system, CYP = cytochrome P450, EPS = extrapyramidal side effects, GABA = gamma-aminobutyric acid, MAOI = monoamine oxidase inhibitor, SOC = standard of care

[a]: Zolpidem 5 to 10 mg/day, zolpidem extended-release 12.5 mg/day, zaleplon 5 to 10 mg/day, zopiclone 3.75 to 7.5 mg/day, or eszopiclone 1 to 3 mg/day was permitted, but not in addition to a benzodiazepine for insomnia.

[b]: Oral olanzapine was allowed during the Screening Period only if the subject was eligible for Phase A.

[c]: Prior use of aripiprazole was allowed, but must have been discontinued prior to the current hospitalization.

9.4.6 Treatment Compliance

Most of the study drugs were administered during the subject's hospitalization or at pre-specified visits and were recorded in the source documentation. Oral aripiprazole usage continuing after

discharge was monitored by self-report to the CSW/SC and by pill counts, when possible, at the next visit after completion of the 14-day oral aripiprazole period.

9.4.7 Accountability

Study drug was not prescribed or administered until the following documentation was provided by the sponsor to OAPI:

- A signed and dated confidentiality agreement
- A copy of the final signed and dated protocol signature page
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB for the institution where the study was to be conducted
- A copy of the IRB-approved ICF and any other documentation provided to the subjects to be used in this study
- A signed and dated curriculum vitae (CV) of the sponsor including a copy of the sponsor's current medical license or medical registration number on the CV
- A signed and dated clinical studies agreement

The sponsor, site investigators, and the study staff were responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) adherence to GCP guidelines and any local or regional requirements.

Under no circumstances was the sponsor or site investigators to allow the study drugs to be used other than as directed by the protocol. Study drugs were not dispensed to any individual who was not enrolled in the study unless that person was a parent or legal guardian for the subject and signed the ICF as such.

The sponsor, or designee, maintained an inventory record of study drugs received, dispensed, administered, disposed of, and returned. The study drugs and inventory records were to be made available, upon request, for inspection by a designated representative of OAPI or a representative of a health authority (e.g., FDA). As applicable, all unused study drugs were returned to the site investigator by the subject.

9.5 STUDY ASSESSMENTS

9.5.1 Assessments

9.5.1.1 Pre-Screening Assessments

RAPID ESTIMATE OF ADULT LITERACY IN MEDICINE-SHORT FORM

The REALM-SF is a 7-item word recognition test to provide investigators with a fast and valid assessment of subject health literacy. The interviewer asked the subject to read each of the words

aloud and reply “blank” if unable to read a particular word. If the subject took more than 5 seconds on a word, the interviewer would say "blank" and point to the next word, if necessary, to move the patient along. If the subject began to miss every word, the interviewer would ask the subject to pronounce the known words only.

The score and grade equivalents for the REALM-SF were: 0 = third grade and below; will not be able to read most low-literacy materials; will need repeated oral instructions, materials composed primarily of illustrations, or audio or video tapes; 1 to 3 = fourth to sixth grade; will need low-literacy materials, may not be able to read prescription labels; 4 to 6 = seventh to eighth grade; will struggle with most patient education materials; will not be offended by low-literacy materials; and 7 = high school; will be able to read most patient education materials.

UNIVERSITY OF CALIFORNIA, SAN DIEGO BRIEF ASSESSMENT OF CAPACITY TO CONSENT

The UBACC is a 10-item scale designed to help investigators identify any subjects with questionable capacity to consent to study participation prior to enrollment in a study. Questions focus on the ability of the subject to understand, appreciate, reason, and express a choice about participating in a particular clinical study.

After explaining the details of the study and the ICF, the interviewer asked each question and rated the subject’s responses on a scale of 0 to 2, with “0” being the lowest (i.e., little to no understanding of this aspect of the study) and “2” being the highest (i.e., clear understanding of this aspect of the study). If a subject had trouble understanding one of the questions on the UBACC, the question could be rephrased.

Subjects were allowed to refer to the ICF when answering these questions, but were encouraged to respond in their own words.

9.5.1.2 Demographics

Subject demographic information was collected at the Screening Visit. Demographic information included date of birth or age, sex, race or ethnicity, and previous hospitalizations or ED visits.

9.5.1.3 Screening Assessments

MEDICAL HISTORY

Medical and surgical history and current medical conditions were recorded at the Screening Visit. All relevant medical and surgical history within 1 year was noted in the CRF.

PSYCHIATRIC HISTORY

A review of the subject’s psychiatric history was performed including all antipsychotic medications used within the 6 months prior to screening. Confirmation of a current diagnosis of schizophrenia, as defined by DSM-5 criteria was obtained. The complete psychiatric history included a clinical interview documented in the medical record and completion of a consensus diagnosis form, where the diagnosis for other records, the study team interview, and the consensus diagnosis were recorded.

ELECTROCARDIOGRAM

A 12-lead ECG was performed while the subject was in a supine position and after having rested for 5 minutes.

DOCUMENTATION OF PREVIOUS HOSPITALIZATIONS

Data regarding psychiatric and non-psychiatric hospitalizations and medical interventions occurring within the 6 months prior to the date of the signing the ICF were obtained by searching MO HealthNet (Medicaid) and the DMH database or confirmed through all available medical records and reliable data from caregivers.

EXCLUSIONARY LABORATORY MEASUREMENTS

At screening, laboratory testing including triglycerides (screening only) were assessed to rule out exclusionary values (see Section 9.3.2). Subjects who had any of the excluded laboratory values were dropped from the study. All other clinical laboratory measurements are described in Section 9.5.1.4.1).

9.5.1.4 Safety Assessments

Safety was assessed by AE reporting, clinical laboratory tests (i.e., hematology, fasting clinical chemistry, and lipid profile), urinalysis, urine pregnancy testing and vital signs measurements. In addition, body weight, BMI, and serum prolactin concentrations were monitored.

The following scales were used to assess for EPS:

- AIMS
- SAS
- BARS

For subjects receiving an injection, the investigator, or qualified designee, assessed the injection site for localized pain, redness, swelling, and induration.

9.5.1.4.1 Clinical Laboratory Tests

The local laboratory was used for all laboratory testing required during the study. Reports from the laboratory were filed with the source documents for each subject. Samples were obtained at the visits designated in Table 3, and as far as possible, samples were drawn at the same time of day at each visit. Additional samples could be collected for further evaluation of safety as warranted by the investigator's discretion. Subjects were to be fasting for a minimum of 10 hours prior to blood draws for assessment of safety, including screening. If non-fasting blood samples were obtained initially for determining eligibility for the study, a fasting blood sample was to be drawn prior to enrollment. The clinical laboratory tests performed during the study are provided in Table 2.

Table 2: Safety Clinical Laboratory Tests

Hematology:	**Serum Chemistry:**
Hematocrit Hemoglobin Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Platelet count Red blood cell (RBC) count White blood cell (WBC) count with differential	Alanine transaminase (ALT) Albumin Alkaline phosphatase (ALP) Aspartate transaminase (AST) Bilirubin, total Blood urea nitrogen (BUN) Calcium Chloride Creatinine Glucose Potassium Protein, total Sodium
Urinalysis:	**Additional Tests:**
Appearance Color Dipstick Microscopic Analysis of RBC and WBC (i.e., per high powered field)] pH Specific gravity	Fasting glucose HbA1c Lipid profile (cholesterol [total, HDL, LDL]) Serum prolactin Triglycerides[a] Urine β-hCG[b] for women of child-bearing potential

β-hCG = beta-human chorionic gonadotropin, HbA1c = glycosylated hemoglobin, HDL = high-density lipoprotein, LDL = low-density lipoprotein

[a]: Triglycerides were measured at screening only, to rule out exclusionary values

[b]: Serum β-hCG was performed if the subject or investigator suspected that the subject may be pregnant

9.5.1.4.2 Vital Signs

Vital sign measurements (i.e., systolic and diastolic blood pressure [BP] [mmHg], heart rate [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) were obtained at the visits designated on the Schedule of Assessments (Table 3) by a validated method. Blood pressure and heart rate were measured after the subject was supine for 5 minutes and again standing for ≥ 1 minute.

9.5.1.5 Adverse Events and Other Events of Interest

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a drug under study. An AE does not necessarily have a causal relationship with the study drug. For this study, the study drug was aripiprazole once monthly and oral aripiprazole.

The criteria for identifying AEs were:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug under study, whether or not considered related to the drug under study
- Any new disease or exacerbation of an existing disease

- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (e.g., ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (e.g., headache) not present pretreatment (i.e., baseline)
- An abnormal laboratory test result was considered an AE if the identified laboratory abnormality led to any type of intervention, whether prescribed in the protocol or not.

A laboratory result was to be considered by the investigator to be an AE if it:

- Resulted in the withdrawal of study drug
- Resulted in withholding of study drug pending some investigational outcome
- Resulted in an intervention, based on medical evaluation (e.g., potassium supplement for hypokalemia)
- Resulted in any out of range laboratory value that in the investigator's judgment fulfills the definitions of an AE with regard to the subject's medical profile

All AEs observed during the study were reported on the CRF. All AEs, regardless of relationship to study drug or procedure, were collected beginning from the time the subject signed the study ICF through the last visit. Serious AEs were collected for 30 days after the last dose or at the Follow-up Visit, whichever came later.

Abnormal laboratory values were not listed as separate AEs if they were considered to be part of the clinical syndrome that is being reported as an AE. Any laboratory abnormality considered to constitute an AE was reported as an AE on the CRF.

It was the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment was to be exercised in deciding whether an isolated laboratory abnormality was classified as an AE.

It was the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constituted an AE. Medical and scientific judgment was to be exercised in deciding whether an isolated suicidality rating scale response was to be classified as an AE (see Other Safety Assessments [Section 9.5.1.7.3] for a description of the C-SSRS).

Every effort was to be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

AEs were graded on a 3-point scale (i.e., mild, moderate, and severe) and reported in the detail indicated on the CRF. The definitions were as follows:

Mild: Discomfort noticed, but no disruption of normal daily activity

Moderate: Discomfort sufficient to reduce or affect normal daily activity

Severe: Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Serious Adverse Events and Other Events of Interest [Section 9.5.1.6] for the definition of an SAE).

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

Related:

Definite: There was a reasonable causal relationship between the study drug and the AE, when the event responded to withdrawal of the study drug (i.e., dechallenge), and recurred with rechallenge by administration of the study drug.

Probable: There was a reasonable causal relationship between the study drug and the AE. The event responded to dechallenge. Rechallenge was not required.

Possible: There was a reasonable causal relationship between the study drug and the AE. Dechallenge was lacking or unclear.

Unrelated:

Not Likely: There was a temporal relationship to study drug administration, but there was not a reasonable causal relationship between the study drug and the event.

Not Related: There was not a temporal or causal relationship to the study drug administration.

9.5.1.6 Serious Adverse Events and Other Events of Interest

An SAE was any untoward medical occurrence that at any dose:

- Resulted in death
- Was life-threatening (i.e., the subject was at immediate risk of death from the adverse event as it occurred; this did not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Required inpatient hospitalization or prolongation of existing hospitalization
- Resulted in persistent or significant disability or incapacity
- Was a congenital anomaly or birth defect in the child of a subject who was exposed to the study drug

Other important medical events that may not have been immediately life-threatening or resulted in death or hospitalization but, when based on appropriate medical judgment, may have jeopardized the subject or may have required intervention to prevent one of the outcomes in the definition of

SAE listed above should also have been considered SAEs. Medical and scientific judgment was to be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, other events of interest included pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error; and any treatment-emergent significant laboratory abnormality. These events of interest were to be captured using the SAE procedures but were to be considered SAEs only if they met one of the above criteria. All AEs associated with events of interest were to be reported on the CRF whether or not they met the criteria for SAEs.

The following hospitalizations were not considered to be SAEs because there is no "adverse event" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent where the condition requiring the hospitalization had not changed post-study drug administration
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study entry

9.5.1.7 Other Safety Assessments

9.5.1.7.1 Injection Site Evaluation

For subjects receiving an injection, the investigator, or qualified designee, assessed the injection site for localized pain, redness, swelling, and induration.

This assessment was completed on the same day the injection was administered.

9.5.1.7.2 Body Weight, Height, Body Mass Index

An assessment for potential of prolactin-related effects was performed via measurement of body weight (kg) and determination of BMI.

The calculation for BMI was:

$$\frac{\text{weight (kg)}}{[\text{height (m)}]^2}$$

9.5.1.7.3 Suicidality

Columbia Suicide Severity Rating Scale

The C-SSRS was designed to distinguish the domains of suicidal ideation and suicidal behavior. The C-SSRS scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicide events and suicidal ideation and a post-baseline or "Since Last Visit" evaluation that focuses on suicidality since the last study visit. The baseline C-SSRS form was completed at baseline of Phase 1. The "Since Last Visit" C-SSRS form was completed at all subsequent visits.

Four constructs were measured:

1. The severity of ideation (i.e., the "severity subscale"), which is rated on a 5-point ordinal scale with 1 = wish to be dead, 2 = nonspecific active suicidal thoughts, 3 = suicidal thoughts with methods, 4 = suicidal intent, and 5 = suicidal intent with plan.

2. The intensity of ideation subscale (i.e., the "intensity subscale"), which is comprised of five items, each rated on a 5-point ordinal scale: frequency, duration, controllability, deterrents, and reason for ideation.

3. The behavior subscale, which is rated on a nominal scale that includes actual, aborted, and interrupted attempts; preparatory behavior; and non-suicidal self-injurious behavior.

4. The lethality subscale, which assesses actual attempts; actual lethality is rated on a 6-point ordinal scale, and if actual lethality is zero, potential lethality of attempts is rated on a 3-point ordinal scale.

9.5.1.7.4 Pregnancy Test

Women of childbearing potential and men who are sexually active must have used an effective method of birth control during the course of the study and for 30 days for a female subject and 90 days for a male subject after the last dose of SOC oral antipsychotics and 150 days for a female subject and 180 days for a male subject after the last dose of aripiprazole once monthly, in a manner such that risk of failure is minimized. Unless the subject and his or her partner(s) are sterile (i.e., women who have had an oophorectomy and/or hysterectomy or have been postmenopausal for at least 12 consecutive months; or men who have had orchiectomy) or remain abstinent, two of the following precautions must have been used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control injection, birth control implant, condom with spermicide, or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, could fail, leading to pregnancy.

Before enrolling women of child-bearing potential in this clinical study, investigators reviewed guidelines about study participation for women of childbearing potential. The topics generally included:

- 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 study enrollment, women of childbearing potential were advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject signed an ICF stating that the above-mentioned risk factors and the consequences were discussed with her.

9.5.1.8 Efficacy Assessments – Clinical Outcome

9.5.1.8.1 Clinical Global Impression–Improvement

The efficacy of study medication was rated for each subject using the CGI-I scale. The rater or investigator rated the subject's total improvement whether or not it was due entirely to drug treatment. All responses were to be compared to the subject's condition at baseline of the appropriate phase. The CGI-I during Phase B would have been assessed relative to the subject's condition at the Phase B baseline visit. Response choices included: 0 = not assessed; 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; and 7 = very much worse.

9.5.1.8.2 Clinical Global Impression–Severity

The severity of illness for each subject was rated using the CGI-S scale. To assess CGI-S, the rater or investigator answered the following question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" Response choices included: 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.

9.5.1.8.3 Personal and Social Performance Scale

The PSP is a 100-point scale divided into 10 subcategories that assesses function using four domains. The domains are: a) socially useful activities including work and study, b) personal and social relationships, c) self-care, and d) disturbing and aggressive behaviors. Each domain is graded using a 6-point scale: absent, mild, manifest, marked, severe, and very severe.

The clinician selects the 10-point category based on a combination of severity in each of the four domains. Higher scores indicate improved functioning. The PSP takes approximately 10 minutes of the clinician's time.

9.5.1.9 Extrapyramidal Side Effects

9.5.1.9.1 Abnormal Involuntary Movement Scale

The AIMS assessment consists of 10 items describing symptoms of dyskinesia. Facial and oral movements (i.e., Items 1 through 4), extremity movements (i.e., Items 5 and 6), and trunk movements (i.e., Item 7) were observed unobtrusively while the subject was at rest (e.g., in the waiting room), and the investigator also made global judgments on the subject's dyskinesias (i.e., Items 8 through 10). Each item was rated on a 5-point scale, with a score of zero representing an absence of symptoms (i.e., for Item 10, no awareness), and a score of four indicating a severe condition (i.e., for Item 10, awareness/severe distress).

9.5.1.9.2 Barnes Akathisia Rating Scale

The BARS assessment consists of four 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 three items were rated on a 4-point scale, with a score of zero representing absence of symptoms and a score of three representing a severe condition. The global clinical evaluation was made on a 6-point scale, with zero representing absence of symptoms and a score of five representing severe akathisia.

9.5.1.9.3 Simpson Angus Scale

The SAS assessment consists of a list of 10 symptoms of parkinsonism (i.e., gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item was rated on a 5-point scale, with a score of one representing absence of symptoms, and a score of five representing a severe condition. The SAS Total Score was the sum of the scores for all 10 items.

9.5.1.10 Pharmacokinetic/Pharmacodynamic Assessments

Not applicable.

9.5.2 Schedule of Assessments

The Schedule of Assessments for the study is provided in Table 3.

Table 3: Schedule of Assessments

Visit			1	2	3	4	5	6	7	8[q]
Study Period	**Screening/ Assessment**	**Phase A (Oral Tolerability Phase[a])**	**Phase B (Treatment Phase)**							
Day	**Variable**	**-3 to -1**	**Baseline Day 1[b,g]**	**15[g]**	**30**	**60**	**90**	**120**	**150**	**180**
Week				**2[e]**	**4**	**8**	**12**	**16**	**20**	**24**
Procedure										
Informed consent	X									
Confirmation of diagnosis of schizophrenia (DSM-5)	X									
Review inclusion/and exclusion criteria	X									
Demographic information	X									
Complete medical history	X									
Complete psychiatric history[c]	X									
Antipsychotic therapy – current use and history[d]	X									
Electrocardiogram	X									
Urine pregnancy test[e]	X									X
Documentation of psychiatric and non-psychiatric hospitalizations and interventions[f]	X									
Contact from the CSW/SC via telephone or in-person[g]			X[g]	X[g]						
Clinical interview and mental status examination[h]					X	X	X	X	X	X
Vital signs[i]	X		X	X	X	X	X	X	X	X
Height, weight, BMI[j]	X		X	X	X	X	X	X	X	X
Screening or safety clinical laboratory testing as needed[k,l,m]	X[m]		X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]
Fasting lipid profile[n]	X		X		X		X			X
HbA1c[l]	X		X		X		X			X
Prolactin[k]			X		X					X
CGI-I			X	X	X	X	X	X	X	X

Table 3: Schedule of Assessments

Visit			1	2	3	4	5	6	7	8[q]
Study Period	**Screening/ Assessment**	**Phase A (Oral Tolerability Phase[a])**	**Phase B (Treatment Phase)**							
Day	**Variable**	**-3 to -1**	**Baseline Day 1[b,g]**	**15[g]**	**30**	**60**	**90**	**120**	**150**	**180**
Week				**2[e]**	**4**	**8**	**12**	**16**	**20**	**24**
Procedure										
CGI-S	X									
AIMS, BARS, SAS	X		X	X	X	X	X	X	X	X
PSP			X							X
C-SSRS[o]	X		X	X	X	X	X	X	X	X
Oral aripiprazole treatment[a,p]		X	X							
Administer aripiprazole once monthly			X		X	X	X	X	X	X
Injection site assessment			X		X	X	X	X	X	X
Reporting of AEs	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X

AE = adverse events, AIMS = Abnormal Involuntary Movement Scale, ALP = alkaline phosphatase, ALT = alanine transaminase, AST = aspartate transaminase, BARS = Barnes Akathisia Rating Scale, BMI = body mass index, BUN = blood urea nitrogen, CBC = complete blood count, CGI-I = Clinical Global Impression–Improvement, CGI-S = Clinical Global Impression–Severity, C-SSRS = Columbia Suicide Severity Rating Scale, CSW = community support worker, DSM-5 = Diagnostic and Statistical Manual, Fifth Edition, ECG = electrocardiogram, ED = emergency department, HbA1c = glycosylated hemoglobin, HDL = high-density lipoprotein, Hgb = hemoglobin, ICF = Informed Consent Form, LDL = low-density lipoprotein, MO = Missouri, PSP = Personal and Social Performance Scale, SAS = Simpson Angus Scale, SC = Study Coordinator, ULN = upper limit of normal

Note: Baseline was considered Day 1, or first day of long-acting injectable treatment in the hospital, of Phase B. However, some subjects may have had their baseline assessments (including clinical laboratory tests) performed any time during or immediately after treatment with oral antipsychotic aripiprazole (unless eligible to skip Phase A in which it was any oral antipsychotic), ideally prior to starting long-acting injectable aripiprazole. Participants were allowed, with Principal Investigator approval, to enter the study after starting treatment with long-acting injectable aripiprazole in the hospital and baseline assessments were performed as soon as feasible within 48 hours of hospital discharge.

[a] The Oral Tolerability Phase lasted for a minimum of 3 days. Subjects who had history of tolerability (e.g., taking at least 3 consecutive doses) with oral aripiprazole and no history of intolerance could receive their aripiprazole once monthly injection immediately upon completion of the screening procedures. All subjects received the first injection of aripiprazole once monthly at Baseline, Day 1.

[b]: Discharge could occur at any time after the first injection of aripiprazole once monthly.

[c]: The complete psychiatric history included a diagnosis reconciliation form on which information from medical records and a clinical interview by a study clinician were recorded.

[d]: Previous medications taken within 7 days prior to starting study drug and all central nervous system-active compounds taken within 30 days preceding the first dose of study drug were recorded. All antipsychotic medications used within 6 months of screening were recorded.

[e]: A urine pregnancy test was performed for women of childbearing potential only at screening, Visit 10, and at the Follow-up visit; subsequent testing was done as is clinically indicated. If a subject or investigator suspected that the subject may be pregnant, a serum pregnancy test would then be performed.

Table 3: Schedule of Assessments

Visit			1	2	3	4	5	6	7	8[q]
Study Period	Screening/ Assessment	Phase A (Oral Tolerability Phase[a])	Phase B (Treatment Phase)							
Day	Variable	-3 to -1	Baseline Day 1[b,g]	15[g]	30	60	90	120	150	180
Week				2[e]	4	8	12	16	20	24
Procedure										

[f]: Data regarding psychiatric and non-psychiatric hospitalizations and medical interventions occurring within the 6 months prior to the date of the signing the ICF were obtained by searching MO HealthNet (Medicaid) and MO Department of Mental Health (DMH) data via collaboration with the Missouri Institute of Mental Health (MIMH); availability of Medicaid data and documentation of at least one inpatient hospitalization or ED visit within the previous 6 months was required for eligibility.

[g]: For subjects who were psychiatrically stabilized and discharged prior to the completion of the required 14-day course of oral aripiprazole, a pre-discharge assignment was given to a CSW or SC. The CSW/SC maintained regular contact with the subject until the Week 2 visit. Following the Week 2 visit, subjects had contact with their assigned CSW/SC based on routine clinical care.

[h]: At all outpatient visits, scheduled or unscheduled.

[i]: Vital signs were recorded daily while hospitalized.

[j]: BMI was calculated as: mass (kg)/height (m2).

[k]: Subjects should have been fasting for a minimum of 10 hours prior to blood draws for all laboratory assessments. Every effort was made to obtain the clinical laboratory samples at the same time of day at each visit. All laboratory testing was performed at local laboratories at the clinical sites.

[l]: Safety clinical laboratory testing was conducted at screening, and as deemed clinically necessary thereafter. Standard clinical safety laboratory testing included: hematology (CBC with differential, and platelet count), chemistry (ALT, albumin, ALP, AST, total bilirubin, BUN, calcium, chloride, creatinine, glucose, potassium, serum prolactin, total protein, and sodium). Urinalysis was a dipstick with microscopic as clinically indicated.

[m]: Exclusionary tests at screening were: platelets ≤ 75,000 mm3, Hgb ≤ 9 g/dL, fasting glucose > 126 mg/dL, HbA1c > 7.0%, absolute neutrophils ≤ 1,000/mm3, ALT > 3x ULN, AST > 3 x ULN, creatinine ≥ 2 mg/dL, diastolic blood pressure > 105 mm Hg, QTc > 475 msec on either the Bazett or Fridericia corrections on ECG, any other abnormal findings that would affect the safety of the subject or interpretation of the study results (Section 9.3.2).

[n]: Lipid profile included: total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides.

[o]: At screening the baseline C-SSRS was completed, at subsequent visits, the "since last visit" version was completed.

[p]: All subjects received 14 days of oral aripiprazole beginning with the first dose of aripiprazole once monthly.

[q]: All subjects who completed or withdrew from the study received a telephone call for safety follow-up at 30 (± 5) days after the last study visit unless they withdrew their consent for participation in the study to assess for any AEs experienced since the last visit (Section 9.1.4.3).

[r]: Clinical laboratory testing only as needed for safety purposes, as determined by the Principal Investigator.

9.5.3 Appropriateness of Measurements

All clinical assessments were standard measurements commonly used in studies of schizophrenia.

The safety assessments performed in the study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs, were standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Other Events of Interest

Collection of safety information was completed from the first administration of the study drug until 28 days after discontinuation, unless otherwise specified in the protocol. The longer of the two timeframes was employed if there was a conflict.

Safety information was defined as any information from any source containing information such as:

- AE or suspicion thereof
- Lack of efficacy
- Overdose/incorrect dosage (i.e., accidental or intentional)
- Abuse/misuse (e.g., patients sharing medication); even without resulting adverse reaction
- Accidental exposure (e.g., child takes parent's medication)
- Medication error
- Withdrawal reactions
- Disease progression/exacerbation of existing disease
- Drug-drug/drug-food interactions
- Exposure to drug during pregnancy, where the embryo or fetus may have been exposed to medicinal products either through maternal exposure or transmission of a medicinal product via semen following paternal exposure
- Exposure to drug during lactation, including uneventful
- Suspected counterfeit product
- Suspected transfer of infectious disease/agent by the medicinal product concerned
- Product Quality Complaint (PQC) with safety related/medically important information
- Pediatric use, if not an approved use

- Occupational exposure
- Off-label use

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, were reported to the following according to the agreement between the investigator and the sponsor, John W. Newcomer, MD, at Florida Atlantic University.

Report all Immediately Reportable Events (i.e., SAEs, potential Hy's Law cases, pregnancies and AEs requiring discontinuation of study drug) to:

Contact: Julie Schweiger (back-up contact Karen Flavin)
Address: 660 South Euclid Avenue, Campus Box 8134, St. Louis, MO 63110
For Medical Emergencies: Tel: 314-362-3153; Fax: 314-747-1160

9.5.5 Completion/Discontinuation of Subjects

A subject could elect to discontinue the study at any time for any reason without prejudice. All subjects who discontinued the study were to complete the study's early discontinuation procedures indicated in the Schedule of Assessments (Table 3) whenever possible.

The investigator promptly explained to the subject involved that the study would be discontinued for that subject and provided appropriate medical treatment and other necessary measures for the subject. A subject who ceased to return for visits was followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms. This information was recorded in the CRF.

Subjects who discontinued early from the study were discontinued for one of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, withdrawal of consent, pregnancy, study termination, or other (to be specified). In addition to the primary reason, the subject could indicate one or more secondary reasons for discontinuation.

A subject removed from the study for any reason could not be replaced.

9.5.6 Confirmation of Medical Care by Another Physician

The investigator instructed subjects to inform site personnel when they were planning to receive medical care by another physician. At each visit, the investigator asked the subject whether he or she had received medical care by another physician since the last visit or was planning to do so in the future. When the subject was going to receive medical care by another physician, the investigator, with the consent of the subject, informed the other physician that the subject was participating in the clinical study.

9.6 DATA QUALITY ASSURANCE

9.6.1 Monitoring

The sponsor had ethical, legal, and scientific obligations to follow the study in a detailed and orderly manner in accordance with established research principles, the ICH GCP Guideline, FDA regulations and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (i.e., maintain current personal knowledge of the progress of the study), an independent group of the sponsor's monitors contracted from Washington University School of Medicine (WUSM), separate from the clinical site staff at WUSM, could visit the site during the study, as well as communicate frequently via telephone and written communications.

9.6.2 Auditing

The OAPI Quality Management Unit (or representative) could conduct study site audits. Audits would include, but were not be limited to, drug supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents. The sponsor agreed to participate with audits.

Regulatory authorities could inspect the sites during or after the study. The sponsor agreed to cooperate with such inspections and to contact the sponsor and OAPI immediately if such an inspection occurs.

9.6.3 Data Collection

The study was expected to start in the spring of 2016 and be completed on or about 01 December 2018. Data collection began when the first subject signed the ICF, on 08 June 2016 and would have been completed on the date at which the last subject's data has been entered into the database and no data queries are outstanding, approximately 01 November 2018.

9.7 STATISTICAL METHODS

The plan analyses are described below. No actual formal statistical analyses were performed.

9.7.1 Statistical and Analytical Plans

9.7.1.1 Primary Endpoint(s)

The primary efficacy endpoint was:

- Comparison of rates of psychiatric re hospitalization for symptoms associated with schizophrenia after receiving aripiprazole once monthly for 30, 90, and 180 days following hospital discharge for acute psychiatric stabilization, compared with retrospective 30-, 90-, and 180-day hospitalization rates, respectively, in subjects previously treated with oral antipsychotic medication.

9.7.1.2 Secondary Endpoint(s)

The secondary endpoints were:

Efficacy:

- Comparison of:
  - 30-, 90-, and 180-day rates of unscheduled psychiatric ED visits compared with prior 30-, 90-, and 180-day unscheduled visits
  - Psychiatric ED visits plus hospitalizations compared with prior 30-, 90-, and 180-day psychiatric visits plus hospitalizations
  - Total psychiatric hospitalization days over the 30-, 90- and 180-day study period compared with the total psychiatric hospitalization days over the prior 30-, 90- and 180-day period
  - Change from baseline in CGI-I, based on the initial CGI-S, and CGI-I scores at 30-, 90-, and 180-days
- Changes from baseline on the following indicators for CMR after receiving aripiprazole once monthly:
  - Weight and BMI
  - Fasting glucose concentrations, HbA1c concentrations, and fasting lipids concentrations (i.e., fasting triglyceride, total cholesterol, HDL, and LDL)

9.7.1.3 Exploratory Endpoints

Safety:

- AEs
- Clinical laboratory tests (i.e., hematology, fasting clinical chemistry, prolactin and urinalysis)
- Vital signs
- PSP
- Injection site reaction (i.e., localized pain, redness, swelling, and induration)
- C-SSRS for suicidality
- EPS assessments, including:
  - AIMS

- SAS
- BARS

9.7.1.4 Definitions of Analysis Sets

Enrolled Sample: All subjects who signed an informed consent form for the study.

Phase A Safety Sample: All subjects who took at least one dose of oral aripiprazole in Phase A and had at least one post-dose safety assessment.

Phase B Safety Sample: All subjects who received at least one dose of aripiprazole once monthly in Phase B.

Phase B Efficacy Sample: The core dataset for all outcome or efficacy analyses was to be the intent-to-treat (ITT) dataset that was to consist of data from all subjects entering Phase B. However, as described in Section 9.7.4.1, in order to handle missing data and restrictions imposed by different types of analyses (e.g., change from baseline), other datasets derived from the ITT dataset could be used for the efficacy analyses.

9.7.1.5 Subject Disposition

The method for summarizing the number (i.e., percentage) of subjects who were screened for the study (i.e., enrolled subjects, or those who signed informed consent) and reasons for screen failure were documented in full using the dedicated Washington University REDCap file for this study, with data fields for Enrollment Tracking, Screen Visits, Screen Failures, and Subject Visit Tracking. These REDCap data fields provided a clear accounting of all subjects who entered the study, the number of subjects screened for inclusion, and a breakdown of the reasons for excluding subjects during screening. In addition, pre-enrollment general pre-screening failures were tracked.

Non-identifying or random numbers were used to identify subjects on the Screening Log and Screen Failure logs. Consented Subjects who met inclusion and exclusion criteria were entered on the Enrollment log with an assigned study number. Completion of each study visit for enrolled subjects through completion of study was documented on the Subject Visit Tracking Log. Subjects not completing the study with a description of the reason for discontinuation were documented on the Subject Visit Tracking Log.

The Excel format of these forms allowed data to be analyzed by investigators at any time during the study and to report progress to the sponsor and regulatory agencies.

9.7.1.6 Demographic and Other Baseline Characteristics

Baseline demographic characteristics including age, race, ethnicity, gender, weight, height and BMI were to be summarized by descriptive statistics (i.e., frequency, mean, median, standard deviation [SD], maximum, minimum, and percentage when applicable).

Baseline disease severity and psychiatric history was also summarized by descriptive statistics.

9.7.1.7 Prior and Concomitant Therapy

The Phase B Efficacy set was used.

9.7.1.8 Safety Analyses

All safety analyses were to be performed on the Safety Analysis Sets. Safety data were summarized on an "as treated" basis using descriptive statistics (e.g., n, mean, standard deviation, median, minimum, maximum for continuous variables; and n [%] for categorical variables). Safety variables included TEAEs, clinical laboratory parameters, vital signs, and 12-lead ECG results. Study Day 1 for all safety analyses was defined as the date of the first dose of study drug.

In general, baseline measurements of safety variables were defined as the last measurements prior to the first dosing of study drug for each phase of the study. Safety analyses were conducted based on the safety populations (Section 9.7.1.4).

9.7.1.8.1 Adverse Events

The AE verbatim descriptions (i.e., investigator terms from the CRF) were to be recorded and entered into the database.

A TEAE was defined as an AE that emerged during treatment, having been absent at pretreatment (i.e., baseline) or

- Reemerged during treatment, having been present at pretreatment (i.e., baseline) but stopped before treatment
- Worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.

Only those AEs that were treatment emergent were to be included in summary tables. All AEs, treatment emergent or otherwise, were presented in subject data listings.

Treatment-emergent AEs were summarized. The incidence of TEAEs was reported as the number (i.e., percentage) of subjects with TEAEs by system organ class and preferred term (PT). A subject was counted only once within a system organ class and PT, even if the subject experienced more than one TEAE within a specific system organ class and PT. The number (i.e., percentage) of subjects with TEAEs was also summarized by maximum severity (i.e., mild, moderate, or severe).

The number (i.e., percentage) of subjects with TEAEs were also summarized by relationship to study drug (i.e., possibly related, probably related, and not related).

9.7.1.8.2 Laboratory Values

Laboratory results were to be summarized using Système International units, as appropriate. For all quantitative parameters listed in Section 9.5.1.4 Safety Assessments, the actual value and the change from baseline to each post-baseline visit and to the end of treatment (i.e., defined as the last on-treatment value) was summarized using descriptive statistics. Qualitative parameters listed

in Section 9.5.1.4 were summarized using frequencies (i.e., number and percentage of subjects), and changes from baseline to each post-baseline visit and to end of treatment were reported. Percentages were based on the number of subjects with both nonmissing baseline and relevant post-baseline results.

Laboratory test results were assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range.

9.7.1.8.3 Vital Signs

Descriptive statistics for vital signs parameters (i.e., diastolic and systolic BP, heart rate, respiration rate, temperature, and weight) and changes from baseline were to be presented by visit.

9.7.1.9 Efficacy Analyses

The primary objective of the study was to evaluate the effect of aripiprazole once monthly on 30-, 90-, and 180-day psychiatric re-hospitalization rates following discharge due to symptoms associated with schizophrenia, compared with retrospective 30-, 90-, and 180-day psychiatric hospitalization rates in subjects previously treated with oral antipsychotic medication.

Because all primary and secondary outcome measures described in the specific aims were continuous and a reflection of a single design configuration involving longitudinal measures, in some cases including retrospective as well as prospective time points, the basic structure of the data analytic strategies was the same for all objectives.

The primary and secondary outcomes were to be analyzed using repeated measures analysis of covariance (ANCOVA) models. For example, in the three primary outcome models, testing for a main effect of time on 30-, 90-, or 180-day pre-hospitalization (i.e., oral antipsychotic) versus 30-, 90-, or 180-day post-hospitalization (i.e., aripiprazole once monthly) rates, respectively. Covariates would have included psychiatric symptoms severity at baseline, measured by CGI-S scores.

Some secondary outcome measures such as BMI, fasting lipid parameters, and glucose that were measured at time points post-hospitalization only (i.e., at baseline, 30-, 90-, and 180-days) were to be evaluated using mixed model repeated measures analysis of variance to determine whether there are changes over time. Other covariates could include race, gender, age, family history of diabetes, and BMI.

Only one primary specific objective was defined, with three time-point comparisons (i.e., 30, 90, and 180 days) with the primary comparison being hospitalization rate for the period of 30 days pre-hospitalization (i.e., at least one, based on the index hospitalization) to 30 days post-hospitalization both because of the importance of that objective and to minimize multiple comparisons concerns. Because of the multiple comparisons issue, p-values associated with the secondary and exploratory analyses performed were to be interpreted cautiously as hypothesis-generating rather than as hypothesis-confirming.

9.7.1.10 Other Analyses

In general, continuous variables were to be summarized by descriptive statistics (i.e., n, mean, median, SD, standard error, maximum, and minimum). The repeated measures ANCOVA was used based on the Phase B sample. The variables relating to hospitalization data were to be comparing retrospective versus prospective data. The number of hospital stays per subject, cumulative duration of hospitalization, mean duration of hospitalization, and the number and mean duration of all other (i.e., non-inpatient) hospitalization programs were to be compared between the SOC and aripiprazole once monthly by ANCOVA and summarized using descriptive statistics. The Kaplan-Meier estimate of the median discontinuous time and the overall Kaplan-Meier curve for the Phase B efficacy sample were to be provided for the time-to-discontinuation due to all causes. In addition, discontinuation rate due to all reasons, change from baseline in CGI-S and CGI-I scores were to be summarized using descriptive statistics for the Phase B efficacy sample.

9.7.2 Determination of Sample Size

The primary endpoints of this study were comparisons of the rate of hospitalization for specified pre-hospitalization (i.e., pre-aripiprazole once monthly) timeframes (i.e., 30-, 90-, and 180-days) to corresponding post-hospitalization timeframes. Based on published results of other studies, it was generally reasonable to assume 30% of subjects would be hospitalized pre-medication switch and 15% would be hospitalized post-switch to aripiprazole once monthly. In this study, 100% of the pre-aripiprazole once monthly subjects would have had at least one hospitalization (i.e., index inpatient hospitalization at least). The estimated sample size of 90 completed subjects would have provided approximately 80% power (alpha = 0.05 two-sided) to detect a clinically relevant difference between pre-switch and post-switch hospitalization rates. The recent Otsuka Mirror study had 121 completers with only a 28% pre-switch hospitalization rate, compared to the present design with a 100% pre-switch hospitalization rate, with highly significant reductions in total psychiatric hospitalization rates in the Mirror study. A medium effect size = 0.5 with a sample size of N = 90 provided approximately 80% power to detect significance at the 5% level (two-tailed test).

9.7.3 Interim Analysis

No interim analysis was planned.

9.7.3.1 Data Safety Monitoring Board

No Data Safety Monitoring Board was planned for this non-randomized, unblinded study.

9.7.4 Other Statistical and Analytical Issues

9.7.4.1 Handling of Missing Data

In order to assess sensitivity of results due to missing data, two types of analyses were to be performed: last observation carried forward (LOCF) and observed case (OC). The primary data set for efficacy analyses by visit was to be the LOCF data set derived from the Phase B efficacy sample. The LOCF data set would have included data recorded at a scheduled Phase B visit or, if no observation was recorded at that visit, data carried forward from the previous scheduled Phase

B time point. Baseline data (i.e., Day 0 in Phase B) were not to be carried forward to impute missing values for the LOCF data set. Analyses based on the OC data set were to be performed. The OC data set would have consisted of the actual observations or hospitalization/ED data recorded at each relevant time point.

9.8 CHANGE TO THE CONDUCT OF THE STUDY OR ANALYSES

9.8.1 Protocol Amendments

There were three amendments to the protocol; major changes are described below.

9.8.1.1 Amendment 1.0, 17 Dec 2015

- Study population recruitment procedures and locations were clarified.
- Updated text to reflect the change in the product labeling that allows for deltoid injections and the reason for administration of oral aripiprazole was added for consistency.
- Pre-Screening assessments to help investigators identify any subjects with literacy or capacity to consent issues prior to study enrollment were added.
- The Follow up Period was eliminated from the study duration.
- Study population recruitment procedures and locations were clarified.
- The IRB requirement regarding consent by a legal representative in addition to the subject as part of the inclusion criteria was eliminated.
- Corrected text to clarify the accountability documentation to OAPI, including the elimination of the need for FDA Form 1572.
- Removed waiting time requirement after IM injection during injection site evaluation.
- Study duration was changed, resulting in elimination of Visit 9.
- Added text regarding the time period for the collection of safety information and the definition of safety information.
- Moved text regarding safety endpoints into a new section as they are considered exploratory endpoints.

9.8.1.2 Amendment 2.0, 26 Feb 2016

- Added text to clarify use of olanzapine and aripiprazole during study duration; text added to clarify the type of antipsychotic allowed during Screening Period; added text to describe decision procedures for aripiprazole once monthly injection administration; added text regarding long-acting antipsychotics as exclusionary medications with the exception of aripiprazole once monthly.
- Added text regarding how data regarding psychiatric and non-psychiatric hospitalizations will be confirmed; text regarding timing of hospitalization and types of documentation to determine eligibility was added for clarification; added text to clarify that DSM-5 diagnosis of schizophrenia must be current.
- Added text regarding aripiprazole dosage decrease.
- Updated inclusion and exclusion criteria.
- Score cap for the UBACC was removed.to allow for greater flexibility for inclusion on the study.

- Updated text to clarify that the diagnosis of schizophrenia according to DSM-5 criteria had to be current; added text describing methods for confirmation of data regarding psychiatric and non-psychiatric hospitalizations and medical interventions.
- The primary efficacy endpoint was reworded for clarity and consistency with other sections (administrative change).

9.8.1.3 Amendment 2.1, 24 Aug 2016

- Added text to clarify when screening for eligibility for entry into the study will occur.
- Added text to clarify that olanzapine is no longer considered an exclusionary medication during the Screening Period, except for those who are eligible for Phase A.
- Added text to clarify the use of long-acting injectable aripiprazole during Phase B for all subjects and eligibility of subjects who were clinically started on long-acting injectable aripiprazole during hospitalization just prior to study entry.
- Updated text to clarify timing and use of baseline assessments for determining tolerability to oral aripiprazole during Phase A of the study; removed text to clarify timing of Phase B baseline/Day 1.
- Added text regarding timing of the collection of baseline data during Phase B for subjects that are enrolled after starting long-acting injectable aripiprazole in the hospital.
- Added text stating that the Study Coordinator can receive a pre-discharge assignment, in addition to a community support worker, for subjects who are psychiatrically stabilized and discharged prior to the completion of the required 14-day course of oral aripiprazole.
- Added text to clarify which clinical laboratory tests require fasting according to when they are performed (i.e., Screening Period versus Baseline Visit)
- Added text regarding the eligibility of subjects already clinically started on long-acting injectable aripiprazole during the hospitalization just prior to study entry.
- Added text regarding the timing of the Baseline Visit and how baseline assessments are to be conducted.
- Updated text regarding how and which baseline assessments will be conducted.
- Updated exclusion criteria.

10 SUBJECT DISPOSITION

A total of nine subjects were enrolled in the study from two of three active sites.

Site	Total Enrolled
Washington University in St. Louis (600-100x)	2
University of Missouri, Columbia	N/A
University of Missouri, Kansas City (600400x)	6
All Sites	**9**

N/A = not applicable

Of the nine enrolled subjects, eight received study drug and their demographic characteristics and study data are provided in Table 4 through Table 7.

Of the nine enrolled subjects, one subject completed the trial (600-1001). Eight subjects discontinued the study prior to completion, with one of those eight discontinuing prior to receiving any study drug. Discontinuations are provided in Table 4:

Table 4: Reasons for Discontinuation

Reason for Discontinuation	Subject ID
Withdrew consent prior to study drug administration	Subject 604001
Withdrew consent (reason not specified)	Subject 600-1002
Terminated early due to study closure	Subject 600-1003 Subject 604003 Subject 604005 Subject 604006
Terminated early by the site investigator in relation to persistent psychotic symptoms, psychiatric hospitalization and clinical decision to use risperidone	Subject 604002
Withdrawn from study due to a TESAE of seizure resulting in hospitalization.	Subject 604004

ID = identification, TESAE = treatment-emergent serious adverse event

11 EFFICACY

This study was terminated due to lack of enrollment. An insufficient number of subjects were enrolled to analyze the data for efficacy. Efficacy data collected are provided in Appendix 2Appendix 1.

12 SAFETY

12.1 BASELINE ASSESSMENTS AND SCREENING

Baseline and screening data collected are provided in Table 5 and Appendix 2.

Table 5: Baseline and Screening Assessments

Baseline Data Category	Result N = 8
Age, mean (SD)	**32.84 (8.69)**
Gender, n (%)	**8 (100.0)**
Male	3 (37.50)
Female	5 (62.50)
Race, n (%)	**8 (100.0)**
Caucasian	2 (25.00)
Black	6 (75.00)
Ethnicity, n (%)	**8 (100.0)**
Hispanic	0 (0.00)
Not Hispanic	8 (100.00)
CGI, Severity of Illness, n (%)	**8 (100.0)**
Moderately Ill	1 (12.50)
Markedly Ill	5 (62.50)
Severely Ill	2 (25.00)
BMI (kg/m^2), mean (SD)	**29.08 (7.88)**
Height (cm), mean (SD)	167.48 (13.40)
Weight (kg), mean (SD)	80.02 (16.36)
Fasting Lipids (mg/dL), mean (SD)	
Total Cholesterol	169.75 (32.38)
Triglycerides	97.63 (58.34)
HDL cholesterol	66.25 (33.97)
LDL choloesterol	84.13 (28.38)
HbA1c (%), mean (SD)	**5.11 (0.28)**

BMI = body mass index, CGI = Clinical Global Impression, HbA1c = glycosylated hemoglobin, HDL = high-density lipoprotein, LDL = low-density lipoprotein, SD = standard deviation

12.2 ADVERSE EVENTS

Four subjects experienced a total of 10 TEAEs, 4 of which were SAEs. Subject 604002 experienced two psychiatric hospitalizations that were not unexpected in this study population; one during study participation leading to discontinuation and one during the immediate post-study follow-up period. Of note, Subject 604002 also experienced two psychiatric ED visits during study participation, not unexpected for this population and coded in the study as a primary outcome rather than as an SAE. Subject 604004 experienced one TESAE during the study, seizure, leading to discontinuation and one AE of generalized weakness during the immediate post-study follow-up

period. The narrative is provided in Section 12.3.2. Adverse event data collected is provided in Table 6 and Appendix 2.

Table 6: Adverse Events

Subject ID	Adverse Event	SAE?	Intensity	Action Taken	Relationship to Study Drug	Onset Date/ End Date[a]	Outcome[a]
604002	Psychiatric hospitalization	Y	Moderate	Aripiprazole stopped, subject discontinued from study, risperidone started	Not related	02 Nov 2016/ 14 Nov 2016	Resolved
	Psychiatric hospitalization	Y	Moderate	None, subject no longer in study	Not related	28 Nov 2016/ 02 Dec 2016	Resolvecd
604004	Seizure	Y	Severe	Aripiprazole stopped, subject discontinued from study	Not likely	11 Jan 2017/ 17 Janu 2017	Resolved
	Generalized weakness	Y	Moderate	None, no longer in study	Not likely	29 Jan 2017/ 3 Feb 2017	Resolved
	Prolonged QTc interval	N	Mild	None, subject discontinued from study	Not likely	13 Jan 2017/ 15 Jan 2017	Resolved
	Insomnia	N	Moderate	None	Not related	10 Jan 2017/ 1 Feb 2017	Resolved
	Cellulitis	N	Moderate	None, no longer in study	Not related	25 Jan 2017/ 29 Jan 2017	Resolved
604003	Sialorrhea	N	Mild	None	Possibly related	18 Jan 2017/ Ongoing	Lost to Follow-up
	Injection site pain	N	Mild	None	Definitely related	30 Jan 2017/ 31 Jan 2017	Resolved
604005	Akthesia	N	Mild	None	Possibly related	13 Mar 2017/ Ongoing	Lost to Follow-up

ID = identification, QTc = corrected QT interval, SAE = serious adverse event
[a:] at the time of last follow-up

12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND ADVERSE EVENTS LEADING TO DISCONTINUATION FROM THE STUDY

One subject (604002) experienced a TESAE of psychiatric symptom increase leading to psychiatric hospitalization, a primary study endpoint and not an unexpected SAE in this population. Another subject (604004) experienced an unexpected TESAE, seizures, during the study, which resulted in discontinuation from the study as described in Section 12.3.2.

12.3.1 Deaths

There were no deaths during the study.

12.3.2 Other Serious Adverse Events

An unexpected TESAE was experienced by only one subject (604004). However, this subject experienced two SAEs, one during the study leading to that subject's study discontinuation and one during the immediate follow up period. This subject was a 40-year-old woman diagnosed with schizophrenia in 2005. Her medical history included a historical diagnosis of Dandy-Walker syndrome, benign occipital lobe cyst, childhood seizures reported to not extend into adulthood, and increased BMI. Concomitant medications were quetiapine, haloperidol and zolpidem for sleep during her initial admission prior to study entry.

The subject was admitted to the behavioral health unit on 05 Jan 2017 with increasing auditory hallucinations and insomnia impairing her functioning. She had trouble with adherence to medication and daytime sedation and a clinical decision was made to transition from quetiapine to oral aripiprazole, 5 mg, per oral every morning. She was enrolled in the study on 10 Jan 2017 entering into Phase B of the study at a dose of 10 mg oral aripiprazole, and received her first injection of long-acting aripiprazole on that day.

The subject had reported not sleeping for 7 days and experienced a fall on 11 Jan 2017 while walking backwards. On that day she experienced a generalized tonic clonic seizure, was cyanotic, and lost consciousness. Oxygen and lorazepam were administered and she was transported to the ED and subsequently admitted to the medical floor. The subject was withdrawn from the study due to the seizure, which resulted in medical hospitalizations. On 13 Jan 2017, she experienced two seizures approximately 6 hours apart; the second immediately following an electroencephalogram (EEG). The seizures were treated with levetiracetam and lorazepam. In addition, lorazepam was given for anxiety. The subjects EEG showed multiple sub-clinical seizures lasting from 10 to 26 seconds. The subject was discontinued from the study on 13 Jan 2017.

She was discharged on 17 Jan 2017 without oral antipsychotic medication and was prescribed levetiracetam, temazepam for insomnia, and hydroxyzine for anxiety. The seizures were considered resolved on 17 Jan 2017.

During the follow-up period, the subject was taking cephalexin from 25 Jan 2017 for cellulitis. She presented to the ED on 29 Jan 2017 with a complaint of generalized weakness which was moderate in severity, resulting in hospital admission during the 30-day period following discontinuation from the study on 13 Jan 2017. Laboratory tests were unremarkable. On 30 Jan

2017, after discharge from the hospital, she received benztropine (indication unknown), hydroxyzine for anxiety and temazepam for insomnia. The subject was restarted on quetiapine on 01 Feb 2017. On 03 Feb 2017 the subject had made a full recovery from the generalized weakness and was ambulating without assistance. The benztropine was discontinued on 14 Feb 2017.

The site investigator assessed the seizures and generalized weakness to be unlikely related to study drug.

12.4 CLINICAL LABORATORY RESULTS

There were no treatment-emergent clinically significant laboratory results reported during the study. There were a number of subjects with elevated laboratory results at screening. Reference ranges and results for out of range screening laboratory values are provided in Appendix 1.

Subject 604002 had a creatinine concentration of 0.68 at screening and returned to within normal range [0.82] on Day 30 (reference range: 0.76 to 1.27 mg/dL; KC LabCorp [Male]). Subject 604002 also had a total bilirubin of 0.2 on Day 30 (reference range: 0.3 to 1.2 mg/dL KC Truman Medical Center EMR; however, this value is defined as normal in the KC Truman Medicla Center Laboratory where the test was completed).

Subject 600-1003 had a low glucose concentration on Day 30 (67 mg/dL; reference range: 70 to 110 mg/dL, KC Truman Medical Center Laboratory). This subjects screening glucose was within the normal range.

None of these reported laboratory results were considered clinically significant. The means and standard deviations for the chemistry safety laboratory data are provided in Table 7; the small sample sizes preclude analyses or any conclusions regarding trends.

Table 7: Blood Chemistry Safety Laboratory Results

Blood Chemistry	Unit	Timepoints			
			Phase B		
		Screening (n = 8)	Day 30 (n = 2)	Day 120 (n =3)	Day 180 (n = 1)
		Mean (SD[a])			
Albumin	g/dL	4.19 (0.43)	4.30 (0.42)	4.70 (0.26)	4.50
Calcium	mg/dL	9.01 (0.71)	9.25 (0.64)	9.70 (0.20)	9.50
BUN	mg/dL	10.88 (3.04)	12.50 (0.71)	12.33 (1.15)	13.00
Total bilirubin	mg/dL	0.44 (0.16)	0.50 (0.42)	0.43 (0.21)	0.60
ALP	U/L	68.88 (17.40)	68.00 (1.41)	80.33 (18.34)	68.00
AST	U/L	17.50 (5.24)	16.50 (2.12)	16.33 (0.58)	22.00
ALT	U/L	16.25 (4.17)	15.50 (0.71)	18.33 (5.86)	23.00
Creatinine	mg/dL	0.76 (0.25)	0.87 (0.07)	0.99 (0.08)	0.86
Sodium	mmol/L	139.88 (3.52)	140.50 (2.12)	141.00 (1.73)	141.00
Potassium	mmol/L	4.08 (0.29)	4.05 (0.35)	4.27 (0.06)	4.00
Chloride	mmol/L	102.25 (3.81)	104.00 (1.41)	103.00 (1.73)	104.00
Carbon dioxide	mmol/L	25.38 (3.62)	25.00 (4.24)	23.67 (2.52)	26.00
Fasting glucose	mg/dL	88.63 (10.36)	90.00 (9.90)	86.00 (16.46)	ND
Total protein	g/dL	7.04 (0.82)	7.30 (0.71)	7.53 (0.50)	7.10

ALP = alkaline phosphatase, ALT = alanine transaminase, AST = aspartate transaminase, BUN = blood urea nitrogen, ND = not done, SD = standard deviation

[a]: Standard deviations were not calculated for Day 180, these data were for an n of 1

12.5 CLINICAL SAFETY VARIABLES

Clinical safety variables are provided in Table 8.

Table 8: Clinical Safety Variables

Clinical Variable	Timepoints										
			Phase B								
	Screening	Phase A	Day 1	Day 15	Day 30	Day 60	Day 90	Day 120	Day 150	Day 180	LOCF
	Mean (SD)										
Total # of psychiatric ER visits per subject	N/A	N/A	N/A	N/A	N/A	3[d]	N/A	N/A	N/A	N/A	3[d]
Total # of psychiatric hospitalizations per subject	N/A	N/A	N/A	N/A	N/A	1[d] A	N/A	N/A	N/A	N/A	1[d]
BMI (kg/m^2)	29.08 (7.88)	N/A	30.134 (8.52)	27.46 (8.47)	27.92 (8.58)	28.57 (9.11)	28.94 (9.72)	29.25 (9.75)	33.71 (ND)	34.37 (ND)	29.18 (8.14)
Height (cm)	167.48 (13.40)	N/A	168.06 (11.19)	167.03 (15.77)	166.76 (16.15)	166.96 (16.01)	171.82 (13.82)	171.82 (13.82)	161.29 (N/A)	161.20 (N/A)	168.36 (14.11)
Weight (kg)	80.02 (16.36)	N/A	83.07 (14.84)	74.89 (16.76)	75.93 (17.11)	77.73 (18.45)	82.50 (15.36)	83.43 (15.40)	87.70 (N/A)	89.30 (N/A)	81.00 (16.50)
HBA1c (%)	5.11 (0.28)	N/A	N/A	N/A	5.03 (0.50)	5.00 (N/A)	5.13 (0.46)	5.27 (0.51)	N/A	5.10 (N/A)	5.18 (0.38)
Total cholesterol (mg/dL)	169.75 (32.38)	N/A	N/A	N/A	186.00 (47.27)	N/A	186.75 (15.97)	175.67 (26.76)	N/A	214 (N/A)	177.80 (30.19)
Triglycerides (mg/dL)	97.63 (58.34)	N/A	N/A	N/A	68.50 (24.09)	N/A	84.75 (22.57)	75.33 (14.84)	N/A	89 (N/A)	70.80 (21.48)
HDL cholesterol (mg/dL)	66.25 (33.97)	N/A	N/A	N/A	63.00 (23.31)	N/A	58.75 (12.84)	55.00 (10.82)	N/A	90 (N/A)	64.40 (17.04)
LDL cholesterol (mg/dL)	84.13 (28.38)	N/A	N/A	N/A	109.50 (29.37)	N/A	111.00 (4.97)	105.33 (15.04)	N/A	106 (N/A)	99.00 (18.01)
Prolactin (ng/mL)	24.15 (12.82)	N/A	21.29 (30.80)	N/A	7.50 (3.63)	5.80 (N/A)	6.30 (5.15)	6.63 (5.65)	N/A	2.70 (ND)	15.93 (25.40)
CGI[a] Severity of illness	5.13 (0.64)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CGI[b] Improvement	N/A	N/A	3.40 (0.55)	3.20 (0.84)	2.80 (1.30)	3.20 (1.64)	2.75 (0.96)	2.75 (0.96)	2.00 (ND)	2.00 (N/A	3.43 (1.40)
AIMS Severity of Abnormal Movements[c]	0.13 (0.35)	0.25 (0.50)	0.00 (0.00)	0.20 (0.45)	0.20 (0.45)	0.20 (0.45)	0.25 (0.50)	0.25 (0.50)	0.00	0.00	0.14 (0.38)
BARS Total score	0.88 (2.47)	0.00 (0.00)	0.60 (1.34)	0.40 (0.55)	0.00 (0.00)	1.00 (2.24)	0.50 (1.00)	0.50 (1.00)	0.00	0.00	0.29 (0.76)
SARS Total score	2.13 (3.09)	1.50 (3.00)	1.40 (2.61)	1.20 (1.30)	2.00 (2.92)	1.60 (1.95)	1.75 (2.2)	2.50 (2.89)	0.00	0,00	2.83 (2.79)

AIMS = abnormal involuntary movement scale, BARS = Barnes Akathisia Rating Scale, BMI = body mass index, CGI = Clinical Global Impression, ER = emergency room, HbA1c = glycosylated hemoglobin, HDL = high-density lipoprotein, LDL = low-density lipoprotein, N/A = not applicable, SARS = Simpson-Angus Rating Scale, SD = standard deviation

Note: Standard deviations not provided for Day 150 and Day 180 data due to n = 1 subject

[a]: Scale = normal, not all ill (1), borderline mentally ill (2), mildly ill (3), moderately ill (4), markedly ill (5), severely ill (6), among the most extremely ill patients (7)

[b]: Scale = very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), very much worse (7)

[c]: Scale = none (0), minimal, maybe extreme normal (1), mild (2), moderate (3). Severe (4)

[d]: Only 1 subject had ER visits (n = 3) and psychiatric hospitalizations (n = 1)

13 ADMINISTRATIVE PROCEDURES AND INSTRUCTIONS

13.1 CHANGES TO THE PROTOCOL

Any change to the protocol required a written protocol amendment or administrative change that must have been approved by the sponsor and OAPI before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study required submission to health or regulatory authorities as well as additional approval by the applicable IRBs. These requirements would in no way prevent any immediate action from being taken by the sponsor or investigators, in the interest of preserving the safety of all subjects included in the study. If the sponsor or investigator determined that an immediate change to or deviation from the protocol was necessary for safety reasons to eliminate an immediate hazard to the subjects, OAPI and the IRB for the site were to be notified immediately. The sponsor would have notified the health or regulatory authority as required per local regulations.

Protocol amendments that affected only administrative aspects of the study might not have required submission to health or regulatory authority or the IRB, but the health or regulatory authority and IRB would be kept informed of such changes as required by local regulations. In these cases, the sponsor might have been required to send a letter to the IRB detailing such changes.

13.2 ADHERENCE TO THE PROTOCOL

The sponsor and investigators conducted the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

13.3 MONITORING PROCEDURES

The sponsor and investigators assured appropriate monitoring of the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (i.e., source documents) were fully available for review by the sponsor's representatives at regular intervals. These reviews verified adherence to study protocol and data accuracy in accordance with local regulations. All records at the site were subject to inspection by the local auditing agency and IRB review.

In accordance with ICH E6, Section 1.52, source documents included, but were not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which were certified for accuracy after production
- Recorded data from automated instruments such as an interactive voice or web response system, x-rays, and other imaging reports, (e.g., sonograms, computed tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, electroencephalographs, polysomnographs, pulmonary function tests) regardless of how these images were stored, including microfiche and photographic negatives

- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (e.g., urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs
- CRF components (e.g., questionnaires) that are completed directly by subjects and serve as their own source

13.4 RECORDING OF DATA

CRFs linked to REDCap were required and completed for each subject by qualified and authorized personnel. All data on the CRF reflected the corresponding source document, except when a section of the CRF itself was used as the source document. Any corrections to entries made on the CRF were documented in a valid audit trail where the correction was dated, the individual making the correction was identified, the reason for the change was stated, and the original data were not obscured. Only data required by the protocol for the purposes of the study were collected.

The investigator signed each CRF.

13.5 IDENTIFICATION OF SOURCE DATA

All data to be recorded on the CRF reflected the corresponding source documents.

13.6 RETENTION OF RECORDS

The circumstances of completion or termination of the study notwithstanding, the investigator was responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (e.g., Form FDA 1572, ICFs, and IRB correspondence). The site retains study documents for the length of time agreed upon in the study contract.

It was requested that at the completion of the required retention period, or should the investigator retire or relocate, the sponsor contact OAPI, allowing OAPI the option of permanently retaining the study records.

13.7 REPORTING OF PRODUCT QUALITY COMPLAINTS

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

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

13.7.1 Information Required for Reporting Purposes

All of the following information would be included when reporting a PQC:

- Description of the complaint(s)
- Reporting party identification (i.e., initial reporting party, such as subject, investigator, or study coordinator)
- Reporter contact information (e.g., address, telephone number, e-mail address)
- Product or compound identification, including name and any product codes, if applicable
- Clinical protocol reference (e.g., collaborative protocol number)
- Dosage form and strength, if known
- Photographs, if available
- Availability for return

13.7.2 Eliciting and Reporting Quality Complaints

The sponsor or designee was required to record all PQCs identified through any means from the receipt of study drug through and including reconciliation and up to destruction, including subject dosing. Identification of a PQC by a subject would be reported to the site investigator, who would report the PQC.

The sponsor or designee was required to notify OAPI within 24 hours of becoming aware of the PQC by e-mail or telephone:

- Online: send the required information to OAPI-EQCProductComplaints@otsuka-us.com
- Telephone: Rocky Mountain Call Center at 1-800-438-6055

13.7.3 Return Process

During the PQC reporting process, it would be indicated if the sample under complaint was available for return. If the sample was available for return, OAPI-EQC would provide a product retrieval package to return the sample in the product retrieval package.

Documentation in the site source documents that a complaint sample for a dispensed product would have been forwarded to OAPI-EQC for complaint investigation.

Assessment and evaluation of PQCs would be handled by the OAPI-EQC Quality Management Group.

13.8 DISCONTINUATION OF STUDY

OAPI reserved the right to discontinue the study for medical reasons or any other reason at any time. If a study was prematurely terminated or suspended, OAPI promptly informed the sponsors or institutions and the sponsor and investigators informed the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB would also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor, investigators, or institution, as specified by the applicable regulatory requirement(s).

The sponsor reserved the right to discontinue the study should his/her judgment so dictate. If the sponsor terminated or suspended a study without prior agreement of OAPI, the sponsor would inform the institution where applicable, and the sponsor or institution would promptly inform all investigators, OAPI, and the relevant IRB and provide OAPI and the IRB with a detailed written explanation of the termination or suspension. Study records were retained as noted above.

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15 APPENDICES

Appendix 1 Reference Ranges

Blood Chemistry	Unit	KC LabCorp	KC Truman Medical Center	Washington University CLCS
Albumin	g/dL	3.5 – 5.5	3.4 – 5.0	3.5 – 5.2
Calcium	mg/dL	8.7 – 10.2	8.5 – 10.1	8.6 – 10.3
BUN	mg/dL	6 - 20	7 - 20	7 - 23
Total bilirubin	mg/dL	0.0 – 1.2	0.0 – 1.0	0.2 – 1.4
ALP	U/L	39 - 117	50 - 136	35 - 129
AST	U/L	0 - 40	15 - 37	11 - 47
ALT	U/L	0 - 32	30 - 65	6 - 53
Creatinine	mg/dL	0.76 – 1.27 (Male) 0.57 – 1.00 (Female)	0.6 – 1.3	0.7 - 1.3 (Male) 0.6 – 1.1 (Female)
Sodium	mmol/L	134 - 144	136 - 145	135 – 145
Potassium	mmol/L	3.5 – 5.2	3.6 – 5.2	3.3 – 5.1
Chloride	mmol/L	97 - 106	98 - 107	95 - 107
Carbon dioxide	mmol/L	18 - 29	21 - 32	21 - 29
Fasting glucose	mg/dL	65 - 99	70 - 110	64 - 99
Total protein	g/dL	6.0 – 8.5	6.4 – 8.2	6.1 – 8.4

Appendix 2: Subject Data

Appendix 3: Signature Page

SIGNATURE PAGE

Study Protocol Number:	031-104-0014
Study Protocol Title:	An Open-label, Multi-center, Longitudinal, Within-subject Comparison Study to Evaluate the Effects of Aripiprazole Once Monthly in Subjects with Schizophrenia on 30-, 90-, and 180-day Re-hospitalization Rates Following Hospital Discharge Compared with Retrospective Re-hospitalization Rates while on Oral Antipsychotic Medication
Drug Under Study:	Abilify Maintena®, aripiprazole

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

John W. Newcomer, MD

Investigator	Signature	Date