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ARIPIPRAZOLE, ABILIFY MAINTENA™ CLINICAL PROTOCOL

A Randomized, Open-Label, Parallel-Group, Study of the Impact of Aripiprazole Once Monthly versus Standard of Care Oral Antipsychotic Medications on Changes in Brain Structure and Metabolism

Protocol No. COL.AOM.2013.002
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CONFIDENTIAL – PROPRIETARY INFORMATION

Drug Development Phase:	4
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2 CLINICAL PROTOCOL SYNOPSIS

Name of Sponsor: The Brain Institute **Name of Product:** Abilify Maintena™, aripiprazole	
Protocol Title:	A Randomized, Open-Label, Parallel-Group, Study of the Impact of Aripiprazole Once Monthly versus Standard of Care Oral Antipsychotic Medications on Changes in Brain Structure and Metabolism
Clinical Phase:	4
Treatment Indication:	Schizophrenia
Objectives:	The primary objective of the study is: • To determine if there are differences in prefrontal white matter fractional anisotrophy (FA) in subjects with schizophrenia after 6 and 12 months of treatment with aripiprazole once monthly compared with standard of care (SOC) oral antipsychotic medications. The secondary objectives of the study are: • To determine if there are differences in water bound pool fraction (BPF) in prefrontal white matter in subjects with schizophrenia after 6 and 12 months of treatment with aripiprazole once monthly as compared with SOC oral antipsychotic medications. • To determine if proton metabolites, specifically gamma-aminobutyric acid (GABA), glutamine, and glutamate, are altered in subjects with schizophrenia after 6 and 12 months of treatment with aripiprazole once monthly compared with SOC oral antipsychotic medications. • To determine if there are differences in regional white matter and gray matter volume in subjects with schizophrenia after 6 and 12 months of treatment with aripiprazole once monthly compared with SOC oral antipsychotic medications. • To determine the effect on clinical and behavioral assessments after 12 months with aripiprazole once monthly compared with SOC oral antipsychotic medications in subjects with schizophrenia. The exploratory objective of the study is: • To determine if there is a demonstrated association between clinical and neurocognitive variables and FA, BPF, and proton metabolite concentrations in subjects with schizophrenia receiving SOC oral antipsychotic medications or once monthly aripiprazole.

Name of Sponsor: The Brain Institute

Name of Product: Abilify Maintena™, aripiprazole

Study Design:

This is a Phase 4, randomized, open-label, parallel-group study designed to assess the clinical and biological effects of 12 months of treatment with long-acting intramuscular (IM) aripiprazole as measured by clinical and behavioral measures, and changes on magnetic resonance imaging (MRI) scans in subjects with schizophrenia compared with SOC oral antipsychotic medications and compared with a healthy control group. A total of 80 subjects are planned to be enrolled in the study in a 3:1 subjects with schizophrenia:control ratio, to allow for an expected 60 completed subjects: approximately 45 subjects with Diagnostic and Statistical Manual, Fourth Edition – Text Revision (DSM-IV-TR) schizophrenia, and approximately 15 healthy control subjects. Attempts will be made to age-, gender-, and education-match the healthy control group with the schizophrenia group. Prospective subjects will undergo a thorough psychiatric and clinical screening phase, including a physical and neurological exam, 12-lead electrocardiogram (ECG), and baseline clinical laboratory testing.

After screening, subjects with schizophrenia will be randomized in a 2:1 aripiprazole once monthly:oral SOC antipsychotics ratio to the aripiprazole once monthly arm or the SOC oral antipsychotic arm of the study. Subjects with schizophrenia who are randomized to the aripiprazole once monthly arm and are not currently receiving oral aripiprazole monotherapy will undergo a medication washout and a conversion (Phase A) to oral aripiprazole monotherapy. In addition, any subject who is still taking a prohibited medication will enter Phase A for the appropriate washout. All subjects with schizophrenia will proceed to Phase B (Stabilization) directly after screening, or after Phase A if conversion to oral aripiprazole or washout from prohibited medications is required. Once stable on SOC oral antipsychotic medications for 2 consecutive visits, the subjects will proceed into Phase C (Treatment). Control subjects will also enter Phase C. All subjects with schizophrenia will undergo neuropsychological testing, clinical ratings, and multimodal MRI acquisition. The MRI scanning protocol includes high-resolution MRI, diffusion tensor (DT)-MRI, water-BPF, and magnetic resonance spectroscopy (MRS). Neuropsychological testing, clinical ratings, and multimodal MRI acquisitions will be performed after 6 and 12 months of treatment. The subjects will be assessed at regularly scheduled visits according to the schedule of assessments (Table 4 through Table 7). Six and 12-month MRI indices in subjects receiving once monthly aripiprazole will be compared with baseline data, the data from subjects with schizophrenia who are receiving SOC oral antipsychotic medications, and the healthy control subjects.

Instruments for the assessment of clinical and behavioral changes are:

Clinical assessments including suicidality, mood, extrapyramidal side effects (EPS), and adverse drug effects are: Abnormal Involuntary Movement Scale (AIMS), Barnes Akathesia Rating Scale (BARS), Clinical and Global Impression – Improvement (CGI-I), Clinical and Global Impression – Severity (CGI-S), Clinical and Global Impression - Severity of Suicidality (CGI-SS), Columbia Suicide Severity Rating Scale (C-SSRS), Hamilton Anxiety Scale (HAM-A), Hamilton Depression Rating Scale (HAM-D), Medication Adherence Questionnaire (MAQ), Monitoring of Side Effects Scale (MOSES), Positive and Negative Symptom Scale (PANSS), Profile of Mood States (POMS), and Simpson Angus Scale (SAS).

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Study Design continued:	In addition to completion of formal rating scales used to assess suicidal ideation and behaviors, suicidal symptomology will be monitored using structured interview questions and follow-up queries. Neuropsychological testing will include: The CogState tests which include Simple Reaction Time, Choice Reaction Time, One-back Working memory, Two-back Working Memory, and Set Shifting. Other neuropsychological tests will be the TrailMaking Test, Tower of London, Continuous Performance Test (CPT) and the Wisconsin Card Sorting Test (WCST). Functional assessments will include: Functional Assessment Test (FAST), Quality of Life Scale (QOLS), Social and Occupational Functioning Assessment Scale (SOFAS), and Life Functioning Questionnaire (LFQ). Healthy control subjects will not receive any investigational medicinal product (IMP); however these subjects will undergo all of the study procedures for comparison with the subjects with schizophrenia. Compliance with SOC drug will be managed using medication possession ratio (MPR) for prescription refills and the MAQ.
Subject Population:	A total of 80 subjects, aged 18 to 35 years will be enrolled to provide for an approximate 60 subjects who complete the study, 45 subjects with DSM-IV-TR schizophrenia and 15 healthy volunteers
Study Drug, Dose, Formulation, Mode of Administration:	Aripiprazole, administered once monthly via gluteal IM injection, as outlined in the product labeling. Oral antipsychotics – (SOC), which includes but is not limited to per oral (PO) administration of the following drugs as prescribed for the treatment of schizophrenia: • aripiprazole (Abilify®) 10 to 30 mg daily • risperidone (Risperdal®) 2 to 8 mg daily • lurasidone HCl (Latuda®) 40 to 160 mg daily • quetiapine fumarate (Seroquel®) 300 to 800 mg daily • olanzapine (Zyprexa®) 10 to 30 mg daily • ziprasidone HCl (Geodon®) 40 to 160 mg daily All SOC oral antipsychotics will be prescribed according to the recommendations contained in their respective product labeling.

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Criteria for Evaluation:	Primary Outcome Variables: Efficacy: The primary endpoint is FA by DT-MRI. Secondary Outcome Variables: Efficacy: The secondary endpoints are: • Volumes by high-resolution MRI • Water-BPF by MRI • Schizophrenia-related instrument scores including suicidality (CGI-SS and C-SSRS), clinical assessment (CGI-I, GAF), symptomology (CGI-I, CGI-S, HAM-A, HAM-D, PANSS, POMS), medication adherence (MAQ, MPR), neuropsychological assessment (Simple Reaction Time, Choice Reaction Time, One-back Working Memory, Set Shifting, TrailMaking Test, Tower of London, CPT, WCST), functional outcomes (FAST, QOLS, SOFAS, LFQ, Hollignshead Index), and side effects (MOSES) • Proton metabolite measurements by MRS
Study Duration:	The clinical trial duration is expected to be approximately 2 years. For subjects who do not require conversion to aripiprazole, the study duration including screening, stabilization, and the treatment phase is expected to be 13 months. For subjects who will require conversion to oral aripiprazole, the duration is expected to be 14.5 months.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
2-D	two-dimensional
ACC	anterior cingulate cortex
ADC	apparent diffusion coefficient
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
BARS	Barnes Akathesia Rating Scale
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BPF	bound pool fraction
BUN	blood urea nitrogen
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical and Global Impression - Severity
CGI-S	Clinical and Global Impression - Schizophrenia
CGI-SS	Clinical and Global Impression - Severity of Suicidality
CFR	Code of Federal Regulations
CNS	central nervous system
CPT	Continuous Performance Test
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
DCF	data clarification form
DSM-IV-TR	Diagnostic and Statistical Manual, Fourth Edition – Text Revision
DSMB	Data Safety Monitoring Board
DT	diffusion tensor
EC	Ethics Committee
ECG	electrocardiogram
EPI	echo-planar imaging
EPS	extrapyramidal side effects
FA	fractional anisotrophy
FAST	Functional Assessment Test
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GABA	gamma-aminobutyric acid
GAF	DSM-IV-TR Global Assessment of Functioning
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLX	glutamate/glutamine
HAM-A	Hamilton Anxiety Scale
HAM-D	Hamilton Depression Rating Scale

ICF	informed consent form
ICH	International Conference on Harmonisation
IM	intramuscular
IMP	investigational medicinal product
IRB	institutional review board
IRE	immediately reportable event
IUD	intrauterine device
LDH	lactate dehydrogenase
LFQ	Life Functioning Questionnaire
MAQ	Medication Adherence Questionnaire
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MD	mean diffusivity
MedDRA	Medical Dictionary for Regulatory Activities
MOSES	Monitoring of Side Effects Scale
MPR	medication possession ratio
MPRAGE	magnetization prepared rapid acquisition gradient echo
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NAA	N-acetyl aspartate
OAPI	Otsuka America Pharmaceutical, Inc.
OPC	Otsuka Pharmaceutical Company
PANSS	Positive and Negative Syndrome Scale
PD	pharmacodynamic
PO	per oral
POMS	Profile of Mood States
QOLS	Quality of Life Scale
RBC	red blood cell
SAE	serious adverse event
SAS	Simpson Angus Scale
SCID-P	Structured Clinical Interview for DSM-N patient version
SOC	standard of care
SOFAS	Social and Occupational Functioning Assessment Scale
TE	echo time
TEAE	treatment-emergent adverse event
TR	repetition time
VAS	visual analog scale
WBC	white blood cell
WCST	Wisconsin Card Sorting Test

5 ETHICS

This study must be conducted in compliance with the protocol, FDA regulations, the ICH GCP Guideline, and all other applicable local laws and regulatory requirements. Each study site will seek approval by an IRB according to regional requirements. The IRB will evaluate the ethical, scientific and medical appropriateness of the study. Further, in preparing and handling CRFs, the investigator, sub-investigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject identification code will be used to identify each subject.

5.1 INFORMED CONSENT

All subjects will have the purpose of the study, study interventions and evaluations, and the potential risks and benefits of participation explained to them and any questions will be answered. If a subject consents to participation in this study, the subject will review and sign the informed consent form (ICF).

Written informed consent will be obtained from all subjects (or their guardian or legal representative, as applicable for local laws). Consent will be documented on a written ICF. The ICF will be approved by the same Institutional Review Board (IRB) that approves this protocol. Each ICF will comply with the Food and Drug Administration (FDA) regulations in Title 21 Code of Federal Regulations (CFR) Part 50, International Conference on Harmonisation (ICH), Good Clinical Practices (GCP), and local regulatory requirements. The investigator agrees to obtain approval from the sponsor of any written ICF used in the study, prior to submission to the IRB.

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

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

6 INVESTIGATORS AND STUDY PERSONNEL

This is an investigator initiated study that will be conducted at The Brain Institute, University of Utah, 36 South Wasatch Drive, Salt Lake City, UT 84112.

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7 INTRODUCTION

Aripiprazole is the first non-D_2 receptor antagonist with clear antipsychotic effects and represents a novel treatment development for psychotic disorders. Aripiprazole possesses serotonergic properties, including partial 5-HT_{1A} agonism, 5-HT_{2A} antagonism, and affinity for the 5-HT_{2C}, 5-HT_6, and 5-HT_7 receptors. Aripiprazole is effective, safe, well tolerated, and has shown efficacy in the treatment of both the positive and negative symptoms of schizophrenia and schizoaffective disorder. Its unique mechanism of action may account for its sustained efficacy and favorable safety and tolerability profile, including a low risk for extrapyramidal symptoms (EPS), cardiac effects, hyperprolactinemia, weight gain, and other metabolic disturbances. Despite the improved side-effect profile of this agent, medication compliance in individuals with schizophrenia is still problematic and may impact symptomatic and cognitive recovery. Improved adherence to psychotropic treatment via long-acting injectable formulations may therefore lead to greater symptomatic improvements in this patient population, which may be detectible not only clinically but via current neuroimaging techniques as well. Therefore, the aim of this study is to examine the structural and metabolic effects of long-acting intramuscular (IM) aripiprazole once monthly and standard of care (SOC) oral antipsychotic medications in subjects with schizophrenia using magnetic resonance imaging (MRI) techniques and to examine these effects in association with cognitive and clinical measures.

Schizophrenia is a chronic illness associated with progressive brain changes over time1. The process underlying tissue loss has been attributed to the course of the illness. However, a study in primates found that loss of gray matter in schizophrenia may be related to antipsychotic medications2. In human studies of schizophrenia, volume losses have been reported for typical antipsychotic medications and volume gains for patients treated with atypical antipsychotic medications3-5. A recent investigation of long-acting depot risperidone versus oral risperidone in first-episode schizophrenia patients found that white matter volume remained stable over the 6-month trial in the long-acting depot patients, while it declined in those individuals taking oral risperidone. Interestingly, the increase in white matter was associated with improved cognitive performance. The authors suggested that the long-acting preparation changed the trajectory of myelination secondary to improved compliance6. Treatment with long-acting atypical antipsychotics has also been associated with improved clinical outcomes, including decreased hospitalizations and duration of hospital stays.

7.1 NOVEL APPROACHES TO UNDERSTANDING BRAIN CHANGES ASSOCIATED WITH MEDICATIONS

While conventional magnetic resonance imaging (MRI) allows for adequate visualization of brain structures and the detection of white matter lesions and hyperintensities, white matter tracts are not readily distinguishable. Diffusion tensor (DT)-MRI is a relatively new MRI modality designed to measure differences in constraints on water diffusion in various types of tissue7. Diffusion tensor imaging has proven effective for observing the relationship between cognitive deficits and structural connectivity in white matter. For example, fractional anisotropy (FA), reflective of tissue organization, degree of myelination, and water mobility, has been extensively used to correlate measures of diffusion with cognitive ability8. In a study of cognitive aging and executive function, Grieve et al. administered a battery of executive tasks and gathered DT-MRI data in a sample of 87 healthy subjects (aged 20 to 73 years) and found a significant negative association between age and average FA values in the frontal, parietal, and temporal lobes9.

Fractional anisotropy was shown to decrease at a rate of approximately 3% per decade in the prefrontal regions of the frontal lobe. Additionally, decreased FA was associated with poorer cognitive performance in executive maze and attention-shifting tasks9. These findings are consistent with earlier correlational work showing a negative association between age and FA values and a positive correlation between FA values and cognitive performance[10].

Determining the precise macromolecular content in neural tissue is crucial for accurately investigating white matter changes associated with anomalous brain development in the central nervous system (CNS)[11]. Recent imaging modalities, such as DT-MRI, provide useful, potential complementary tools that may aid in this process, but they are not without their limitations. For instance, DT-MRI indices, which measure the directionality of water diffusion in white matter through measures of FA, apparent diffusion coefficient (ADC) and mean diffusivity (MD), may or may not in fact be indicative of compromised brain tissue. Furthermore, there is still some disagreement over what exactly FA and ADC measure. Nevertheless, DT-MRI and other techniques have yielded promising findings, which may be aided by other novel approaches, such as T_1 bound pool fraction (BPF). Bound pool fraction, a T_1 measurement, may hold particular utility in the assessment of white matter tissue integrity, as it is a more direct measure of myelin content[12]. There is already convincing evidence, including some from the demyelinating disease, multiple sclerosis, that BPF is directly linked to the composition and density of myelin[13-15], a dielectric material that enables rapid and efficient conduction of neural signals[16-18]. Relevant to this proposal, Soellinger and colleagues' recent work demonstrated that, at 3 Tesla, BPF showed high repeatability and low variance in several investigated regions and thus appears to be a useful tool in investigating changes in myelin content or microstructural changes in brain tissue longitudinally[11]. The potential for BPF and DT-MRI to complement each other in such investigations was recently demonstrated by Stikov, et al[12]. In their study, they combined BPF macromolecular content estimates with measurements of diffusivity within human white matter tracts and found modest correlations between BPF and the diffusion indices FA and radial diffusivity. These findings suggest that the two techniques may, in fact, constitute complementary findings, which will clarify the mechanisms underlying white matter changes associated with the atypical antipsychotic agent, aripiprazole.

Magnetic resonance spectroscopy (MRS) methods allow identification and quantification of chemical compounds in tissue. The application of proton (^{1}H) MRS is widely used for *in vivo* measurement of human brain chemistry because nearly all metabolites contain protons, allowing for a large number of important neurochemicals to be detected and measured. Proton (^{1}H) MRS can measure cerebral concentrations of *N*-acetyl aspartate (NAA), choline (Cho)-containing compounds, glutamate/glutamine (Glx), myo-inositol (mI), lactate, and gamma-aminobutyric acid (GABA), which plays a central role in maintaining inhibitory function[19]. The primary inhibitory neurotransmitter, GABA, is distributed ubiquitously throughout the mammalian CNS. Altered GABAergic neurotransmission has been implicated in a wide range of human CNS disorders including epilepsy, schizophrenia, anxiety, and substance abuse disorders[20]. The pharmacological manipulation of GABAergic neurotransmission is a common target for many of these disorders and Proton (^{1}H) MRS approaches have successfully demonstrated normalized post-treatment GABA levels in depression[21], epilepsy[22], and substance abuse disorders[23]. To date, there have been no studies on the relationship between brain GABA levels and aripiprazole treatment in humans, which constitutes an important gap in the MRS literature. However, a recent study evaluating the effect of a variety of psychotropic drugs, including aripiprazole, on

rat brain metabolites found increased NAA concentrations (a marker of neuronal viability and activity) in the frontal cortex and striatum[24].

Seminal work completed by Koenig et al.[13] has provided strong evidence that BPF is directly linked to the local density of myelin and is thought to reflect efficient neuronal signal conduction. This method complements DT-MRI-based tractography, which allows for the evaluation of the integrity of specific white matter tracts and their connectivity[25]. Furthermore, the application of two-dimensional MRS provides a technique for the simultaneous measurement of localized neuronal metabolites, including GABA, glutamate, glutamine, and lactate[26]. Taken together these methods are ideally suited for evaluating changes in the structure and chemistry of the brain in relation to aripiprazole treatment. Although DT-MRI approaches have begun to examine aberrant white matter connectivity, changes accompanied by alterations in the macromolecular content of tissue are not observable using DT-MRI or conventional MRI. To our knowledge, no previous investigation has explored the impact of aripiprazole on the relationship between macromolecular content of white matter, DT-MRI measures of white matter integrity, and concentration of neuronal metabolites in the brain. In addition, we propose to examine the relationship between white matter integrity and neurocognitive and functional outcomes in relation to changes in brain structure and metabolic function.

7.2 ABILIFY® (ARIPIPRAZOLE)

Aripiprazole (ABILIFY®) is a dopamine partial agonist discovered by Otsuka Pharmaceutical Company (OPC) and co-developed by Bristol-Myers Squibb and OPC. Otsuka Pharmaceutical Company and H. Lundbeck A/S are jointly developing the IM once monthly 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 (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 symptoms (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 once monthly formulation. The aripiprazole IM once monthly formulation was recently approved for treatment of schizophrenia in the US.

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

7.3 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 extrapyramidal symptoms (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)[27] for information regarding nonclinical toxicity and pharmacokinetic (PK) studies conducted using aripiprazole in animals.

7.4 Relevant Clinical Studies

7.4.1 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[28] and 31-97-202)[29] each included 2 fixed doses of aripiprazole (15 mg and 30 mg for 31-97-201 and 20 mg and 30 mg for 31-97-202), an active comparator, for comparison of safety profiles, and placebo. Review of the data from these 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)[30] 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[31,32] 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 $\geq$ 5, PANSS scores for hostility or uncooperativeness $\geq$ 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)[33,34] of aripiprazole 30 mg versus haloperidol 10 mg were conducted in acutely relapsing schizophrenic subjects with the intention of pooling the data for analysis. On the primary efficacy measure (time to failure to maintain response in responders) no difference was seen between aripiprazole and haloperidol. However, analysis of secondary efficacy measures showed that aripiprazole 30 mg was superior to haloperidol 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)[35]. A separate open-label study (CN138152)[36,37] compared aripiprazole (10 to 30 mg daily) with SOC treatment (clinician-prescribed olanzapine, risperidone, or quetiapine) in community-treated schizophrenic subjects for whom an alteration in antipsychotic medication was clinically warranted. Aripiprazole demonstrated superior effectiveness as measured by the Investigator's Assessment Questionnaire, which provides an overall assessment of efficacy and tolerability[38].

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 Investigator's Brochure.[27]

7.4.2 Agitation Studies with Injectable Aripiprazole

The efficacy of immediate-release IM aripiprazole for the treatment of agitation was established in three short-term (24-hour) placebo-controlled studies[39]. 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.

7.4.3 Clinical Studies in Schizophrenia with Aripiprazole IM

Protocol CN138020, a clinical study conducted by Bristol-Myers Squibb, assessed the safety, tolerability, and PK of single doses of the aripiprazole IM once monthly formulation. This was an open-label, 2-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 IM once monthly formulation, followed by safety and PK monitoring. The IM once monthly 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. conducted a phase 1B study (Protocol 31-05-244) to assess the safety, tolerability, and PK of multiple doses of the aripiprazole IM once monthly formulation in subjects with schizophrenia. The results showed that once-monthly administration of the 400-mg and 300-mg IM once monthly 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 3 doses of aripiprazole IM once monthly (200, 300, and 400 mg) demonstrated acceptable safety, tolerability, and potential effectiveness[40].

A phase 3 study (Protocol 31-07-246) was conducted to evaluate the efficacy and safety of aripiprazole IM once monthly compared with placebo in schizophrenic subjects who had maintained stability on aripiprazole IM once monthly for at least 12 weeks. Aripiprazole IM once monthly 400 or 300 mg administered as monthly injections was effective for the maintenance treatment of schizophrenia in adults as demonstrated by a statistically significant difference, compared with placebo, in the primary efficacy endpoint of time to impending relapse. The percentage of subjects who met the criteria for impending relapse was significantly lower in the aripiprazole IM once monthly group than in the placebo group. The maintenance of stability was also demonstrated by statistically significant differences favoring aripiprazole IM once monthly in PANSS and CGI scores that remained significant throughout the double-blind, placebo-controlled phase. In addition, the Personal and Social Performance Scale (PSP) total score, cognitive function assessments, and IAQ score were supportive of the efficacy of aripiprazole IM once monthly treatment. Aripiprazole IM 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 IM 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.

7.4.4 Known and Potential Risks and Benefits

As of 10 Jun 2010, 15,088 adult patients were treated with aripiprazole oral tablet formulation in Phase 2, 3, and 4 studies (representing 8577 patient-exposure years). Of these, 3901 (25.9%) patients were treated with aripiprazole for 180 days or longer; 2259 (15.0%) patients received

aripiprazole for at least 360 days, with 933 (6.2%) patients 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. Akathesia 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[32].

In the pooled analysis of the two 52-week studies comparing aripiprazole with haloperidol, the incidence of EPS-related AEs was significantly higher for haloperidol (58%) compared with aripiprazole (27%). In the one 52-week study in which prolactin levels were measured, significantly fewer aripiprazole-treated subjects (3.4%) experienced prolactin elevations above the upper limit of normal compared with the haloperidol group (61%)[34].

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[41].

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 United States (US) package insert.

7.5 STUDY RATIONALE

Aripiprazole is a second-generation antipsychotic with a mechanism of action that may be attributed to a partial agonism at dopamine D_2 receptors. Aripiprazole also possesses serotonergic properties, including partial 5-HT_{1A} agonism, 5-HT_{2A} antagonism, and affinity for the 5-HT_{2C}, $5HT_6$, and $5HT_7$ receptors. Its unique mechanism of action may account for its sustained efficacy and favorable safety and tolerability profile, including a low risk for EPS, cardiac effects, hyperprolactinemia, weight gain, and other metabolic disturbances. Despite the improved side-effect profile of this agent, compliance in individuals with schizophrenia is problematic and may impact recovery. Improved adherence to psychotropic treatment may therefore lead to greater symptomatic improvements in this patient population. By nature of the method of administration, once monthly aripiprazole should produce improved treatment compliance compared with oral antipsychotics.

It is hypothesized that improved treatment compliance will lead to fewer white matter changes in the brain. Fewer white matter changes will be demonstrated via neuroimaging as increased FA and BPF values in the prefrontal region, and an increase in metabolites in a voxel centered on the anterior cingulate cortex (ACC) as seen with MRS. Therefore, the aim of this study is to examine the structural and metabolic effects of aripiprazole once monthly in patients with schizophrenia using MRI techniques and to examine these effects in association with cognitive and clinical measures.

8 STUDY OBJECTIVES

8.1 PRIMARY OBJECTIVE(S)

The primary objective of the study is:

- To determine if there are differences from baseline in prefrontal white matter FA after 6 and 12 months of treatment with once monthly aripiprazole in subjects with schizophrenia compared with SOC oral antipsychotic medications.

8.2 SECONDARY OBJECTIVE(S)

The secondary objectives of the study are:

- To determine if there are differences from baseline in water BPF in prefrontal white matter after 6 and 12 months of treatment with once monthly aripiprazole in subjects with schizophrenia compared with SOC oral antipsychotic medications.
- To determine if proton metabolites, specifically GABA, glutamine, and glutamate, are altered after 6 and 12 months of treatment with once monthly aripiprazole in subjects with schizophrenia compared with SOC oral antipsychotic medications, compared with baseline.
- To determine if there are differences from baseline in regional white and gray matter volume after 6 and 12 months of treatment with once monthly aripiprazole in subjects with schizophrenia compared with SOC oral antipsychotic medications.
- To determine the effect on clinical and behavioral assessments of schizophrenia after 12 months with aripiprazole once monthly compared with SOC oral antipsychotic medications, compared with baseline.

8.3 EXPLORATORY OBJECTIVE(S)

The exploratory objective of the study is:

- To determine if there is a demonstrated association between clinical and neurocognitive variables and FA, BPF, and metabolite concentrations in subjects with schizophrenia receiving SOC oral antipsychotic medications or once monthly aripiprazole.

9 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN

This is a Phase 4, randomized, open-label, parallel-group study designed to assess the clinical and biological effects of 12 months of treatment with aripiprazole once monthly as measured by clinical and behavioral measures, and changes on MRI scans in subjects with schizophrenia, compared with standard of care (SOC) oral antipsychotic therapy. A total of 80 subjects are planned to be enrolled in the study in a 3:1 subjects with schizophrenia:control ratio, to allow for 60 completed subjects: 45 subjects with Diagnostic and Statistical Manual of Mental Disease – Fourth Edition, Text Revised (DSM-IV-TR) schizophrenia, and 15 age-, gender-, and education-matched healthy control subjects. Prospective subjects will undergo a thorough psychiatric and clinical screening phase, including a physical and neurological examination, 12-lead electrocardiogram (ECG), and clinical laboratory testing. All subjects with schizophrenia will be evaluated using appropriate rating scales for psychosis, negative symptoms, depression, suicidality, and psychosocial functioning.

After screening, subjects with schizophrenia will be randomized in a 2:1 aripiprazole once monthly:oral SOC antipsychotics ratio to the aripiprazole once monthly arm or the SOC oral antipsychotics arm of the study. Subjects with schizophrenia who are randomized to the aripiprazole once monthly arm of the study and are not currently receiving oral aripiprazole monotherapy will undergo a medication washout and a conversion (Phase A) to oral aripiprazole monotherapy. In addition, any subject who is still taking prohibited medication will enter Phase A for the appropriate washout. All subjects with schizophrenia will proceed to Phase B (Stabilization) directly after screening, or after Phase A if conversion to oral aripiprazole or washout from prohibited medications is required. For those subjects in the oral SOC antipsychotic arm, once stable on SOC oral antipsychotic medications for 2 consecutive visits, the subjects will proceed into Phase C (Treatment). Control subjects will enter Phase C directly after screening. All subjects with schizophrenia will undergo neuropsychological testing, clinical ratings, and multimodal MRI acquisition. The MRI scanning protocol includes high-resolution MR, diffusion tensor (DT)-MRI, water-BPF, and magnetic resonance spectroscopy (MRS). Neuropsychological testing, clinical ratings, and multimodal MRI acquisitions will be performed after 6 and 12 months of treatment. The subjects will be assessed at regularly scheduled visits according to the schedules of assessments (Table 4 through Table 7). Six and 12-month MRI indices in subjects receiving once monthly aripiprazole will be compared with baseline data, the data from subjects with schizophrenia who are receiving SOC oral antipsychotic medications, and the healthy control subjects.

Clinical assessments including suicidality, mood, extrapyramidal side effects (EPS), and adverse drug effects are: Abnormal Involuntary Movement Scale (AIMS), Barnes Akathesia Rating Scale (BARS), Clinical and Global Impression – Improvement (CGI-I), Clinical and Global Impression – Severity (CGI-S), Clinical and Global Impression - Severity of Suicidality (CGI-SS), Columbia Suicide Severity Rating Scale (C-SSRS), Hamilton Anxiety Scale (HAM-A), Hamilton Depression Rating Scale (HAM-D), Medication Adherence Questionnaire (MAQ), Monitoring of Side Effects Scale (MOSES), Positive and Negative Symptom Scale (PANSS), Profile of Mood States (POMS), and Simpson Angus Scale (SAS).

In addition to completion of formal rating scales used to assess suicidal ideation and behaviors, suicidal symptomology will be monitored through structured interview questions and follow-up queries. During the initial structured interview, subjects will be asked about historical and current suicidal thoughts and self-directed violence. During study conduct, subjects will be asked during each call and at each visit if they had experienced a wish to die, or had any intention of engaging in self-directed violence. Additionally, subjects will be queried regarding feelings of sadness, helplessness, and hopelessness, as each of these have been related to suicidal ideation and suicide attempts. Expression of suicidal ideation or behaviors will be followed up verbally or, depending on the severity, through further clinical action.

Neuropsychological testing will include: The CogState tests which include Simple Reaction Time, Choice Reaction Time, One-back Working memory, Two-back Working Memory, and Set Shifting. Other neuropsychological tests will be the TrailMaking Test, Tower of London, Continuous Performance Test (CPT) and the Wisconsin Card Sorting Test (WCST).

Functional assessments will include: Functional Assessment Test (FAST), Quality of Life Scale (QOLS), Social and Occupational Functioning Assessment Scale (SOFAS), and Life Functioning Questionnaire (LFQ).

Healthy control subjects will not receive any study drug; however these subjects will undergo MRI imaging for comparison with the subjects with schizophrenia.

Compliance with SOC antipsychotic drugs will be managed using medication possession ratio (MPR) for prescription refills, and the self-reported MAQ.

The trial schematic is provided in Figure 1.

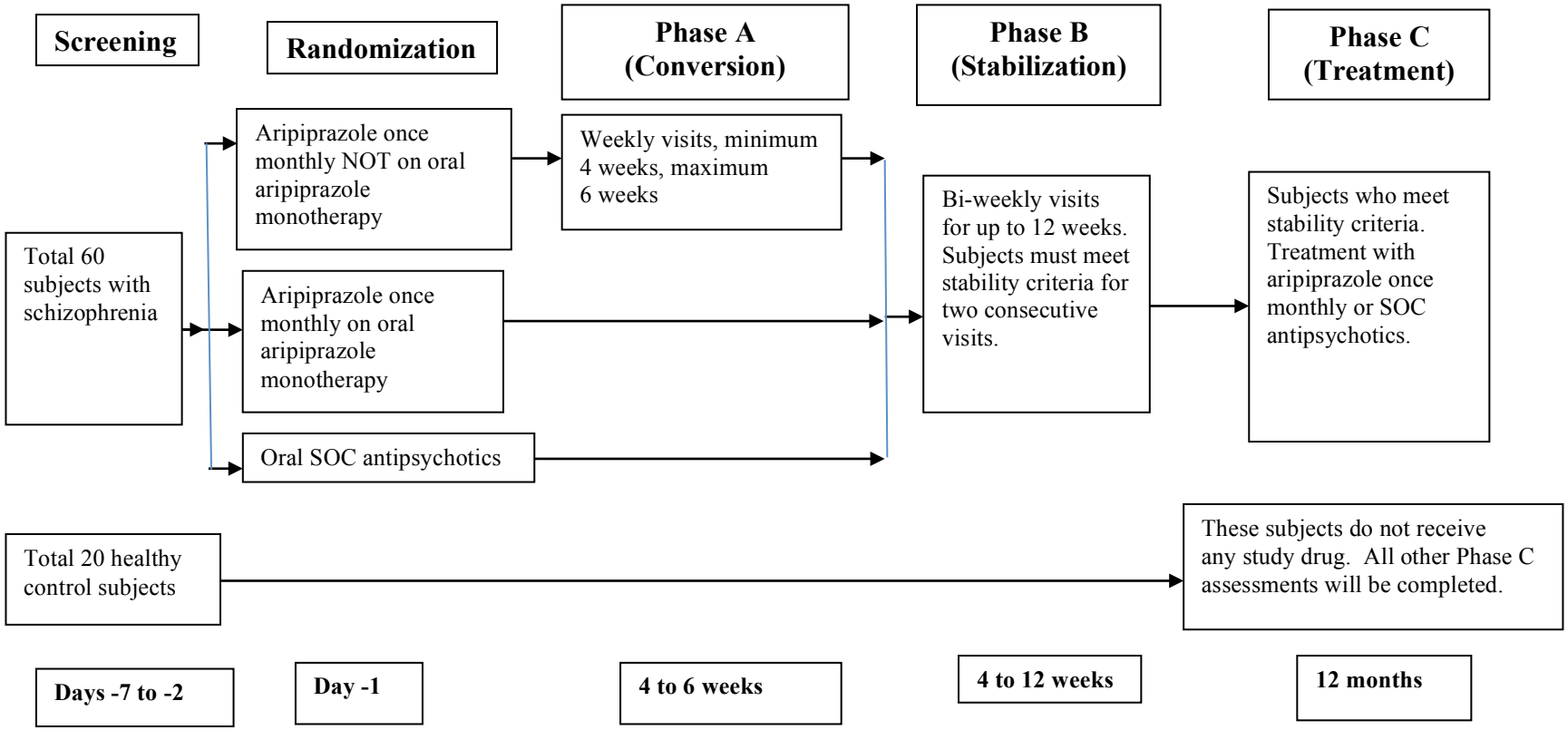

Figure 1 Study Schematic

9.1.1 Screening Period

All recruitment methods will conform to the guidelines of the IRB at the clinical site. Study recruitment materials will be posted at all included treatment facilities. Contact between subjects and clinical research staff will be initiated by the subjects. An initial pre-screening visit will be held to describe the study and, if interested, subjects will be asked to sign a study ICF.
The subjects participating in this study must be capable of understanding the nature of this study. The ICF contains a full description of the procedures and their associated risks. Subjects will be 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 will be given the opportunity to ask questions. Subjects will be asked to paraphrase the ICF. When ready, subjects will be asked to give written consent to participate in the study. After the ICF is signed by both the subject and the investigator, each subject will be given a copy of the signed ICF. The PI will have full responsibility for all issues pertaining to assent and informed consent.

The Screening Visit will occur on Days -7 to -2. Eligibility for the study will be determined via the following:

- Review of the inclusion and exclusion criteria
- Complete medical history and demographic data
- Assessment of current antipsychotic treatment and the stability of the current medication regimen
- Structured Clinical Interview for DSM-IV Patient Version (SCID-P) to determine Axis I disorders including substance use/dependence disorders
- Serum beta human chorionic gonadatropin (βhCG) pregnancy test for all women of childbearing potential to ensure that individuals are appropriate for imaging. Subjects who are found to be pregnant or have metal implants, pacemakers, prosthetic devices, or other situations or conditions that preclude the ability to participate in the imaging studies will not be entered into the study.
- Physical examination, including height and weight, and vital signs (body temperature, supine and sitting blood pressure, and heart rate) measurements
- Baseline clinical laboratory tests (See Section 9.5.1.3.1 for a complete list)
- Serum prolactin concentration
- 12-lead electrocardiogram (ECG)
- Urine drugs of abuse screen
- Blood alcohol content

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 will be recorded. Concomitant medications including details (e.g., drug name, dose, and frequency) of all current antipsychotic medication(s) will be recorded.

Washout from prohibited concomitant medications will begin, if applicable.

9.1.2 Baseline

Screening and the first baseline visit can occur on the same day if appropriate, and the assessments to be completed for the baseline visits will occur as outlined in Table 4, Table 5, and Table 6. For subjects who enter Phase A after screening, the baseline visit for Phase B will occur during the last visit for Phase A; all other subjects will have their baseline visit for Phase B either at the screening visit or on Day 1 of Phase B. At the Baseline Visits, the inclusion and exclusion criteria, current antipsychotic therapy, and concomitant medication use will be reviewed and recorded. Vital signs and body weight will be measured and body mass index (BMI) will be calculated.

The following core measures will be assessed:

1. Clinical Outcomes
    a. Positive and Negative Syndrome Scale (PANSS)
    b. Medication Adherence Questionnaire (MAQ)
    c. Clinical and Global Impression - Severity (CGI-S)
    d. Clinical and Global Impression - Severity of Suicidality (CGI-SS)
    e. Clinical and Global Impression – Improvement (CGI-I)
    f. Columbia Suicide Severity Rating Scale (C-SSRS)
    g. DSM-IV-TR Global Assessment of Functioning (GAF)
2. Mood
    a. Profile of Mood States (POMS)
    b. Hamilton Anxiety Scale (HAM-A)
    c. Hamilton Depression Rating Scale (HAM-D)
3. Extrapyramidal Side Effects
    a. Simpson Angus Scale (SAS)
    b. Abnormal Involuntary Movement Scale (AIMS)
    c. Barnes Akathesia Rating Scale (BARS)
4. Adverse Drug Effects

a. Monitoring of Side Effects Scale (MOSES)

Subjects will be given prescriptions for their oral SOC antipsychotic medications.

At the end of the baseline visit, for subjects who were randomized to aripiprazole once monthly who were not receiving oral aripiprazole monotherapy, cross-titration will begin (Phase A). In addition, any subjects who must undergo a washout from prohibited medications (see Section 9.4.5**Error! Reference source not found.**) will enter Phase A to complete the washout.

Subjects with schizophrenia who are randomized to the SOC oral antipsychotic arm who do not need to undergo washout from prohibited medications will move directly into Phase B.

9.1.3 Randomization

All subjects with schizophrenia will be randomized to the aripiprazole once monthly arm or the SOC oral antipsychotic arm in a 2:1 ratio at screening. Blocking will be used to ensure relatively equal distribution of subjects in each arm. It is expected that 80 subjects will be enrolled to compensate for any subjects that are lost-to-follow up, discontinue the study, or fail to meet conversion or stability criteria.

This will be an open-label study. All clinical personnel, investigators, and subjects will be knowledgeable regarding the study treatment.

9.1.3.1 Overall Treatment

- Aripiprazole once monthly at an approved dose based on the investigator's judgment and in accordance with product labeling, administered via gluteal IM injection once monthly.

- SOC oral antipsychotic medications (PO) will be prescribed by the study physician based on the investigator's judgment and in accordance with product labeling and include but are not limited to aripiprazole (Abilify®), risperidone (Risperdal®), lurasidone HCl (Latuda®), quetiapine fumarate (Seroquel®), olanzapine (Zyprexa®), and ziprasidone HCl (Geodon®).

9.1.3.2 Phase A – Conversion

During Phase A, all subjects randomized to aripiprazole once monthly that are not currently receiving aripiprazole monotherapy will undergo cross-titration to receive oral aripiprazole monotherapy, 10 to 20 mg PO, daily.

Subjects receiving SOC aripiprazole monotherapy can receive oral aripiprazole at doses ranging from 10 to 30 mg PO daily.

In addition, any subject requiring washout from prohibited medications will enter Phase A and prohibited medications will be withdrawn on a schedule based on the investigator's judgment.

9.1.3.3 Phase B – Stabilization

During Phase B, all enrolled subjects will be receiving SOC oral antipsychotic medication until stability criteria are met for two consecutive visits. All oral antipsychotic medications will be prescribed using doses consistent with their respective product labeling.

9.1.3.4 Phase C – Treatment

During Phase C:

- A total of 30 to 40 subjects with schizophrenia will receive aripiprazole once monthly, at a starting dose of 400 mg IM or an approved dose based on the investigator's judgment and in accordance with product labeling. In addition, these subjects will continue to receive oral aripiprazole at the dose (10 to 20 mg PO, daily) given prior to Phase C for 14 days.

- A total of 15 to 20 subjects will receive SOC oral antipsychotic medications, PO daily, in accordance with their respective product labeling.

9.1.4 Follow-Up Period

All subjects who receive at least one dose of study drug and who are discontinued from the study for any reason will be followed for safety reasons for 30 days following the last dose of drug.

9.2 Discussion of Study Design, Including Choice of Control Groups

The study design is based on published findings with respect to long-acting injectable neuroleptic medications and was selected based on prior imaging findings for competitor compounds[4,5]. Prior investigations suggest that the effect sizes will be large enough to see differences in imaging parameters between oral and once monthly injectable medication with the sample size proposed in this protocol[6]. Imaging findings in patients treated with aripiprazole will be compared to those observed in patients treated as usual with oral antipsychotic medications. The study will also include a non-psychiatric control group as normal aging has been shown to be associated with progressive brain structural changes including changes in white matter fiber tracts[43]. This study is not powered to provide evidence for or against clinical inferiority of the depot preparation. Choice of both primary and secondary endpoints for this study is consistent with published reports of changes in brain white matter integrity, localized brain volumes, and cognition after treatment with neuroleptic medications[4-6].

A data safety monitoring board (DSMB) will oversee the current study. Monitoring will include completion of a site initiation visit, interim monitoring visits, submission of monitoring reports, oversight of regulatory paperwork, and oversight of IRE/SAE review of monthly enrollment logs.

The scanning methods to be employed in this study are superior to those utilized in previous investigations as the current protocol will use higher magnetic resonance imaging field strength to collect data and more advanced analytical strategies for image analysis. As such, the effect sizes are expected to be larger and, because multimodal imaging protocols will be implemented, it is expected that this study will produce a number of significant, complimentary clinical findings.

This is an open-label study. Randomization is used in the study to mitigate the potential for bias in allocation of study drug.

9.3 SELECTION OF STUDY POPULATION

Approximately 80 subjects are planned for enrollment into the study at the Brain Institute. There will be up to 60 subjects with a diagnosis of DSM-IV-TR schizophrenia and 15 to 20 age-, gender-, and education-matched healthy control subjects enrolled in a 3:1 subjects with schizophrenia:control subjects ratio. This, accounting for drop-outs, will allow for 60 completed subjects: 45 subjects with schizophrenia and 15 healthy control subjects. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug. After screening, subjects with schizophrenia will be randomized in a 2:1 aripiprazole once monthly:SOC oral antipsychotics ratio.

The enrollment estimates for the study are provided in Table 1:

Table 1: Estimated Enrollment - Subjects Completed Per Year

	Year 1	Year 2	Total
Subject type	**n**		
Healthy controls	7	8	15
SCZ subjects treated with depot aripiprazole	15	15	30
SCZ subjects treated with SOC oral antipsychotics	7	8	15
Total	29	31	60

SCZ = schizophrenia, SOC = standard of care

9.3.1 Inclusion Criteria

9.3.1.1 Inclusion Criteria for All Subjects

1 Are able to provide written informed consent.

2 Are male and female subjects 18 to 35 years of age, inclusive, at time of informed consent.

9.3.1.2 Inclusion Criteria for Subjects with Schizophrenia

1. Have a current diagnosis of schizophrenia as defined by DSM-IV-TR criteria and a history of the illness for at least 1 year prior to screening and at least two prior psychotic episodes based on medical records or a qualified and reliable health care provider.

2. Require, in the investigator's judgment, chronic treatment with an antipsychotic medication.

3. Are able to understand the nature of the study and follow protocol requirements, including the prescribed dosage regimens, tablet ingestion, IM depot injection, and discontinuation of prohibited concomitant medications, read and understand the written

word in order to complete subject-reported outcomes measures, and be reliably rated on assessment scales.

4. Are male and female subjects who are surgically sterile (i.e., have undergone orchiectomy or hysterectomy, respectively; female subjects who have been postmenopausal for at least 12 consecutive months; or male and female subjects who agree to remain abstinent or to practice double-barrier forms of birth control from trial screening through 30 days (for females) and 90 days (for males) from the last dose of IMP for SOC oral antipsychotics and 150 days for females and 180 days for males for aripiprazole depot. If employing birth control, two of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injections, condom, or sponge with spermicide.

9.3.2 Exclusion Criteria

9.3.2.1 Exclusion Criteria All Subjects

1. Presence of any metal implants, pacemakers, unremovable prosthetic device, or other device or situation that may preclude imaging
2. History of a head injury with loss of consciousness > 5 minutes
3. Has a significant medical condition that would expose the subject to undue risk or interfere with study assessments.

9.3.2.2 Exclusion Criteria for Subjects with Schizophrenia

1. Has a current DSM-IV-TR diagnosis other than schizophrenia, including schizophreniform disorder, schizoaffective disorder, major depressive disorder, bipolar disorder, delirium, dementia, amnestic or other cognitive disorders. Also excluded are subjects with borderline, paranoid, histrionic, schizotypal, schizoid, or antisocial personality disorder.
2. Is considered resistant/refractory to antipsychotic treatment by history (failed two prior antipsychotic medication trials) or response only to clozapine.
3. Has a significant risk of violent behavior or a significant risk of committing suicide based on history or investigator's discretion.
4. Has met DSM-IV-TR criteria for any significant substance use disorder within 3 months prior to screening, excluding caffeine, nicotine, or marijuana.
5. Is known to be allergic, intolerant, or unresponsive to prior treatment with aripiprazole or other quinolinones, or hypersensitivity to antipsychotic agents, including aripiprazole.

6. Has a history of neuroleptic malignant syndrome or clinically significant tardive dyskinesia at screening per the investigator's discretion.
7. Has a history of seizures or any other medical condition that would expose the subject to undue risk or interfere with study assessments.
8. Is involuntarily incarcerated.
9. Has undergone electroconvulsive therapy in the 2 years prior to enrollment in the study.
10. Has used an investigational agent or has participated in a clinical study with aripiprazole IM depot or any other antipsychotic depot preparation within 30 days of screening.
11. Has clinically significant abnormalities in laboratory test results, vital signs, or ECG results.
12. Requires more than one benzodiazepine beyond screening (e.g., lorazepam and oxazepam).
13. Fails to washout from prohibited concomitant medications, including the use of or CYP3A4 inducers, a second antipsychotic, antidepressants (including monoamine oxidase inhibitors), and mood stabilizers.

9.3.3 Removal of Subjects From Therapy or Assessment

9.3.3.1 Entire Study or Treatment Arm(s)

If the investigator terminates or suspends the study for safety or unanticipated other reasons, prompt notification will be given to OAPI, IRBs, and regulatory authorities in accordance with regulatory requirements.

9.3.3.2 Individual Center

The investigator will notify OAPI promptly if the study is terminated by the investigator or the IRB at the site.

9.3.3.3 Individual Subject

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

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

All subjects have the right to withdraw at any point during treatment without prejudice. The investigator can discontinue a subject's participation in the study at any time if medically necessary. In addition, subjects meeting the following criteria must 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, warrants 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 becomes pregnant; or

6. subject is lost to follow-up.

The Investigator will notify OAPI promptly when a subject is withdrawn.

9.4 TREATMENTS

9.4.1 Treatments Administered

Aripiprazole once monthly and oral aripiprazole from commercial sources will be prescribed and administered according to recommendations contained in their respective product labeling, including dosing adjustments based on CYP2D6 status and concomitant medication use. All other SOC oral antipsychotic medications will be prescribed and administered according to recommendations contained in their respective product labeling.

The following treatments will be administered to subjects in this study:

- Aripiprazole (IM), 300 or 400 mg administered via gluteal injection, once monthly.
- SOC oral antipsychotic medications (PO) including but not limited to:
    - Aripiprazole (Abilify®), 10 mg to 30 mg, daily
    - Risperidone (Risperdal®), 2 to 8 mg daily
    - lurasidone HCl (Latuda®), 40 to 160 mg daily
    - quietapine fumarate (Seroquel®), 300 to 800 mg daily
    - olanzapine (Zyprexa®) 10 to 30 mg daily
    - ziprasidone HCl (Geodon®) 40 to 160 mg daily

9.4.1.1 Dosage Adjustments for Missed Doses of Aripiprazole Once Monthly

If the second or third doses are missed:

- If > 4 weeks and < 5 weeks have elapsed since the last injection, administer the injection as soon as possible.
- If > 5 weeks have elapsed since the last injection, restart concomitant oral aripiprazole for 14 days with the next administered injection.

If the fourth or subsequent doses are missed:

- If > 4 weeks and < 6 weeks have elapsed since the last injection, administer the injection as soon as possible.
- If > 6 weeks have elapsed since the last injection, restart concomitant oral aripiprazole for 14 days with the next administered injection.

9.4.2 Identity and Storage of Investigational Product(s)

Study drugs will not be stored at the clinical site. If, on occasion, study drug is stored at the site for any reason, all drug will be securely locked in a cabinet or enclosure according to the storage instructions on the product labeling. Access will be limited to the investigators and their designees. Neither investigators nor any designees may provide study drugs to any subject not participating in this protocol.

9.4.3 Method of Assigning Subjects to Treatment Groups

A total of 80 subjects are planned to be enrolled in the study in a 3:1 subjects with schizophrenia:control ratio, to allow for 60 completed subjects: 45 subjects with schizophrenia, and 15 age-, gender-, and education-matched healthy control subjects.

9.4.4 Blinding

The study will not be blinded.

9.4.5 Prohibited Medication

Medications that are prohibited or restricted prior to screening and/or during the study are listed in Table 2.

Table 2: Prohibited and Restricted Medications

Medication	Prohibition or Restriction
Antipsychotics	No more than one SOC antipsychotic allowed
Antidepressants including MAOIs	Not allowed
Benzodiazapine	The use of one benzodiazapine is allowed.
Mood stabilizers	Not allowed
Non-benzodiazapine sleep aids[a]	Allowed
Anitcholinergics	≤ 4 mg/day benztropine or equivalent; not within 12 hours of any rating scales.
Propanolol for akathisia or tremor	Maximum 60 mg/day; not within 8 hours of any rating scales. Subjects receiving propanolol for heart disease may remain on stable, pre-study doses, as needed as long as the dose does 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 are allowed, however, the investigator may adjust the dose of the study drug per the prescribing instructions. CYP3A4 inducers are not allowed
Hydroxyzine and diphenhydramine	Not allowed for the treatment of agitation, anxiety, insomnia, or EPS; Allowed for the treatment of allergy.

AE – adverse event, CNS = central nervous system, CYP = cytochrome P450, EPS = extrapyramidal side effects, GABA = gamma aminobutyric acid, IM = intramuscular, MAOI = monoamine oxidase inhibitor
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 is permitted, but not in addition to a benzodiazepine for insomnia.

9.4.6 Treatment Compliance

Compliance with SOC drug will be managed using the MPR (Section **Error! Reference source not found.**) for prescription refills and the MAQ (Section **Error! Reference source not found.**).

9.4.7 Accountability

Study drug will not be prescribed or administered until the following documentation has been provided by the investigator 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 is to be conducted
- A copy of the IRB-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the investigator and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae (CV) of the investigator including a copy of the investigator's current medical license or medical registration number on the CV
- A signed and dated clinical studies agreement

The investigator and the study staff will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the, and adherence to, Good Clinical Practice (GCP) guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be administered or prescribed to any individual who is not enrolled in the study.

The investigator, or designee, must maintain an inventory record of trial drugs (including study drug, active control, or placebo) received, dispensed, administered and returned.

The study drugs and inventory records must 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 are to be returned to the investigator by the subject.

9.5 STUDY ASSESSMENTS

9.5.1 Assessments

9.5.1.1 Demographics

Subject demographic information will be collected at the Screening Visit. Demographic information includes date of birth (or age), sex, race or ethnicity.

9.5.1.2 Screening Assessments

MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. All relevant medical and surgical history within 10 years must be noted in the CRF.

PSYCHIATRIC HISTORY

A review of the subject's psychiatric history will be performed including all antipsychotic medications used within the 6 months prior to screening. Confirmation of the diagnosis of schizophrenia, as defined by DSM-IV-TR criteria.

9.5.1.3 Safety Assessments

Safety will be assessed by adverse event (AE) reporting, clinical laboratory tests (hematology and fasting clinical chemistry), urinalysis, 12-lead ECG, vital signs, and physical examination. In addition, body weight, BMI, and serum prolactin concentrations will be monitored.

The MOSES will be utilized to assess for side effects, and the following scales will be used to assess for EPS: AIMS, SAS, and BARS.

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

9.5.1.3.1 Clinical Laboratory Tests

The local laboratory will be used for all laboratory testing required during the study. Reports from the laboratory should be filed with the source documents for each subject. Samples will be obtained at the visits designated in Table 4 through Table 6, and as far as possible, samples should be drawn at the same time of day at each visit. Additional samples may be collected for further evaluation of safety as warranted by the investigator's discretion. Subjects should be fasting for a minimum of 10 hours prior to blood draws for assessment of safety, including screening. If non-fasting blood samples are obtained initially for determining eligibility for the study, a fasting blood sample should be drawn prior to enrollment. The clinical laboratory tests performed during the study are provided in Table 3.

Table 3. Safety Clinical Laboratory Tests

Hematology: White Blood Cell (WBC) count with differential Red Blood Cell (RBC) count Hematocrit Hemoglobin Mean Corpuscular Volume (MCV) Mean Corpuscular Hemoglobin Concentration (MCHC)	Serum Chemistry: Alanine Transaminase (ALT) Alkaline Phosphatase (ALP) Aspartate Transaminase (AST) Bilirubin, Total Blood Urea Nitrogen (BUN) Calcium Cholesterol Creatinine Gamma Glutamyl Transferase (GGT) Glucose Lactic Dehydrogenase (LDH) Potassium Protein, Total Sodium Triglycerides
Urinalysis: Color Appearance pH Specific gravity Microscopic Analysis of RBC/WBC (per high powered field)]	Additional Tests: Urine β-hCG[a] for women of child-bearing potential Serum prolactin

β-hCG = beta human chorionic gonadatropin
a: Serum β-hCG will be performed if the subject or investigator suspects that the subject may be pregnant.

9.5.1.3.2 Physical Examination

Physical examinations (comprehensive or symptom directed) will be performed as designated on the Schedules of Assessments (Table 4 through Table 6). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation. Significant findings at the Screening Visit will be recorded on the CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF. ECG Assessments

A 12-lead ECG will be performed in triplicate while the subject is in a supine position and after having rested for 5 minutes.Adverse Events and Other Events of Interest

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the study product. For this study, the study drugs are aripiprazole once monthly and SOC oral antipsychotics.

The criteria for identifying AEs are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product
- 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 (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, whether prescribed in the protocol or not.

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

- Results in the withdrawal of study drug
- Results in withholding of study drug pending some investigational outcome
- Results in an intervention, based on medical evaluation (e.g., potassium supplement for hypokalemia)
- Results 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 will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit. Serious AEs will be collected for 30 days after the last dose.

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

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

It is the responsibility of the investigator to review the results of the C-SSRS and CGI-SS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Other Safety Assessments [Section 9.5.1.6] for a description of the C-SSRS and CGI-SS).

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

During the study, all women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual cycle).

Assessing Severity of Adverse Events

Standard Text

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are 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 9.5.1.5] for the definition of an SAE).

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

Related:

Definite: There is a reasonable causal relationship between the study drug and the AE, when the event responds to withdrawal of the study drug (dechallenge), and recurs with rechallenge by administration of the study drug.

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

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

Unrelated:

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

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

9.5.1.5 Serious Adverse Events and Other Events of Interest

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

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

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, other events of interest include 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 are to be captured using the SAE procedures but are to be considered SAEs only if they meet one of the above criteria. All AEs associated with events of interest are to be reported on the CRF whether or not they meet the criteria for SAEs.

The following hospitalizations are 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 has 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

9.5.1.6 Other Safety Assessments

9.5.1.6.1 Injection Site Evaluation

For subjects receiving an injection, two assessments of the most recent injection site will be completed at each visit at which an injection is administered: an investigator assessment and a subject-rated visual analog scale (VAS) assessment of the pain at the injection site.

For the investigator assessment, the investigator, or qualified designee, will assess the injection site for localized pain, redness, swelling, and induration. For the subject-rated VAS assessment, the subject will mark the scale with one vertical line across the bar of the VAS to indicate the degree of injection site discomfort.

These assessments will occur as the last evaluations of the visit, approximately 1 hour (± 15 minutes) after the gluteal IM once monthly injection.

For the subject-rated assessment of pain at the injection site, the subject will complete the VAS approximately 1 hour (± 15 minutes) post-injection to assess the injection site.

The evaluations must be completed on the same day (i.e., the day the injection is administered).

9.5.1.6.2 Body Mass Index and Waist Circumference

An assessment for potential of prolactin-related effects will be performed via determination of BMI, and measurement of waist circumference.

The calculation for BMI is:

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

9.5.1.6.3 Vital Signs

Vital sign measurements (i.e., systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated on the Schedules of Assessments (Table 4 through Table 6) by a validated method. Blood pressure and pulse will be measured after the subject has been supine for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

9.5.1.6.4 Schizophrenia Assessments

DSM-IV-TR Global Assessment of Functioning (GAF)

The GAF is used to assess global functioning using a scale from 1 (worst) to 100 (best). An intraclass correlation coefficient of 0.81 has been reported.

Structured Clinical Interview for DSM-IV, Patient Version (SCID-P)

The SCID-P is a semi-structured interview for making the major DSM-IV Axis I diagnoses. The instrument is designed to be administered by a clinician or trained mental health professional. The SCID-P is broken down into separate modules corresponding to categories of diagnoses. Most sections begin with an entry question that would allow the interviewer to "skip" the associated questions if not met. However, to be sensitive to subthreshold syndromes we will query further even if the entry questions appears negative. For all diagnoses symptoms are coded as present, subthreshold, or absent.

9.5.1.6.5 Suicidality

Clinical Global Impression – Severity of Suicidality (CGI-SS)

The CGI-SS is a two-part scale that assesses severity of suicidality over the week prior to the evaluation.

The CGI-SS Part 1 has 5 levels of severity of suicidality: 1 = not at all suicidal, 2 = mildly suicidal, 3 = moderately suicidal, 4 = severely suicidal, and 5 = attempted suicide.

The CGI-SS Part 2 has 7 levels of change in suicidality: 1 = very much improved since the initiation of treatment, 2 = much improved, 3 = minimally improved, 4 = no change since the initiation of treatment, 5=minimally worse, 6= much worse, 7=very much worse since the initiation of treatment.

All evaluations for Part 2 of the CGI-SS will use the baseline of the appropriate phase as a reference for judging change in suicidality. For the purpose of this study, a score of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or a score of 6 (much worse) or 7 (very much worse) on Part 2 will be considered an exacerbation of psychotic symptoms/impending relapse and may result in immediate withdrawal from the study at the investigator's discretion.

Columbia Suicide Severity Rating Scale (C-SSRS)

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/"Since Last Visit" evaluation that focuses on suicidality since the last study visit. The baseline C-SSRS form will be completed at baseline of Phase 1. The "Since Last Visit" C-SSRS form will be completed at all subsequent visits.

Four constructs are measured:

1. The severity of ideation (the "severity subscale"), which is rated on a 5-point ordinal scale in which 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 (the "intensity subscale"), which comprises 5 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 nonsuicidal 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 0, potential lethality of attempts is rated on a 3-point ordinal scale.

9.5.1.6.6 Pregnancy Test

Women of childbearing potential and men who are sexually active must use an effective method of birth control during the course of the trial and for 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/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 be used: vasectomy, tubal ligation, vaginal diaphragm, IUD, birth control pills, birth control depot injection, birth control implant, condom, or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy.

Before enrolling women of child-bearing potential in this clinical study, investigators must review guidelines about trial participation for women of childbearing potential. The topics should generally include:

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

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

9.5.1.6.7 Urine Screen for Drugs of Abuse

A 30-mL urine sample will be collected at designated time points as specified in the Schedules of Assessments (Table 4 through Table 6). This sample will be tested for drugs of abuse: e.g., marijuana, cocaine, opiates, oxycodone, phencyclidine, amphetamines, barbiturates, benzodiazapines, methadone, and propoxyphene (ARUP laboratories; see Section 6). An aliquot

of the urine sample will be prepared and shipped for confirmation and quantification of drug levels via enzyme immunoassay/gas chromatography-mass spectrometry/liquid chromatography-tandem mass spectrometry.

In addition, a blood sample will be obtained to test for blood alcohol content.

9.5.1.6.8 Monitoring of Side Effects Scale (MOSES)

The MOSES scale is a Division of Social and Health Services Scale consisting of seven body system symptom domains: ears, eyes, head; mouth; nose, throat, chest; gastrointestinal; musculoskeletal and neurological; skin; and urinary and genital; and one psychological symptom domain, in which the examiner will check boxes for symptoms present on a scale of 0 to 4 in which 0 = none and 4 = severe.

9.5.1.7 Efficacy Assessments – Clinical Outcome

9.5.1.7.1 Clinical Global Impression – Improvement

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

9.5.1.7.2 Clinical Global Impression – Severity

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

9.5.1.7.3 Positive and Negative Syndrome Scale (PANSS)

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

Positive Subscale (7 positive symptom constructs: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility),

Negative Subscale (7 negative symptom constructs: blunted affect, emotional withdrawal, poor rapport, passive pathetic withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking),

General Psychopathology Subscale (16 symptom constructs: somatic concern, anxiety, guilt feelings, tension, mannerism and posturing, depression, motor retardation, uncooperative, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance).

All efforts are to be made to ensure that the same rater administers the PANSS for a given subject. The number of raters within each study center is to be kept to a minimum. Instructions for administering this instrument will be provided to the site. A copy of the PANSS assessment with complete rating criteria is required as source documentation.

9.5.1.8 Efficacy Assessments – Extrapyramidal Symptoms

9.5.1.8.1 Abnormal Involuntary Movement Scale (AIMS)

The AIMS assessment consists of 10 items describing symptoms of dyskinesia. Facial and oral movements (items 1 through 4), extremity movements (items 5 and 6), and trunk movements (item 7) will be observed unobtrusively while the subject is at rest (e.g., in the waiting room), and the investigator will also make global judgments on the subject's dyskinesias (items 8 through 10). Each item will be rated on a 5-point scale, with a score of 0 representing absence of symptoms (for item 10, no awareness), and a score of 4 indicating a severe condition (for item 10, awareness/severe distress).

9.5.1.8.2 Barnes Akathisia Rating Scale (BARS)

The BARS assessment consists of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the subject, subject distress due to akathisia, and global evaluation of akathisia. The first 3 items will be rated on a 4-point scale, with a score of 0 representing absence of symptoms and a score of 3 representing a severe condition. The global clinical evaluation will be made on a 6-point scale, with 0 representing absence of symptoms and a score of 5 representing severe akathisia.

9.5.1.8.3 Simpson Angus Scale (SAS)

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

9.5.1.9 Efficacy Assessments – Mood

9.5.1.9.1 The Hamilton Anxiety Scale (HAM-A)

Rating scale developed to quantify the severity of anxiety symptomatology, often used in psychotropic drug evaluations.

9.5.1.9.2 The Hamilton Depression Rating Scale (HAM-D)

Proven useful for determining the level of depression before, during, and after treatment[32]. It is based on the clinician's interview with the patient and probes symptoms such as depressed mood, guilty feelings, suicidal ideation, sleep disturbances, anxiety levels and weight loss. Research has demonstrated a validity coefficient of .85.

9.5.1.9.3 The Profile of Mood States (POMS)

Self-report inventory in which respondents rate a series of mood states. The POMS Standard form contains 65 items and takes approximately 10 minutes to complete. Internal consistency scores have ranged from .84 to .95.

9.5.1.10 Efficacy Assessments – Medication Adherence

9.5.1.10.1 Medication Adherence Questionnaire (MAQ)

The MAQ is a validated, 4-item, self-reported measure to determine adherence to treatment. The four behavioral questions of the MAQ are designed to assess different sources of noncompliance (e.g., forgetfulness, carelessness, symptom driven compliance), with positive responses indicating nonadherence to medication regimens. Responses to each question will be "Yes" (score of 1) or "No" (score of 0), thus the MAQ total score will range from 0 to 4.

9.5.1.10.2 Medication Possession Ratio (MPR)

Medication Possession Ratio (MPR) measures the percentage of time a subject has access to medication.

9.5.1.11 Other Assessments

9.5.1.11.1 Neuropsychological Measures

COGSTATE COMPUTERIZED TESTING

Simple Reaction Time

Simple reaction time will be assessed by means of the Detection Task section of the CogState computerized assessment. This task is used to assess psychomotor functioning as well as speed of processing. During this task a face down deck of cards is presented electronically to the subject. The card on the top of the pile is then flipped over to reveal the face of the card. The subject is asked to indicate when this has happened by pressing a "yes" button. Subjects are instructed to make this indication as quickly as possible. If the subject fails to make an indication, or presses the button prior to the face of the card becoming visible, an error sound is heard.

Choice Reaction Time

Choice reaction time will be assessed by means of the Identification Task section of the CogState computerized assessment. This task is used to assess visual attention as well as vigilance. This task is presented similar to the simple reaction time task with the additional instruction that the

subject only presses the "yes" button when the card presented is red. As with the previous task, subjects are instructed to make this indication as quickly as possible.

One-back Working Memory

The one back task is a CogState task that will be used to assess attention and working memory. During this task, subjects are presented with an electronic deck of cards face down. A card is turned over revealing the face of the card and then is returned to the deck. Following each card, the subject is instructed to indicate whether or not the most recent card is identical to the previous card by pressing either "yes" or "no" on the keyboard. The subject is encouraged to work quickly and accurately.

Set Shifting

This test is a Cog State test designed to determine executive function. During this task, the subject is presented with a playing card in the center of the computer screen. The subject is asked to guess whether the card is the "target" or "correct" card. A target card is a card which contains a color or a number. If the guess is correct the card is flipped over. If not correct, an error noise will sound and the card will not flip over. At this point, the subject must guess again. Once the subject has made their way through a set of cards, the target or correct stimulus dimensions changes without the subject's knowledge and the subject must relearn the rule. There are multiple set shifts within the task, and the order of the set shifts is pseudo-randomized to create multiple alternate forms of the task.

Unit of measurement: total number of errors. Accuracy of performance and total number of errors across five rounds are measured; a lower score = better performance

OTHER NEUROPSYCHOLOGICAL TESTS

TrailMaking Test

This test is designed to measure visual conceptual and visual-motor tracking, as well as maintenance of cognitive set. The subject must first draw lines to connect consecutively numbered circles on one work sheet (Part A) and then connect the same number of consecutively numbered and lettered circles on another work sheet by alternating between the two sequences (Part B). TrailMaking B is the more sensitive of the two tests -- particularly to frontal-lobe dysfunction -- as scores on this section are indicative of the subject's ability to shift sets and process concurrent stimuli.

Tower of London

The Tower of London task will be used to assess executive function. This assessment will be presented electronically during with the subject will be presented with a screenshot containing three balls of differing colors on three pegs. The subject will be asked the amount of times the balls in one picture must be moved in order to match a second image. The complexity of the task will increase over the course of the trials.

Continuous Performance Test (CPT)

Computerized test of sustained attention. The test requires subjects to attend vigilantly to a series of target and distracter stimuli for 14-minutes. Generated scores include reaction time, omission errors, commission errors, and an index of overall performance. An alpha score of .84 has been reported along with an intraclass correlation coefficient of .91.

Wisconsin Card Sorting Test

Assesses a person's ability to form abstract concepts, utilize feedback, and shift and maintain set. This test has been shown to be sensitive to frontal lobe dysfunction. Dependent variables include total number of categories correct (color, form, or number) and perseverative errors. The measure has a test retest generalizability coefficient of > 90.

9.5.1.11.2 Functional Outcomes and Quality of Life

FUNCTIONING ASSESSMENT SHORT TEST (FAST):

The FAST is a 24-item, clinician administered assessment used to assess functional impairment with a focus on the main problems experienced by psychiatric populations. The timeframe for this measure refers to the subjects last 15 days before assessment. The assessment is broken down into 6 specific areas of functioning including: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time.

QUALITY OF LIFE SCALE (QOLS):

The QOLS is a measure designed to determine the impact of health care. This measure consists of 16 questions (the original 15 QOLS questions, with the addition of a chronic illness component) delivered as a self-report measure. The QOLS assesses factors related to (1) relationships and material well-being, (2) personal, social and community commitment, and (3) health and functioning.

SOCIAL AND OCCUPATIONAL FUNCTIONING ASSESSMENT SCALE (SOFAS):

The SOFAS is a new scale that assesses a subject's individual level of social and occupational functioning. Similar to the GAF, the SOFAS is a scaled score that ranges from 0 to 100, but differs from the GAF such that it is specific to social and occupational functioning and is not directly influenced by a subject's psychiatric illness symptom severity. This scale can be used in terms of current functioning, but can also be used over a timeframe detailing highest and lowest level of social and occupational functioning.

LIFE FUNCTIONING QUESTIONNAIRE (LFQ):

The LFQ is a 14-item, gender-neutral, self-report questionnaire used to assess functional outcome in patients with psychiatric illness in terms of role function. The assessment measures four domains, which include: workplace, duties at home, leisure time with family, and leisure time with friends.

HOLLINGSHEAD FOUR FACTOR INDEX OF SOCIAL POSITION:

The Hollingshead Index is a report of socioeconomic status, used with modifications. Intermeasure correlations range from r = .86 to .91.

9.5.1.12 Pharmacokinetic/Pharmacodynamic Assessments

PHARMACOKINETIC ASSESSMENTS

Not applicable.

PHARMACODYNAMIC ASSESSMENTS

Measurements of FA, BPF, and proton metabolites will occur using imaging techniques as described below. All structural scans will be read and interpreted by a clinical neuroradiologist. Structural data will be utilized in three ways: to ensure specific regions of interest are visible and localized for correlation with T1 mapping of the BPF, DT-MRI and MRS data. In addition, cortical reconstruction and volumetric segmentation and parcellation will be performed with the FreeSurfer image analysis suite, which is documented and available for download online (http://surfer.nmr.mgh.harvard.edu/), to obtain volumetric and cortical thickness measures for brain regions of interest, including the cingulum.

Magnetic Resonance Imaging

All subjects will undergo an MRI protocol on a Siemens Trio 3 Tesla Scanner at baseline, 6 months, and 12 months during Phase C. This protocol includes a high-resolution structural MRI protocol. The structural acquisitions include a T1-weighted 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence acquired sagittally, with TE/TR/TI = 3.38ms/2.0s/1.1s, 8°flip, 256 x 256 acquisition matrix, 256 mm^2 field of vision, 160 slices, 1.0 mm slice thickness.

Diffusion Tensor Imaging (DT-MRI)

A single-shot spin-echo echo-planar imaging (EPI) sequence with diffusion-weighting will be used to acquire diffusion tensor images. To describe the intensity and direction of diffusion anisotropy, MR images with 25 non-collinear diffusion gradients and without diffusion gradient will be acquired. B-factor will be set to be 1000 sec/mm^2. Acquisition parameters include FOV = 256 mm, matrix = 128 x 128, resulting 2-mm isotropic in-plane resolution. TR/TE = 7000/84, pixel bandwidth = 1346 Hz, and averages = 4.

Magnetic Resonance Spectroscopic (MRS) Imaging

Proton (^1H) magnetic resonance spectroscopic imaging measurements will be acquired using a 3.0 Tesla Siemens (Erlangen, Germany) Verio™ whole-body MRI scanner.
^{1}H-MRS spectra will be acquired using a manufacturer-supplied 12-channel head coil, following high-resolution MPRAGE image acquisition to facilitate accurate voxel positioning. A modified point-resolved spectroscopy sequence (two-dimensional *J*-resolved spectroscopy) is used: repetition time/echo time (TR/TE) range 2400/31 to 229 ms; 100 TE steps; Vector size 2048; Bandwidth 2000/500 Hz) acquires MRS spectra with 128 and 4 signal averages per TE step for metabolite and water non-suppressed data. An 18.75 mL (2.5 x 2.5 x 3.0 cm^3) voxel is placed at the ACC and the parietal-occipital cortex. Parietal occipital cortex data serves as a control region. Automated and manual shimming ensures unsuppressed water signal linewidths of <9 Hz.

9.5.2 Schedules of Assessments

Table 4 provides the Schedule of Assessments for Phase A of the study. Table 5 provides the Schedule of Assessments for Phase B of the study. Table 6 provides the Schedule of Assessments for Phase C of the study. Table 7 provides the neurological assessments to be completed During Phase C.

Table 4 Schedule of Assessments – Phase A – Screening and Conversion Phase

Assessments	STUDY VISIT							
	Screening (Days -7 to -2)	Conversion to Oral Aripiprazole (Phase A)						
		Baseline Day 1[i]	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6[g]
		± 2 days						
STANDARD STUDY ASSESSMENTS								
Informed consent	X							
Review inclusion/exclusion criteria	X							X
Medical history	X							
Demographics	X							
Physical examination, including height	X							X
Vital signs	X	X	X	X	X	X	X	X
Body weight and waist circumference		X						X
Calculate BMI[a]		X						X
12-lead ECG	X							X
Clinical laboratory tests[b]	X							X
Prolactin level	X							X
Urine βhCG[c]	X							X
Screen for drugs of abuse[d]	X							X
Prior medication history	X							
Concomitant medications	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
SCHIZOPHRENIA-RELATED ASSESSMENTS								
SCID-P	X							
Current antipsychotic therapy[e]	X	X	X	X	X	X	X	X
Clinical Outcome								
CGI-I, CGI-S , CGI-SS, C-SSRS, GAF, MAQ, PANSS	X	X	X	X	X	X	X	X
Mood								
HAM-A, HAM-B, POMS	X	X	X	X	X	X	X	X
Extrapyramidal Side Effects								
AIMS, BARS, SAS	X	X	X	X	X	X	X	X

Table 4 Schedule of Assessments – Phase A – Screening and Conversion Phase

Assessments	STUDY VISIT							
	Screening (Days -7 to -2)	Conversion to Oral Aripiprazole (Phase A)						
		Baseline Day 1[i]	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6[g]
		± 2 days						
Adverse Drug Effects								
MOSES	X	X	X	X	X	X	X	X
CONVERSION TO ARIPIPRAZOLE[g]								
Dispense oral aripiprazole[h]		X	X	X	X	X	X	X
Cross-titration[h]		X	X	X	X	X	X	
Taper off other psychotropic medications[f]		X	X	X	X	X	X	X
Assess eligibility for Phase B				X	X	X	X	X

AIMS = Abnormal Involuntary Movement Scale, ALT = alanine aminotransferase, AST = aspartate aminotransferase, βhCG = human chorionic gonadotropin, BARS = Barnes Akathesia Rating Scale, BMI = body mass index, BUN = blood urea nitrogen, CGI-I = clinical and global Impression – Improvement, CGI-S = Clinical and Global Impression – Severity, CGI-SS = Clinical and Global Impression for Severity of Suicidality, C-SSRS = Columbia Suicide Severity Rating Scale, CYP = cytochrome P, DSM = Diagnostic and Statistical Manual, ECG = electrocardiogram, GAF = DSM-IV-TR Global Assessment of Functioning, GGT = gamma glutamyltransferase, HAM-A = Hamilton Anxiety Scale, HAM-D = Hamilton Depression Rating Scale, LDH – lactate dehydrogenase, MAQ = Medication Adherence Questionnaire, MOSES = Monitoring of Side Effects Scale, PANSS = Positive and Negative Symptom Scale, POMS = Profile of Mood States, RBC = red blood cell, SAS = Simpson Angus Scale, SCID-P = structured clinical interview for DSM-IV Patient Version, WBC = white blood cell

a: BMI is calculated as: mass (kg)/height (m^2)

b: clinical laboratory tests include hematology (WBC with differential, RBC, hemoglobin, hematocrit, mean corpuscular volume and mean corpuscular hemoglobin concentration), serum chemistry (ALT, alkaline phosphatase, AST, total bilirubin, BUN, calcium, cholesterol, creatinine, GGT, glucose, LDH, potassium, total protein, sodium, and triglycerides), and urinalysis (color, appearance, specific gravity, pH, microscopic for RBCs and WBCs per high-powered field.

c: Urine pregnancy test for women of childbearing potential only. If a subject or investigator suspects that the subject may be pregnant, a serum pregnancy test should be performed.

d: Urine will be collected for drugs of abuse testing for: marijuana, cocaine, opiates, oxycodone, phencyclidine, amphetamines, barbiturates, benzodiazapines, methadone, and propoxyphene on the day of MR imaging (ARUP Drugs of Abuse Panel 9: ARUP Laboratories, Salt Lake City, UT). An aliquot of this urine sample will also be sent for confirmation and quantification of drug levels via Enzyme Immunoassay/Gas Chromatography-Mass Spectrometry/Liquid Chromatography-Tandem Mass Spectrometry. Note: the presence of benzodiazapines in the results of the drugs of abuse screening will not be cause for the discontinuation of the subject from the study if they are part of the subject's treatment regimen; subjects will be excluded for significant substance use per the investigator's discretion. In addition, blood will be collected to test for blood alcohol content.

e: Subjects with schizophrenia only

f: Subjects on SOC oral antipsychotic medications that areparticipating in Phase A due to washout from more than one benzodiazepine, or prohibited concomitant medications such as CYP3A4 inducers, antidepressants including monamine oxidase inhibitors, and mood stabilizers, will also be evaluated during Phase A.

g: The final visit of Phase A will be the baseline for Phase B for those subjects whoparticpated in Phase A.

h: For subjects with schizophrenia only, who were randomized to the aripiprazole once monthly arm in Phase C and aren't currently receiving oral aripiprazole monotherapy.

i: Screening and baseline can occur on the same day if appropriate.

Table 5: Schedule of Assessments Phase B – Oral Stabilization Phase

Assessments	Baseline[a]	Week 2[b]	Week 4[h]	Week 6[c,h]	Week 8[c,h]	Week 10[c,h]	Week 12[c,h]
		(± 1 day)					
STANDARD STUDY ASSESSMENTS							
Confirm inclusion/exclusion criteria	X						X
Physical examination, including height	X						X
Vital signs	X	X	X	X	X	X	X
12-lead ECG	X						X
Body weight and waist circumference	X	X	X	X	X	X	X
Calculate BMI[d]	X		X		X		X
Clinical laboratory tests[e]	X						X
Prolactin concentration	X						X
Urine βhCG[f]	X		X		X		X
Screen for drugs of abuse[g]	X		X		X		X
Concomitant medications	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X
SCHIZOPHRENIA-RELATED STUDY ASSESSMENTS							
CLINICAL OUTCOME							
CGI-I, MAQ, PANSS	X	X	X	X	X	X	X
MOOD SCALES							
HAM-A, HAM-D, POMS							
EXTRAPYRAMIDAL SIDE EFFECTS							
AIMS, BARS, SAS							
ADVERSE DRUG EFFECTS							
MOSES							
BASELINE ASSESSMENTS FOR PHASE C							
Neuropsychological Testing[i]							
Functional Outcomes Assessments[j]							
STUDY MANAGEMENT							
Assess stability criteria		X	X	X	X	X	X
Drug accountability (MPR)		X	X	X	X	X	X
Administer aripiprazole once monthly[c,i]							X
Evaluate injection site[j]							X

AIMS = Abnormal Involuntary Movement Scale, ALT = alanine aminotransferase, AST = aspartate aminotransferase, βhCG = human chorionic gonadotropin, BARS = Barnes Akathisia Rating Scale, BMI = body mass index, BUN = blood urea nitrogen, CGI-I = Clinical and Global Impression – Improvement, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, GGT = gamma glutamyltransferase, HAM-A = Hamilton Anxiety Scale, HAM-D = Hamilton Depression Rating Scale, IM = intramuscular, LDH – lactate dehydrogenase,

Table 5: Schedule of Assessments Phase B – Oral Stabilization Phase

MAQ = Medication Adherence Questionnaire, MPR = medicine possession ratio, MOSES = Monitoring of Side Effects Scale, MRI = magnetic resonance imaging, PANSS = Positive and Negative Syndrome Scale,POMS = Profile of Mood States, RBC = red blood cell, SAS = Simpson Angus Scale, VAS = visual analog scale, WBC = white blood cell

a: For subjects not converting to oral aripirazole, subjects move directly to Phase B after screening. Screening and baseline can occur on the same day if appropriate.

b: For subjects who participated in Phase A, baseline assessments are completed during the last visit of Phase A; Week 1 is the first visit of Phase B

c: Subjects who are stable for 2 consecutive visits can be moved directly into Phase C; subjects unable to be stabilized after 12 weeks will be discontinued from the study

d: BMI is calculated as: mass (kg)/height (m^2)

e: Clinical laboratory tests include hematology (WBC with differential, RBC, hemoglobin, hematocrit, mean corpuscular volume and mean corpuscular hemoglobin concentration), serum chemistry (ALT, alkaline phosphatase, AST, total bilirubin, BUN, calcium, cholesterol, creatinine, GGT, glucose, LDH, potassium, total protein, sodium, and triglycerides), and urinalysis (color, appearance, specific gravity, pH, microscopic for RBCs and WBCs per high-powered field).

f: Urine pregnancy test for women of childbearing potential only. If a subject or investigator suspects that the subject may be pregnant, a serum pregnancy test should be performed.

g: Urine will be collected for drugs of abuse testing for: marijuana, cocaine, opiates, oxycodone, phencyclidine, amphetamines, barbiturates, benzodiazapines, methadone, and propoxyphene on the day of MR imaging (ARUP Drugs of Abuse Panel 9: ARUP Laboratories, Salt Lake City, UT). An aliquot of this urine sample will also be sent for confirmation and quantification of drug levels via Enzyme Immunoassay/Gas Chromatography-Mass Spectrometry/Liquid Chromatography-Tandem Mass Spectrometry. Note: the presence of benzodiazapines in the results of the drugs of abuse screening will not be cause for the discontinuation of the subject from the study if they are part of the subject's treatment regimen. A subject will be excluded for significant substance use per the investigators discretion. In addition, blood will be collected to test for blood alcohol content.

h: The final visit of Phase B will be the Baseline visit for Phase C. Neuropsychological testing, functional outcomes testing, and the first dose of aripiprazole depot will be administered. MRI will be completed.

i: Neuropsychological testing includes: CogState testing (simple reaction time, choice reaction time, one-back working memory, two-back working memory, and set shifting), TrailMaking Test, Tower of London, Continuous Performance Test, and Wisconsin Card Sorting Test. See Table 7.

j: Functional outcomes assessments include: Functional Assessment Test, Quality of Life Scale, Social and Occupational Functioning Assessment Scale, Life Functioning Questionnaire

k: For subjects who are entering into Phase C and are randomized to aripiprazole once monthly, the first dose of aripiprazole once monthly will be administered IM at the last visit in Phase B. All study drug will be administered at the end of the visit.

Table 6: Schedule of Assessments Phase C - Treatment Phase

Assessments	Study Week																	
	1	2	3	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52
	(± 3 days)																	
STANDARD STUDY ASSESSMENTS																		
Physical examination											X							X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and waist circumference	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BMI[a]	X			X		X		X	X	X	X	X	X	X	X	X	X	X
12-lead ECG											X							X
Clinical laboratory tests[b]											X							X
Prolactin level											X							X
Urine Pregnancy test[c]				X		X		X	X	X	X	X	X	X	X	X	X	X
Screen for drugs of abuse[d]								X			X							
VAS pain at injection site[e]				X		X		X	X	X	X	X	X	X	X	X	X	X
Investigator rating of injection site[e]				X		X		X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SCHIZOPHRENIA-RELATED ASSESSMENTS																		
CLINICAL OUTCOME																		
CGI-I, CGI-S , CGI-SS, C-SSRS, GAF, MAQ, PANSS								X			X			X			X	X
MOOD SCALES																		
HAM-A, HAM-D, POMS	X			X		X		X	X	X	X	X	X	X	X	X	X	X
EXTRAPYRAMIDAL SIDE EFFECTS																		
AIMS, BARS, SAS				X		X		X	X	X	X	X	X	X	X	X	X	X
ADVERSE DRUG EFFECTS																		
MOSES	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
STUDY-SPECIFIC ASSESSMENTS AND MANAGEMENT																		
Assess stability criteria[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MRI Imaging	X[i]										X							X
Administer IM once monthly aripiprazole[h]				X		X		X	X	X	X	X	X	X	X	X	X	
Drug accountability with SOC oral anti-psychotics (MPR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 6: Schedule of Assessments Phase C - Treatment Phase

Assessments	Study Week (± 3 days)																	
	1	2	3	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52

AIMS = Abnormal Involuntary Movement Scale, ALT = alanine aminotransferase, AST = aspartate aminotransferase, βhCG = human chorionic gonadotropin, BARS = Barnes Akathesia Rating Scale, BMI = body mass index, BUN = blood urea nitrogen, CGI-I = clinical and global Impression – Improvement, CGI-S = Clinical and Global Impression – Severity, CGI-SS = Clinical and Global Impression for Severity of Suicidality, C-SSRS = Columbia Suicide Severity Rating Scale, DSM = Diagnostic and Statistical Manual, DT-MRI = diffusion tensor magnetic resonance imaging, ECG = electrocardiogram, EPS = extrapyramidal side effects, fMRI = functional magnetic resonance imaging, GGT = gamma glutamyltransferase, HAM-A = Hamilton Anxiety Scale, HAM-D = Hamilton Depression Rating Scale, LDH – lactose dehydrogenase, MAQ = Medication Adherence Questionnaire, MOSES = Monitoring of Side Effects Scale, MPR = medication possession ratio, MRI = magnetic resonance imaging, MRS = magnetic resonance spectroscopy, PANSS = Positive and Negative Symptom Scale, POMS = Profile of Mood States, RBC = red blood cell, SAS = Simpson Angus Scale, WBC = white blood cell

a: BMI is calculated as: mass (kg)/height (m^2)

b: clinical laboratory tests include hematology (WBC with differential, RBC, hemoglobin, hematocrit, mean corpuscular volume and mean corpuscular hemoglobin concentration), serum chemistry (ALT, alkaline phosphatase, AST, total bilirubin, BUN, calcium, cholesterol, creatinine, GGT, glucose, LDH, potassium, total protein, sodium, and triglycerides), and urinalysis (color, appearance, specific gravity, pH, microscopic for RBCs and WBCs per high-powered field.

c: Urine pregnancy test for women of childbearing potential only. If a subject or investigator suspects that the subject may be pregnant, a serum pregnancy test should be performed.

d: Drug screen for drugs of abuse includes: amphetamines, barbiturates, benzodiazapines, cannabinoids, cocaine metabolites, opiates, ethanol, and methadone. Note: the presence of benzodiazapines in the results of the drugs of abuse screening will not be cause for the discontinuation of the subject from the study if they are part of the subject's treatment regimen.

e: For subjects administered once monthly aripiprazole only. For visits at which no injection is administered, the assessments are done once, using the most recent injection site. For visits in which an injection is administered, the area of the most recent injection will be assessed approximately 30 minutes prior to the injection (or in the case of the first injection, the area to be injected), and one hour (± 15 minutes) after the injection. On injection days, these assessments will be the last assessments completed.

f: Neuropsychological testing includes: CogState testing (simple reaction time, choice reaction time, one-back working memory, two-back working memory, and set shifting), TrailMaking Test, Tower of London, Cognitive Performance Test, and Wisconsin Card Sorting Test. See Table 7.

g: Functional outcomes assessments include: Functional Assessment Test, Quality of Life Scale, Social and Occupational Functioning Assessment Scale, Life functioning Questionnaire

h: aripiprazole will be administered at the end of the visit

i: MRI imaging includes MRI, MRS, fMRI, DT-MRI

Table 7: Neuropsychological Measures for the Treatment Phase (Phase C)

Neuropsychological Measure	Baseline	6 Months	12 Months
CogState Tests			
Simple Reaction Time	X	X	X
Choice Reaction Time	X	X	X
One-back Working Memory	X	X	X
Two-back Working Memory	X	X	X
Set-Shifting	X	X	X
Other Neuropsychological Tests			
TrailMaking Test	X	X	X
Tower of London	X	X	X
CPT	X	X	X
WCST	X	X	X

CPT = Continuous Performance Test, WCST = Wisconsin Card Sorting Test

9.5.3 Appropriateness of Measurements

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

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

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

9.5.4.1 Reporting of Serious Adverse Events

All serious adverse events, regardless of their relationship to study treatment, must be reported to OAPI on a completed SAE form by email or fax as soon as possible but no later than 24 hours from the date the investigator becomes aware of the event.

Deaths and life-threatening events should be reported immediately by telephone. The immediate report should be followed up within 24 hours by emailing or faxing the completed SAE form.

Serious adverse events, regardless of causality assessment, must be collected through the last visit. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

Report IREs (serious adverse events, potential Hy's Law cases, pregnancies and adverse events requiring discontinuation of trial drug) to:

Clinical Safety and Pharmacovigilance
Otsuka Pharmaceutical Development & Commercialization, Inc.
Khaled Bannout, MD

2440 Research Boulevard
Rockville, Maryland 20850, United States
Hotline: 240-683-3115
Fax: 301-721-7115
For Medical Emergencies (use only if Otsuka personnel listed above are unavailable): 301-990-0030

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the OAPI to be filed in the OAPI Study Master File.

9.5.4.2 Immediately Reportable Events (IRE)

Immediately Reportable Event (IRE):

- Any SAE
- Any AE that necessitates discontinuation of study drug
- Potential Hy's Law cases (any increase of AST or ALT ≥ 3 times the upper normal limit or screening value with an increase in total bilirubin ≥ 2 times the upper normal limit or screening value)
- Pregnancies are also defined as IREs, although normal pregnancy is not an AE, it will mandate study drug discontinuation and must be reported on an immediately reportable event (IRE) form to OAPI. Pregnancy will only be documented on the AE-CRF if there is an abnormality or complication.

The investigator must immediately report any serious adverse event (SAE), potential Hy's law cases, or confirmed pregnancy, by telephone or by fax to OAPI as outlined in Section 9.5.4.1 after either the investigator or site personnel become aware of the event. An IRE form must be completed and sent by fax or overnight courier to OAPI within 24 hours of knowledge of the event by the site. (Please note that the IRE form is NOT the AE CRF.)

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

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

POTENTIAL HY'S LAW CASES

For a subject that experiences an elevation in AST or ALT that is ≥ 3 times the upper limit of normal (ULN) or whose levels increase ≥ 3 times their initial screening value, a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN or ≥ 2 times their screening value, complete an IRE form with all values listed and also report as an AE on the CRF.

9.5.4.3 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

During the trial, all women of childbearing potential should be instructed to contact the investigator immediately, but no later than 3 days, if they suspect they might be pregnant (e.g., missed or late menstrual cycle).

If a subject or investigator suspects that the subject may be pregnant prior to study drug administration, the study drug administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the study drug and must not be enrolled in the study. If pregnancy is suspected while the subject is taking study drug, the study drug must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy is known. If pregnancy is confirmed, the study drug will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety) and the subject withdrawn from the study. Exceptions to study discontinuation may be considered for life-threatening conditions only after consultations with OAPI's Clinical Safety and Pharmacovigilance Department (see Section 9.5.4.1 for contact information).

The investigator must immediately notify OAPI of any pregnancy associated with study drug exposure, including 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, and record the event on the IRE form and forward it to OAPI. The OAPI contact will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

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

9.5.4.4 Reporting of Safety Information and Other Events of Interest

All non-serious AEs will be reported to OAPI at the end of the study or at the request of OAPI.

REPORTING OF ADVERSE EVENTS ASSOCIATED WITH STUDY DRUG OVERDOSE, MISUSE, ABUSE, OR MEDICATION ERROR

Safety Information is defined as any information from any source containing information such as:

- Adverse event or suspicion thereof
- Lack of efficacy
- Overdose, abuse, misuse (even without resulting adverse reaction)
- Medication error
- Exposure during pregnancy or lactation (including uneventful) and reports 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)
- Counterfeit product
- Transfer of infectious disease by the medicinal product concerned
- Product complaint report which includes medically important information
- Pediatric use
- Occupational exposure
- Off-label use

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the prescribed or authorized dose, route of administration, or indication(s) or use of prescription-only study drug without a prescription
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of the healthcare professional, subject, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems including prescribing; order communication; product labeling,

packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

All AEs associated with an overdose should be captured on the CRF. Adverse events associated with overdose, misuse, abuse, or medication error should be reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the CRF.

9.5.4.5 Regulatory Reporting of Adverse Events

Adverse events will be reported by the investigator or a third party acting on behalf of the investigator to regulatory authorities in compliance with the law and established guidance and will be reported to OAPI at least 2 weeks prior to submission of an aggregate safety report. The format of these reports will be dictated by the local requirements.

9.5.5 Database Reconciliation

The investigator or designee will request contact information for the OAPI safety officer to whom this protocol is assigned. The safety officer will provide listings of SAES and non-serious AEs from OAPI to the investigator or designee for review and potential reconciliation of the safety data. This review will occur at specified time points and at the end of the study for final reconciliation.

The OAPI contact will be copied on all correspondence regarding attempts to reconcile the safety database.

9.5.6 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason without prejudice. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedules of Assessments (Table 4 through Table 7) whenever possible.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be 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 will be recorded in the CRF.

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

A subject removed from the study for any reason may be replaced.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 DATA QUALITY ASSURANCE

9.6.1 Monitoring

The OAPI has ethical, legal, and scientific obligations to follow this trial 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 (maintain current personal knowledge of the progress of the trial), OAPI's monitors may visit the site during the trial, as well as communicate frequently via telephone and written communications.

9.6.2 Auditing

The OAPI Quality Management Unit (or representative) may conduct trial site audits. Audits will include, but are not be limited to, drug supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents. The investigator agrees to participate with audits.

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

9.6.3 Data Collection Duration

Data collection begins when the first subject signs the ICF and is complete on the date at which the last subject’s data has been entered into the database and no data queries are outstanding.

9.7 STATISTICAL METHODS

All statistical analyses will be performed by the investigator or designee after the study is completed and the database is locked and released and randomization codes have been released. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Additional details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

9.7.1.1 Primary Endpoint(s)

The primary efficacy endpoint is change from Phase C baseline in prefrontal white matter FA measured by DT-MRI. The primary time point will be the Week 52 assessment. Secondary Endpoint(s)

The secondary efficacy endpoints will include:

- Change from Phase C baseline in volumes by high-resolution MRI. This variable will be analyzed using the methods employed for the primary endpoint.
- Change from Phase C baseline in Water-BPF by MRI. This variable will be analyzed using the methods employed for the primary endpoint.
- Changes from Phase C baseline in schizophrenia-related instrument scores, if appropriate. These variables will be analyzed using the methods employed for the primary endpoint.
- Changes from Phase C baseline in neuropsychological measures. These variables will be analyzed using the methods employed for the primary endpoint.

9.7.1.2 Exploratory Endpoint(s)

Exploratory endpoints such as proton metabolite measurements by MRS will be analyzed as appropriate. Additional analyses will be performed as appropriate.

9.7.1.3 Definitions of Analysis Sets

Three analysis populations will be considered in this study, safety, intent-to-treat (ITT), and per protocol (PP) populations.

- Safety population: includes all subjects with any safety assessments
- ITT population: includes all subjects with some Phase C baseline and post-baseline efficacy assessments
- PP population includes: all ITT subjects without major protocol deviations

Unless otherwise stated, the primary safety analyses will be based on the safety population and the primary efficacy and pharmacodynamic analyses will be based on the ITT population.

The primary comparisons will be made between the SOC oral antipsychotic arm and the aripiprazole depot arm during Phase C.

9.7.1.4 Subject Disposition

Descriptive statistics will be utilized. By-subject listings and summary tables will be provided.

9.7.1.5 Demographic and Other Baseline Characteristics

Descriptive statistics will be utilized. By-subject listings and summary tables will be provided.

9.7.1.6 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). The number (percentage) of subjects who took prior and concomitant medications will be summarized by treatment group, Anatomical Therapeutic Chemical (ATC) class (i.e., nervous system class and therapeutic class), and WHO DD preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's last dose. All medications will be presented in subject data listings.

9.7.1.7 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, presented by treatment group will be summarized on an "as treated" basis using descriptive statistics (e.g., n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include physical examinations, neurologic evaluations, treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, 12-lead ECG results, and injection site reactions. Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

9.7.1.7.1 Extent of Exposure

By-subject listings and summary tables will be provided.

9.7.1.7.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

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

Treatment-emergent AEs (TEAEs) will be summarized by treatment group and overall. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within a SOC and PT, even if the subject

experienced more than one TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

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

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be possibly or probably related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

Adverse events will be summarized using the Safety Analysis Set. The number of AEs and number and incidence (%) of subjects with AEs will be summarized by cohort/dose level and overall. To obtain the incidence (%), the number of subjects with at least 1 event and the percentage of subjects with AEs by system organ class (SOC) and by preferred term (PT) will be calculated. Incidence (%) by causal relationship with study drug and by severity will also be calculated. For clinically significant events, time of onset, and recovery will be reported.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.7.3 Laboratory Values

Summary statistics for changes from baseline and the incidence of potentially clinically significant values in the routine clinical laboratory measurements will be provided.

9.7.1.7.4 Physical Examination and Vital Signs

By-subject listings will be provided for physical examination. Summary statistics for change from baseline and incidence of potentially clinically significant results in vital signs will be provided.

9.7.1.7.5 Electrocardiograms

Mean change from baseline and incidence of clinically significant changes in ECG parameters will be calculated.

9.7.1.7.6 Other Safety Analyses

Summary statistics will be provided for the change from baseline in SAS, AIMS, and BARS when applicable. Summary statistics for VAS score and injection site reaction will be provided when applicable. Suicidality data collected on the C-SSRS will be summarized as appropriate.

9.7.1.8 Efficacy Analyses

9.7.1.8.1 Primary Efficacy Analysis

The primary endpoint will be analyzed by an analysis of variance (ANOVA) model with treatment effect. The treatment effects, treatment differences, and the 95% confidence intervals of the treatment differences will be presented.

9.7.1.8.2 Secondary Efficacy Analyses

The secondary endpoints will be analyzed by an analysis of variance (ANOVA) model with treatment effect. The treatment effects, treatment differences, and the 95% confidence intervals of the treatment differences will be presented.

Correlations between the imaging parameters, especially the primary endpoints and the neuropsychological measures (e.g., reaction time) will be analyzed.

9.7.1.8.3 Exploratory Efficacy Analyses

Exploratory endpoints such as proton metabolite measurements by MRS will be analyzed as appropriate. Additional analyses will be performed as appropriate.

9.7.1.9 Pharmacokinetic/Pharmacodynamic Analyses

9.7.1.9.1 Pharmacokinetic Analyses

Not applicable.

9.7.1.9.2 Pharmacodynamic Analyses

The PD endpoints will be analyzed by an analysis of variance (ANOVA) model with treatment effect. The treatment effects, treatment differences, and the 95% confidence intervals of the treatment differences will be presented.

9.7.2 Determination of Sample Size

After screening subjects with schizophrenia will be randomized in a 2:1 (aripiprazole once monthly:/SOC oral antipsychotics) ratio to the aripiprazole once monthly arm or the SOC oral antipsychotic arm of the study. A sample size of 42 (28 in the depot arm and 14 in the oral arm) will provide 90% power to detect a treatment difference for the primary endpoint at a two-sided 5% significance level. In the sample size calculation, it was assumed a treatment difference of 0.7 and a common standard deviation of 0.64. Approximately 60 subjects with schizophrenia will be randomized (40 in the depot arm and 20 in the oral arm) to account for the expected dropouts. Up to 20 normal healthy subjects will also be enrolled to serve as the control.

9.7.3 Interim Analysis

No interim analysis is planned.

9.7.3.1 Data Safety Monitoring Board

In addition, a DSMB will be created in compliance with the University of Utah IRBs guidances.

9.7.3.1.1 Functions of the Data and Safety Monitoring Board

The DSMB will function as an independent body charged with monitoring the safety of subjects, and ensuring that the scientific goals of the study are met. To support these goals, the DSMB will review proposed amendments to the study protocol, monitor AEs and report to the IRB, review subject withdrawals and the reasons for withdrawal, determine whether study procedures should be changed or the study should be stopped for reasons related to subject safety, and conduct reviews of the completeness and validity of study data. The DSMB will also monitor subject privacy and data confidentiality, and will recommend added protections if necessary.

9.7.3.1.2 Monitoring of Data Quality by the DSMB

On a quarterly basis, the DSMB will receive a report prepared by the research team on data quality and completeness. This will include an overview of recruitment and retention, a summary report describing subject adherence to the protocol's procedures and study-drug compliance, and a summary of the completeness and quality of the data elements needed to characterize the subjects and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the adequacy of the research team's data capture and management to support scientifically valid analysis. The DSMB will make recommendations to improve data management as needed.

The PI will review all unanticipated problems involving risk to subjects or others, SAEs, and any subject deaths; and provide an unbiased written report of the event within 5 calendar days. The medical monitor will comment on the outcome of the AEs and relationship of the event to the study drug.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP requires revision after the study starts, the investigator will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 ADMINISTRATIVE PROCEDURES AND INSTRUCTIONS

10.1 CHANGES TO THE PROTOCOL

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

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

10.2 ADHERENCE TO THE PROTOCOL

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

10.3 MONITORING PROCEDURES

The investigator will assure 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 (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB review.

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

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (e.g., sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are 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

10.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF.

10.5 Identification of Source Data

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

10.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is 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 should plan to retain study documents for the length of time agreed upon in the study contract.

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

10.7 Auditing Procedures and Inspection

In addition to the routine monitoring procedures, the OAPI Clinical Quality Assurance department conducts audits of clinical research activities in accordance with OAPI's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform OAPI immediately.

10.8 Reporting and Publication of Results

A clinical study report will be finalized within one year of the end of data collection.

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by OAPI in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Study Agreement between OAPI and the institution/investigator. The review is aimed at protecting OAPI's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between the investigator and OAPI, as appropriate.

10.9 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of OAPI. No data collected as part of this study will be used in any written work, including publications, without the written consent of OAPI. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Study Agreement executed between OAPI and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Study Agreement executed between the institution/investigator and OAPI.

10.10 Discontinuation of Study

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

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of OAPI, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform OAPI and the IRB and provide OAPI and the IRB with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

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