1 TITLE PAGE

ARIPIPRAZOLE, ABILIFY MAINTENA®
COLLABORATIVE CLINICAL PROTOCOL

A Cluster Randomized, Multi-center, Parallel-group, Rater-blind Study Comparing Treatment with Aripiprazole Once Monthly and Treatment as Usual on Effectiveness in First-Episode and Early Phase Illness in Schizophrenia

Collaborative Protocol No. COL.AOM.2013.005

G-Port No.

CONFIDENTIAL – PROPRIETARY INFORMATION

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29 July 2014, Original Protocol
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REVISION HISTORY

29 July 2014	Original Protocol
20 July 2015	Amendment 0.1
	• Title Page: Added amendment version number and date for revisions to the protocol. • Section 2: Changes in baseline visit assessments and procedures, including timing, and the criteria that needs to be met before scheduling the once monthly visits; Canadian sites were removed from the study; randomization procedures were clarified; the criteria for calculation for the inpatient psychiatric hospitalization secondary endpoint was clarified; change from baseline in quality of life using the QLS was missing as a secondary endpoint; and additional inclusion and exclusion criteria were added. • Section 6: Additional site information will be provided in the PI's trial master file only (removed FDA form requirement). • Table 1: Key Study Personnel and Contributors was updated to include the appropriate names for Other PI Study Staff and DSMB. • Section 9.1: Changes in baseline visit assessments and procedures, the criteria that needs to be met before scheduling the once monthly visits, and additional information regarding recruitment methods for each cohort was added. • Figure 1: Procedures during the Screening, Baseline 1, Baseline 2, and Treatment Visits were changed or updated. • Section 9.1.1: Changes in baseline visit assessments and procedures and added text regarding timing of initial aripiprazole injection. • Section 9.1.2: Section updated to reflect that the Canadian sites were removed from the study; further clarification of the randomization procedure; and the inclusion of the SCID-5, QLS, and Premorbid Adjustment Scale as assessments being remotely conducted. • Section 9.1.3.1: Treatment and analysis procedures for subjects at LAI sites was clarified. • Section: 9.1.3.1.1: Clarification of timing for the remote assessments of BPRS, CGI S, RBANS, QLS, and C SSRS to be conducted. • Section 9.1.4: Addition of the QLS to the list of assessments conducted during Month 24 Visit/Early Termination. • Section 9.2: Removed training information for sites randomized to aripiprazole once monthly because it was already included in Section 9.1.3.1. • Section 9.3.1: Additional inclusion criteria was added. • Section 9.3.2: Additional exclusion criteria was added. • Section 9.4: Source of study drug was clarified. • Section 9.4.2: Storage procedures for study drug was updated. • Section 9.4.3: Section updated to reflect that the Canadian sites were removed from the study. • Section 9.5.1: Text regarding timing of the study assessments at Screening and Baseline Visits were added; the exact version of the SCID was added. • Section 9.5.1.5: Hospitalization for administration of study drug or insertion of access for administration of study drug was removed from list of hospitalizations that are not considered SAEs. • Section 9.5.1.6.3: Removed description of C SSRS scale and updated timing of the C-SSRS assessment.

	• Section 9.5.1.8: Added the Premorbid Adjustment Scale to the assessments for neuropsychiatric function. • Section 9.5.2.1: Procedures for structural and diffusion tensor imaging was updated. • Section 9.5.2.2 and 9.5.2.3: Section removed; task-based fMRI acquisition is not being used in this study. • Section 9.5.2.4: Procedures for fMRI acquisition were changed; section was renumbered due to removal of previous sections; new section added for MRI assessments (replaced previous Sections 9.5.2.2 and 9.5.2.3). • Table 3 and Table 4: The Schedule of Assessments for Year 1 and Year 2 were updated, including new assessments, timing of assessments, and footnote changes; footnotes were then reordered for clarity.' • Section 9.6.3: Data collection dates were updated. • Section 9.7.1.2: Text was added to clarify the definition of "total times" and "gap times" and that only inpatient psychiatric hospitalization will be calculated for each subject as part of the secondary endpoints. • Section 9.7.1.3: Definition of the Full Analysis Set was updated; text was added to describe the procedures for subgroup analyses of subjects at LAI sites. • Section 9.7.1.5: Removal of the presentation of demographics of the Safety Analysis Set if there is more than a 5% difference from the Full Analysis Set. • Section 9.7.1.8.2: Text was added to clarify that only inpatient psychiatric hospitalization will be calculated for each subject as part of the secondary endpoints. • Section 9.7.1.8.4: Updated the criteria for the *a priori* sensitivity analyses. • Section 9.7.5: Addition of requirement to send any changes to the SAP to the DSMB for review. • Section 10: Any changes in the protocol that affect the safety of subjects, the scope of the investigation, or the scientific quality of the study must also be approved by the DSMB in addition to the applicable IRBs. • Various sections: Random typographical errors corrected for reader clarity; no effect on safety or study conduct.
29 October 2015	• Amendment 2.0
	• Synopsis page 8: added "or deltoid" • Section 9.3.3.1 (Overall treatment): added "or deltoid" • Section 9.4.1 (Treatments Administered): added "or deltoid IM"

2 CLINICAL PROTOCOL SYNOPSIS

Name of Sponsor: Vanguard Research Group **Name of Product:** Abilify Maintena®, aripiprazole	
Collaborative Protocol Title:	A Cluster Randomized, Multi-center, Parallel-group, Rater-blind Study Comparing Treatment with Aripiprazole Once Monthly and Treatment as Usual on Effectiveness in First-Episode and Early Phase Illness in Schizophrenia
Treatment Indication:	Schizophrenia
Objective(s):	The primary objective of the study is: • To determine the effectiveness of treatment with aripiprazole once monthly compared with treatment as usual (TAU) as defined by time to first hospitalizations. The secondary objectives of the study are to: • Determine the effect of treatment with aripiprazole once monthly compared with TAU on brain structure volumes and white matter integrity over the 2-year study duration • Determine the effectiveness of treatment with aripiprazole once monthly compared with TAU on clinical outcomes beyond time to first hospitalization. The outcomes are: o Reducing the number of days in the hospital during the 2 years of follow-up o Reducing the time to all episodes of psychiatric hospitalization o Reducing psychopathology o Lowering cost of care o Improving neuropsychological functioning
Study Design:	This is a cluster randomized, two-arm, rater-blind, multi-center, parallel-group study designed to compare the effectiveness and changes in brain structure volumes of aripiprazole once monthly compared with TAU in subjects with first-episode and early phase (EP) schizophrenia. Approximately 40 sites will participate in the study in order to enroll approximately 500 subjects during 1 year of recruiting. Subjects will be recruited into two cohorts: the first-episode cohort and the EP cohort, with approximately 250 subjects in each cohort. Ongoing evaluation of the numbers of subjects for each cohort will continue until target enrollment is reached. Enrollment of subjects into the first-episode and EP cohort will be discontinued when the appropriate number for the target is reached. Sites, as a cluster, will be randomized, with half of the sites assigned to the long-acting injectable (LAI) aripiprazole once monthly and half of the sites assigned to TAU medications. One screening visit will occur over approximately 1 week. After providing written informed consent, subjects will be screened for general eligibility by the clinical team at the site. Basic demographic data will be collected to determine suitability for inclusion into the study and to account for subjects screened, but not included in the study. The site will complete an information interview comprising of data regarding symptomology and history to enable the remote centralized assessment team to conduct their assessments. After screening, two baseline visits will occur, which will be no more than 4 weeks apart.

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Study Design continued:

Baseline Visit 1 will include:

- Establish diagnostic eligibility with the Structured Clinical Interview for Diagnostic and Statistical Manual, Fifth Edition (DSM-5) Disorders (SCID-5) by the remote centralized assessment team
- Evaluate psychopathology using the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impression-Severity (CGI-S) scale by the remote centralized assessment team
- Completion of the Heinrichs-Carpenter Quality of Life Scale (QLS) by the remote centralized assessment team
- Completion of the Columbia Suicide Severity Rating Scale (C-SSRS) assessment by the remote centralized assessment team
- Completion of the Premorbid Adjustment Scale by the remote centralized assessment team
- Begin oral aripiprazole (LAI sites only)
- Urine pregnancy test will be performed
- If eligible per the SCID-5, LAI sites will start to assess tolerability to oral aripiprazole. Visits will occur weekly until the clinician determines tolerability.

Baseline Visit 2 is the final baseline visit and will include:

- Magnetic resonance imaging (MRI) will be completed for subjects in the MRI substudy
- Completion of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
- Collection of study-specific demographic information
- Recording of medical and psychiatric histories
- Collection of information on use of services, insurance status, work, school attendance, and other service use outcomes will be assessed using the Service Utilization and Resources Form (SURF)
- Height, body weight, waist circumference, temperature, pulse and blood pressure will be measured
- Body mass index (BMI) will be calculated
- Fasting blood samples for clinical laboratory testing will be collected, including a lipid panel (i.e., cholesterol: total, high-density lipoprotein [HDL] low-density lipoprotein, [LDL], and triglycerides), a metabolic profile, prolactin and insulin concentrations, and a complete blood count (CBC) with differential, glycosylated hemoglobin (HbA1c)
- Urinalysis with microscopic analysis
- Completion of the Medication Visit Record
- Record current medications
- Completion of the Hospitalization and Emergency Room Visit (HEC) form

All Baseline Visit 2 assessments must occur within 4 weeks of Baseline Visit 1. Baseline Visit 2 will be considered completed when all assessments have been performed.

The initial aripiprazole injection will be given at some point after the Baseline Visit 1 once tolerability to oral aripiprazole is established. Future injections of aripiprazole will still be administered monthly; however, the injections may not coincide with the scheduled monthly visits.

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Study Design continued:

Aripiprazole once monthly will be prescribed and administered according to recommendations contained in the product labeling.

Following the baseline visits and once tolerability has been established, subjects at the LAI sites will be scheduled for once monthly medication visits for aripiprazole once monthly injections, and subjects at the TAU sites will be scheduled for medication visits as required based on their TAU medications (i.e., at a minimum of every 3 months). All subjects will receive bimonthly phone calls inquiring about any visits to emergency rooms and hospitalizations. All subjects will receive phone calls every 4 months to complete the SURF. The calls will be conducted by the local site research assistant or study coordinator and are not linked to participation in treatment. All subjects are required to attend an in-person visit every 6 months (i.e., 6, 12, 18, and 24 months) during the 2-year study duration. Subjects who prefer in-person visits at any time when a telephone visit is scheduled may request them at any time. At the 6-, 12-, 18-, and 24-month visits, the following assessments will be performed:

- Information on use of services, insurance status, work, school attendance, and other service use outcomes will be assessed using the SURF (i.e., 12- and 24-month visits only)
- Height, body weight, waist circumference, temperature, pulse and blood pressure will be measured
- Fasting blood samples for clinical laboratory testing will be collected including a lipid panel (i.e., cholesterol: total, HDL, LDL, and triglycerides), a metabolic profile, prolactin and fasting insulin concentrations, and a CBC with differential
- Urine pregnancy test
- Assessments for psychopathology using BPRS and CGI-S (i.e., 12- and 24- month visits only)
- Completion of C-SSRS (i.e., 12- and 24-month visits only)
- Administration of LAI medications including aripiprazole once monthly or prescription dispensation
- Completion of the Medication Visit Record, including details of dispensing, prescribing, and administration information where appropriate
- Reporting and recording of adverse events
- Completion of the RBANS to measure neuropsychological function (i.e., 12- and 24-month visits only)
- Completion of QLS (i.e., 12- and 24-month visits only)

Because subjects with schizophrenia have an estimated 8.5-fold greater risk of suicide than the general population, with young patients particularly at risk, subjects in this study will be monitored closely for suicidality at each study visit. Instances of suicidality will be captured using an expanded serious adverse event form, and potential for suicidality will be monitored using the C-SSRS at the 12- and 24-month visits and at any other appropriate time, per the investigator's judgment.

In addition, a subset of an expected 114 first-episode and EP subjects at approximately 10 clinical sites will undergo MRI at the baseline, 12- and 24-month visits to measure brain structure volumes and white matter integrity.

The MRI sites (i.e., Five TAU and Five LAI) will be selected based on close proximity to centers with research MRI capabilities. The first 57 subjects at both the TAU and LAI sites consenting to MRI will be enrolled into the MRI portion of the study.

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Subject Population:

An estimated 500 subjects with schizophrenia will be enrolled over a 1-year recruitment period to recruit an expected 0.5 to 1 subject with first-episode schizophrenia and 0.5 to 1 subject with EP schizophrenia per month, allowing for an anticipated 250 subjects in the first-episode cohort and 250 subjects in the EP cohort. Randomization at the 40 sites will be stratified by 1) urban versus non-urban treatment setting and 2) ethnic composition of the population served by the site. All sites will provide detailed information about the ethnic composition of their patient population prior to randomization. Half of the sites (i.e., 20/40) will be randomly assigned to administer aripiprazole once monthly and the remaining 50% of the sites will be randomly assigned to administer TAU antipsychotic medications.

In addition, a subset of 114 first-episode and EP subjects at approximately 10 of the clinical sites will undergo MRI to measure brain structure volumes and white matter integrity. The MRI sites (i.e., five TAU and five LAI) will be selected based on close proximity to centers with research MRI capabilities. The first 57 subjects at both the TAU and LAI sites consenting to MRI will be enrolled into the MRI portion of the study.

All subjects will have a current diagnosis of schizophrenia as defined by the DSM-5 criteria. The first-episode subjects are defined as those subjects with < 1 year of antipsychotic treatment and the EP subjects are defined as subjects with a 1- to 5-year history of antipsychotic treatment.

Subjects will be selected by approaching all eligible patients at the participating clinics. The inclusion criteria are as broad as possible within an EP population. Subjects must meet the following inclusion criteria to be eligible for the study:

1. Are able to provide written informed consent
2. Have a confirmed diagnosis of schizophrenia as defined by DSM-5 criteria using the SCID-5
3. Are between the ages of 18 and 35, inclusive
4. Have the following history with antipsychotic medications
    a. First episode subjects: < 1 year of lifetime exposure to antipsychotic medication and only one episode of psychosis
    b. EP subjects: between 1 year and 5 years of lifetime exposure to antipsychotic medication or subjects with < 1 year of lifetime antipsychotic medication and more than one episode of psychosis
5. Subjects at LAI sites must be willing to accept an injectable form of treatment.

Subjects must not have any of the following criteria to be eligible for the study:

1. Have a current primary DSM-5 diagnosis other than schizophrenia, including schizophreniform disorder, schizoaffective disorder, major depressive disorder, bipolar disorder, delirium, dementia, and amnestic or other cognitive disorders.
2. Subjects at LAI sites: have a known allergy or intolerance to aripiprazole, or a past negative response to aripiprazole that is not explained by nonadherence
3. Be pregnant or lactating
4. Have any unstable medical condition that, in the opinion of the investigator, would be detrimental to the subject or would confound the results of the study
5. Past or current treatment with clozapine
6. Subjects in the MRI subset only who have:
    a. Received an LAI antipsychotic in the last 6 months
    b. Any metal implants, pacemakers, irremovable prosthetic device, or other device or situation that may preclude imaging

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Study Drug, Dose, Formulation, Mode of Administration:	All aripiprazole study drug will be purchased by the investigator. Medication at the TAU sites will be prescribed based upon usual site practices. In order not to influence or restrict which medications are prescribed at TAU sites, medications for TAU subjects will not be supplied by the study. Reimbursement for medications at TAU sites will be by usual mechanisms (e.g., private or public insurance). The following medications will be administered: • Aripiprazole administered once monthly via gluteal or deltoid intramuscular (IM) injection, as outlined in the product labeling. • Oral antipsychotics administered per oral including, but not limited to: o aripiprazole (Abilify®) o risperidone (Risperdal®) o lurasidone HCl (Latuda®) o quetiapine fumarate (Seroquel®) o olanzapine (Zyprexa®) o ziprasidone HCl (Geodon®) • Long-acting injectable medications administered intramuscular include but are not limited to:: o risperidone (Risperdal® Consta®) o haloperidal decanoate (Haldol® decanoate) o olanzapine (Zyprexa® Relprevv™) o paliperidone palmitate (Invega® Sustenna®) o fluphenazine decanoate (Prolixin® decanoate)

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Criteria for Evaluation:	Primary outcome variables: Efficacy: • Time to the first hospitalization Secondary outcome variables: Efficacy: • Change from baseline to the 1-year and 2-year time points in gray matter and white matter volume, and cortical thickness. The 2-year time point is the primary time point • Time to all episodes of psychiatric hospitalization, including total times (e.g., time from randomization to first, second, or any subsequent hospitalizations) as well as gap times (e.g., time between first and second hospitalization, second and third hospitalization, etc.) • Total number of days of inpatient psychiatric hospitalization per quarter for each subject for the duration of the study • Change from baseline in BPRS and CGI-S • Cost of care from the SURF • Change from baseline in neuropsychological function (i.e., RBANS) • Change from baseline in quality of life (i.e., QLS) Safety: • Treatment-emergent adverse events • Blood pressure • Clinical laboratory testing including prolactin and lipid profiles • Body weight, height, and BMI • C-SSRS assessment for suicidality Pharmacodynamic: • Change from baseline to the 1-year and 2-year time points in gray matter and white matter volume, and cortical thickness with the 2-year time point as the primary time point
Study Duration:	The study is expected to be approximately 3 years in duration. Subject recruitment is expected to occur over 1 year and the study conduct is approximately 2 years in duration for individual subjects.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BPRS	Brief Psychiatric Rating Scale
CBC	complete blood count
CGI-S	Clinical Global Impression-Severity
CR	competing risk
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
DS	dorsal striatum
DSM-5	Diagnostic and Statistical Manual, Fifth Edition
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EP	early phase
EPI	echo planar imaging
EPS	extrapyramidal side effects
EQC	Ethics, Quality, and Compliance
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GCP	Good Clinical Practice
HbA1c	glycosylated hemoglobin
HDL	high-density lipoprotein
HEC	Hospitalization and Emergency Room Visit
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IM	intramuscular

Abbreviation	Term
IRB	institutional review board
LAI	long-acting injectable
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
OAPI	Otsuka America Pharmaceutical, Inc.
OPC	Otsuka Pharmaceutical Co., Ltd
PANSS	Positive and Negative Syndrome Scale
PHREG	proportional hazards regression
PI	Principal Investigator
PK	pharmacokinetic
PO	per oral
PQC	product quality complaint
PT	preferred term
QLS	Heinrichs-Carpenter Quality of Life Scale
QT	interval from beginning of the QRS complex to end of the T wave in the frontal plane
QTc	corrected QT interval
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCT	randomized clinical trial
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety Analysis Set
SCID-5	Structured Clinical Interview for DSM -5 Disorders
SURF	Service Utilization and Resources Form
TAU	treatment as usual
TEAE	treatment-emergent adverse event
US	United States
VS	ventral striatum

5 ETHICS

This study must be conducted in compliance with the protocol, Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline, and all other applicable local laws and regulatory requirements. Each study site will seek approval by an institutional review board (IRB) according to regional requirements. The IRB will evaluate the ethical, scientific, and medical appropriateness of the study. Further, in preparing and handling case report forms (CRFs), the investigator, sub-investigator, and their staff 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. Subjects will also complete a written study review questionnaire that covers key aspects of the study (e.g., the ability to withdraw at any time). If a subject consents to participation in this study, the subject will review and sign the informed consent form (ICF). When ready, and after having satisfactorily answered all questions on the study review questionnaire indicating understanding of the study procedures, subjects will be asked to give written consent to participate in the study. After both the subject and the investigator sign the ICF, each subject will be given a copy of the signed 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 IRB that approves this protocol. Each ICF will comply with the FDA regulations in Title 21 Code of Federal Regulations Part 50 ICH, 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 determination of eligibility for this study, including withdrawal from current medication(s).

Once the 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 (i.e., investigator or designee), as well as by any other parties required by the IRB. The subject will receive a copy of the signed ICF and the original shall be kept on file by the investigator.

5.1.1 Magnetic Resonance Imaging Consent

Subjects enrolled for the magnetic resonance imaging (MRI) portion of the study must give separate informed consent before any MRI procedures can be performed.

6 INVESTIGATORS AND STUDY PERSONNEL

This is a collaboratively designed, investigator-sponsored study that will be conducted at approximately 40 sites across North America.

The Principal Investigator (PI) and study staff at the PI site are listed below along with information for other key contributors to the study. Information regarding the additional sites will be provided in the PI's trial master file.

Table 1: Key Study Personnel and Contributors

<table>
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<tr><td>The Zucker Hillside Hospital</td><td>Independent DSMB
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</table>

DSMB = Data Safety Monitoring Board, IRB = Institutional Review Board, PI = Principal Investigator,

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7 INTRODUCTION

Non-adherence remains an enormous challenge in schizophrenia. Long-acting injectable (LAI) antipsychotics have been shown in some mirror image, naturalistic, and randomized clinical trials (RCTs) to significantly reduce rates of relapse and re-hospitalization in comparison with oral antipsychotics. However, a recent meta-analysis1 of RCTs did not show an overall advantage. This change from a previous analysis published only 2 years ago[2] is largely due to the findings of two recent studies funded by the Veteran's Administration and National Institutes of Mental Health[3,4], which were both unable to demonstrate superiority for LAIs, despite state-of-the-art methodology. Given the apparent disconnect between some naturalistic data[5,6] and recent RCTs, it is important to consider the possibility that the types of RCTs that have traditionally been conducted do not really succeed in recruiting representative patients or in fully achieving an effectiveness treatment trial model for LAIs. A well-designed effectiveness trial that overcomes the limitations of prior studies is necessary to better address the question of the utility of LAIs in settings that approximate real world care. Health policy makers, payers and providers, particularly those in the United States (US), will be less likely to actively facilitate the use of LAIs, unless there is compelling evidence to support their use, including cost effectiveness data.

Given the increasing recognition that early and effective interventions hold the greatest promise for improving the overall trajectory and outcome of schizophrenia, including rates of recovery, it is particularly important to determine the impact of "guaranteed medication" in the earliest possible phases of illness. This is underscored by the well-documented enormous challenge of medication acceptance and adherence among first-episode and early phase (EP) patients. In addition, there are some suggestions that LAI medication administration may be particularly effective in the early phase of schizophrenia7[-10].

Aripiprazole once monthly is particularly well suited to a large simple trial because monthly administration more closely mirrors clinical practice. In both recent LAI studies, risperidone microspheres were used, which require biweekly administration. Moreover, the relatively lower side effect burden of aripiprazole once monthly when compared with most other first line agents, including paliperidone, the only other once-monthly second generation antipsychotic, increases its acceptability for and utility in EP patients.

7.1 BRAIN CHANGES IN SCHIZOPHRENIA

Antipsychotic medications are widely prescribed for the treatment of schizophrenia and related psychotic disorders; thus, understanding their potential impact on the brain has significant health implications. Moreover, better understanding of how brain changes relate to long-term antipsychotic treatment could improve our understanding of the mechanisms of antipsychotic efficacy (especially in the developing brain), inform neurobiological models of schizophrenia, and translate into improved clinical care by clarifying their impact on long-term cognitive and functional outcome. The early phase of psychosis is likely the most critical period for treatment intervention, and the ideal time to study key mechanisms associated with brain plasticity.

There is now considerable evidence that both typical and atypical antipsychotic medications may be associated with structural and functional changes in the brain. Initial longitudinal studies conducted by our group and others suggested that basal ganglia volumes increase over time

following treatment with typical antipsychotics, and that this enlargement may be reversed or normalized following treatment with clozapine[11-14]. Comprehensive literature reviews indicate that antipsychotics may contribute to the genesis of some of the structural abnormalities that are usually attributed to schizophrenia[15]. Furthermore, several longitudinal neuroimaging studies reported white matter volume reductions in association with greater exposure to antipsychotic medications[16] and reductions in white matter integrity in treatment-naïve patients following antipsychotic treatment[17-19].

A critical limitation of prior neuroimaging studies assessing the impact of antipsychotics on brain structure and function is the lack of information regarding medication compliance and the possibility that such purported neuroanatomic changes may reflect illness progression. Few studies in the literature have addressed this critical issue. Of particular relevance to this study is work by Bartzokis et al[20], who examined the impact of antipsychotic formulations on white matter volume during a 6-month trial of LAI risperidone versus oral risperidone in first-episode schizophrenia patients. White matter volume remained stable in the patients treated with LAI risperidone, but decreased significantly among patients treated with oral risperidone. This work was subsequently extended by Bartzokis et al[21] to indicate that frontal lobe intracortical myelin volume increased significantly among patients receiving LAI risperidone, but no significant longitudinal effects were evident among patients treated with oral risperidone. Notably, patients receiving LAI risperidone had better medication adherence and greater intracortical myelin increases.

Conclusions gleaned from prospective studies examining the relationship between antipsychotic treatment and brain integrity in schizophrenia must be interpreted in the context of research demonstrating a deleterious effect of psychosis on the brain independent of antipsychotic medication exposure. For example, Ziermans et al[22] reported that those individuals who were at ultra-high risk for psychosis and became psychotic demonstrated a greater reduction in total brain and white matter volume over time, compared with healthy controls and individuals who did not become psychotic. Other studies suggest that a greater duration of untreated psychosis may be neurotoxic to the brain. Filippi et al[23] reported that 43 first-episode, drug-naïve patients with schizophrenia demonstrated gray and white matter structural alterations, which were associated with a longer duration of untreated psychosis and positive symptom severity compared with healthy volunteers. In addition, Cahn et al[24] found that a greater duration of psychosis was associated with gray matter volume reductions and ventricular volume increases among 48 first-episode schizophrenia patients scanned at the onset of illness, and then again 5 years later. Similarly, Malla et al[25] reported that individuals with a greater duration of untreated psychosis had significantly greater grey matter volume reductions in the bilateral medial frontal and rectal gyrus compared with patients with a short duration of untreated psychosis. Taken together, these studies suggest that untreated psychosis is a contributing factor to brain volumetric abnormalities identified in patients with schizophrenia.

The proposed study will test the hypothesis that better antipsychotic medication compliance using aripiprazole once monthly will be associated with less severe progression of neuroanatomic deficits over the course of illness in schizophrenia.

7.2 ABILIFY® (ARIPIPRAZOLE)

Aripiprazole (ABILIFY®) is a dopamine partial agonist discovered by Otsuka Pharmaceutical Co., Ltd., (OPC) and co-developed by Bristol-Myers Squibb and OPC. OPC and H. Lundbeck A/S are jointly developing the intramuscular (IM) injection formulation of aripiprazole. Aripiprazole oral tablets are approved in the US for the treatment of adults and adolescents with acute schizophrenia, maintenance of stability in adults with schizophrenia, treatment of acute manic episodes associated with bipolar I disorder in adults and pediatric patients, maintenance of efficacy in adults with bipolar I disorder, and as adjunctive treatment of major depressive disorder. Aripiprazole is also approved for the treatment of schizophrenia in the European Union (EU), Australia, and a number of countries in Asia, Europe, and Latin America. The aripiprazole immediate-release IM injection formulation is approved for agitation in schizophrenia and bipolar mania in the US and EU. In addition, an oral solution formulation and orally disintegrating (i.e., dispersible) tablets have been approved and marketed for use in the US and EU. The favorable side effect profile of oral aripiprazole, including its low incidence of extrapyramidal side effects (EPS), low risk of prolactin elevation, decreased adrenergic and anticholinergic side effects, and minimal weight gain, makes it an excellent candidate for an LAI formulation. The aripiprazole once monthly formulation was recently approved for treatment of schizophrenia in the US.

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

7.3 RELEVANT NONCLINICAL STUDIES

The mechanism of action of aripiprazole differs from that of currently marketed typical and atypical antipsychotics. It has been proposed that the effectiveness of aripiprazole 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 D_3 and serotonin 5-HT_{1A} and 5-HT_{2A} receptors, and moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha$_1$-adrenergic, and histamine H_1 receptors, and the serotonin reuptake site. Aripiprazole also displays 5-HT_{1A} partial agonist and 5-HT_{2A} antagonist activity in nonclinical studies. The emerging literature for other antipsychotics indicates that 5-HT_{1A} and 5-HT_{2A} activity may be correlated with the clinical observation of effectiveness against negative symptoms in subjects with schizophrenia. It seems likely that the favorable safety and tolerability profile of aripiprazole, including its low incidence of EPS, lack of prolactin elevation, decreased adrenergic and anticholinergic side effects, and decreased weight gain, is also mediated by its unique profile of interaction with central neuroreceptors. Please refer to the Investigator's Brochure (IB)[26] 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. These 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 in doses of 10, 15, 20, and 30 mg for the treatment of acute relapse of schizophrenia or schizoaffective disorder. The two 4-week studies (i.e., 31-97-201[27] and 31-97-202[28]) each included two fixed doses of aripiprazole (i.e., 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 (i.e., CN138001)[29] 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[30,31] 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 score ≥ 5, PANSS scores for hostility or uncooperativeness ≥ 5, or $\geq 20\%$ increase in PANSS total score. The results indicated that subjects treated with aripiprazole 15 mg daily experienced a significantly longer time to relapse over the 26-week assessment period compared with those receiving placebo. Two 52-week studies (i.e., 31-98-217 and 31-98-304-01)[32,33] of aripiprazole 30 mg versus haloperidol 10 mg were conducted in acutely relapsing schizophrenic subjects with the intention of pooling the data for analysis. On the primary efficacy measure (i.e., time to failure to maintain response in responders), no difference was seen between aripiprazole and haloperidol. However, analysis of secondary efficacy measures showed that aripiprazole 30 mg was superior to haloperidol for negative symptoms, depressive symptoms, and discontinuation for any reason.

The subject-rated and investigator-rated acceptability of aripiprazole treatment was examined in several 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 studies (i.e., CN138087 and CN138100)[34]. A separate open-label study (i.e., CN138152)[35,36] compared aripiprazole 10 to 30 mg daily with standard of care treatment (i.e., 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[37].

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 daily schedule without regard to meals. Aripiprazole has been systematically evaluated and shown to be effective in a dose range of 10 to 30 mg/day; however, there is no evidence that doses higher than 15 mg/day are associated with increased efficacy. Additional details of results of clinical studies with aripiprazole in other indications are provided in the IB[26].

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 (i.e., 24-hour) placebo-controlled studies[38]. 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-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 Once Monthly

CN138020, a clinical study conducted by Bristol-Myers Squibb, assessed the safety, tolerability, and PK of single doses of the aripiprazole once monthly formulation. This was an open-label, two-phase, nonrandomized, ascending dose, sequential panel study in subjects with a confirmed diagnosis of chronic schizophrenia or schizoaffective disorder. Subjects received a single 5 mg dose of the standard IM formulation, followed by safety and PK monitoring. After a minimum 28-day washout, subjects who qualified (i.e., based on no significant adverse events [AEs] or clinical laboratory abnormalities) received a single dose of 15, 50, 100, 200, 300, or 400 mg of aripiprazole once monthly formulation, followed by safety and PK monitoring. The IM formulation appeared to be well tolerated. Peak plasma concentrations in most subjects were observed after approximately 100 hours. Most AEs were mild (43%) to moderate (33%) in severity. The most commonly reported treatment-emergent adverse events (TEAEs) 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) (i.e., attempted suicide and exacerbation of schizophrenia) that were considered to be unrelated to study drug.

Otsuka Pharmaceutical Development & Commercialization, Inc. conducted a Phase 1B study (i.e., 31-05-244) to assess the safety, tolerability, and PK of multiple doses of the aripiprazole once monthly formulation in subjects with schizophrenia. The results showed that once monthly administration of the 400-mg and 300-mg IM injections resulted in mean aripiprazole trough and average plasma concentrations that were comparable to the therapeutic concentrations of 10 to 30 mg oral aripiprazole administered daily to schizophrenic subjects. All three doses of aripiprazole once monthly (i.e., 200, 300, and 400 mg) demonstrated acceptable safety, tolerability, and potential effectiveness[39].

A Phase 3 study (i.e., 31-07-246) was conducted to evaluate the efficacy and safety of aripiprazole once monthly compared with placebo in schizophrenic subjects who had maintained stability on aripiprazole once monthly for at least 12 weeks. Aripiprazole once monthly 400 mg or 300 mg administered as monthly gluteal injections was effective for the maintenance treatment of schizophrenia in adults as demonstrated by a statistically significant difference, when compared with placebo, in the primary efficacy endpoint of time to impending relapse. The percentage of subjects who met the criteria for impending relapse was significantly lower in the aripiprazole once monthly group than in the placebo group. The maintenance of stability was also demonstrated by statistically significant differences favoring aripiprazole once monthly in PANSS and CGI scores, which remained significant throughout the double-blind, placebo-controlled phase. In addition, the Personal and Social Performance Scale total score, cognitive function assessments, and Investigator Assessment Questionnaire score were supportive of the efficacy of aripiprazole once monthly treatment. Aripiprazole once monthly was well tolerated by adult subjects with schizophrenia, as demonstrated by an AE profile similar to placebo. Most TEAEs were either mild or moderate in severity. Tremor was the only TEAE with an incidence of at least twice that of placebo and reported by ≥ 5% of subjects receiving aripiprazole once monthly. 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 subjects were treated with aripiprazole oral tablet formulation in Phase 2, 3, and 4 studies, representing 8,577 subject-exposure years. Of these, 3,901 (25.9%) subjects were treated with aripiprazole for 180 days or longer, 2,259 (15.0%) subjects received aripiprazole for at least 360 days, and 933 (6.2%) subjects continued aripiprazole treatment for at least 720 days.

Across the short-term, double-blind, placebo-controlled studies conducted in schizophrenic subjects, the AE profile of oral aripiprazole was generally comparable to that of placebo. There was little difference in the incidence of discontinuation due to AEs between aripiprazole-treated (7%) and placebo-treated (9%) subjects. Akathisia was the only commonly observed AE that occurred in ≥ 5% of aripiprazole-treated subjects and with an incidence of more than twice that of placebo (8% versus 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[31].

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%)[33].

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[40].

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. Since 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 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 post-marketing 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 (i.e., up to 195 mg) in children were received with no fatalities. The potentially medically serious signs and symptoms reported included somnolence and transient loss of consciousness. In the patients who were evaluated in hospital settings, there were no reported observations indicating clinically important adverse changes in vital signs, laboratory assessments, or ECGs. Additional information can be obtained from the ABILIFY US® package insert.

7.5 STUDY RATIONALE

Aripiprazole once monthly is particularly well suited to a large simple trial because monthly administration more closely mirrors clinical practice. We hypothesize that treatment with aripiprazole once monthly will have significantly greater effectiveness than treatment as usual (TAU) based on time to hospitalization due to increased medication adherence and compliance.

The proposed study will also test the hypothesis that better antipsychotic medication compliance using aripiprazole once monthly will be associated with less severe progression of neuroanatomic deficits over the course of illness in schizophrenia. Ultimately, the identification of *in vivo* biomarkers, such as change in brain structure volumes or cortical thickness, that reflect these processes could help clarify mechanisms of action for effective treatment intervention.

In addition, we believe that treatment with aripiprazole once monthly will have significantly greater effectiveness than TAU due to increased medication adherence and compliance in the following:

- Reducing total number of days in hospital during the 2 years of follow-up
- Reducing psychopathology than TAU
- Significantly lower cost of care than TAU
- Improve cognitive functioning and quality of life

We believe that LAIs are grossly under used in much of the world and should be the TAU standard for patients receiving antipsychotics. The current design directly addresses the question if a clinician has a patient on oral medication should they keep that patient on their ongoing oral regime or switch to an LAI? The answer to this question could change current clinical practice.

Regarding the risk of deterioration, in the 52-week, placebo-controlled trial of aripiprazole once monthly[41], there was a 3% "lack of efficacy" discontinuation rate in the switch to oral aripiprazole and a 2% "lack of efficacy" discontinuation rate in the switch from oral to aripiprazole once monthly. We believe that the 3% discontinuation rate is relevant to the present discussion, whereas the 2% discontinuation rate is an inevitable part of the process of switching to the LAI formulation of the same drug.

In this study (i.e., COL.AOM.2013.005), we will employ training for all LAI sites on the proper process for switching from oral medications to LAIs using a two-stage model that 1) facilitates engagement and development of a therapeutic alliance, followed by 2) completion of enrollment in the study and administration of LAI aripiprazole. This model has been used successfully in prior trials and is designed to provide information regarding the possibilities and potential value of LAI treatment7.

In the Stroup et al. study[42], patients with schizophrenia or schizoaffective disorder with a body mass index (BMI) ≥ 27 and non-high-density lipoprotein (HDL) cholesterol ≥ 130 mg/dl who were on a stable treatment dosage of olanzapine, quetiapine, or risperidone were randomly assigned to switch to aripiprazole (N = 109) for 24 weeks or stay on their current medication (N = 106).

Patients had a mean PANSS total score of 66.0 ± 16.3 and a mean CGI-S score of 4.0 ± 0.9. Twenty-two (20.6%) of the patients who switched and 18 (17.0%) of the patients who stayed on their medication experienced protocol-defined efficacy failure. Although overall more patients in the switch versus stay arm discontinued the study prematurely (43.9% versus 24.5%), it is important to note that there was no significant difference in time to efficacy failure (i.e., hazard ratio for switching = 0.747; 95% confidence interval = 0.395 – 1.413, p = 0.3703). There were also no differences between groups in psychopathology changes as measured by the PANSS total score, change in CGI-S score, or change in the Medical Outcomes Study 12-Item Short-Form Health Survey mental health scores.

In a 16-week, double-blind study, 173 subjects with schizophrenia or schizoaffective disorder who were previously treated with olanzapine were randomly assigned to switch to aripiprazole (n = 88) or stay on olanzapine (n = 85)[43]. Primary and secondary endpoints were mean weight change from baseline and percentage change from baseline in fasting triglyceride levels, respectively. Patients must have been on olanzapine monotherapy for 1 to 24 months, have a BMI of at least 24 and a CGI-S score of ≤ 4 (i.e., moderately ill, mean = 3.0 ± 0.9) to be included in the study. In this study, 56 (63.6%) of the 88 patients who switched to oral aripiprazole and 63 (74.1%) of 85 patients who stayed on their previous olanzapine treatment completed the 16-week study. This was a difference of 9.5% when switching from one of the most antihistaminergic and anticholinergic second-generation antipsychotics. Specifically, discontinuations in the switch arm from olanzapine to aripiprazole and in the stay arm on olanzapine were 8% and 9% for intolerability and 8% versus 0% for inefficacy, respectively.

Although there were some increased rates of discontinuation in the switch arm compared with the stay arm in both studies reviewed above, the differences were not large. Moreover, in our opinion, this risk would be even lower in first-episode and EP patients, as they tend to be more responsive to medications in general and less likely to deteriorate when switched from one drug to another. This argument is further supported by the lack of a difference in efficacy between antipsychotics in first-episode schizophrenia, including even clozapine as a comparator[44,45].

In addition, for stable EP patients, there is no ethically acceptable rationale to require a change in medication from one oral formulation to another, unless there are side effects or clinical symptoms justifying such a change. Parenthetically, a switch due to intolerability or inefficacy may very well be an outcome in the naturalistic oral antipsychotic comparison group during the duration of the trial, so that at the end the two groups will not be as polarized as 100% switch versus 0% switch.

On the other hand, the change from oral to an LAI is ethically justifiable, as we are hypothesizing that for stable patients this will lead to a better long-term outcome. If we required all patients to be appropriate for a medication change, based on lack of efficacy or intolerability, this would limit an already precious sample to a degree that would make the study impossible to do. Moreover, as suggested above, the thrust of this study of using LAI formulations as a preemptive and preventive step in all patients who can be expected to relapse as time goes on would be undermined.

8 STUDY OBJECTIVES

8.1 PRIMARY OBJECTIVE

The primary objective of the study is:

- To determine the effectiveness of treatment with aripiprazole once monthly compared with TAU as defined by time to first hospitalization.

8.2 SECONDARY OBJECTIVES

The secondary objectives of the study are to:

- Determine the effect of treatment with aripiprazole once monthly compared with TAU on brain structure volumes and white matter integrity over the 2-year study duration
- Determine the effectiveness of treatment with aripiprazole once monthly compared with TAU on clinical outcomes beyond time to first hospitalization. The outcomes are:
  - Reducing the number of days in the hospital during 2 years of follow-up
  - Reducing the time to all episodes of psychiatric hospitalization in subjects with schizophrenia
  - Reducing psychopathology
  - Lowering cost of care
  - Improving neuropsychological functioning

9 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN

This is a cluster randomized, two-arm, rater-blind, multi-center, parallel-group study designed to compare the effectiveness and changes in brain structure volumes of aripiprazole once monthly compared with TAU in subjects with first-episode and EP schizophrenia.

Approximately 40 sites will participate in the study in order to enroll an estimated 500 subjects with schizophrenia over a 1 year recruitment period to recruit an expected 0.5 to 1 subject with first-episode schizophrenia and 0.5 to 1 subject with EP schizophrenia per month, allowing for an anticipated 250 subjects in the first episode cohort and 250 subjects in the EP cohort. Ongoing evaluation of the numbers of subjects for each cohort will continue until target enrollment is reached. Enrollment of subjects into the first-episode and EP cohort will be discontinued when the appropriate number for the target is reached.

Randomization will occur by site, with half of the sites assigned to the LAI aripiprazole once monthly and half of the sites assigned to TAU medications. Prior to randomization, one screening visit will occur over approximately 1 week. After providing written informed consent, subjects will be screened for general eligibility by the clinical team at the site. Basic demographic data will be collected to determine suitability for inclusion into the study and to account for subjects screened, but not included in the study. The site will complete an information interview comprising of data regarding symptomology and history to enable the remote centralized assessment team to conduct their assessments. After screening, two baseline visits will occur at no more than 4 weeks apart to confirm the diagnosis of schizophrenia, evaluate psychopathology, collect demographic information, record baseline histories, take study measurements, collect blood samples for PK and clinical safety laboratory testing, and for the LAI sites only, determine tolerability to aripiprazole. For the LAI sites, the first dose of oral aripiprazole will be given at the first baseline visit after the diagnosis of first-episode or EP schizophrenia is confirmed. Once the clinical team determines tolerability to oral aripiprazole at the second baseline visit, the first dose of aripiprazole once monthly will be administered and the subjects will next be seen at the Month 1 Visit (i.e., medication visit) of the treatment phase. Aripiprazole once monthly will be prescribed and administered according to recommendations contained in its respective product labeling. Subjects at the TAU sites will attend both baseline visits while continuing on their TAU medications.

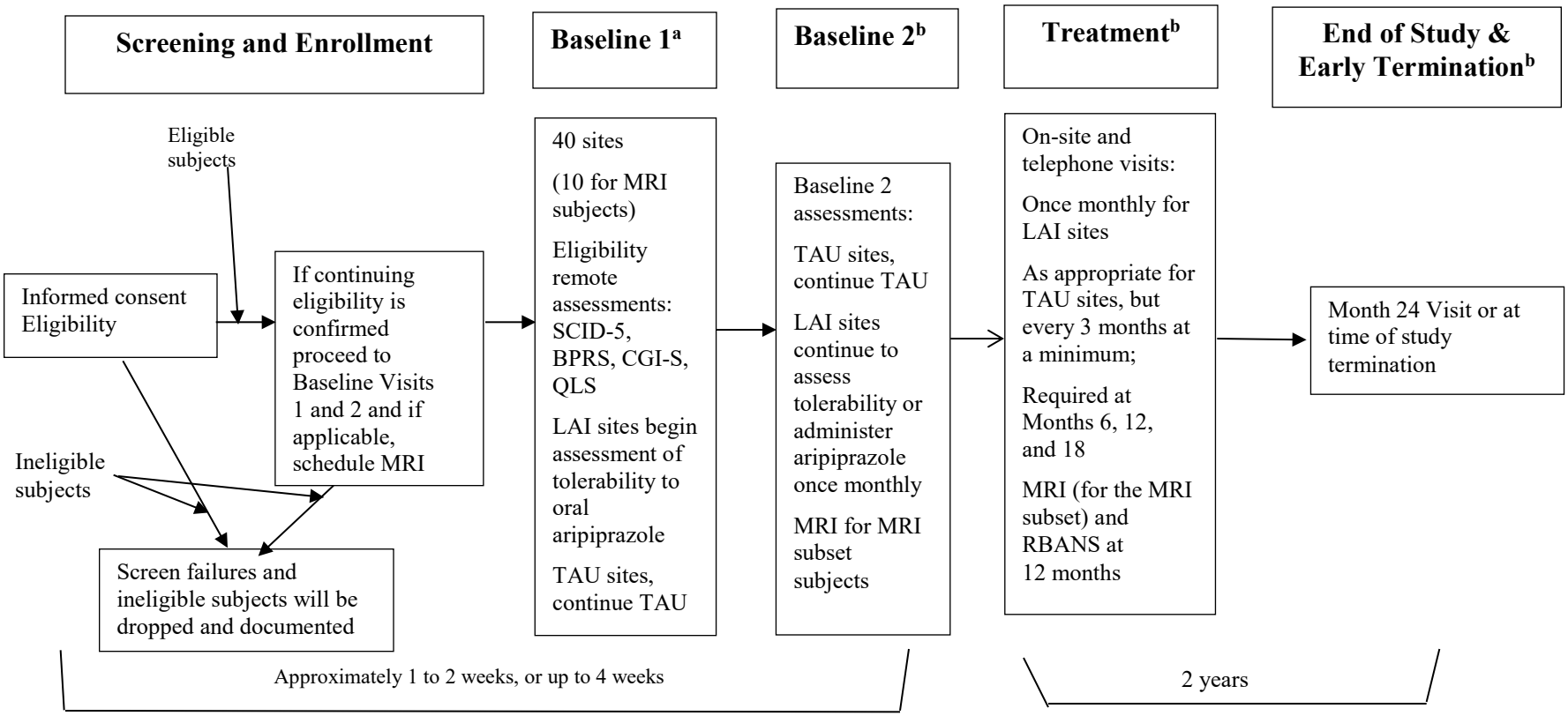
Following the baseline visits and once tolerability has been established, subjects at the LAI sites will be scheduled for medication visits once monthly for aripiprazole once monthly injections and subjects at the TAU sites will be scheduled for medication visits as required based on their TAU medications at a minimum of every 3 months. All subjects will receive bimonthly phone calls inquiring about any visits to emergency rooms and hospitalizations for completion of the Hospitalization and Emergency Room Visit Form (HEC). All subjects will receive phone calls every 4 months to complete the Service Utilization and Resources Form (SURF). The calls will be conducted by the local site research assistant or study coordinator and are not linked to participation in treatment. All subjects are required to attend an in-person visit every 6 months (i.e., 6, 12, 18, and 24 months) during the 2-year study duration for the completion of the HEC and the SURF, to take study measurements, and collect blood samples for clinical safety laboratory

testing. Measurements of psychopathology using the Brief Psychiatric Rating Scale (BPRS), CGI-S, and the Heinrichs-Carpenter Quality of Life Scale (QLS) will be completed at the 12- and 24-month visits only. Measurement of neuropsychological function using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) will be completed at the 12- and 24-month visits only. Subjects who prefer in-person visits at a time when a telephone visit is scheduled may request them at any time.

Because subjects with schizophrenia have an estimated 8.5-fold greater risk of suicide than the general population, with young patients particularly at risk, subjects in this study will be monitored closely for suicidality, at each study visit. Instances of suicidality will be captured using an expanded SAE form, and potential for suicidality will be monitored using the Columbia Suicide Severity Rating Scale (C-SSRS) at every annual (i.e., 12 and 24 months) in-person visit and at any other appropriate time, per the investigator's judgment.

In addition, a subset of 114 first-episode and EP subjects at approximately 10 clinical sites will undergo MRI at the baseline, 12- and 24-month visits to measure brain structure volumes and white matter integrity. The MRI sites (i.e., five TAU and five LAI) will be selected based on close proximity to centers with research MRI capabilities. The first 57 subjects at both the TAU and LAI sites consenting to MRI will be enrolled into the MRI portion of the study.

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



AE = adverse event, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impression–Severity, DSM-5 = Diagnostic and Statistical Manual, Fifth Edition, LAI = long-acting injectable, MRI = magnetic resonance imaging, QLS = Heinrichs-Carpenter Quality of Life Scale, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, SCID-5 = Structured Clinical Interview for DSM-5 Disorders, TAU = treatment as usual

a: Sites are randomized to either LAI or TAU. Subjects will not be randomized; study-drug allocation is determined by the site at which they enter the study

b: Adverse events will be elicited and recorded at the 6-, 12-, 18-, and 24-month visits. Spontaneous reports will be recorded and assessed when the site is notified, per the AE reporting section. Serious AEs will be reported as outlined in Section 9.5.5.

Figure 1: Study Schematic

9.1.1 Screening and Baseline Visits

All recruitment methods will conform to the guidelines of the IRB at the clinical site. 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 a briefing on the reasons for the research, their rights as a subject, and the risks involved, the subjects will be given the opportunity to ask questions. Subjects will be asked to paraphrase the ICF. Subjects will also complete a written study review questionnaire that covers key aspects of the study (e.g., the ability to withdraw at any time). When ready, and after having satisfactorily answered all questions on the study review questionnaire indicating understanding of the study procedures, subjects will be asked to give written consent to participate in the study. After both the subject and the investigator sign the ICF, each subject will be given a copy of the signed ICF. The investigator will have full responsibility for addressing all issues pertaining to informed consent. Procedures to be followed when obtaining informed consent are detailed in Section 5.1.

Eligibility for the study will be determined over a series of screening and baseline visits. During the Screening Visit, the following procedures will be completed according to Table 3:

- Review of the inclusion and exclusion criteria
- Preliminary demographic information
- An information interview will be conducted comprising data regarding symptomology and history to enable the remote centralized assessment team to conduct their assessments

During Baseline Visit 1, the following assessments will be performed remotely:

- Structured Clinical Interview for Diagnostic and Statistical Manual, Fifth Edition (DSM-5) Disorders (SCID-5)
- BPRS
- CGI-S
- C-SSRS
- QLS
- Premorbid Adjustment Scale

A urine pregnancy test will be performed on all women of childbearing potential during Baseline Visit 1. In addition, a subset of 114 first-episode and EP subjects at approximately 10 clinical sites (i.e., five LAI sites [n = 57 subjects] and five TAU sites [n = 57 subjects]) will be scheduled to undergo MRI at the baseline, 12-, and 24-month visits to measure brain structure volumes and white matter integrity. The MRI sites will be selected based on close proximity to centers with research MRI capabilities. The first 57 subjects at both the TAU and LAI sites consenting to MRI

will be enrolled into the MRI portion of the study. The MRI can be completed at any time following completion of the Baseline Visit 1 assessments, but no later than at Baseline Visit 2.

Once the diagnosis of first-episode or EP schizophrenia is confirmed at Baseline Visit 1, subjects at the LAI sites who are not already taking oral aripiprazole once monthly will be given oral aripiprazole and will be assessed for tolerability to oral aripiprazole. Visits will occur weekly until the clinician determines tolerability. Tolerability will be based upon the clinical judgment of the research prescriber. Subjects who do not tolerate aripiprazole based upon clinical judgment will discontinue aripiprazole treatment and be given clinician choice treatment and continue study outcome assessments. Subjects at the LAI sites who enter the study currently taking aripiprazole once monthly will be continued on their clinically appropriate aripiprazole once monthly schedule, if the subject is tolerating aripiprazole once monthly.

The Baseline Visit 2 will be scheduled a maximum of 1 month following the Baseline Visit 1. During Baseline Visit 2, complete demographic data and medical and psychiatric histories will be recorded. The SURF, HEC form, medication visit record, and the RBANS will be completed. Body weight, height, and blood pressure will be measured and BMI will be calculated.

Current medications will be reviewed and recorded. 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) and any antipsychotic medications taken within 30 days of screening will be recorded.

Blood samples for clinical laboratory tests will be obtained. All attempts should be made to obtain blood samples at the same time of day for each visit. Subjects should come to the clinic after an overnight fast of ≥ 10 hours; however if they are not fasting, samples will be collected and the subject will be reminded to fast for the next visit. Non-fasting samples will be recorded as such in the source documents and CRFs.

All Baseline Visit 2 assessments must occur within 4 weeks of Baseline Visit 1. Baseline Visit 2 will be considered completed when all assessments have been performed.

The initial aripiprazole injection will be given at some point after the Baseline Visit 1 once tolerability to oral aripiprazole is established. Future injections of aripiprazole will still be administered monthly; however, the injections may not coincide with the scheduled monthly visits.

9.1.2 Randomization

Randomization will be by site rather than by individual subject and will be stratified by relevant sociodemographic variables to assure appropriate representativeness. Randomization at the 40 sites will be stratified by 1) urban versus non-urban treatment setting and 2) ethnic composition of the population served by the site. All sites will provide detailed information about the ethnic composition of their patient population prior to randomization. Sites will be randomized in a 1:1 ratio to either the LAI treatment (i.e., aripiprazole once monthly) or TAU. Each subject enrolled at the site will receive the type of treatment (i.e., either aripiprazole once monthly or TAU) allocated for that site.

This will be a rater-blind study. The investigator and the subjects will not be blinded to study treatment; however, the remote assessment team responsible for conducting the SCID-5, BPRS, QLS, Premorbid Adjustment Scale, and CGI-S will be blinded to study treatment.

9.1.3 Treatment

9.1.3.1 Overall

- Aripiprazole once monthly, administered via gluteal or deltoid IM injection, at a starting dose based on the investigator's judgment and in accordance with product labeling.
- Oral antipsychotic medications taken per oral (PO) including, but not limited to:
  - aripiprazole (Abilify®)
  - risperidone (Risperdal®)
  - lurasidone HCl (Latuda®)
  - quetiapine fumarate (Seroquel®)
  - olanzapine (Zyprexa®)
  - ziprasidone HCl (Geodon®)
- LAI antipsychotic medications including, but not limited to:
  - risperidone (Risperdal® Consta®)
  - haloperidal decanoate (Haldol® decanoate)
  - olanzapine (Zyprexa® Relprevv™)
  - paliperidone palmitate (Invega® Sustenna®)
  - fluphenazine decanoate (Prolixin® decanoate)

For LAI subjects who were not taking aripiprazole once monthly at study entry, the first dose of aripiprazole once monthly will be administered once tolerability to oral aripiprazole is established. In addition, these subjects allocated to aripiprazole once monthly will continue to receive oral aripiprazole for 14 days following the first injection. Those subjects allocated to TAU will continue with their TAU medications.

Subjects at LAI sites who do not agree to an injection of aripiprazole once monthly when tolerability is established will be continued in the study. These subjects will be given continued education about aripiprazole once monthly and given the opportunity to start aripiprazole once monthly later in the study.

Sites that are randomly assigned to administer aripiprazole once monthly will receive training on proper switching to aripiprazole and LAI processes using a two-stage model that 1) facilitates engagement and development of a therapeutic alliance, followed by 2) completion of enrollment in the study and administration of LAI aripiprazole. This model has been used successfully in prior trials and is designed to provide information regarding the possibilities and potential value of LAI treatment7. Sites allocated to LAI will be instructed on appropriate methods for administering the injection, and standard follow-up for the site should be used to remind the subjects to return for their monthly injections.

9.1.3.1.1 2-year Treatment Period

During the 2-year Treatment Period, assessments will be performed according to Table 3 and Table 4 at regularly scheduled intervals. For the LAI group, monthly visits are mandatory for aripiprazole once monthly injections. For the TAU group, visits will be conducted in a combination of telephone and clinic visits, dependent on their particular treatment modality and if applicable, their preference, at any time for attending visits at the clinic versus a telephone visit.

For all groups, attendance at the clinic is required at the 6-, 12-, and 18-month time points for clinical laboratory testing and measurements of body weight, waist circumference, temperature, pulse, and blood pressure. Remote assessments of BPRS, CGI-S, RBANS, QLS, and C-SSRS will occur at the 12- and 24-month visit. All subjects are required to attend the final visit, which occurs at the 24-Month Visit. Adverse events will be elicited and recorded at the 6-, 12-, 18-, and 24-month visits. Spontaneous reports will be recorded and assessed when the site is notified, per the AE reporting section. Serious AEs will be reported as outlined in Section 9.5.5.

In addition, MRI will occur at the 12- and 24-month visits for those subjects in the subset who are participating in the imaging portion of the study.

9.1.4 Final Visit – Month 24 and Early Termination

All subjects who complete the study are required to attend this final study visit. In addition, any subject that is discontinued from the study for any reason should have the final visit (i.e., Month 24) procedures completed if possible. Procedures to be completed will be performed according to Table 4 and include clinical laboratory testing; measurements of body weight, waist circumference, temperature, pulse , and blood pressure; and remote BPRS, CGI-S, QLS, and C-SSRS assessments.

9.1.5 Follow-up Period

All subjects who receive at least one dose of study drug and who are discontinued from the study for any reason, including completion, will be followed for safety reasons for approximately 30 days following the last dose of study drug. At 30 (± 3) days, each subject will be contacted by telephone or will attend a visit at the clinic for safety follow-up.

9.2 Discussion of Study Design, Including Choice of Control Groups

Non-adherence remains an enormous challenge in schizophrenia. Long-acting injectable antipsychotics have been shown in some mirror image, naturalistic, and RCTs to significantly

reduce rates of relapse and rehospitalization in comparison with oral antipsychotics. However, the most recent meta-analysis[1] of RCTs did not show an overall advantage. The proposed large simple trial is designed to address the limitations of conventional RCTs that compare LAI and oral antipsychotics. Cluster (i.e., site) randomization is utilized to eliminate bias in perceived subject preference; subjects either consent to the study treatment at that site or continue with their care as usual at the clinic and are not enrolled in the study. Sites randomized to TAU will not see the study subjects at a frequency typical to a conventional RCT. Assessments will be infrequent, occurring every 6 months. Given that investigators will not be blinded to treatment, centralized ratings have been incorporated into the study to allow for blinded assessment of psychopathology outcomes. In addition, the subjects eligible for the study are those who are early in the course of the illness, and for whom prior data suggest that early intervention provides potential for a higher likelihood of improved outcome[6-10].

Twenty-four patients with first-episode psychosis underwent resting state functional MRI (fMRI) scanning and symptom ratings while acutely psychotic and after 12 weeks of treatment with either risperidone or aripiprazole. In addition, baseline and follow-up resting state fMRI exams were obtained in 24 age-, sex-, and handedness-matched controls. Antipsychotic treatment resulted in a significant reduction in positive symptoms, as measured by the Thought Disturbance factor of the BPRS. We present data on resting-state connectivity based on seeds, defined by the Harvard-Oxford Structural Atlas, placed in the caudate (i.e., dorsal striatum [DS]) and nucleus accumbens (i.e., ventral striatum [VS]). Consistent with prior literature[41], our healthy volunteers demonstrated strong correlations between DS and dorsal prefrontal cortex, including both lateral and medial aspects, and between VS and ventral prefrontal cortex (i.e., primarily medial). Importantly, upon re-scanning after 12 weeks, healthy subjects showed no significant longitudinal changes in functional interactions of DS or VS. As symptoms improved in patients, both of the striatal structures showed an increase in correlative activity within the prefrontal cortex in the "normal" dorso-ventral pattern (Figure 2). Specifically, DS showed an increase in functional connectivity in a region within the dorsolateral prefrontal cortex as positive symptoms improved. Similarly, as positive symptoms improved, functional connectivity of VS was increased to a region within the ventral prefrontal cortex. Overall, these results suggest that "frontalization" and normalization of frontostriatal connections may underlie the successful treatment of psychosis.

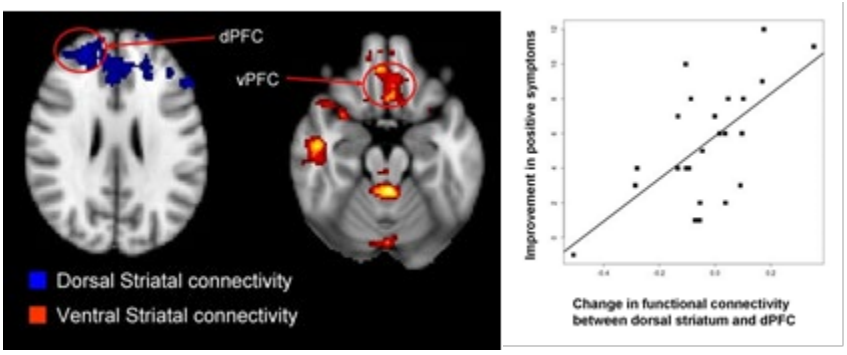


Figure 2: Functional Connectivity Correlations

Note: all activations are thresholded at $p < 0.005$) in the imaging photo; in the scatter plot $r^2 = 0.41$

Based on these data, fMRI scanning is an appropriate measure to evaluate progression of neuroanatomic deficits and evaluate the utility of biomarkers, such as brain structure volumes and cortical thickness, as mechanisms of action for effective treatment intervention.

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment.

9.3 SELECTION OF STUDY POPULATION

Approximately 500 subjects will be enrolled at approximately 40 sites. 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. Subjects will be selected by approaching all eligible patients at the participating clinics. The inclusion criteria are as broad as possible within an EP population.

9.3.1 Inclusion Criteria

Subjects must meet the following inclusion criteria to be eligible for the study:

1. Are able to provide written informed consent
2. Have a confirmed diagnosis of schizophrenia as defined by DSM-5 criteria using the SCID-5
3. Are between the ages of 18 and 35, inclusive
4. Have the following history with antipsychotic medications
    a. First-episode subjects: < 1 year of lifetime exposure to antipsychotic medication and only one episode of psychosis
    b. EP subjects: between 1 year and 5 years of lifetime exposure to antipsychotic medication or subjects with < 1 year of lifetime antipsychotic medication and more than one episode of psychosis
5. Subjects at LAI sites must be willing to accept an injectable form of treatment

9.3.2 Exclusion Criteria

Subjects must not have any of the following criteria to be eligible for the study:

1. Have a current primary DSM-5 diagnosis other than schizophrenia, including schizophreniform disorder, schizoaffective disorder, major depressive disorder, bipolar disorder, delirium, dementia, and amnestic or other cognitive disorders
2. Subjects at LAI sites: have a known allergy or intolerance to aripiprazole, or a past negative response to aripiprazole that is not explained by nonadherence
3. Be pregnant or lactating

4. Have any unstable medical condition that, in the opinion of the investigator, would be detrimental to the subject or would confound the results of the study

5. Past or current treatment with clozapine

6. Subjects in the MRI subset only who have:

    a. Received an LAI antipsychotic in the last 6 months

    b. Any metal implants, pacemakers, irremovable prosthetic devices, or other devices or situations that may preclude imaging

9.3.3 Removal of Subjects from Therapy or Assessment

9.3.3.1 Entire Study or Treatment Arms

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

9.3.3.2 Individual Center

The investigator will notify OAPI promptly if the investigator or the IRB at the site terminates the study.

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 investigator's 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 any of the following criteria must be withdrawn from the study:

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

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

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

4. Subject becomes pregnant

5. Subject is lost to follow-up

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

9.4 TREATMENTS

The investigator will purchase or be supplied with the aripiprazole study drugs. Medication at the TAU sites will be prescribed based upon usual site practices. In order not to influence or restrict which medications are prescribed at TAU sites, medications for TAU subjects will not be supplied by the study. Reimbursement for medications at TAU sites will be by usual mechanisms (e.g., private or public insurance).

9.4.1 Treatments Administered

Aripiprazole once monthly 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 once monthly administered via gluteal or deltoid IM injection.
- TAU oral antipsychotic medications administered PO including, but not limited to:
  - aripiprazole (Abilify®)
  - risperidone (Risperdal®)
  - lurasidone HCl (Latuda®)
  - quietapine fumarate (Seroquel®)
  - olanzapine (Zyprexa®)
  - ziprasidone HCl (Geodon®)
- LAI antipsychotic medications administered IM including, but not limited to:
  - risperidone (Risperdal® Consta®)
  - haloperidal decanoate (Haldol® decanoate)
  - olanzapine (Zyprexa® Relprevv™)
  - paliperidone palmitate (Invega® Sustenna®)
  - fluphenazine decanoate (Proloxin® decanoate)

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 can be stored at the clinical site as long as the medication is kept in a securely locked cabinet in an area with a minimum/maximum thermometer that constantly monitors temperature. All study drug will be kept 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 500 subjects are planned to be enrolled in the study at approximately 40 sites. Randomization within the group of 40 US sites will be balanced by 1) urban versus non-urban treatment setting and 2) ethnic composition of the population served by the site. Sites will be randomized in a 1:1 ratio to either the LAI treatment (i.e., aripiprazole once monthly) or TAU. Each subject enrolled at the site will receive the type of treatment (i.e., either aripiprazole once monthly or TAU) allocated for that site.

9.4.4 Blinding

This is a rater-blind study. The investigator and the subjects will not be blinded to study treatment; however, the remote assessment team responsible for conducting the SCID-5, BPRS, CGI-S, and QLS will be blinded to study treatment.

9.4.5 Treatment Compliance

No formal measures of compliance will be performed.

9.4.6 Accountability

Study drug will not be prescribed or administered until the investigator has provided the following documentation to OAPI:

- 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
- A signed and dated clinical studies agreement

The investigator and the study staff will be responsible for the accountability of all study drugs (i.e., dispensing, inventory, and record keeping), and following and adhering to 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 dispensed to any individual who is not enrolled in the study.

The investigator, or designee, must maintain an inventory record of all study 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, age, sex, and race or ethnicity. Study-specific demographic information will be collected at the Baseline 2 Visit.

9.5.1.2 Screening and Baseline Assessments

MEDICAL HISTORY

Medical history, surgical history, and current medical conditions will be recorded at the Baseline 2 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 lifetime use of antipsychotic medications, at the Baseline 2 Visit.

STRUCTURED CLINICAL INTERVIEW FOR DSM DISORDERS

Study diagnoses will be established using the SCID-5 interview. The SCID-5 is a semi-structured interview for making the major DSM-5 Axis I diagnoses. The instrument is designed to be administered by a clinician or trained mental health professional. The SCID-5 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. For all diagnoses symptoms are coded as present, subthreshold, or absent.

The SCID-5 will be administered remotely at the Baseline 1 Visit only.

INFORMATION INTERVIEW

An information interview will be conducted for each subject at each site to record symptomology and history to enable the remote team to conduct their assessments. This interview will be conducted during screening.

9.5.1.3 Safety Assessments

Safety will be assessed by AE reporting, clinical laboratory tests (i.e., hematology and fasting clinical chemistry), and vital signs. In addition, body weight, BMI, and serum prolactin concentrations will be monitored.

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 3 and Table 4, 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. Fasting samples should be collected whenever possible; however, if they are not fasting, samples will be collected and the subject will be reminded to fast for the next visit. Non-fasting samples will be recorded as such in the source documents and CRFs.

Standard clinical laboratory tests will be performed if clinically indicated. Clinical laboratory tests that may be performed during the study are provided in Table 2.

Table 2: Safety Clinical Laboratory Tests

Hematology: Hematocrit Hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count Red blood cell count White blood cell count with differential	Fasting Serum Chemistry: Alanine transaminase Alkaline phosphatase Aspartate transaminase Bilirubin, total Blood urea nitrogen Calcium Cholesterol (total, LDL, and HDL), triglycerides Creatinine Fasting lipid profile Gamma glutamyl transferase Glucose Glycosylated hemoglobin (HbA1c) Lactate dehydrogenase Potassium Protein, total Sodium
Additional Tests: Fasting insulin Serum prolactin Urinalysis with microscopic analysis[a] Urine β-hCG[b] for women of child-bearing potential	

β-hCG = beta-human chorionic gonadotropin, HDL = high-density lipoprotein, LDL = low-density lipoprotein
a: Sample for urinalysis will be collected and analyzed when clinically indicated.
b: Serum β-hCG will be performed if the urine pregnancy test is positive or if the subject or investigator suspects that the subject may be pregnant.

9.5.1.3.2 Blood Pressure

Blood pressure measurements (i.e., systolic and diastolic blood pressure [mmHg]) will be obtained at the visits designated on the Schedules of Assessments (Table 3 and Table 4) by a validated method. Blood pressure will be measured after the subject has been sitting for 5 minutes and then standing after 3 minutes, but no longer than 5 minutes. All blood pressure measurements should be performed on the same arm, preferably by the same person.

9.5.1.4 Adverse Events and Other Events of Interest

An 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 drug. For this study, the study drugs are aripiprazole once monthly and any other antipsychotic treatment.

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 (i.e., 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 or at the Follow-up Visit, whichever comes later.

Abnormal laboratory values should not be listed as separate AEs if they are considered 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 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).

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

ASSESSING SEVERITY OF ADVERSE EVENTS

AEs will be graded on a 3-point scale (i.e., mild, moderate, and severe) and reported in detail as 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 (i.e., 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 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

An 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 AE 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 or incapacity
- Is a congenital anomaly or birth defect in the child of a subject who was exposed to the study drug

Other important medical events that may not 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
- Hospitalization planned before informed consent where the condition requiring the hospitalization has not changed post-study drug administration
- 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 Body Weight, Body Mass Index, Height

An assessment for potential of prolactin-related effects will be performed via measurement of body weight (kg), height (m, for determination of BMI), and determination of BMI.

The calculation for BMI is:

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

9.5.1.6.2 Prior and Concomitant Therapies

Prior and concomitant therapies will be collected via self-report using the SURF. The SURF Medication Visit Record is a standardized form on which the medication name, dose, and regimen are recorded for prescribed medications.

9.5.1.6.3 Suicidality

All subjects will be treated as usual in the clinic for any suspected suicidality or suicidal ideation, irrespective of study involvement. For the purposes of the study, in these cases, suicidality information will be collected on the SAE form, and a clinical intervention assessment of risk will be performed per the PI's judgment.

In addition, the C-SSRS will be performed at 12-month intervals during the study.

COLUMBIA SUICIDE SEVERITY RATING SCALE

The C-SSRS was designed to distinguish the domains of suicidal ideation and suicidal behavior. The baseline C-SSRS form will be completed at baseline of Phase 1. Later C-SSRS assessments will be completed at 1 year and 2 years.

Four constructs are measured:

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

2. The intensity of ideation subscale (i.e., the "intensity subscale") rates frequency, duration, controllability, deterrents, and reason for ideation on a 5-point ordinal scale.

3. The behavior subscale rates actual, aborted, and interrupted attempts; preparatory behavior; and non-suicidal self-injurious behavior on a nominal scale.

4. The lethality subscale 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.

9.5.1.6.4 Pregnancy Test

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

- General information
- ICF
- 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 study participation and the potential risk factors for an unintentional pregnancy. Specifically, investigators will review with subjects all applicable information about pregnancy and lactation in the FDA-approved prescribing information for medications in the protocol. The subject must sign an ICF stating that the above-mentioned risk factors and the consequences were discussed with her.

9.5.1.7 Efficacy Assessments

9.5.1.7.1 Hospitalization and Emergency Room Visit Form

The HEC form is a subject interview form in which the subject is asked to answer a "yes" or "no" question regarding each one of nine settings pertaining to inpatient, emergency room, and crisis stabilization treatment. If the subject answers "yes" to any of the questions, additional information regarding the "yes" answer is elicited. The questions are:

> Did you spend any nights in the following treatment settings: 1) medical program, 2) surgical program, 3) psychiatric program, 4) substance use program, 5) nursing home, 6) halfway house or staffed residence, 7) emergency room for medical reason, 8) emergency room for psychiatric or substance abuse reason, and 9) crisis stabilization for psychiatric or substance abuse reason.

For "yes" answers, the total number of times and the total number of nights are recorded. In addition, continuing for inpatient care, and the longest duration of the emergency room stay and overnight stay status is also recorded.

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 Brief Psychiatric Rating Scale

The BPRS is a rating scale that a clinician or researcher may use to measure psychiatric symptoms such as depression, anxiety, hallucinations, and unusual behavior. Each symptom is rated 1 (not present) to 7 (extremely severe). A zero is entered if the item is not assessed.

9.5.1.8 Other Assessments – Neuropsychiatric Function

PREMORBID ADJUSTMENT SCALE

The Premorbid Adjustment Scale is a rating scale designed to evaluate the degree of achievement of developmental goals at each of several periods of a subject's life before the onset of schizophrenia. The Premorbid Adjustment Scale has been found to be useful in identifying patients likely to become chronically hospitalized or at high risk for readmission.

The scale is divided into a general scale and four developmental age periods:

1. Childhood to age 11 years old
2. Early adolescence to age 15 years old

3. Late adolescence to age 18 years old

4. Adulthood

Rating items in childhood, early adolescence, and late adolescence include sociability and social withdrawal, peer relationships, scholastic performance, adaption to school, and ability to form socio-sexual relationships. Rating items in adulthood include social relationships, educational achievement, and level of interest and enjoyment of major life activities.

REPEATABLE BATTERY FOR THE ASSESSMENT OF NEUROPSYCHOLOGICAL STATUS

The RBANS is a brief neurocognitive battery with four alternate forms that measures immediate and delayed memory, attention, language, and visuospatial skills. It is broadly used for clinical diagnostic purposes and is increasingly employed as an endpoint in clinical trials of medications that may have an impact on neurocognitive status. The RBANS was developed for two primary applications:

1. As a stand-alone "core" battery for the detection and neurocognitive characterization of dementia.

2. As a brief neurocognitive battery for the detection and tracking of neurocognitive deficits in a variety of disorders.

The RBANS consists of ten subtests that give five scores, one for each of the five domains tested (i.e., immediate memory, visuospatial/constructional, language, attention, and delayed memory). The RBANS requires approximately 25 minutes to administer, and is a "pencil-and-paper" test, with only a stimulus booklet and record form needed for administration and scoring.

SERVICE UTILIZATION AND RESOURCES FORM

The SURF questionnaire is comprised of seven domains with 49 questions. The domains are:

- Work
- General Health
- Outpatient Mental Health Visits
- Use of Outpatient Medical/Surgical Treatment Services
- Substance Use
- Justice System Contacts
- Insurance Coverage

All questions in the SURF refer to the 30 days prior to the date of the interview. The subjects are asked questions with either "yes" or "no" answers, a rating scale to circle all that apply, or

requesting specific information (e.g., hours worked or total earnings), depending on the domain and the information in question.

9.5.1.9 Other Assessments – Quality of Life

HEINRICHS-CARPENTER QUALITY OF LIFE SCALE

The QLS is a 21-item semi-structured interview designed to be used by trained interviewers to assess functioning based on the subject's self-report and the interviewer's judgment based on all available information. The QLS combines subjective reports and objective data, and raters are instructed to weight their assessment more heavily than the subject's self-assessment. The QLS assesses four domains: 1) interpersonal relations, 2) instrumental role functioning, 3) intrapsychic foundations (i.e., cognitive-emotional functioning), and 4) common objects and activities (i.e., extent of involvement with routine daily life activities). Each item is rated on a 0 to 6 Likert-type scale with a higher score indicating a higher level of functioning. The QLS has become the standard instrument for assessing change in quality of life in clinical trials and, based on our preliminary work, provides an optimal balance between subjective and objective perspectives.

9.5.2 Pharmacodynamic Assessments

The dependent measures will include volumes of brain structure (e.g., gray matter, white matter, and subcortical regions), white matter integrity assessed using diffusion tensor imaging, and indices of fMRI task-based and resting state activity.

To accomplish scanner stability, each site will purchase and employ the Magphan® Quantitative Imaging Phantom, commonly known as the ADNI phantom (http://www.phantomlab.com/products/magphan_adni.php).

9.5.2.1 Structural and Diffusion Tensor Imaging

Each exam will include acquisition of structural images, including a sagittal localizer and high-resolution T1-weighted sequence. In addition, we will collect diffusion-weighted, spin-echo echo planar imaging (EPI) scans, and a reference T2-weighted image. Functional imaging will utilize a gradient echo, EPI sequence sensitive to the blood-oxygen-level-dependent signal, acquired along the anterior/posterior commissure. A field map will be collected to control for distortions in the EPI images.

9.5.2.2 Resting State fMRI Acquisition

Resting state fMRI will be collected in the absence of task demands and subjects will be instructed to keep their eyes open. This permits the assessment of functional connectivity while the subjects are at rest.

9.5.2.3 MRI Assessments

EDINBURGH HANDEDNESS INVENTORY

The Edinburgh Handedness Inventory is a scale used to assess the dominance of a person's right or left hand in everyday activities. The inventory will be completed by the patients self-reporting hand use. The inventory will be completed only at the Baseline 2 Visit.

MRI FORM

The MRI form will capture patient date of birth, gender, summary of the Edinburgh Handedness Inventory, medications taken the day of the scan, and any substances use 24 hours prior to the scan.

9.5.3 Schedules of Assessments

The Schedule of Assessments for screening, baseline, and Year 1 of the study is provided in Table 3.

The Schedule of Assessments for Year 2 of the study is provided in Table 4.

Table 3: Schedule of Assessments Year 1

Procedure	Screening	Baseline Visits Visits 1 and 2[j]	Month (each visit ± 3 days)[k]											
	~ 1 week	Up to 4 weeks	1	2	3	4	5	6	7	8	9	10	11	12
On-site Assessments														
Informed consent	X													
Eligibility and demographic information	X													
Information interview	X													
Demographics and Psychiatric History			X											
Medical history			X											
Current medication			X											
SURF			X				P			P				X
HEC Form			X		P		P		X		P		P		X
Clinical laboratory testing[a]			X						X						X
Urine pregnancy testing[b]		X							X						X
Body weight, height, BMI, waist circumference, temperature, pulse			X						X						X
Blood pressure[c]			X						X						X
RBANS			X												X
MRI[d]			X												X
Edinburgh Handedness Inventory[d]			X												
MRI Form[d]			X												X
Oral aripiprazole[e]		X	X	X											
Tolerability[f]		X	X												
LAI injection[e]			X	X	X	X	X	X	X	X	X	X	X	X	X
Medication Visit Record[g]			X	X	X	X	X	X	X	X	X	X	X	X	X
AEs[h]									X						X
Remote Assessments[l]														
SCID-5		X													
BPRS		X													X
CGI-S		X													X
C-SSRS		X													X
Heinrichs-Carpenter QLS		X													X
Premorbid Adjustment Scale[i]		X	X												

AE = adverse event, BMI = body mass index, BPRS = Brief Psychiatric Rating Scale, CBC = complete blood count, CGI-S = Clinical Global Impression-Severity, C-SSRS = Columbia Suicide Severity Rating Scale, HbA1c = glycosylated hemoglobin, HDL = high-density lipoprotein, HEC = Hospitalization and Emergency Room Visit, LAI = long-acting injectable, LDL = low-density lipoprotein, MRI = magnetic resonance imaging, P = phone visit, QLS = Heinrichs-Carpenter Quality of Life Scale, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, SCID-5 = Structured Clinical Interview for DSM-5 Disorders, SURF = Service Utilization and Resources Form, TAU = treatment as usual, X = clinic visit

a: Clinical laboratory testing includes a fasting lipid panel (i.e., cholesterol: total, HDL, LDL, and triglycerides), metabolic profile, prolactin and fasting insulin concentrations, HbA1c, and a CBC with differential. Samples for urinalysis tests will be collected and analyzed as clinically indicated.

b: 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.

c: Blood pressure will be measured sitting after 5 minutes, and then standing after 3 minutes.

d: For the MRI subset of subjects only.

e: At the LAI sites only. Oral aripiprazole will continue for 14 days after the first aripiprazole once monthly injections.

f: The initial aripiprazole injection will be given at some point after the Baseline Visit 1 once tolerability to oral aripiprazole is established. Future injections of aripiprazole will still be administered monthly; however, the injections may not coincide with the scheduled monthly visits.

g: The Medication Visit Record will be completed monthly at the LAI sites and whenever a medication visit occurs at the TAU sites.

h: Adverse events will be elicited and recorded at the 6-, 12-, 18-, and 24-month visits. Spontaneous reports will be recorded and assessed when the site is notified, per the AE reporting section. Serious AEs will be reported as outlined in Section 9.5.5.

i: The Premorbid Adjustment Scale will be administered at Baseline Visit 1 or Baseline Visit 2 for those clients who have a family member or support.

j: All Baseline Visit 2 assessments must occur within 4 weeks of Baseline Visit 1. Baseline Visit 2 will be considered completed when all assessments have been performed.

k: Visit windows are for data management purposes only. Subjects will not be discontinued if visit windows are not adhered to.

l: Remote assessments will be conducted by a centralized assessment team from Vanguard Research Group, while the subject is at the clinic.

Table 4: Schedule of Assessments Year 2

Procedure	Month (each visit ± 3 days)[h]												
	13	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24[i]**	**30-day Follow-up**
On-site Assessments													
SURF				P				P				X	
HEC Form		P		P		X		P		P		X	
Clinical laboratory testing[a]						X						X	
Body weight, height, BMI						X						X	
Blood pressure[b]						X						X	
Urine pregnancy testing[c]						X						X	
RBANS												X	
MRI[d]												X	
MRI Form[d]												X	
LAI injection[e]	X	X	X	X	X	X	X	X	X	X	X	X	
Medication Visit Record[f]	X	X	X	X	X	X	X	X	X	X	X	X	
AEs[g]						X						X	
Remote Assessments[j]													
BPRS												X	
CGI-S												X	
C SSRS												X	
Heinrichs-Carpenter QLS												X	
Telephone call													X

AE = adverse event, BMI = body mass index, BPRS = Brief Psychiatric Rating Scale, CBC = complete blood count, CGI-S = Clinical Global Impression–Severity, C-SSRS = Columbia Suicide Severity Rating Scale, HbA1c = glycosylated hemoglobin, HDL = high-density lipoprotein, HEC = Hospitalization and Emergency Room Visit, LAI = long-acting injectable, LDL = low-density lipoprotein, MRI = magnetic resonance imaging, P = phone visit, QLS = Heinrichs-Carpenter Quality of Life Scale, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, SURF = Service Utilization and Resources Form, TAU = treatment as usual, X = clinical visit

a: Clinical laboratory testing includes a fasting lipid panel (i.e., cholesterol: total, HDL, LDL, and triglycerides), a metabolic profile, prolactin and fasting insulin concentrations, HbA1c, and a CBC with differential. Samples for urinalysis tests will be collected and analyzed as clinically indicated.

b: Blood pressure will be measured after sitting for 5 minutes, and then standing for 3 minutes.

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: For the MRI subset of subjects only.

e: At the LAI sites only.

f: The Medication Visit Record will be completed monthly at the LAI sites and whenever a medication visit occurs at the TAU sites.

g: Adverse events will be elicited and recorded at the 6-, 12-, 18-, and 24-month visits. Spontaneous reports will be recorded and assessed when the site is notified, per the AE reporting section. Serious AEs will be reported as outlined in Section 9.5.5.

h: Visit windows are for data management purposes only. Subjects will not be discontinued if visit windows are not adhered to.

i: Subjects who terminate early from the study will be asked to complete the Month 24 assessments.

j: Remote assessments will be conducted by a centralized assessment team from the Vanguard Research Group, while the subject is in the clinic.

9.5.4 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, and assessment of AEs, are standard evaluations to ensure subject safety.

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

9.5.5.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported to the PI's study manager 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.

The SAE is reviewed for completeness, and if necessary, queries are issued to the site for additional or corrected information. Once the SAE form is reviewed by the study manager, the site is instructed to enter the SAE information into the electronic database.

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.

Report immediately reportable events (SAEs, potential Hy's Law cases, pregnancies, and AEs requiring discontinuation of study drug) to:

Vanguard Research Group
Fax: 212-913-9850
e-mail: cgomes@nshs.edu
Tel: 347-804-3605

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.

As updated information becomes available, an updated SAE form is sent from the site to the study manager to review for completeness. Once reviewed, the study manager informs the site and instructs them to enter the data into the electronic database.

The PI will notify the IRB of the occurrence of the SAE, in writing, if the SAE meets the IRB reporting criteria.

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).

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 early discontinuation procedures indicated in the Schedule of Assessments (Table 4) 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 termination, 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 or 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 investigator has ethical, legal, and scientific obligations to follow this study in a detailed and orderly manner in accordance with established research principles, the ICH GCP Guideline, FDA regulations and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (i.e., maintain current personal knowledge of the progress of the study), investigator's monitors may visit the site during the study, as well as communicate frequently via telephone and written communications.

9.6.2 Auditing

The OAPI Quality Management Unit, or a representative, may conduct study 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 study. The investigator will cooperate with such inspections and will contact the sponsor and OAPI immediately if such an inspection occurs.

9.6.3 Data Collection

The study is expected to start on or about 01 December 2014 and be completed on or about 15 March 2018. Data collection will begin when the first subject signs the ICF, on approximately 01 December 2014, 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, on approximately 01 March 2018.

9.6.3.1 Cross-site Data Integration

Data management for the project will be performed by the Nathan Kline Institute for Psychiatric Research. Data are transmitted to the data center through a secure, password-protected web portal. Nathan Kline Institute has an up-to-date information system security plan developed under the guidance of federal document NIST Special Publication 800-18: "Guide for Developing Security Plans for Federal Information Systems". Nathan Kline Institute has also completed a thorough security self-assessment, under the guidance of federal document NIST 800-53A: "Guide for Assessing the Security Controls in Federal Information Systems Questionnaire".

9.7 STATISTICAL METHODS

The investigator or designee will perform all statistical analyses after the study is completed and the database is locked and released. Statistical analyses will be performed using the Statistical Analysis System software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP). Unless otherwise stated, all hypothesis tests will be performed at a two-sided 0.05 significance level.

9.7.1 Statistical Considerations

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

The primary endpoint of the study is:

- Time to the first hospitalization

9.7.1.2 Secondary Endpoints

Secondary endpoints of the study are:

- Change from baseline to the 1- year and 2-year time points in gray matter and white matter volume, and cortical thickness. The 2-year time point is the primary time point.

- Time to all episodes of psychiatric hospitalization, including total times (e.g., time from randomization to first, second, or any subsequent hospitalizations) as well as gap times (e.g., time between first and second hospitalization, second and third hospitalization, etc.)

- Total number of days of inpatient psychiatric hospitalization per quarter for each subject for the duration of the study

- Change from baseline in BPRS and CGI-S

- Cost of care from the SURF

- Change from baseline in neuropsychological function (i.e., RBANS)

- Change from baseline in quality of life (i.e., QLS)

9.7.1.3 Definitions of Analysis Sets

The Safety Analysis Set (SAS) is the group of subjects who received at least one dose of study drug and had at least one postdose safety assessment.

The Full Analysis Set (FAS) is the group of randomized subjects who meet all of the inclusion criteria and none of the exclusion criteria.

The Randomized Set is the group of subjects who were randomized.

The Per Protocol Set is the group of subjects who sufficiently complied with the protocol. Details of the evaluability criteria will be determined before database lock and will be specified in the SAP.

Subjects at LAI sites who do not agree to an injection of aripiprazole once monthly will be continued in the study. These subjects will be given continued education about aripiprazole once monthly and given the opportunity to start aripiprazole once monthly later in the study.

For subgroup analyses of subjects at LAI sites, two groups are being specified prior to the start of data analysis. The tolerated aripiprazole once monthly group consists of LAI site subjects who the prescriber deemed as tolerating aripiprazole once monthly after a maximum of 6 weeks of initiating treatment with aripiprazole within the study (i.e., tolerability can be declared at times earlier than 6 weeks). The timely initiation of aripiprazole once monthly group consists of LAI site subjects who received at least one injection of aripiprazole once monthly within 3 months of the prescriber declaring that the subject tolerates aripiprazole.

9.7.1.4 Subject Disposition

The summary of subject disposition for all enrolled subjects will be provided for the study overall and by site. The summary will include the number of subjects enrolled, completed, and discontinued, including the reason for discontinuation.

9.7.1.5 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the FAS will be summarized for each treatment group using descriptive statistics.

Continuous variables, such as age, will be summarized by N (i.e., sample size), mean, standard deviation, minimum, median, and maximum. Categorical variables, such as sex, will be summarized by frequency counts and percentages.

9.7.1.6 Prior and Concomitant Therapy

Medical history and medication history will be summarized. The use of aripiprazole in the TAU group will be accounted for in the SAP.

9.7.1.7 Safety Analyses

All safety analyses will be performed on the SAS. 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, and maximum for continuous variables; n [%] for categorical variables). Safety variables, such as TEAEs, clinical laboratory parameters, and vital signs will be summarized. 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

Treatment exposure will be characterized according to the number of subjects exposed, the duration of exposure, and the dose to which they were exposed.

9.7.1.7.2 Adverse Events

The AE verbatim descriptions (i.e., 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 (Version 15.1 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class are also captured in the database.

A TEAE is defined as an AE that:

- Emerges during treatment, having been absent at pretreatment (i.e., baseline)
- Reemerges during treatment, having been present at pretreatment (i.e., baseline) but stopped before treatment

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

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

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

Adverse events will be summarized using the SAS. The number of AEs and number and incidence (%) of subjects with AEs will be summarized by cohort or dose and overall. To obtain the incidence (%), the number of subjects with at least one event and the percentage of subjects with AEs by system organ class and by 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 (i.e., percentage) of subjects with TEAEs leading to death will be summarized by MedDRA system organ class and PT for each treatment group. A subject data listing of all AEs leading to death will be provided.

The number (i.e., percentage) of subjects with SAEs will be summarized by MedDRA system organ class and PT for each treatment group. A subject data listing of all SAEs will be provided.

The number (i.e., percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA system organ class 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

Laboratory results will be summarized using Système International units, as appropriate. For all quantitative parameters listed in Section 9.5.1.3 Safety Assessments (Laboratory Measurements), the actual value and the change from baseline to each postbaseline visit and to the end of treatment (i.e., defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.3 will be summarized using frequencies (i.e., number and percentage of subjects), and changes from baseline to each

postbaseline visit and to end of treatment will be reported. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high classification according to whether the value was below, within, or above the laboratory parameter's reference range.

9.7.1.7.4 Blood Pressure

Descriptive statistics for blood pressure parameters (i.e., diastolic and systolic) and changes from baseline will be presented by visit and treatment group.

9.7.1.8 Efficacy Analyses

9.7.1.8.1 Primary Efficacy Analysis

Hazard functions related to the first hospitalization will be analyzed using competing risk (CR) modeling strategies proposed by Fine and Gray[49]. The proportional hazards regression (PHREG) procedure in the Statistical Analysis System software will be utilized for this analysis. The newly available random effects option in the PHREG procedure will be explored to incorporate the within-cluster correlations. We will also consider a recently proposed population average CR regression model for clustered data[50] using the crrSC package in R. Percent CIF macro in the Statistical Analysis System software will be used to implement Gray's method[51] for testing differences of the cumulative incidence functions between the two treatment groups. The SRATA parameter in the %CIF macro will also be used to perform the stratified version of Gray's test[51]. In the event that a subject dies from causes unrelated to schizophrenia before a hospitalization, the death will be considered a competing event instead of a censoring event. Subjects discontinued without an event (i.e., hospitalization) will be censored on the last known day without an event. We will also assess for the misspecification of the regression model for the subdistribution hazard of a CR using the diagnostic plots recommended by Latouche et al[52].

9.7.1.8.2 Secondary Efficacy Analysis

Time to hospitalization and days of inpatient hospitalization will be evaluated as part of the secondary efficacy analysis using the following:

- Time to hospitalizations: Total times (e.g., time from randomization to first, second, or any subsequent hospitalizations) as well as gap times (e.g., time between first and second hospitalization, second and third hospitalization, etc.) will be considered. The conditional models of Prentice, Williams, and Peterson will be used, with the risk set for the $(k + 1)^{st}$ hospitalization restricted to subjects who already had k hospitalizations, to compare the total time endpoints between the treatment groups. For comparison of gap time endpoints, a marginal approach proposed by Wei, Lin, and Weissfeld will be used.

- Days of inpatient psychiatric hospitalization: The total number of days of inpatient psychiatric hospitalization occurring in each quarter (i.e., every 3 months) of the 2-year study period will be counted. This will generate longitudinal measurements with eight time points (i.e., corresponding to eight quarters) for each subject.

If the subject drops out partially or completely for any quarter, the outcome for that particular quarter will be considered a missing value. The linear mixed effects model with time x group interaction will be used to compare the longitudinal trajectories of number of days of psychiatric hospitalization every quarter between the two treatment groups.

Change from baseline or postbaseline assessments in psychopathology (e.g., BPRS and CGI-S), cost of care from the SURF, quality of life from the QLS, and change from baseline at the 1-year and 2-year time points in neuropsychological functioning (e.g., RBANS) will be analyzed using linear contrasts in a mixed model with a nested design (e.g., subjects nested within clusters). This design will take into account the within-cluster correlations as well as within-subject correlations. The treatment effects, treatment differences, and the associated 95% confidence intervals will be presented.

9.7.1.8.3 Pharmacodynamic Analyses

Change from baseline to the 1-year and 2-year time points in gray matter and white matter volume, and cortical thickness will be analyzed using linear contrasts in a mixed model with a nested design (e.g., subjects nested within clusters). This design will take into account the within-cluster correlations as well as within-subject correlations. The 2-year time point will be the primary time point for this variable.

9.7.1.8.4 *a priori* Analyses

In addition to an intent-to-treat analysis including all FAS subjects, an *a priori* sensitivity analyses of the data will be conducted. The first will exclude patients who discontinue for any reason during the first 2 months after determination of study eligibility. The second will exclude patients who have a psychiatric emergency room visit or a psychiatric inpatient hospitalization during the first 2 months after determination of study eligibility. The third will exclude patients who do not meet criteria for inclusion into the timely initiation of aripiprazole once monthly group.

9.7.2 Determination of Sample Size

The total number of subjects will be 500. There will be approximately 250 subjects in the aripiprazole once monthly arm and 250 subjects receiving TAU. Each group will be further divided into a first-episode cohort and an EP cohort.

In a unique 2-year longitudinal epidemiological study of subjects receiving community-based treatment in the US for first-episode psychosis, differences among diagnostic groups in the interval from first psychotic symptom to hospitalization were analyzed. The rate of rehospitalization for subjects with schizophrenia followed for 2 years after the first psychiatric admission was 53.5%[46], which was similar to the 53.7% cited by Robinson et al[47] in a previous study. These rehospitalization rates are for subjects recruited at the time of first initiating treatment for psychosis. Subjects for the proposed study include subjects who are slightly more advanced in the course of their illness. Therefore, we project a 60% rehospitalization rate for subjects in our TAU treatment group. In addition, a subset of 114 first-episode and EP subjects at approximately 10 sites will undergo imaging studies during the 2-year study duration. The sample size calculation was based on the formula provided by Fitzmaurice, Laird, and Ware (2004) for a longitudinal study. We assume that changes in neuroanatomic measures can be expressed in terms

of a linear trend over time, in years, and that these effects can be expressed as the difference between slopes in the treatment conditions (i.e., δ). We based our analysis on data provided in Bartzokis et al[20], which reported study standard deviations for the rate of change in neuroanatomic measures ranging from 0.66 to 0.98, for an LAI antipsychotic versus oral administration. For our calculations, we assume that the between-subject standard deviation of the slopes is 0.90 and within-subject variability to be 2.0. With these values, we would be able to detect a minimum treatment effect δ of 1.25 (effect size = 0.75) with 80% power (alpha = 0.05), with a sample size of 28 in each treatment arm at the 2-year follow-up. Assuming a 30% drop-out rate, the sample size needed at baseline would be 57 per group. Included in the 30% drop-out rate are dropouts for the imaging analyses, subjects who drop out of the study completely (i.e., all study procedures), and those that drop out of the imaging component only.

Sample size calculations were done using the formula developed by Latouche et al[48] proportional hazards modeling of CR. The proportion of "failures of interest" (i.e., first hospitalization) was set at 60% for the TAU arm. For the sample size calculation, we hypothesized the corresponding proportion in the LAI arm to be 30% so that the overall proportion of the patients hospitalized at least once, in both treatment arms combined, is 45%. The minimum detectable subdistribution hazard ratio at 80% power and a 5% significance level with 398 subjects equally allocated in the two treatment arms is 1[48]. Accounting for a 20% drop-out from the rehospitalization analyses, the corresponding sample will be 498, or 249 per treatment group. With 400 completed subjects (i.e., 200 per group), the cause-specific hazard ratio that could be estimated at 80% power and 5% significance level was 1.38. The 1.38 hazard ratio is conventionally considered to be close to a small effect size, but it is large enough that it would influence both prescriber decisions about individual patients but also crucially health policy makers' decisions about the advantages of treatment with aripiprazole once monthly.

The numbers of subjects per site and treatment arm are provided in Table 5.

Table 5: Number of Subjects per Site per Treatment Arm

Treatment Group	Number of sites	First-episode[a]	EP[b]	Total
Aripiprazole once monthly (LAI)	20	125	125	250
TAU	20	125	125	250
Total	40	250	250	500

EP = early phase, LAI = long-acting injectable, TAU = treatment as usual
a: < 1 year of antipsychotic treatment
b: between 1 and 5 years of antipsychotic treatment

9.7.3 Interim Analysis

No interim analyses are planned.

9.7.4 Multiple Comparison Adjustment

No multiple comparisons are required as there is only one primary endpoint.

9.7.4.1 Data Safety Monitoring Board

The study will be monitored by a Data Safety Monitoring Board (DSMB) organized by The Zucker Hillside Hospital. The DSMB will independently review the protocol and consent documents, AEs, and outcome data as needed, for the proposed study. The DSMB will evaluate issues related to subject safety and the adequacy and integrity of accumulated data. The DSMB will meet once per year to review the study. Data reports will be prepared by the central coordinating team and the data management center to support the work of the DSMB.

The data coordinating center will create tables for the DSMB to review every 6 months. The tables will include enrollment, demographic information by treatment arm, abnormal laboratory results, SAEs, and missing data. After each annual meeting, the DSMB will issue a memo documenting any action items for the team. Copies will be provided to OAPI upon request.

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 affects the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report. Any changes to the SAP will be sent to the DSMB for review.

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 and the DSMB. 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 (i.e., source documents) are to be fully available for review by the PI'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 that have been certified for accuracy after production
- Recorded data from automated instruments, such as Interactive Voice and Web Response System, x-rays, and other imaging reports, (e.g., sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalographies, polysomnographs, and 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 correction 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 IB, 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 REPORTING OF PRODUCT QUALITY COMPLAINTS

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

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

10.7.1 Information Required for Reporting Purposes

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

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

10.7.2 Eliciting and Reporting Quality Complaints

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

The investigator or designee must notify OAPI Ethics, Quality, and Compliance (EQC) within 24 hours of becoming aware of the PQC by e-mail or telephone:

- Online – send the required information to OAPI-EQC ProductComplaints@otsuka-us.com
- Telephone – Rocky Mountain Call Center – 1-800-438-9927

10.7.3 Return Process

During the PQC reporting process, indicate if the sample under complaint is available for return. If the sample is available for return, OAPI-EQC will provide a product retrieval package. Return the sample in the product retrieval package.

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

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

10.8 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 terminated or suspended prematurely, OAPI will promptly inform the investigators or 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 or institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his or 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 or 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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12 APPENDICES

Appendix 1: SIGNATURE PAGE

Study Protocol Number:	COL.AOM.2013.005
Study Protocol Title:	A Cluster Randomized, Multi-center, Parallel-group, Rater-blind Study Comparing Treatment with Aripiprazole Once Monthly and Treatment as Usual on Effectiveness in First-Episode and Early Phase Illness in Schizophrenia
Investigational Product Name:	Abilify Maintena®, aripiprazole

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

Feinstein Institute for Medical Research

Medical Institution

John M. Kane, MD

Investigator	Signature	Date