CLINICAL STUDY PROTOCOL

Study Title:	Aripiprazole lauroxil for Preventing Psychotic Relapse After an Initial Schizophrenia Episode (APPRAISE)
Document Status:	Final
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PROCEDURES IN CASE OF EMERGENCY

Table 1: Study Contact Information

Role in Study	Name	Telephone Number
To contact the treating psychiatrists during regular business hours, call the main line for the Aftercare Research Program. Case managers may also be contacted through this main number.	Laurie Casaus, M.D. or Margaret Distler, M.D.	+1 (310) 206-3142
To contact the treating psychiatrists outside of business hours, call the 24-Hour Emergency Live Answering Service/ Page Operator. One of the two treating psychiatrists is always on call. Call schedule rotates and is provided to the answering service. Case managers also have a rotating after hours call and may be contacted through this same answering service.	Laurie Casaus, M.D. or Margaret Distler, M.D.	+1 (310) 825-6301

2. SYNOPSIS

<table>
<tr><td colspan="2">Sponsor: University of California, Los Angeles (UCLA)</td></tr>
<tr><td colspan="2">Investigational Products:
• aripiprazole lauroxil long-acting injectable (AL-LAI; ARISTADA®)
• aripiprazole lauroxil NanoCrystal® Dispersion (AL-NCD; ARISTADA INITIO®)</td></tr>
<tr><td colspan="2">Active Ingredient: aripiprazole lauroxil</td></tr>
<tr><td colspan="2">Study Title: Aripiprazole lauroxil for Preventing Psychotic Relapse After an Initial Schizophrenia Episode (APPRAISE)</td></tr>
<tr><td colspan="2">Study Center: UCLA</td></tr>
<tr><td colspan="2">Investigator: Kenneth Subotnik, Ph.D.</td></tr>
<tr><td>Study Period (years):
Estimated date first patient’s consent: TBD
Estimated date last patient’s visit: TBD + 48 months</td><td>Phase of development: Phase 4</td></tr>
<tr><td colspan="2">Objectives:
<u>Primary:</u>
The primary objective is to assess whether schizophrenia patients who recently experienced their first psychotic episode that are randomized to AL-LAI are less likely to experience a re-emergence of positive psychotic symptoms compared to those randomized to oral aripiprazole (ARI-ORAL).
<u>Secondary:</u>
The secondary objectives are to:
1. Examine differences in functional outcome between the two treatment groups. We anticipate that role functioning will improve more in the group randomized to AL-LAI than those assigned to the ARI-ORAL group.
2. Evaluate and compare the cognitive changes of the AL-LAI vs. ARI-ORAL group over the 12-month Treatment period. It is hypothesized that patients assigned to AL-LAI will demonstrate relatively better performance on a standardized measure of cognition than those assigned to ARI-ORAL.
<u>Exploratory:</u>
Additional exploratory objectives are to determine whether the two medication groups differ in other symptoms domains, adherence, and tolerability (eg, negative symptoms, suicidality, self-reported awareness of having a mental disorder, service engagement, sexual/prolactin-related side effects, treatment engagement, and quality of life).</td></tr>
<tr><td colspan="2">Study Design/Methods:
This is a single-site study with all assessments and treatment to take place at the UCLA Aftercare Research Program (300 UCLA Medical Plaza, Los Angeles, CA 90095), which is a program that specializes in the treatment and study of individuals with a recent onset of schizophrenia. Patients entering the program will have extensive diagnostic and treatment evaluations, and eligible patients meeting diagnostic criteria will be invited to participate in a 12-month open-label randomized study comparing AL-LAI with ARI-ORAL. The flow for each patient after initial enrollment and evaluation will involve a Stabilization period of up to 90 days with at least the final 2 weeks on oral aripiprazole</td></tr>
</table>

as the sole antipsychotic medication, after which the patients will be randomly assigned to treatment with either ARI-ORAL or AL-LAI for a 12-month Treatment period.

Overview of the Randomized Treatment Groups:

Patients successfully completing the Stabilization period will be randomized to one of two medications groups: converting from oral antipsychotic to AL-LAI vs continuing on (ARI-ORAL). Randomization will be automated by UCLA. Patients successfully completing the Stabilization period will be randomized to one of two medications groups: converting from oral antipsychotic to AL-LAI vs continuing on (ARI ORAL). Each treatment group will be further randomized to computerized cognitive training with or without aerobic exercise.

Randomization to AL-LAI: Initiation of AL-LAI will begin with a one-day initiation regimen (one intramuscular injection of 675 mg AL-NCD and one single-dose of 30 mg oral aripiprazole). Subsequent dosing of AL-LAI will be flexible based on clinician judgment. The first AL-LAI injection may be administered on the same day as the one-day initiation regimen or up to 10 days thereafter. Treatment with AL-LAI can be initiated at a dose of 441 mg, 662 mg or 882 mg; 441 mg administered monthly, 882 mg administered every 6 weeks or 1064 mg administered every two months.

Randomization to ARI-ORAL: Patients will continue with ARI-ORAL doses within the recommended oral dosage range for the treatment of schizophrenia (10-30mg/day) with the usual starting dosage of 10 mg/day. ARI-ORAL dosage will be flexible and dosage will be at the discretion of the treating psychiatrist. Patients assigned to this treatment arm will receive a written prescription for a 30-day supply along with a medication coupon so there will be no medication cost to the patient.

Discontinuation of Assigned Treatment

Both groups will remain on their assigned treatment for 12 months or discontinue their assigned medication early. The reason(s) for early discontinuation of initial antipsychotic will be recorded, including whether it is initiated by the clinician or patient, and whether it is efficacy or tolerability related. Patients will be assessed for the reason for discontinuation using a version of the All-Cause Discontinuation (ACD) measure that was the primary outcome of the CATIE schizophrenia study. If a switch to another antipsychotic medication is warranted, the new therapy will be determined by the prescribing psychiatrist's judgment using the medication selection recommendation adapted from NAVIGATE pharmacologic treatment manual developed as part of the Recovery After an Initial Schizophrenia Episode (RAISE) study intervention groups. Patients discontinuing study drug after Randomization, but remaining in active treatment and follow-up, may be prescribed any first-line oral antipsychotic within the prescribing information dosage for schizophrenia. Patients will be encouraged to stay in the study for the remainder of the 12-month Treatment period and will be administered all of the scheduled assessments even if the initial randomly assigned antipsychotic medication is discontinued by the treating psychiatrist.

Symptom assessments will occur every two weeks, functional endpoint will occur every three months, and the cognitive endpoint will occur at baseline and at the 6- and 12-month points. All patients participating in the protocol will be invited to concurrently participate in a separate NIMH-funded psychosocial intervention protocol comparing the effectiveness of computerized cognitive training with and without aerobic exercise training.

Number of Patients Planned: Approximately 128 patients enrolled into the Stabilization period for final randomized sample of 90 (45 in each group) with a target of 14 relapses

Main Criteria for Inclusion:

Men and women aged 18 to 45 years, inclusive, with current diagnosis of schizophreniform disorder, schizophrenia, or schizoaffective depressed subtype disorder as defined by DSM-5 with the first psychotic episode having occurred within the last 24 months prior to Screening.

Reference Therapy, Dosage, Duration, and Mode of Administration:

ARI-ORAL treatment will be initiated for all patients during the Stabilization period per the label recommended range for the treatment of schizophrenia ARI-ORAL will continue to be prescribed for patients randomly assigned to the ARI-ORAL group during the Treatment period.

AL-LAI treatment will be initiated with the one-day initiation regimen (675 mg AL-NCD and 30 mg oral aripiprazole), but may alternatively be initiated with 21 consecutive days of supplementation with ARI-ORAL if clinically appropriate or preferable. The first AL-LAI injection may be administered on the same day as AL-NCD or up to 10 days thereafter as per clinical judgment. AL-LAI will be flexibly dosed for 12 months per label and can be initiated at a dose of 441 mg, 662 mg or 882 mg administered monthly, 882 mg administered every 6 weeks or 1064 mg administered every two months.

Duration of Study: ~15 months (3 months Stabilization period and 12 month Treatment period)

Criteria for Efficacy Evaluation:

Primary Endpoint

The primary endpoint will be time to first positive symptom exacerbation and/or relapse following a period of absence or relatively low levels of psychotic symptoms based on the expanded 24-item version Brief Psychiatric Rating Scale.

Secondary Endpoints

Functional assessment: The Role ratings on the Global Functioning Scale (GFS: Role) will serve as the measure of functional outcome. The GFS: ROLE will be administered every three months throughout the 12-month Treatment period.

Cognitive assessment: The Overall Composite T-score from the MATRICS Consensus Cognitive Battery (MCCB) will be the overall index of cognitive performance. The MCCB will be administered every six months throughout the 12-month Treatment period.

Exploratory Endpoints

Endpoints include Quality of Life, negative symptoms, self-reported awareness of having a mental disorder, service engagement, prolactin-related side effects, treatment satisfaction, and family/caregiver medication administration burden.

Safety Assessments

Extrapyramidal symptoms will be assessed on three scales (Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, and the Extrapyramidal Symptom Rating Scale). Adverse events (including serious and AEs of special interest), and suicidality will be monitored.

Statistical methods:

Sample Size Considerations:

Ninety first-episode patients will be randomized (1:1) fashion to either AL-LAI or ARI-ORAL, and based on our previous RCT, assume a 20% attrition rate over 12 months. 45 randomized patients (36 completers) in each group provides at least 80% power. Statistical power considerations are based on the effect sizes observed when comparing long-acting injectable risperidone vs oral risperidone (survival analysis for psychotic relapse: 5% relapse in the risperidone long-acting injectable group and 33% relapse in the oral risperidone group). On the basis of hazard function rates of 5.0% (AL-LAI)

and 33% (ARI-ORAL), the study has 87% power (α=0.05). On a more conservative basis of hazard function rates of 7.5% (AL-LAI) and 33% (ARI-ORAL), the study has 78% power (α=0.05).

For the secondary hypothesis for the relative changes in the MCCB Composite score and the GFS: Role, we will use a two-sided significance level of α=0.025 to account for type 1 error inflation. For the MCCB Composite score, assuming a within-patient correlation between repeated measurements of r=0.89 (based on a prior study), the proposed design provides us sufficient power (>=0.80) for Group X Time interaction effects as small as Cohen's f=0.09. Based on our previous work, we anticipate a medium effect size (Cohen's f=0.25 or d=0.50), and this design provides a power of >0.99 for an effect of this size. For the GFS rating, if we assume a within-patient correlation of r=0.5, with α=0.025, our GLMM will have 80% power to detect an interaction corresponding to an effect size of f=0.20. Based on a prior study, we anticipate an effect size of f=0.32 or d=0.63 for the GFS: Role ratings, for which we would have >99% power.

Thus, for both primary and secondary outcome measures we will be able to detect differential treatment effects based on our proposed design and expected sample size.

Analysis of Efficacy:

The primary hypothesis is that the hazard function (i.e. the risk of an event per unit of time) of the two medication groups differs between AL-LAI and the ARI-ORAL group. The hypothesis will be examined in a Cox regression model on the time to first relapse. We will include medication group membership, participation status in the NIMH exercise study, and length of stabilization period as predictors in the model.

The secondary hypotheses of the MCCB composite score and the GFS (Role) rating will be examined in general linear mixed models (GLMMs). We will include participation status in the NIMH exercise study, medication group as a between-patient variable and time as a within-patient variable in the model, and time*group as a within-between interaction term. Additionally, we will include length of stabilization period as a person level time invariant covariate. The primary effect of interest is the difference in the pattern of change over time of the dependent variable between the medication groups (i.e. the time*group interaction term). GLMMs properly account for correlations induced by repeated measurements within patients and automatically handle missing data, producing unbiased estimates as long as observations are missing at random. The GLMM will use Satterthwaite's approximation to estimate degrees of freedom for the tests of the fixed and random effects, and model the variance-covariance matrix as a Toeplitz matrix. If this assumption does not lead to convergence we will instead use compound symmetry. The secondary analyses will compare the change in the MCCB Composite score and GFS (Role) ratings between the two medication groups over the 12-month study period.

The data analytic methods for the exploratory measures will in general parallel those of the secondary measures.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACD	All-cause discontinuation
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
AL-LAI	Aripiprazole lauroxil, long-acting injectable (ARISTADA®)
AL-NCD	Aripiprazole lauroxil NanoCrystal® Dispersion (ARISTADA INITIO®)
ARI-ORAL	Oral aripiprazole
BARS	Barnes Akathisia Rating Scale
BPRS	Brief psychiatric rating scale
C-SSRS	Columbia suicide severity rating scale
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CGI-S	Clinical global impression – severity
CYP	Cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EPS	Extrapyramidal symptoms
ESRS-A	Extrapyramidal symptom rating scale
FDA	Food and Drug Administration
GASS	Glasgow Antipsychotic Side-effect Scale
GFS	Global functioning scale
GLMM	General linear mixed models
ICF	Informed consent form
IRB	Institutional review board
IM	Intramuscular
ITT	Intent-to-treat
MCCB	Matrics consensus cognitive battery
MSQ	Medication satisfaction questionnaire
NIMH	National Institute of Mental Health
PANSS	Positive and Negative Syndrome Scale
PSP	Personal and Social Performance
QLS	Quality of Life Scale
RAISE	The Recovery After an Initial Schizophrenia Episode (study)
SAE	Serious adverse event

Abbreviation	Definition
SANS	Scale for the Assessment of Negative Symptoms
SCID	Structured Clinical Interview for DSM-5
SES	Service engagement scale
SIStat	Semel institute biostatistics core
SUI-Brief	Brief substance use inventory
SUMD-R	Scale to Assess Unawareness of Mental Disorder-Revised
UCLA	University of California, Los Angeles
WTAR	Wechsler Test of Adult Reading

4. INTRODUCTION

Long-acting injectable antipsychotic medications are a critical tool for clinicians treating schizophrenia patients. There is a growing consensus that long-acting injectable options should not be reserved only for the very ill who have demonstrated nonadherence to oral antipsychotic medication. Additional research into their effectiveness may be required in order to inform physicians of the use long-acting injectable medications early in the course of the disorder. Ensured adherence using long-acting injectables allows the clinician to better judge the effectiveness of the medication and dosage, and guide the pharmacologic treatment early in disease.

Aripiprazole lauroxil, long-acting injectable (AL-LAI; ARISTADA®) is an atypical long-acting injectable for the treatment of schizophrenia. It is a covalently bonded, non-ester modification of aripiprazole, a second generation atypical antipsychotic agent, to form *N*-lauroyloxymethyl aripiprazole. It is formulated as an extended-release suspension to be administered via intramuscular (IM) injection into either the gluteal or deltoid muscles. After injection, aripiprazole lauroxil is converted to aripiprazole by dissolution of the aripiprazole lauroxil drug crystal from the injection site and subsequent enzyme-mediated cleavage, ultimately releasing aripiprazole into the plasma circulation.

Therapy may be initiated by a one-day initiation regimen (a single IM injection of 675 mg aripiprazole lauroxil NanoCrystal® Dispersion [AL-NCD; ARISTADA INITIO®] with a single-dose of 30 mg oral aripiprazole [ARI-ORAL]) or by 21 consecutive days of supplementation with ARI-ORAL. AL-NCD is a different IM formulation of AL. The two IM formulations predominantly differ in the particle size of the drug substance, the AL-LAI in the micrometer range and AL-NCD in the nanometer range. The smaller particle size of the AL-NCD formulation is designed to accelerate the rate of dissolution of AL to provide earlier appearance of circulating aripiprazole following administration compared to the micron formulation.

In clinical trials, treatment with AL-LAI demonstrated statistically significant reductions from baseline in Positive and Negative Syndrome Scale (PANSS) total scores at Week 12, compared with placebo. AL-LAI was generally well tolerated for patients with schizophrenia at monthly IM dosing of 441 mg and 882 mg with the most common adverse events (AEs) being insomnia, akathisia, and headache.

This study is an open label, 12-month prospective evaluation comparing ARI-ORAL to AL-LAI conducted by the University of California, Los Angeles (UCLA).

5. STUDY OBJECTIVES

5.1. Primary Objective

The primary objective is to assess whether schizophrenia patients who recently experienced their first psychotic episode that are randomized to AL-LAI are less likely to experience a re-emergence of positive psychotic symptoms compared to those randomized to ARI-ORAL.

5.2. Secondary Objectives

The secondary objectives are to:

1. Examine differences in functional outcome between the two treatment groups. We anticipate that role functioning will improve more in the group randomized to AL-LAI than those assigned to the ARI-ORAL group.
2. Evaluate and compare the cognitive changes of the AL-LAI vs. ARI-ORAL group over the 12-month Treatment period. It is hypothesized that patients assigned to AL-LAI will demonstrate relatively better performance on a standardized measure of cognition than those assigned to ARI-ORAL.

5.3. Exploratory Objectives

Additional exploratory objectives are to determine whether the two medication groups differ in other symptoms domains, adherence, and tolerability (eg, negative symptoms, suicidality, self-reported awareness of having a mental disorder, service engagement, sexual/ prolactin-related side effects, treatment engagement, and quality of life).

6. SELECTION AND WITHDRAWAL OF PATIENTS

Approximately 128 patients will be recruited for the study as defined by consenting to a full screening assessment with the goal of randomization to a treatment group. Based on prior long-acting injectable versus oral studies, we expect an attrition rate of 30% prior to Randomization, so that a total of 90 eligible patients will be randomized to either ARI ORAL (N=45) or AL-LAI (N=45).

6.1. Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be qualified to participate in this study.

3. Is willing and able to provide informed consent.
4. Is between 18 and 45 years of age, inclusive, at Screening.
5. Has a diagnosis of schizophreniform disorder, schizophrenia, or schizoaffective disorder, depressed type, as defined by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [DSM-5] (American Psychiatric Association 2013) criteria at Screening.
6. Has a first episode of a psychotic illness that occurred within the 24 months before entry into the UCLA Aftercare Research Program.
7. Sufficient acculturation and fluency (oral and written) in the English language to avoid invalidating research measures of thought, language, and speech disorder or of verbal abilities.
8. Exhibits tolerability to ARI-ORAL during the Stabilization period, according to Investigator judgment (to be randomized).
9. Resides within commuting distance of the UCLA Aftercare Research Program in a stable living situation where the patient can be located.
10. Agrees to abide by the contraceptive requirements of the protocol.

6.2. Exclusion Criteria

Each patient must not have any of the following conditions to be qualified to participate in this study.

1. Evidence of a known neurological disorder (e.g., epilepsy) or significant head injury with loss of consciousness of more than one hour.
2. Has mental retardation (i.e., premorbid IQ less than 70) as estimated by the Wechsler Test of Adult Reading (WTAR) completed at screening or as documented in medical records conducted in childhood. The WTAR assesses word pronunciation, which is thought to be unaffected by cognitive decline associated with neurological damage and is thus a good proxy for premorbid intelligence.
3. Is currently pregnant or breastfeeding, or is planning to become pregnant during the study.

4. Is currently on a long-acting injectable antipsychotic medication and it is clinically contra-indicated due to the risk of becoming a danger to self or others if the patient discontinued treatment with the long-acting injectable in order to participate in this trial.
5. Has a history of poor or inadequate response to an adequate trial of oral or injectable aripiprazole (does not exclude patients whose aripiprazole exposure was too brief or at sub-therapeutic doses).
6. Has received AL-LAI or IM depot aripiprazole within two months prior to Randomization (unless Stabilization period is extended beyond 90 days to accommodate).
7. Has alcohol or substance abuse as a prominent clinical problem or makes the primary diagnosis not possible to confirm. Evidence of alcohol or substance use is not, in and of itself, exclusionary.
8. Is currently being treated with clozapine.
9. Has participated in a clinical trial involving any drug within the past two months prior to screening, or is currently participating in a clinical trial involving an investigational medication.
10. Has a history of psychopathology based on the screening SCID other than schizophreniform disorder, schizophrenia, or schizoaffective disorder, mainly depressed type as indicated by any primary DSM-5 diagnosis within the 12 months prior to Screening or Randomization (e.g. primary diagnosis of bipolar disorder, schizoaffective disorder, bipolar type, bipolar disorder, or neurocognitive disorder) based on our research diagnostic procedures.
11. Is in the opinion of the Investigator or prescribing psychiatrist, the patient is an imminent danger to himself/herself. Patient must not be an imminent danger to himself/herself for two weeks prior to entry. The Stabilization period may be extended until the potential patient participant has not been in imminent danger to himself/herself for at least two consecutive weeks. A prior history of suicidal ideation or suicidal attempt is not exclusionary.
12. Has any of the following conditions or abnormalities at screening: History of neuroleptic malignant syndrome, malignant hyperthermia, or clinically significant tardive dyskinesia.

6.3. Discontinuation of Assigned Medication

If the randomly assigned medication must be discontinued and/or switched to a different antipsychotic medication, the patient may remain in the study until the 12-month assessment point. End of Assigned Treatment assessment point measures will be completed as close to and if possible, just prior to, the discontinuation/switch. Decision to switch medication will be recorded on a modified Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) All-Cause Discontinuation (ACD) assessment completed by the treating psychiatrist (Stroup et al, 2003). The switch to another antipsychotic medication will be guided by clinician judgment using the mediation selection recommendation adapted from the oral antipsychotic guidance used in the RAISE study (Kane et al, 2015). The date the new medication is prescribed will be recorded and used in the analyses. Patients who choose to discontinue study medication will be allowed to re-

initiate study medication at any time during the 12-month follow-up. All other regular assessments will be completed throughout the remainder of the 12-month study.

6.4. Over-enrollment of Patients

Over-enrollment (beyond 90 patients) will occur to ensure that there are at least 14 patients who had a relapse in the 12-month Treatment period.

7. STUDY DESIGN

7.1. Overall Study Design

This is an open-label study of approximately 90 patients with schizophrenia who will be randomly assigned to 12 months of treatment with either ARI-ORAL or AL-LAI to take place at the UCLA Aftercare Research Program (300 UCLA Medical Plaza, Los Angeles, CA 90095), which is a program that specializes in the treatment and study of individuals with a recent onset of schizophrenia. The study design is presented in Figure 1. Potential patients will be evaluated for eligibility according to the inclusion and exclusion criteria at Screening.

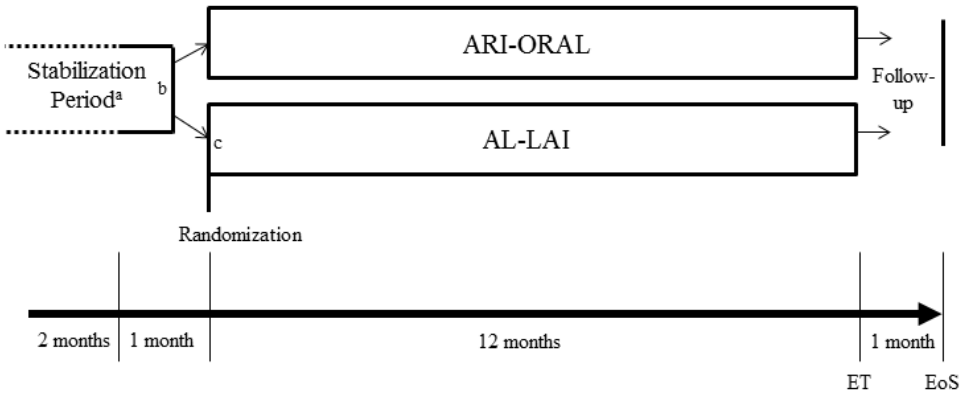
For patients who have never taken aripiprazole, tolerability must be established during the Stabilization period. The Stabilization period will be once-a-day ARI-ORAL with flexible dosing. All patients will receive ARI-ORAL for at least two weeks to establish full tolerability before Randomization, and patients who cannot tolerate ARI-ORAL 10 mg/day will not be randomized. Eligibility to be randomized will be determined at the end of the Stabilization period of up to 90 days.

The Stabilization period will allow time for the oral antipsychotic medication to be cross-tapered to ARI-ORAL, if needed, and allow time for the patient to obtain some clinical stability prior to Randomization. Further, the Stabilization period will allow the baseline testing for this and the overlapping National Institute of Medical Health (NIMH) protocol to occur at a pace appropriate for someone who is in the middle, or tail-end of, a psychotic episode.

Randomization (1:1 [AL-LAI: ARI-ORAL]) will take place after the Stabilization period. The NIMH overlapping study is a psychosocial intervention treatment. To balance the overlapping NIMH treatment groups in the AL-LAI and ARI-ORAL treatment groups, the randomization of patients in the APPRIASE study will be stratified by their participating role in the NIMH study (randomized to computerized cognitive training with or without aerobic exercise). Once randomized, patients will be treated per prescribing recommendations for a 12-month Treatment period.

Efficacy will be evaluated based on the Brief Psychiatric Rating Scale (BPRS) scored for symptom exacerbation or relapse following Subotnik et al. (Subotnik et al, 2015) and Nuechterlein et al. (Nuechterlein et al, 2006). Because patients will not be withdrawn from the study if relapse criteria are met, there will be no need to score the BPRS for relapse contemporaneously throughout the study. Secondary outcomes will be role functioning and cognition. Exploratory outcomes will be negative symptoms, suicidality, awareness of having a mental disorder, extrapyramidal and prolactin-related side effects, service engagement, treatment satisfaction, and quality of life. Safety assessments will be collected and monitored.

Figure 1: Study Design



[a] 1 to 3 months of stabilization on oral aripiprazole.
[b] For 2 weeks prior to Randomization, all patients must be on oral aripiprazole
[c] Initiation of treatment per Section 7.2.2
Abbreviations: ARI-ORAL: aripiprazole oral; AL-LAI = aripiprazole lauroxil long-acting injectable; ET = End Treatment; EoS = End of Study

7.2. Treatment Initiation

During the last two weeks of the Stabilization period, all patients must be on ARI-ORAL to assess tolerability. At the initiation of ARI-ORAL during the Stabilization period, patients will be provided a prescription and prescription coupon to cover aripiprazole costs.

7.2.1. Initiation of ARI-ORAL Treatment Arm after Randomization

Patients will start or continue (from the Stabilization period) with ARI-ORAL doses within the recommended oral dosage range for the treatment of schizophrenia per the prescribing information (Abilify USPI). ARI-ORAL dosage will be flexible and dosage will be at the discretion of the treating psychiatrist. Patients assigned to this treatment arm will receive a written prescription for a 30-day supply along with a medication coupon so there will be no medication cost to the patient.

7.2.2. Initiation of AL-LAI Treatment Arm after Randomization

Initiation of AL-LAI will begin with a one-day initiation regimen (675 mg AL-NCD and 30 mg oral aripiprazole) per prescribing information (Initio USPI) unless the alternative initiation is selected (see Section 8.3.4.1.2). Dosing of AL-LAI will be flexible based on clinician judgment per prescribing information (Aristada USPI). The first AL-LAI injection may be administered on the same day as the one-day initiation regimen or up to ten days thereafter. Treatment with AL-LAI can be initiated at a dose of 441 mg, 662 mg or 882 mg administered monthly, 882 mg administered every six weeks or 1064 mg administered every two months. Patients assigned to the AL-LAI treatment arm will return to the clinic for injections during scheduled visits.

7.3. Continuation of Treatment

Both treatment arms will be seen for routine monthly medication management visits with the prescribing psychiatrist who is affiliated with the UCLA program, and urgent visits can be scheduled as per clinical circumstances.

7.4. Study Procedures

7.4.1. Visit and Assessment Schedule

The schedule of assessments is shown in Table 2. For a missed visit, the site should attempt to contact the patient to reschedule.

Table 2: Schedule of Visits and Assessments

	Screening	Stabilization	Treatment Period[1]					Month 13 Follow-up
			Day 1 (Randomization baseline)	Months 1-5[2]	Month 6	Months 7-11	Month 12 EoT/EoAT[3]	
Clinical Visit Number	**V1**		**V2**	**V3, 4,5,6,7**	**V8**	**V9,10,11,12,13**	**V14**	**V15**
Study Drug Administration		Ongoing throughout study						
Psychiatrist Medication Visit	X	Every month throughout study						
Informed Consent	X							
Eligibility Criteria Review	X		X					
Demographics and Medical History[4]	X							
SCID-5	X							
ARI-ORAL 2-Week Tolerability Assessment[5]		X						
Pregnancy Testing[6]	X		X	X (3 months)	X	X (9 months)	X	X
Urine Drug Screen	X		X		X	An additional test if needed for clinical purposes		
Physical Exam[7]	X							
AE Monitoring		Ongoing throughout study						X
Concomitant Medication Review	X	Every month throughout study						X
Vital Signs[8], Weight, Waist Circumference	X		Every 3 months throughout study					X
Fasting Clinical Lab Tests[9]	X		X		X		X	
Plasma aripiprazole measurement					X		X	
MCCB			X		X		X	
GFS:Role[10]	X		X	Every 3 months throughout study				
QLS[10]			X		X		X	
SUI-Brief[11]	X		X	X	X	X	X	

	Screening	Stabilization	Treatment Period[1]					Month 13 Follow-up
			Day 1 (Randomization baseline)	Months 1-5[2]	Month 6	Months 7-11	Month 12 EoT/EoAT[3]	
Clinical Visit Number	**V1**		**V2**	**V3, 4,5,6,7**	**V8**	**V9,10,11,12,13**	**V14**	**V15**
Modified MSQ			X		X		X	
ESRS	X		X		X		X	X
AIMS	X		X		X		X	X
BARS	X		X	X	X	X	X	X
GASS			X		X		X	
C-SSRS[12]	X		X	X	X	X	X	X
SES			X		X		X	
CGI-S			X		X		X	
BPRS	X		X	Every 2 weeks throughout study				
MCCB			X		X		X	
SANS			X		X		X	
PSP			X		X		X	
SUMD-R			X		X		X	
Hassles			X		X		X	
ACD			Ongoing throughout study if assigned medications are discontinued					

Abbreviations: ACD= Modified Version of the All-Cause Discontinuation; AIMS = Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; BPRS= Brief Psychiatric Rating Scale; CGI-S= Clinical Global Impressions-Severity; C-SSRS= Columbia Suicide Severity Rating Scale; GASS= Glasgow Antipsychotic Side-effect Scale; EoT= end of study treatment; ESRS-A=Abbreviated Extrapyramidal Symptom Rating Scale; EoAT = end of aripiprazole treatment; GFS: Role=Global Functioning Scale: Role; Hassles= Family Caregiver Medication Administration Hassles Scale; MCCB=MATRICS Consensus Cognitive Battery; MSQ= Medication Satisfaction Questionnaire (Modified); QLS = Quality of Life Scale; PSP= Personal and Social Performance Scale; SAE = Serious Adverse Event; SANS= Scale for the Assessment of Negative Symptoms; SCID-5= Structured Clinical Interview for DSM-5; SUI-Brief=Brief Substance Use Inventory; SUMD-R= Scale to Assess Unawareness of Mental Disorder-Revised; SES= Services Engagement Scale

[1] For all visits other than Screening and Day 1, the visit will be anchored to the previous visit (based on dosing regimen schedule)

[2] In the event that a visit is missed or skipped, the additional assessments required at the visit should be conducted (via unscheduled assessment) at the patient's next visit

[3] EoT= end of study treatment (may include therapies other than aripiprazole, if changed); EoAT = end of aripiprazole treatment

[4] The Psychiatric and Social History Schedule will be administered to record basic demographic information as well as past work and school history.

[Assessment5]ARI-ORAL will be prescribed with flexible dosing. The first dose should be administered at the UCLA Aftercare Research Program.

[6] Urine pregnancy testing will be completed for ALL women. At Visit 1 and 14, a serum pregnancy test will be performed. At Visit 1, the pregnancy test should be completed prior to the administration of the first ARI-ORAL dose. A urine pregnancy test will be conducted at mid-study indicated time points.
[7] Full physical examination at screening; brief physical examination on Day 1; symptom directed physical exams may be performed as needed at the Investigator's discretion.
[8] Vital signs include blood pressure, heart rate, respiratory rate, and body temperature
[9] Clinical Lab Tests include biochemistry (including prolactin) and hematology
[10]Will be administered at baseline, Month 3, Month 6, Month 9, and Month 12/ET
[11] Will be administered every 2 weeks throughout the treatment period
[12] "Baseline/Screening" version used at screening; "since last visit" used at all subsequent visits

7.4.2. Informed Consent

The nature of the study and its risks and benefits will be explained to the patient by the Principal Investigator or designated study personnel as outlined in Section 13.3.

Prior to the administration of any study-specific procedures, authorized study personnel will obtain written informed consent from each potential patient and caregiver.

7.4.3. Eligibility Review

An eligibility review will be conducted by the Investigator at the visits specified in Table 2 using the patient inclusion criteria in Section 6.1 and exclusion criteria in Section 6.2. The Structured Clinical Interview for DSM-5 (SCID; (First et al, 2002)) will be used to establish entry diagnosis. The SCID was developed for use in research by trained clinicians. The SCID incorporates the use of obligatory questions, operational criteria from the DSM-5, a categorical system for rating symptoms, and an algorithm for arriving at a final diagnosis. The SCID is organized in sections that include an overview of the individual's psychiatric history, an assessment of mood disorder symptoms, psychotic symptoms, anxiety, alcohol abuse, substance abuse, and other Axis I disorders. The SCID has two sections that provide an algorithm for making a differential diagnosis of psychosis and mood disorder. Recent modifications of the SCID allow the interviewer to incorporate all relevant sources of information that are gathered from the patient's chart and reliable informants in making a diagnosis. Published levels of inter-rater reliability when using the SCID were very high for schizophrenia (kappa = 0.94) and major depression (kappa = 0.93; (Skre et al, 1991)). The SCID interview takes 1-2 hours to complete.

7.4.4. Demographics and Medical History

Patient demographic data and medical history will be reviewed and documented at the time point(s) specified in Table 2. The Psychiatric and Social History Schedule will be administered at the Screening to record basic demographic information as well as past work and school history.

7.4.5. Prior and Concomitant Medication Review

At Screening, all medications (prescription and nonprescription, including vitamins and herbal supplements) taken by a given patient within 30 days prior to screening through follow-up will be recorded. At all other time point(s) specified in Table 2, prospective patients will be asked about the medications they have taken since the last visit and are currently taking (including prescription and nonprescription medications, vitamins, and supplements).

The Investigator will record the following data on all medications used by the patient: name, dose, regimen, route of administration, start and stop dates, and the indication for use.

7.4.5.1. Substance Use

The Brief Substance Use Inventory (SUI-Brief) will be administered every two weeks during the randomized treatment period to document amount and frequency of alcohol, substance, and tobacco use.

7.4.6. Primary Endpoint Measurements

The primary endpoint will be time to first positive symptom exacerbation and/or relapse following a period of absence or relatively low levels of psychotic symptoms based on the expanded 24-item version Brief Psychiatric Rating Scale (BPRS) (published UCLA relapse criteria (Nuechterlein et al, 2006) that are summarized below).

7.4.6.1. APPRAISE Study Criteria for Reemergence of Positive Symptoms

The BPRS is a semi-structured instrument that is internationally recognized and accepted for rating the presence and severity of psychiatric symptoms. The BPRS assesses various domains of psychiatric symptoms. Ratings are based on information obtained from self-report and observation of the patient's behavior and speech. Symptoms and signs are rated along a severity and impairment in functioning dimension using a seven point rating scale. The BPRS has been used extensively to assess changes over time in the severity of the symptoms of schizophrenia and other major psychiatric disorders. In a comprehensive review, Hedlund and Vieweg (Hedlund Jl 1980) found that most studies reported excellent inter-rater reliability for the BPRS. Median Pearson and Intraclass correlation coefficients on the BPRS have ranged from 0.67 to 0.88 (Bech et al, 1988; Tarell and Schulz 1988). The UCLA research team has developed a training and quality program for the expanded BPRS that has led to excellent inter-rater reliability at the completion of training (Ventura et al, 1993). The case managers will complete the BPRS at Screening and every two weeks as identified in Table 2.

The BPRS includes ratings from 1 to 7 on each of these symptom dimensions. However, for positive symptom exacerbation, the three key BPRS ratings for predicting and evaluating psychotic relapse or significant exacerbation are:

1. Hallucinations
2. Unusual Thought Content
3. Conceptual Disorganization

It is these three items that are scored into the relapse algorithm.

Because patients will vary based on their relative stability over time as well as the degree of change in positive symptom severity, the actual relapse outcome will be based on *both* current and prior BPRS evaluations as specified by one of the three exacerbation/relapse categories. Meeting criteria for any of the following three categories will be considered a psychotic relapse/exacerbation.

Criteria for relapse or exacerbation of symptoms are summarized in Table 3. These criteria have established reliability, predictive validity and reactivity to medication nonadherence. Assessments are done every 2 weeks and scoring done by computer program.

Table 3: Criteria for Relapse or Exacerbation of Symptoms

Remission followed by relapse	Remission followed by 1 psychotic item ≥ 6 (severe) at any BPRS assessment visit	Section 7.4.6.1.1
Remission followed by significant exacerbation	Remission followed by 1 psychotic item rated 5 (marked) for more than 4 weeks (2 consecutive BPRS assessments)	Section 7.4.6.1.2
Persistent symptoms followed by significant exacerbation	Psychotic item rated 4 or 5 and then ≥ 2 point increase to severe level (6 or 7) at any BPRS assessment visit	Section 7.4.6.1.3

7.4.6.1.1. Remission Followed by Relapse

The patient achieves remission on all BPRS key symptoms by being rated 3 (which is below clinical threshold) or lower for more than four consecutive weeks at some point following project entry. A rating of ≥ 6 (severe) on any one of these items following this period of remission would meet this relapse criterion.

7.4.6.1.2. Remission Followed by Significant Exacerbation of Symptoms

The patient is rated 3 or lower on the BPRS key symptom items for more than four weeks and the patient subsequently (a) is rated 5 on one of the key symptom items and increases at least two points on another key symptom item within the same four-week period while the initial exacerbating symptom is still in the clinical range (4 or higher) or (b) is rated 5 on one of the key symptom items for more than four weeks.

7.4.6.1.3. Persisting Symptoms Followed by Significant Exacerbation of Symptoms

The patient has persisting clinically significant symptoms in the 4 to 5 range on one or more BPRS key items but not in the 6 or 7 range for more than four weeks (not necessarily always the same item) during the Treatment period without achieving remission (by criteria above), and:

a. shows an increase of two points within an eight-week period to a rating of 6 or 7, or
b. shows an increase of one point on this item to a 6 and an accompanying two-point increase on another key symptom item within the same four-week period.

These criteria are not made in real time, but are entered into the database and determined at a later time.

7.4.7. Secondary Endpoint Measurements

The secondary endpoints of this study are:

- Role ratings on the Global Functioning Scale (GFS: Role)
- Overall Composite T-score MATRICS Consensus Cognitive Battery (MCCB)

7.4.7.1. Functional Assessment -The Role ratings on the Global Functioning Scale

The GFS: Role (Cornblatt et al, 2007; Niendam et al, 2006) will serve as the measure of functional outcome for this secondary objective. The GFS: Role is a 10-point rating scale for evaluating school and job functioning. This outcome scale has strong psychometric characteristics and the anchors were developed to be appropriate for adolescents and young adults in a large prodromal schizophrenia study, and are especially suited for the younger age group of our young-adult first-episode sample. GFS: Role will be administered at entry, baseline, and every three months throughout the 12-month Treatment period.

7.4.7.2. Cognitive Assessment- The MATRICS Consensus Cognitive Battery

The Overall Composite T-score from the MCCB is a secondary endpoint and will be the overall index of cognitive performance. This battery is the result of the efforts of a national committee of experts to develop a NIMH-recommended battery for evaluation of interventions designed to improve cognition in schizophrenia (Kern et al, 2008; Nuechterlein et al, 2008). By using the MCCB, the results of our attempts to improve cognition in schizophrenia can be directly compared to attempts to do so through pharmacological and other learning-based interventions. The Overall Composite Score summarizes performance across 10 tests of Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning, Visual Learning, Reasoning and Problem Solving, and Social Cognition (Nuechterlein et al, 2008).

7.4.8. Exploratory Endpoint Measurements

The exploratory endpoints of this study are:

- Heinrichs-Carpenter Quality of Life Scale (QLS)
- Personal and Social Performance Scale (PSP)
- Clinical Global Impressions-Severity (CGI-S)
- Scale for the Assessment of Negative Symptoms (SANS)
- Scale to Assess Unawareness of Mental Disorder-Revised (SUMD-R)
- Glasgow Antipsychotic Side-effect Scale (GASS)
- Modified Medication Satisfaction Questionnaire (Modified MSQ)
- Service Engagement Scale (SES)
- Family Caregiver Medication Administration Hassles scale
- Modified Version of the ACD

7.4.8.1. Heinrichs-Carpenter Quality of Life Scale

The QLS is a clinician-rated scale based on a patient's report during a semi-structured interview. It is used to assess health-related quality of life and functioning in patients with schizophrenia during the preceding four weeks (Heinrichs et al, 1984). The QLS consists of 21 items in four major domains (Intrapsychic Foundations, Interpersonal Relations, Instrumental Role, and Common Objects and Activities). Following a semi-structured interview, each item is rated on a 7-point scale, from 0 (severe impairment) to 6 (normal or unimpaired functioning). Reported

inter-rater reliabilities range from 0.84 to 0.97 on the summary scales. The QLS will be completed every three months after the onset of randomized treatment. This measure revealed an advantage for aripiprazole monohydrate compared to paliperidone palmitate for improving quality of life in schizophrenia (Naber et al, 2015). The Intrapsychic Foundations subscale will be the primary one analyzed for this objective. This scale will be completed at the time points specified in Table 2.

7.4.8.2. Personal and Social Performance Scale

The Investigator or designee will complete the 5-point PSP scale (Patrick et al, 2009) at the time points identified in Table 2.

7.4.8.3. Clinical Global Impressions-Severity

The Investigator or designee will complete the CGI-S scale (Guy 1976) at Screening and at the time points as identified in Table 2.

7.4.8.4. Scale for the Assessment of Negative Symptoms

A SANS manual describes each symptom and provides anchor point definitions. Each of the SANS items are scored on a 6-point Likert-type scale (from 0 to 5). The SANS contains 20 items within five domains of negative symptoms: Alogia; Affective flattening; Avolition-Apathy; Anhedonia-Asociality; and Attention. Each group of symptoms has several component items relevant to the assessment of positive symptoms and a global rating. Negative symptoms will be rated during the administration of the SANS and will be based on observations, information provided by the patient, and from all reliable sources of information. The SANS manual contains a set of specific interview questions, supplemented by our group that will be used by the assessment team to elicit reported negative symptoms (eg, impersistence and asociality). This scale will be completed at the time points specified in Table 2.

7.4.8.5. Scale to Assess Unawareness of Mental Disorder-Revised

The SUMD-R will be used to assess insight in the early course of schizophrenia. To reduce the time burden on patients, the SUMD-R has been shortened to include key items found to be the most useful in previous studies. The SUMD-R measures three aspects of insight for each psychiatric symptom: unawareness that the symptom is present, the attribution as to the cause of the symptom, and unawareness of whether others would perceive the symptom as being present. Unawareness of concentration, memory, and speed of processing deficits are also assessed. The Overall Unawareness of Mental Illness item will be the primary one used for this outcome measure. This scale will be completed at the time points specified in Table 2.

7.4.8.6. Glasgow Antipsychotic Side-effect Scale

The GASS scale will be completed by the patient at the time points specified in Table 2.

7.4.8.7. Modified Medication Satisfaction Questionnaire

The Modified MSQ is a 3-item self-report patient satisfaction questionnaire which assesses the level of patient satisfaction with medication. Patients rate their satisfaction with their current medication, their preference for their current medication versus the one taken prior to the study,

and their opinion on the side effects of their current medication versus the one taken prior to the study. Ratings are on a 5-point Likert scale. The Modified MSQ will be collected every six months following randomization. This scale will be completed at the time points specified in Table 2.

7.4.8.8. Service Engagement Scale (SES)

The SES is a 14-item questionnaire to evaluate engagement with clinical services and to evaluate areas of engagement difficulties that might pose obstacles to treatment. The scale has been shown to have good validity and test-retest reliability (Tait et al, 2002; Tait et al, 2018). This scale will be completed at the time points specified in Table 2.

7.4.8.9. The Family Caregiver Medication Administration Hassles Scale

The Family Caregiver Medication Administration Hassles scale is a 24-item scale that identifies hassles and frustrations that occur for family caregivers who are responsible for administering medications to their family members. Four subscales have been identified: Information Seeking/Information Sharing, Safety Issues, Scheduling logistics, and Polypharmacy. The overall scale reliability is 0.95, and the test-retest reliability at 2 weeks is 0.84 (Travis et al, 2003). This scale will be completed at the time points specified in Table 2.

7.4.8.10. Modified Version of the All-Cause Discontinuation

A modified version of the ACD measure used in the CATIE schizophrenia study will be used to track the reasons for medication changes. The modification of this measure pertains to the addition of further nuances in the decision-making process.

7.4.9. Safety Assessments

7.4.9.1. Overview of Safety Assessment Procedures

Each patient will have a treating psychiatrist who is a part of the clinical team for UCLA Aftercare Research Program. The psychiatrist will be responsible for the medical and psychopharmacologic management of patients. The one-on-one medication assessment appointments are scheduled at least monthly, and may be more frequent as per the clinical status and needs of the individual patient. The treating psychiatrists have specialty practice experience in schizophrenia and psychotic disorders, and will be trained in all of the ongoing safety assessments for the study, including:

- Extrapyramidal symptoms (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], and the Extrapyramidal Symptom Rating Scale [ESRS-A])
- Columbia Suicide Severity Rating Scale (C-SSRS)
- AE collection
- Serious adverse event (SAE) reporting

The treating psychiatrists also attend the UCLA Aftercare Research Program weekly case conferences where the entire clinical team, including the clinical assessors, meets to review the clinical status of all patients in the program. Patients will be reviewed for any SAEs or other

clinical changes on a weekly basis. However, the BPRS assessments that are the basis of the relapse criteria are not specifically reviewed within the case conferences, but salient clinical information gleaned from the biweekly BPRS ratings will be shared at that time and will be used along with all other relevant clinical information for further medication management and patient treatment decisions.

Semi-annual review of all safety assessment responses will be conducted by a Data and Safety Monitoring Committee at UCLA who are not study investigators per the UCLA IRB standards.

7.4.9.2. Extrapyramidal Symptoms

Extrapyramidal Symptom Scales will include AIMS, BARS, and ESRS-A. The Investigator or designee will administer the extrapyramidal symptom scales at time points specified in Table 2.

After administration of the first dose of study drug, if a patient complains of extrapyramidal symptoms (EPS) on days when the abnormal movement scales are not scheduled to be performed, an unscheduled assessment should be performed.

The AIMS will primarily be used to assess dyskinesia. The BARS will primarily be used to assess akathisia. The ESRS-A will primarily be used to assess Parkinsonism and dystonia.

7.4.9.3. Columbia Suicide Severity Rating Scale

The Investigator or designee will administer the C-SSRS according to the schedule in Table 2. At Screening, the "Baseline/Screening" version will be administered (Mundt et al, 2013; Posner et al, 2009; Posner et al, 2011), and at all other visits, the "Since Last Visit" version will be administered (Posner K et al, 2009). For "Since Last Visit" versions, patients should be asked to report on ideation and behavior since the last scheduled C-SSRS assessment. The C-SSRS will be administered by a clinician trained to assess and manage suicidal ideation and behavior.

7.4.9.4. Laboratory Assessments

7.4.9.4.1. Drug Testing

A urine drug test for drugs of abuse, including amphetamines, barbiturates, cocaine, methamphetamine, opiates, and phencyclidine will be performed at the time points specified in Table 2. Results must be negative, or if positive, there must be additional evidence that the abuse is not persistent and will not make treatment in this outpatient program contraindicated.

7.4.9.4.2. Hematology, Biochemistry, Metabolic, and Prolactin Assessments

Blood and urine samples for laboratory assessments will be collected at the time points specified in Table 2. Specific hematology, biochemistry, metabolic, and prolactin assessments are listed in Table 4. Samples will be collected in accordance with the site's usual procedures at the UCLA Department of Pathology phlebotomy station on the first floor of the 200 UCLA Medical Plaza building next door to the Aftercare Research Program, thereby facilitating convenient blood drawing for laboratory tests.

Table 4: Clinical Laboratory Assessments

Hematology	Biochemistry
Hematocrit Hemoglobin Red blood cell count Total and differential (absolute) white blood cell count Platelets	Sodium Potassium Glucose Creatinine Total protein Blood urea nitrogen Albumin Total bilirubin Alanine transferase Aspartate transferase Lactic dehydrogenase Gamma-glutamyl transferase Alkaline phosphatase Creatinine phosphokinase A1c Blood sugar Fasting lipid panel Prolactin

7.4.9.4.3. Plasma Aripiprazole Concentrations

Plasma samples will be collected at the visits indicated in Table 2 and will be kept for measurement of aripiprazole concentrations in plasma assays. The clinicians will not be updated on the outcome of the measurement.

7.4.9.4.4. Pregnancy Testing

A serum pregnancy test will be conducted at Screening and at the last study visit for all women. A urine pregnancy test will be administered to all women every 3 months during the Treatment period, as specified in Table 2. At the Screening visit, results must be negative for the patient to be eligible for the study.

7.4.10. Vital Signs

Vital signs (i.e., blood pressure, pulse, respiratory rate, and oral body temperature) will be assessed at the time points specified in Table 2. Blood pressure, pulse, and respiratory rate will be measured after the patient has been resting in a seated or supine position for at least five minutes.

7.4.11. Physical Examination, Body Height, Weight

A physical examination will be performed at the time points specified in Table 2.

7.4.12. Adverse Event Monitoring

Continuous monitoring of AEs will take place from the time a patient signs the informed consent document until the completion of the final study visit. Additional information on the assessment of safety is provided in Section 11.

7.4.13. Randomization

Randomization will occur after the Stabilization period in a 1:1 ratio by an automated method at UCLA. Patients successfully completing the Stabilization period will be randomized to one of two medications groups: converting from oral antipsychotic to AL-LAI vs continuing on (ARI ORAL). Each medication group will be further randomized to the cognitive remediation or healthy behavior training condition. Patients do not need to be free of psychosis at the time of randomization and the severity of psychosis is not a variable for stratification.

7.5. Study Requirements and Restrictions

Prohibited medications are defined in Section 7.5.1. Other restrictions are outlined in the Exclusion Criteria (Section 6.2). If at any point a patient is no longer eligible per the entry criteria, they will be discontinued from the study.

7.5.1. Prohibited Medications and Restricted Concomitant Medications

Prohibited mediations and restrictions are detailed in Table 5. Refer to the prescribing information for the study drug (Abilify USPI ; Aristada USPI ; Initio USPI) and each concomitant medication for interactions and dose restrictions.

Concomitant use of potent oral CYP3A4 inhibitors **and** CYP2D6 inhibitors is to be avoided. In addition, patients with known CYP2D6 poor metabolism should not receive strong oral CYP3A4 inhibitors during the study. During the study, dose adjustment may be necessary in the event of use of potent oral CYP2D6 inhibitor, or a CYP3A4 inhibitor or inducer. For example, the use of CYP3A4 inducers may require dose escalation. Investigators should consult the prescribing information for questions regarding any such dose adjustments.

Table 5: Prohibited Medications: Pre- and Post-randomization

Class (medication)	Prescribed before randomization	Started Post-randomization
Antipsychotics		
Other first-line oral antipsychotic	all prior (non-aripiprazole) antipsychotics must be discontinued within 2 weeks prior to the Randomization visit	Not allowed[123]
Clozapine	Not allowed	Not allowed
Other long-acting injectables	Not allowed	Not allowed
Antidepressants		

Class (medication)	Prescribed before randomization	Started Post-randomization
	Generally allowed but sertraline (Zoloft®), citalopram (Celexa®) or escitalopram (Lexapro®) preferred	Sertraline (Zoloft®), citalopram (Celexa®) or escitalopram (Lexapro®) preferred
Mood Stabilizers (Starting mood stabilizer not encouraged)		
Lithium carbonate	Allowed	Allowed
Lamotrigine	Allowed	Allowed
Valproate	Allowed for men Not allowed for women	Allowed for men Not allowed for women
Carbamazepine/oxcarbazapine	Not allowed	Not allowed
Anti-anxiety medications		
Lorazepam PRN anxiety/insomnia	Allowed	Allowed[4]
Lorazepam standing	Allowed	Allowed
Clonazepam PRN	Not allowed	Not allowed
Clonazepam standing	Allowed[5]	Allowed
Alprazolam	Not allowed	Not allowed
Diphenhydramine (for insomnia)	Allowed[6]	Allowed
Anti-EPS and anti-akathisia		
Propranolol (akathisia only)	Allowed	Allowed/preferred
Lorazepam (akathisia or acute dystonia only)	Allowed	Allowed
Benztropine (antipsychotic-induced parkinsonism)	Allowed	Allowed
Diphenhydramine (akathisia and acute dystonia only)	Allowed	Allowed
ADHD therapies		
Methylphenidate-based ADHD treatments	Allowed with review	Not allowed
Amphetamine-based ADHD treatments	Not allowed	Not allowed

Abbreviations: PRN= as needed; ADHD= Attention-deficit/hyperactivity disorder; EPS= Extrapyramidal symptoms

[1] For patients in the ARI-ORAL arm, dose increases for persistent symptoms and/or symptom exacerbations is permitted. However, prescribing another non-aripiprazole oral antipsychotic for "rescue" medication will be criteria for stopping the treatment assignment.

[2] For patients in the AL-LAI arm, ARI-ORAL for ≤ 2 weeks will be allowed for transient exacerbations that are deemed to be caused by external stressors. ARI-ORAL prescribed for > 2 weeks will be criteria for AL-LAI failure
[3] Patients receiving up to 2 days of oral or short acting antipsychotic IM medication because they presented to an ER or crisis facility outside of the UCLA program will not be criteria for discontinuation of treatment assignment
[4] Maximum 4mg day Total Daily Dose (TDD)
[5] Maximum is 3mg/day Total Daily Dose (TDD)
[6] Max 100mg

7.5.2. Contraception and Pregnancy

All male and female patients must agree to use an acceptable method of contraception for the duration of the study and 30 days after the final dose of oral study drug, and 90 days following the final dose of long-acting injectable antipsychotic unless they are surgically sterile or postmenopausal (see below). The following are considered acceptable methods of contraception:

1. Double-barrier protection (eg, a condom with spermicide or a diaphragm with spermicide)
2. Intrauterine device
3. Oral contraceptive pills or other hormonal methods (eg, a vaginal ring, contraceptive patch, contraceptive implant); oral contraceptives should have been initiated at least 30 days prior to Screening.

Patients who are abstinent are eligible, provided they agree to use an acceptable contraceptive method should they become sexually active.

Patients who are surgically sterile are exempt from the requirement to use contraception. Women who have undergone a hysterectomy, bilateral tubal ligation, or bilateral salpingo-oophorectomy are considered surgically sterile. Men who have undergone a vasectomy or bilateral orchiectomy are considered surgically sterile. Partner vasectomy is not considered an approved acceptable method of contraception for a female patient.

If a patient becomes pregnant while participating in the study, she will be promptly discontinued from study drug. Pregnancy is not considered an AE, however pregnancy, whether a female study patient or the partner of a male study patient, must be immediately documented on a Pregnancy Form and reported to Alkermes, Inc., within 24 hours of the Investigator becoming aware of the pregnancy as outlined in Section 11.3. Additional follow-up may be required.

The pregnancy will be followed until completion or termination, if feasible. If the outcome of the pregnancy meets the criteria for classification as a SAE it should be reported following the SAE procedure (Section 11.3).

8. TREATMENT OF PATIENTS

Each patient will be provided a prescribing psychiatrist and a case manager/therapist to monitor clinical status and provide treatment. Study visits will occur weekly at Screening and Stabilization period, and then every two weeks throughout the 12-month randomized Treatment period (at each clinical visit and between each clinical visit). The total study duration for each patient will be approximately 70 weeks, including a Screening period (up to four weeks), up to 90-day Stabilization period, and a 12-month randomized Treatment period.

If the patient is not already on ARI-ORAL at Screening, any prestudy oral antipsychotic medication can begin to be tapered off during the Stabilization period, while ARI-ORAL is initiated. During the Stabilization period, all patients will receive flexible dosing of ARI-ORAL. Patients who find ARI-ORAL intolerable during the Stabilization period will not be randomized.

8.1. Study Drug Dose and Administration

During the 12-month Treatment period, patients who tolerate the study medication but find that after adequate duration and dosage, it is inadequately efficacious per clinical judgment, may be switched to another oral antipsychotic at the discretion of the Investigator. Patients who miss scheduled injections or visits are allowed to continue in the same assigned treatment group.

8.1.1. AL-LAI and AL-NCD Administration

Refer to the prescribing information for AL-NCD administration (Initio USPI). Administer 675mg AL-NCD in either the deltoid or gluteal muscle.

Refer to the prescribing information for AL-LAI administration (Aristada USPI). In summary, administer AL-LAI either in the deltoid muscle (441 mg dose only) or gluteal muscle (441 mg, 662 mg, 882 mg or 1064 mg) (Table 6). Clinical staff administering AL-LAI will be licensed to give IM injections in the state of California and will be trained and certified on proper injection technique for AL-LAI and AL-NCD administration.

Table 6: AL-LAI Dosing Frequency and Site of Injection

Dose	Dosing Frequency	Site of Intramuscular Injection
441 mg	Monthly	Deltoid or Gluteal
662 mg	Monthly	Gluteal
882 mg	Monthly or every 6 weeks	Gluteal
1064 mg	Every two months	Gluteal

Refer to the current prescribing information for ARISTADA for the recommended starting dose based on ARI-ORAL total daily dose, handling of missed doses of AL-LAI, early dosing of AL-LAI and dose adjustments for CYP450 considerations for AL-LAI (Aristada USPI).

Schedule changes, from monthly to every six weeks (or the reverse) will also be allowed after the second injection. Dose changes due to the medical need to initiate concomitant CYP modulators may be performed at any time if the concomitant medication is necessary for more than two weeks.

8.1.2. ARI-ORAL Drug Dose and Administration

Patients in the ARI-ORAL group will receive vouchers that will need to be given to the pharmacy at the time that the study oral antipsychotic medication is first dispensed. When ARI-ORAL is prescribed, the generic formulation will be prescribed, instead of the commercially available Abilify® brand. This voucher will have instructions for the pharmacy to bill Alkermes directly for the medication. Pharmacy billing will also be captured by Alkermes and shared with the study team for use as medication possession data, which will be an additional source of information used to make medication adherence ratings for the ARI-ORAL group patients.

8.2. Measurement of Medication Treatment Adherence

All study drug injections will be directly administered by clinical study staff. The date, time, dosage, and location of each injection will be recorded by the clinical staff. Study staff will address non-adherence with the patient as needed.

Adherence to oral medication will be rated by a team of research assistants who will not inform the clinical team of their ratings or determinations. The oral antipsychotic medication adherence ratings will rely primarily on pill counts. Patients will be asked to bring their pill bottles to clinic appointments, for pills to be counted by a separate, nonclinical staff. Medication poss++ession information will be captured through the pharmacy voucher billing and used as an additional source of information in the all sources consensus adherence ratings. Adherence ratings will be a consensus rating based on all sources of information (pill counts, plasma assays, patient self-report, clinician judgment based on the occurrence or change in side effects, family or caregiver collateral information, and pharmacy billing). Retroactive changes to the all sources consensus adherence ratings based on new information is allowed. No changes will be made to the quantitative pill counts based on changes in the patient or caregiver reports. Oral medication adherence will also be tracked in this way for any other oral antipsychotic medications if the initially assigned ARI-ORAL medication needs to be switched.

8.3. Study Drug Dose Adjustment and Stopping Rules

8.3.1. Aripiprazole Prospective Tolerability Screening

After Screening but before Randomization (Stabilization period), the patient's current and past medication history will be reviewed carefully. Patients with current or prior exposure to oral aripiprazole meeting criteria of a reliable history at least two weeks given at >10 mg day for a two-week period will be assessed for their efficacy and tolerability to aripiprazole.

Tolerability path will involve flexibly dosed aripiprazole prescribed ≥ 2 weeks. Patients will be eligible for Randomization upon completing this (and other) required screening procedures.

8.3.2. Cross-Over from Other Oral Antipsychotics

For patients on other [non-aripiprazole] oral antipsychotics, the clinician and patient can choose a cross-taper switch plan ranging from immediate discontinuation to a delayed cross-over during Stabilization period.

8.3.2.1. Other Concomitant Medications

Most adjunctive psychotropic medications can be continued during the cross-over and after the cross-over. Patients receiving anti-EPS or anti-akathisia medications will have these medications continued for at least 30 days and then will be evaluated for possible taper and discontinuation if the patient has been on ARI-ORAL for ≥ 30 days without EPS or akathisia.

8.3.3. Treatment for Patients Randomly Assigned ARI-ORAL

8.3.3.1. Starting Dose of ARI-ORAL

The recommended starting dose for ARI-ORAL should be determined per the prescribing information (Abilify USPI). Patients will start ARI-ORAL as soon as possible, after filling their ARI-ORAL prescription at the local pharmacy. The reasons for dosage changes will be documented.

8.3.4. Treatment for Patients Randomly Assigned to AL-LAI

8.3.4.1. Starting dose of AL-LAI

The recommended starting dose for AL-LAI should be determined per the prescribing information (Aristada USPI).

8.3.4.1.1. Initiation Regimen

The preferred method of initiating AL-LAI is the one-day initiation regimen consisting of a single-dose injection of 675 mg AL-NCD IM plus a single 30 mg oral aripiprazole.

8.3.4.1.2. Exceptions to the One-day Initiation Regimen

The alternative to the one-day initiation regimen is prescribing 21-days of oral aripiprazole in conjunction with the first injection of AL-LAI. This method will be allowed but needs to be documented, with reasons including:

1. Presence of genetic or drug-drug interactions regarding CYP interactions that exclude one-day initiation regimen
2. Patient refusal to accept the one-day initiation regimen (but agrees to accept the AL-LAI starting dose during the same visit)

8.3.4.1.3. Timing of the First AL-LAI Treatment

When starting with the one-day initiation regimen, the starting dose of AL-LAI can be given within 60 minutes of AL-NCD. Patients will also be asked to take the 30 mg aripiprazole tablet with the injections, but clinicians will have the option of giving the oral dose to the patient to be taken at bedtime if the patient has family members willing to supervise.

8.3.5. Does Adjustments

8.3.5.1. ARI-ORAL Dose Adjustments

Dose adjustments of ARI-ORAL should be made per prescribing recommendations (Abilify USPI).

8.3.5.2. AL-LAI Dose Adjustments

Patients who have successfully received three or more monthly AL-LAI without significant tolerability problems will be eligible to change to a 1064 mg/two month interval regimen. Dose adjustments should be made per prescribing information (Aristada USPI). The following are also required to dose adjust:

- Patient request with clinician assent
- Clinician recommendation

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Storage

Study drug must be stored in a locked area at 20°C to 25°C (68°F to 77°F); excursions between 15°C and 30°C (59°F and 86°F) are permitted.

Note that AL-NCD has a specific instruction "Do not freeze" on its packaging.

9.2. Handling of Study Drug

9.2.1. AL-LAI Medication Group

AL-LAI and AL-NCD will be provided by Alkermes, Inc. and should be shipped to:

UCLA Investigational Drug Pharmacy

Ronald Reagan UCLA Medical Center

Dept. Of Pharmaceutical Services

662 Gayley Ave., B1-504A

Los Angeles, CA 90095

Phone Number: 310-267-8522

AL-LAI and AL-NCD will be stored and dispensed by the UCLA Investigational Drug Pharmacy. Both will be stored in a locked cabinet after it is dispensed up until the time of injection.

9.2.2. ARI-ORAL Medication Group

The ARI-ORAL group will be given paper or electronic prescriptions, or the prescription may be telephoned to, or faxed to, the pharmacy of the patient's choice. Prescriptions will typically be for 30 day supplies, unless otherwise indicated by the treating psychiatrist. Side-effect medications, such as anti-parkinsonians, beta-blockers, and benzodiazepines will also be billable through the voucher system. The patient will be provided a payment coupon that s/he will present to the pharmacy. The payment coupon will direct the pharmacist to Alkermes for reimbursement. Subsequent refills will not require a new coupon. Patients will be seen by the Aftercare Research Program clinical team every two weeks. This prescribing routine as outlined for this study is consistent with standard pharmacologic treatment for patients in clinical care at the same site who are prescribed oral antipsychotic medication.

Deliberate over-prescribing or stockpiling is not permitted. Patients who are discontinuing ARI-ORAL will be allowed to overlap antipsychotic for a maximum of one month; otherwise co-prescribing two oral antipsychotics is not allowed.

10. ASSESSMENT OF EFFICACY

10.1. Primary Endpoint

10.1.1. Primary Endpoint Measurements

The primary endpoint will be time to first positive symptom exacerbation and/or relapse following a period of relative remission of psychotic symptoms based on expanded 24-item version Brief Psychiatric Rating Scale (BPRS) (published UCLA relapse criteria (Nuechterlein et al, 2006) that are summarized in Section 7.4.6.

10.1.2. Primary Endpoint Rationale

The expanded BPRS (Ventura et al, 1993) will be rated every two weeks, with each item rated from 1 (not present) to 7 (extremely severe). Positive symptom exacerbation or relapse will be identified based on increases of the BPRS items Unusual Thought Content, Hallucinations, or Conceptual Disorganization using computer scoring algorithms (Nuechterlein et al, 2006). The three scoring categories considered to be a psychotic symptom return are: "Remission Followed by Relapse", "Remission Followed by Significant Exacerbation", or "Persisting Symptoms Followed by Significant Exacerbation." These definitions do not consider other aspects of outcome often part of "treatment failure" definitions, such as: hospitalization or increased treatment to prevent hospitalization; harm to self, others, or property; arrest; or treatment discontinuation, as these other negative outcomes might not be secondary to psychotic symptoms per se. These classifications have been shown to be sensitive measures of the return of psychotic symptoms and differentiated oral and long-lasting injectable treatment groups in our previous research (Subotnik et al, 2015). Patients in the proposed study will continue in the protocol even if a psychotic relapse or exacerbation occurs, although the medication regimen might change at the discretion of the Aftercare Research Program treating psychiatrist. Our experience has been that the majority of psychotic exacerbations or relapses can be managed on an outpatient basis unless the patient has concurrent imminent suicidality, and often the prescribed medication does not change (although the dosage might). Continuing patients in the protocol after a return of symptoms will allow us to assess secondary outcomes at the 6- and 12-month points.

10.2. Secondary Endpoints

10.2.1. Secondary Endpoint Measurements

The secondary endpoints of this study are:

- GFS: Role
- Overall Composite T-score MCCB

10.3. Exploratory Endpoints

10.3.1. Exploratory Endpoint Measurements

The exploratory endpoints of this study are:

- Heinrichs-Carpenter QLS

- PSP
- CGI-S
- SANS
- SUMD-R
- GASS
- Modified MSQ
- SES
- Family Caregiver Medication Administration Hassles scale
- Modified Version of the ACD

11. ASSESSMENT OF SAFETY

11.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient who has been administered a pharmaceutical product. The occurrence may or may not have a causal relationship with the investigational treatment, may include any clinical or laboratory change that does not commonly occur in that patient and is considered clinically significant.

Pregnancy is not considered an AE, although a patient will be withdrawn from the study if a pregnancy occurs. The pregnancy, including a partner's pregnancy, must be reported to Alkermes, and additional follow-up may be required.

11.2. Definition of Serious Adverse Events

An SAE is any AE, occurring at any dose and regardless of causality, that:

- Results in death
- Is life-threatening. The patient is at immediate risk of death from the reaction as it occurs. This does not include reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (eg, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be immediately life threatening, or require hospitalization may be considered to be SAEs when, based upon appropriate medical judgment, may jeopardize the patient and may require intervention to prevent one of the other outcomes listed above.

Admission to a hospital or an inpatient unit for a non-medical reason (i.e., social stay admission) during the study in the absence of untoward medical occurrence will not be considered as an SAE.

Hospitalization due to worsening of behavioral health related issues should be reported as an SAE.

11.3. Reporting of Serious Adverse Events and Pregnancy

Investigator is responsible for timely reporting of Adverse Drug Experiences, Serious Adverse Drug Experiences and pregnancy in a Study patient to the Food and Drug Administration (FDA), Institutional Review Board (IRB), data safety monitoring board, Institution, grant agency, etc. as applicable to the Study and according to FDA, Institution and/or grant agency guidelines and procedures.

12. STATISTICS

12.1.1. Sample Size Considerations

Ninety first-episode patients will be randomized (1:1) fashion to either AL-LAI or ARI-ORAL, and based on our previous RCT, assume a 20% attrition rate over 12 months. Statistical power considerations are based on the effect sizes observed when comparing long-acting injectable risperidone vs. oral risperidone (survival analysis for psychotic relapse: 5% relapse in the risperidone long-acting injectable group and 33% relapse in the oral risperidone group). On the basis of hazard function rates of 5.0% (AL-LAI) and 33% (ARI-ORAL), the study has 87% power (α=0.05). On a more conservative basis of hazard function rates of 7.5% (AL-LAI) and 33% (ARI-ORAL), the study has 78% power (α=0.05) (Table 6).

For the secondary hypothesis for the relative changes in the MCCB Composite score and the GFS: Role, we will use a two-sided significance level of α=.025 to account for type 1 error inflation. For the MCCB Composite score, assuming a within-patient correlation between repeated measurements of r=0.89 (based on a prior study), the proposed design provides us sufficient power (>=0.80) for Group X Time interaction effects as small as Cohen's f=0.09. Based on our previous work, we anticipate a medium effect size (Cohen's f=0.25 or d=0.50), and this design provides a power of >0.99 for an effect of this size. For the GFS rating, if we assume a within-patient correlation of r=0.5, with α=0.025, our GLMM will have 80% power to detect an interaction corresponding to an effect size of f=.20. Based on a prior study, we anticipate an effect size of f=0.32 or d=0.63 for the GFS: Role ratings, for which we would have >99% power.

Thus, for both primary and secondary outcome measures we will be able to detect differential treatment effects based on our proposed design and expected sample size.

Table 7: Power Calculations by Analysis with N=35 Each Group (N=28 at completion)

Clinical assumption for each group			Power	Alpha
Primary Analyses	Hazard ratio between the two groups	Difference in hazard functions similar to that of our previous RCT: Long-acting injectable: 5%, oral antipsychotic: 33%	87%	.05
		For rates of hazard function rates of 7.5% (AL-LAI) and 33% (ARI-ORAL)	78%	
Secondary Analyses: MCCB Overall Composite score	change from BL in MCCB Overall Composite score	Based on our previous work, we anticipate a medium effect size (Cohen's f=.25 or d=.50)	>99%	.025
Secondary Analyses: GFS Role Functioning	Change from BL in GFS Role Functioning	Based on a prior RCT, we anticipate an effect size of f=.32 or d=.63 for the GFS: Role ratings.	>99%	.025

12.2. General Statistical Methodology

12.2.1. Intent-to-Treat Population

The Intent-to-treat (ITT) population will include all patients in the AL-LAI group who received at least one dose of AL-LAI, and all patients in the ARI-ORAL antipsychotic medication group who filled at least one prescription of ARI-ORAL after random treatment assignment. This population will be used for efficacy and safety analyses.

12.2.2. Medication Adherence as a Dimension

The measurement of medication adherence (see Section 8.2) will allow analyses within the oral medication group, as well as within the total combined sample, to examine the relationship of the variables of interest with degree of medication adherence.

12.3. Demographics and Baseline Data

Demographics and baseline characteristics such as gender, age, race, weight, height, and body-mass index will be summarized using descriptive statistics. Medical history will be summarized using the number of observations and percentage of patients reporting each category. Concomitant medications as well as any protocol deviations will be recorded.

12.4. Efficacy Analysis

The primary hypothesis, that the hazard function (i.e. the risk of an event per unit of time) of the two medication groups differs between AL-LAI than the ARI-ORAL group, will be examined in a Cox regression analysis on the time to first relapse. We will include medication group membership, participation status in the NIMH exercise study, and length of stabilization period as predictors in the model.

For the secondary hypotheses involving the MCCB composite score, the GFS: (Role) we will use general linear mixed models (GLMMs). We will include participation status in the NIMH exercise study, medication group as a between-patient variable and time as a within-patient

variable in the model, and time*group as a within-between interaction term. Additionally, we will include length of stabilization period as person level time invariant covariate. The primary effect of interest is the difference in the pattern of change over time of the dependent variable between the medication groups, i.e. the time*group interaction term. GLMMs properly account for correlations induced by repeated measurements within patients and automatically handle missing data, producing unbiased estimates as long as observations are missing at random. The GLMM will use Satterthwaite's approximation to estimate degrees of freedom for the tests of the fixed and random effects, and model the variance-covariance matrix as a Toeplitz matrix. If this assumption does not lead to convergence we will instead use compound symmetry. The secondary analyses will compare the change in the MCCB Composite score and GFS: (Role) ratings between the two medication groups over the 12-month study period.

The data analyses for the exploratory measures will parallel those of the secondary measures.

All statistical tests and confidence intervals, unless stated otherwise, will be two-sided and will be set at $\alpha=0.05$.

12.5. Safety and Tolerability Analyses

The following safety and tolerability measures monitored throughout the study and summarized:

- AEs
- EPS Scales (AIMS, BARS, and ESRS-A)
- Presence of akathisia
- C-SSRS

13. ETHICAL CONSIDERATIONS

13.1. Ethics Review

The study, the informed consent procedures, and the informed consent form (ICF) must be approved by the UCLA IRB prior to enrolling patients into the study. The Investigator is responsible for submitting all protocol changes and SAE reports to the IRB according to local procedures. At a minimum, all SAEs requiring an investigational new drug safety report must be immediately reported according to IRB requirements.

13.2. Ethical Conduct of the Study

This study will be conducted in accordance with the protocol and all applicable local regulatory requirements. UCLA is committed to assuring that the rights, safety, and well-being of study patients will be protected, consistent with the principles having their origin in the Declaration of Helsinki.

13.3. Written Informed Consent

Each prospective patient (or the patient's legal representative) will be given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the study. Each prospective patient will receive an IRB-approved ICF that summarizes the pertinent study information and will be given ample time to read the form and ask questions about the study. All information is to be provided in a language understandable to the patient and must not include any language that waives the patient's legal rights. Prospective patients must also be informed of their right to withdraw consent without prejudice at any time during the study. If the patient chooses to participate, he or she must sign the ICF before any study-specific procedures are conducted. The Investigator must maintain the original signed ICF in the patient's source documents. A copy of the signed ICF must be given to the patient.

Significant changes to the protocol or product safety information may require a revision of the ICF, which must be reviewed and approved by the IRB. The revised ICF will be signed by current patients for who the significantly revised procedures and risks apply.

14. DATA HANDLING AND RECORD KEEPING

Quality control of data, protocol deviation process, data monitoring and auditing will be UCLA standard operating procedures and/or IRB requirements.

14.1. Data Capture

The Semel Institute Biostatistics Core (SIStat) will be responsible for study data management, storage, and statistical analysis. SIStat has developed and maintains a centralized database for the PI's projects that is available on a secure, password-protected dynamic website on the Internet. All systems are on the UCLA network and reside behind the UCLA School of Medicine (Mednet) firewall. All the SIStat servers have 128-bit SSL certificates installed to provide security for transmission of any sensitive or confidential data. Administrative control is built into the databases by establishing password-protected classes of users with access privileges appropriate to their study roles. The systems support both manual entry and electronic upload of data generated by external sources. Use of a centralized LAN makes the data instantly available to all authorized researcher personnel. Data or summary reports are immediately available for viewing and automatically "updated" as the database changes. Extensive JavaScript-based validity checking is built in to maximize data quality.

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