CLINICAL STUDY PROTOCOL

ALK9072-A306

Study title:	A Phase 3b, Multicenter, Randomized, Double-blind Study to Evaluate the Efficacy and Safety of Aripiprazole Lauroxil or Paliperidone Palmitate for the Treatment of Schizophrenia in Subjects Hospitalized for Acute Exacerbation
Document date:	v 2.0 (incorporates Amendment 1.0): 04 Jan 2018 Original Protocol: 24 Aug 2017
Sponsor:	Alkermes, Inc. 852 Winter Street Waltham, MA 02451 USA

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PROCEDURES IN CASE OF EMERGENCY

Table 1: Study Contact Information

Role in Study	Name	Address and Telephone Number
Alkermes Medical Monitor	PPD	Alkermes, Inc. 852 Winter Street Waltham, MA 02451 USA Office: PPD Mobile: PPD
Alkermes Global Safety Officer	PPD	Alkermes, Inc. 852 Winter Street Waltham, MA 02451 USA Office: PPD PPD
CRO Medical Monitor and 24-Hour Emergency Contact	PPD	PPD Raleigh, NC 27604 USA Office: PPD Mobile: PPD PPD 24-hour Emergency Hotline: PPD
CRO Unblinded Medical Monitor	PPD	PPD PPD Raleigh, NC 27604 USA Office: PPD PPD
SAE and Pregnancy Reporting	PPD Drug Safety	Email: PPD Phone Number: PPD FAX Number: PPD

Abbreviations: CRO=contract research organization; SAE=serious adverse event

2. SYNOPSIS

Name of Sponsor/Company: Alkermes, Inc.

Name of investigational product: aripiprazole lauroxil (AL; ARISTADA®), aripiprazole lauroxil NanoCrystal® Dispersion (AL-NCD)

Name of active ingredient: aripiprazole lauroxil

Title of study: A Phase 3b, multicenter, randomized, double-blind study to evaluate the efficacy and safety of aripiprazole lauroxil or paliperidone palmitate for the treatment of schizophrenia in subjects hospitalized for acute exacerbation

Investigator(s): This study will be conducted at multiple sites in the United States.

Study period (years):	**Phase of development:**
Estimated date first patient enrolled: November 2017 (First Subject First Visit) Estimated date last patient completed: August 2019 (Last Subject Last Visit)	Phase 3b

Objectives:

Primary:

- To evaluate the efficacy of AL-NCD initiation regimen (30 mg oral aripiprazole + 662 mg AL-NCD intramuscular [IM]) followed by AL 1064 mg IM during the first 4 weeks of treatment of patients hospitalized for an acute exacerbation of schizophrenia.

Secondary:

- To compare the efficacy of AL-NCD initiation regimen followed by AL 1064 mg IM with paliperidone palmitate initiation dosing (PP; Invega® Sustenna®; 234 mg + 156 mg IM) during the first 4 weeks of treatment of patients hospitalized for an acute exacerbation of schizophrenia
- To evaluate the safety, efficacy, and tolerability of AL 1064 mg IM after 6 months of treatment with AL for schizophrenia
- To compare the safety, efficacy, and tolerability of AL 1064 mg IM with monthly PP 156 mg IM after 6 months of treatment with AL or PP for schizophrenia

Exploratory:

- To characterize subject and caregiver centered outcomes, such as quality of life, work readiness, satisfaction with medication, resource utilization, and caregiver burden after 6 months of treatment with AL or PP for schizophrenia

Methodology: This is a multicenter, randomized, double-blind study evaluating the efficacy and safety of AL and PP in approximately 180 subjects experiencing an acute exacerbation of schizophrenia. In total, subjects will participate for approximately 26 weeks, including up to 1 week of inpatient screening and 25 weeks of treatment (which includes an initial 2-week inpatient stay). Potential subjects will be evaluated for eligibility according to the inclusion and exclusion criteria at a Screening visit (up to a 7 day period) and Baseline visit prior to randomization. Prior antipsychotic medications should be discontinued after screening upon inpatient admission. Subjects will be randomized to either the AL Treatment Group or the PP Treatment Group and receive dosing with AL or PP.

Number of subjects planned: Approximately 180 subjects (90 subjects per group)
Main criteria for inclusion: Men and women 18 through 65 years of age (inclusive) with a diagnosis of schizophrenia, who are experiencing an acute exacerbation or relapse of symptoms requiring hospitalization with onset less than 2 months prior to screening may be eligible for this study. Subjects must be willing and able to be confined to an inpatient study unit for up to 3 or 4 weeks (clinically dependent).
Investigational product, dosage, duration, and mode of administration: Aripiprazole lauroxil (AL) is a covalent non-ester modification of aripiprazole to form *N*-lauroyloxymethyl aripiprazole. The AL drug product is a white to off-white aqueous extended-release suspension for IM provided as single-use prefilled syringes (PFS) in a dose strength of 1064 mg every 2 months. Aripiprazole lauroxil NanoCrystal Dispersion (AL-NCD) is an alternative formulation of AL designed to provide faster dissolution than the AL formulation and is provided in single-use PFS containing a dose strength of 662 mg. Aripiprazole lauroxil NanoCrystal Dispersion (AL-NCD) is intended as a starting dose to initiate treatment with AL. For subjects with no history of tolerated exposure to aripiprazole, oral test doses will be commercially available aripiprazole 5 mg tablets, provided in commercial packaging provided to the site by Alkermes. Oral aripiprazole for use in dose initiation will be aripiprazole 30 mg tablets (overencapsulated to maintain study blind), which will be provided in bottles to the site by Alkermes. On Day 1, subjects randomized to the AL Treatment Group will receive 662 mg AL-NCD (single IM gluteal injection) plus IM placebo (PBO; single IM deltoid injection) plus a 30 mg oral aripiprazole tablet. On Day 8, subjects will receive AL 1064 mg (single IM gluteal injection) plus IM PBO (single IM deltoid injection). On Days 64 and 120, subjects will receive AL 1064 mg (single IM gluteal injection), and on Days 36, 92, and 148 will receive IM PBO (single IM gluteal injection).
Reference therapy, dosage, duration, and mode of administration: Paliperidone palmitate is available as a white to off-white aqueous extended-release injectable suspension for IM injection provided as a single-use PFS in dose strengths of 156 mg and 234 mg. For subjects with no history of tolerated exposure to risperidone or paliperidone, risperidone for use as oral test doses will be commercially available risperidone 1.0 mg tablets, provided in commercial packaging provided to the site by Alkermes. Oral PBO for use in dose initiation will be empty gelatin capsules that visually match the overencapsulated aripiprazole 30 mg tablets (to maintain study blind), which will be provided in bottles to the site by Alkermes. On Day 1, subjects randomized to the PP Treatment Group will receive PP 234 mg (single IM deltoid injection) plus IM PBO (single IM gluteal injection) plus an oral PBO tablet. On Day 8, subjects will receive PP 156 mg (single IM deltoid injection) plus IM PBO (single IM gluteal injection). Subjects randomized to the PP Treatment Group will receive PP 156 mg (single IM gluteal injection) on Days 36, 64, 92, 120, and 148.
Duration of study: The overall study duration is approximately 26 weeks and includes up to 1 week of inpatient screening and 25 weeks of treatment (which includes an initial 2-week inpatient stay post randomization/baseline).

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint:

- Change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score at Week 4 (within treatment groups)

Secondary efficacy endpoints:

- Change from baseline in PANSS total score at Week 4 (between treatment groups)
- Change from baseline in PANSS total score at Week 9 and Week 25 (within treatment groups)
- Change from baseline in PANSS total score at Week 9 and Week 25 (between treatment groups)

Other efficacy endpoints:

- Change from baseline in PANSS total score at each visit
- Change from baseline in PANSS subscales (positive, negative, general, or other subscales) at each visit
- Change from baseline in Clinical Global Impression-Severity Scale (CGI-S) at each visit
- Time from randomization to Readiness for Discharge

Safety endpoints:

- Incidence of treatment-emergent adverse events (TEAEs)
- Change from baseline in clinical laboratory parameters (chemistry, hematology, and urinalysis), vital signs, and electrocardiograms (ECGs)
- Number and percentage of subjects with potentially clinically significant values in chemistry, hematology, vital signs and ECGs
- Change from baseline in abnormal movement scales scores (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], and Simpson-Angus Scale [SAS])
- Columbia-Suicide Severity Rating Scale (C-SSRS) scores
- Number and percentage of injection site reactions (ISRs)
- Udvalg for Kliniske Undersøgelser Side Effect Self-Rating Scale - Patient (UKU-SERS-PAT) – Sexual Side Effects Subscale score
- Epworth Sleepiness Scale (ESS) total score

Other subject or caregiver centered endpoints:

- Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q-SF) total score
- Number and percentage of response to each modified Medication Satisfaction Questionnaire (MSQ) question
- Change from baseline in total Burden Assessment Score
- Number and percentage of response to Work Readiness Questionnaire (WoRQ) question
- Total resource utilization value

- Handwriting Movement Kinematics score
- Wrist actigraphy scores from each collection period

Statistical methods:

Efficacy analysis will be based on the Full analysis set (FAS), which will include all subjects in the Safety population who have at least one postbaseline assessment of PANSS.

The Safety population will include all subjects who received at least one dose of study drug (AL injection, AL-NCD injection, 30 mg oral aripiprazole, oral PBO, PBO injection, or PP injection). Safety analysis will be based on the Safety population.

Efficacy:

Primary endpoint:

The change from baseline in PANSS total score at Week 4 will be tested against no improvement using the one-sample T test for the AL and PP Treatment Groups separately.

Secondary endpoints:

The change from baseline in PANSS total score at Week 9 and Week 25 will be tested against no improvement using the one-sample T test for the AL and PP groups separately.

The change from baseline in PANSS total score at Week 4, Week 9, or Week 25 will be compared between the two treatment groups using an analysis of covariance (ANCOVA) with last observation carried forward (LOCF) imputation for missing data. The ANCOVA model will include treatment group, baseline PANSS total score, stratification factor, and the pooled study sites as covariates.

Other efficacy endpoints:

The continuous outcomes (change from baseline in PANSS subscales, CGI-S) will be analyzed using the same ANCOVA with LOCF model. The time from randomization to Readiness for Discharge will be summarized using a Kaplan-Meier plot.

Safety endpoints:

Evaluation of safety will be based on adverse events (AEs), vital signs, clinical laboratory parameters (chemistry, hematology, and urinalysis), ECGs, abnormal movement scales scores (AIMS, BARS, and SAS), C-SSRS scores, ISRs, UKU-SERS-PAT – Sexual Side Effects Subscale scores, and ESS total scores. Reported AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and system organ classes. Concomitant medications will be categorized using the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) classification system.

Analysis of other subject or caregiver centered endpoints:

The change from baseline at each visit in Q-LES-Q-SF total score will be summarized by treatment group. The Burden Assessment Score will be summarized by treatment group or by caregiver type. The number and percentage of response for the modified MSQ and WoRQ will be summarized by treatment group. The number and percentage of subjects who had an ER visit, arrest, or have been incarcerated will be summarized by treatment group. Handwriting Movement Kinematics and wrist actigraphy results will be summarized by treatment group. Further analysis details will be specified in the Statistical Analysis Plan (SAP).

Sample size considerations:

No formal sample size calculations have been performed. The sample size is based on practical and clinical considerations.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: List of Abbreviations and Definition of Terms

Abbreviation or Term	Full Form of Definition
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
AL	Aripiprazole lauroxil
AL-NCD	Aripiprazole lauroxil NanoCrystal Dispersion
ANCOVA	Analysis of covariance
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
CGI-S	Clinical Global Impression-Severity Scale
CSA	Clinical Study Agreement
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
C-VISA	Clinical-Validation Inventory for Study Admission
CYP	Cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of study
EOT	End of treatment
End of Trial	Date of last subject's last visit
EPS	Extrapyramidal symptoms
ESS	Epworth Sleepiness Scale
ET	Early termination
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

Table 2: List of Abbreviations and Definition of Terms (Continued)

Abbreviation or Term	Full Form of Definition
IM	Intramuscular
IRB	Institutional Review Board
ISR	Injection site reactions
LAI	Long-acting injectable
LOCF	Last observation carried forward
MDMA	3,4-methylendioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MINI v 7.0.2	Mini-International Neuropsychiatric Interview-7.0.2 for Schizophrenia and Psychotic Disorder Studies
MSQ	Medication Satisfaction Questionnaire
PANSS	Positive and Negative Syndrome Scale
PBO	Placebo
PFS	Prefilled syringe
PP	Paliperidone palmitate
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form
QTcF	QT interval corrected for heart rate using Fridericia's formula
RDQ	Readiness for Discharge Questionnaire
SAS	Simpson-Angus Scale
SAE	Serious adverse event
SAP	Statistical Analysis Plan
TEAE	Treatment-emergent adverse event
UKU-SERS-PAT	Udvalg for Kliniske Undersøgelser Side Effect Self-Rating Scale – Patient
US	United States
WHO-ATC	World Health Organization-Anatomical Therapeutic Chemical
WoRQ	Work Readiness Questionnaire

5. INTRODUCTION

Schizophrenia is a severe mental disorder characterized by abnormalities in the perception or expression of reality. Aripiprazole is a second generation, atypical antipsychotic with demonstrated efficacy for the symptoms of schizophrenia (Abilify USPI, 2017). Although aripiprazole and other antipsychotics are effective for managing schizophrenia when used regularly, poor adherence to oral antipsychotic treatment regimens is widespread and presents a major limitation to successful treatment (Keith and Kane 2003). Nonadherence has been associated with relapse and worsening long-term functional and mental outcomes (Ascher-Svanum et al, 2006; Ascher-Svanum et al, 2010). Long-acting injectable (LAI) antipsychotic formulations, such as risperidone (Risperdal® Consta®), paliperidone palmitate (PP; Invega® Sustenna®), olanzapine (Zyprexa® Relprevv®), and aripiprazole (Abilify® Maintena®; ARISTADA®), were developed to promote treatment adherence, and have been demonstrated to improve adherence relative to oral medication, and thus improve outcomes and reduce long term costs (Kane et al, 2013).

Aripiprazole lauroxil (AL; ARISTADA) is a covalently bonded, non-ester modification of aripiprazole to form *N*-lauroyloxymethyl aripiprazole. It is formulated as an extended-release suspension to be administered via intramuscular (IM) injection into the gluteal or deltoid muscle. In clinical trials, treatment with AL demonstrated statistically significant reductions from baseline in Positive and Negative Syndrome Scale (PANSS) total scores at Week 12, compared with placebo. Aripiprazole lauroxil 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.

Due to the delayed appearance of aripiprazole in systemic circulation following AL administration, treatment with AL currently requires a concurrent 21-day oral lead-in regimen (oral initiation regimen; ie, oral aripiprazole once daily for 21 days after AL administration) to ensure adequate pharmacological activity to cover the initial lag of aripiprazole appearance with the first IM injection. Aripiprazole lauroxil NanoCrystal Dispersion® (AL-NCD) is an alternative IM formulation of AL under investigation that has been developed for the initiation of treatment with AL in order to eliminate the need for the current oral initiation regimen. This study is designed to 1) evaluate the efficacy of the AL-NCD initiation regimen followed by the AL 1064 mg/every 2 months dose regimen for acute symptoms of schizophrenia, and 2) compare the safety and efficacy of AL to PP (ie, ARISTADA and Invega Sustenna).

This study is a double-blind, 25-week evaluation of the safety and efficacy of AL or PP for the treatment of schizophrenia in subjects hospitalized for acute exacerbation.

5.1. Disease Overview

Schizophrenia is a chronic, severe mental disorder characterized by debilitating psychotic symptoms, physical and psychiatric comorbidities, and increased mortality. Symptoms are characterized by a mix of "positive symptoms" such as hallucinations, delusions, and thought disorders, and by "negative symptoms" such as flat or blunted affect, poverty of speech, inability to experience pleasure, lack of desire to form relationships, and reduced motivation (American Psychiatric Association 2013). Effective antipsychotic medications are available to treat this

condition; for example, in patients with schizophrenia, aripiprazole has demonstrated efficacy for both the positive and negative symptoms of schizophrenia (Abilify USPI, 2017). Although aripiprazole and other antipsychotics are effective for managing schizophrenia when used regularly, poor adherence to oral antipsychotic treatment regimens is widespread and presents a major barrier to achieving optimal pharmacologic outcomes (Keith and Kane 2003).

5.2. Study Rationale

Aripiprazole lauroxil is an injectable extended-release formulation of an atypical antipsychotic developed by Alkermes for the treatment of schizophrenia. Five dose regimens of AL are currently approved by the United States (US) Food and Drug Administration (FDA) for the treatment of schizophrenia as follows: 441 mg/monthly, 662 mg/monthly, 882 mg/monthly, 882 mg/every 6 weeks, and 1064 mg/every 2 months.

Aripiprazole lauroxil NanoCrystal Dispersion (AL-NCD) is an alternative IM formulation of AL under investigation that has been developed for the initiation of treatment with AL in order to eliminate the need for the current 21-day oral initiation regimen. The AL-NCD initiation regimen comprises a single 662 mg IM dose of AL-NCD coadministered with a single 30 mg oral dose of aripiprazole. This regimen was developed based on pharmacokinetic modeling, and AL-NCD was found to be well tolerated when tested in a clinical study in subjects with schizophrenia.

This study is being conducted to evaluate the efficacy of the AL-NCD initiation regimen for acute symptoms followed by initiation of the 1064 mg/every 2 months dose regimen. It will also compare the safety and efficacy of AL to PP (ie, ARISTADA and Invega Sustenna), two atypical LAI antipsychotics with different mechanisms of action. Paliperidone palmitate is approved by the US FDA for the treatment of schizophrenia. In multiple clinical studies, PP has been found to be efficacious in patients with an acute exacerbation of schizophrenia (Gopal et al, 2010; Nasrallah et al, 2010; Pandina et al, 2010). An active drug with a known efficacy profile is a useful comparator for evaluating new drugs while avoiding the ethical dilemmas associated with placebo.

Therefore, this study is being conducted to assess the efficacy, safety, and tolerability of AL and PP in subjects hospitalized for acute exacerbation of schizophrenia.

5.3. Dose Selection

The AL dose of 1064 mg IM every 2 months and the PP doses of 234 mg IM initiation and 156 mg IM monthly were selected because they are approved doses used for the treatment of patients with schizophrenia.

For the AL-NCD initiation regimen, the dose of 662 mg IM coadministered with a single 30 mg oral aripiprazole dose has been shown to provide aripiprazole concentrations comparable to daily administration of 15 mg oral aripiprazole administered during the first 21 days of AL treatment.

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of AL-NCD initiation regimen (30 mg oral aripiprazole + 662 mg AL-NCD IM) followed by AL 1064 mg IM during the first 4 weeks of treatment of patients hospitalized for an acute exacerbation of schizophrenia.

6.2. Secondary Objectives

The secondary objectives of this study are to:

- Compare the efficacy of AL-NCD initiation regimen followed by AL 1064 mg IM with PP initiation dosing (Invega® Sustenna®; 234 mg + 156 mg IM) during the first 4 weeks of treatment of patients hospitalized for an acute exacerbation of schizophrenia
- Evaluate the safety, efficacy, and tolerability of AL 1064 mg IM after 6 months of treatment with AL for schizophrenia
- Compare the safety, efficacy, and tolerability of AL 1064 mg IM with monthly PP 156 mg IM after 6 months of treatment with AL or PP for schizophrenia

6.3. Exploratory Objective

The exploratory objective of this study is to characterize subject and caregiver centered outcomes, such as quality of life, work readiness, satisfaction with medication, resource utilization, and caregiver burden after 6 months of treatment with AL or PP for schizophrenia.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

Each subject must meet all of the inclusion and none of the exclusion criteria to be qualified to participate in this study.

7.1. Subject Inclusion Criteria

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

7.1.1. General Criteria

1. Subject is willing and able to give informed consent; subject has signed the informed consent form (ICF) before initiation of any study-specific procedures
2. Subject is ≥18 and ≤65 years of age and is willing and able to provide government-issued identification at screening
3. Subject has a body mass index (BMI) between 18.0 kg/m^2 and 40.0 kg/m^2, inclusive, at screening
4. Subject is willing to abide by the contraception requirements that will be defined in the protocol for the duration of the study (males and females; please refer to Section 8.4.1 in the protocol)
5. Subject is fluent (oral and written) in the language of the Investigator and study site staff in order to be reliably evaluated and rated using standardized tests
6. Subject is willing and able to follow the study procedures as outlined in the protocol

7.1.2. Psychiatric Criteria

7. Subject has a diagnosis of schizophrenia per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association 2013) criteria as confirmed by Mini International Neuropsychiatric Interview 7.0.2 for Schizophrenia and Psychotic Disorder Studies (MINI v 7.0.2)
8. Subject is experiencing an acute exacerbation or relapse of symptoms, with onset less than 2 months prior to screening
    a. The subject requires hospitalization for this acute exacerbation or relapse of symptoms
    b. If already inpatient at screening, has been hospitalized for less than 2 weeks for the current exacerbation at the time of screening
        – Involuntarily hospitalized subjects who request and are granted voluntary status prior to signing informed consent may participate, provided criteria above are met
9. Subject is willing and able to be confined to an inpatient study unit for up to 3 or 4 weeks (clinically dependent)
10. PANSS that meets the following criteria at screening and baseline:

a. Total score between 80 and 120, inclusive
b. Score of ≥4 (moderate or greater) for ≥2 of the following Positive Scale (P) items:
   - Item 1 (P1; delusions)
   - Item 2 (P2; conceptual disorganization)
   - Item 3 (P3; hallucinatory behavior)
   - Item 6 (P6; suspiciousness/persecution)

11. Clinical Global Impression-Severity Scale (CGI-S) score ≥4 at screening and baseline
12. Subject has experienced at least one previous hospitalization for schizophrenia
13. Subject has had a past history of clinically significant beneficial response (improvement in schizophrenia symptoms), as determined by the Investigator, to treatment with an antipsychotic medication other than clozapine
14. Subject meets either one of the two tolerability criteria below for aripiprazole:
    a. Has a history of tolerated use of aripiprazole
    b. If there is no tolerability history, then has demonstrated tolerability to oral test doses of aripiprazole during screening
15. Subject meets either one of the two tolerability criteria below for either risperidone or paliperidone:
    a. Has a history of tolerated use of risperidone or paliperidone (Note: history of tolerating either medication will fulfill this criteria)
    b. If there is no tolerability history, then has demonstrated tolerability to oral test doses of risperidone during screening
16. Subject has been able to achieve outpatient status for more than 3 consecutive months in the past year
17. Subject resides in a stable living situation when not hospitalized, in the opinion of the Investigator
18. Subject has an identified reliable informant (caregiver) who is willing and able to provide informed consent by signing the caregiver ICF

7.2. Subject Exclusion Criteria

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

1. Subject has any finding that in the view of the Investigator may compromise the safety of the subject or affect their ability to adhere to the protocol visit schedule or fulfill visit requirements

7.2.1. Psychiatric Criteria

2. Subject has a history of psychopathology other than schizophrenia as indicated by any of the following:
    a. Has any current primary DSM-5 diagnosis other than schizophrenia within the 12 months prior to screening (confirmed using MINI v 7.0.2 at screening)
    b. Has a DSM-5 diagnosis of moderate to severe substance use disorder (except tobacco or cannabis use disorder) within the 12 months prior to screening (confirmed using MINI v 7.0.2 at screening)
3. Subject poses a current suicide risk in the opinion of the Investigator or as confirmed by the following:
    a. Answers "Yes" on items 4 or 5 (Columbia-Suicide Severity Rating Scale [C-SSRS]-ideation) with the most recent episode occurring within the 2 months prior to screening, or answers "Yes" to any of the 5 items (C-SSRS-behavior) with an episode occurring within the 12 months prior to screening. Non-suicidal self-injurious behavior is not exclusionary.

7.2.2. Criteria Based on Treatment History

4. Subject has a history of treatment resistance defined as failure to respond to 2 adequate courses of pharmacotherapy (a minimum of 4 weeks at an adequate dose per the label) or required clozapine within the last 12 months
5. Subject has a known or suspected hypersensitivity, or history of intolerable side effects attributed to one or more of the following: aripiprazole, risperidone, or paliperidone, per the Investigator's judgment
6. Subject has a history of poor or inadequate clinical response to one or more of the following: aripiprazole, risperidone, or paliperidone, when subject was known to be adherent to the antipsychotic for a full course (a minimum of 4 weeks at an adequate dose per the label) per the Investigator's judgment
7. Subject has received a LAI antipsychotic (eg, paliperidone palmitate) in the past 3 months or received ARISTADA 1064 mg or Invega Trinza® in the past 6 months
8. Subject initiated first antipsychotic treatment within the past 12 months or <1 year has elapsed since the initial onset of the active-phase of schizophrenia symptoms
9. Current involuntary hospitalization or incarceration
10. Subject has had psychiatric hospitalization(s) for more than 30 days (cumulative) during the 90 days before screening

7.2.3. Criteria Based on Drug/Alcohol Use and Concomitant Medications

11. Subject has a positive urine drug test for illicit use of amphetamines, methamphetamines, 3,4-methylenedioxymethamphetamine (MDMA), barbiturates, benzodiazepines, cocaine, opioids, or phencyclidine at screening (cannabinoids are not exclusionary). Use of prescribed medications (eg, benzodiazepines or opioids) that account for the positive urine drug test results are not exclusionary.

12. Subject has used potent oral cytochrome P450 (CYP) 3A inducers or inhibitors or CYP2D6 inhibitors (prescription medications, over-the-counter medications, or dietary supplements) over the 14 days prior to Day 1 (Section 21 and Section 22).
13. Subject requires treatment with a prohibited medication (refer to Section 8.4.4)

7.2.4. Criteria Based on Medical Conditions/Medical History

14. Subject has a history or current evidence of a clinically significant medical illness, condition, or disorder that would be anticipated to potentially compromise subject safety or adversely affect the evaluation of efficacy, including, but not necessarily limited to, the following:
    a. Clinically significant hypotension or hypertension not stabilized by medical therapy per the Investigator's judgment
    b. Unstable thyroid dysfunction in the past 6 months (eg, hypothyroidism, hyperthyroidism, or thyroiditis that was untreated or discovered, and treatment was initiated within the 6 months prior to screening)
    c. Malignant tumor within the last 5 years (exception: dermal squamous or basal cell carcinoma or cervical carcinoma in situ allowable)
    d. Neurologic conditions including the following:
        – History of seizure disorder or condition associated with seizures, with the exception of febrile seizure history
        – History of brain tumor, subdural hematoma, or other clinically significant neurological condition within the past 12 months
        – Head trauma with loss of consciousness within 12 months before screening
        – Active acute or chronic central nervous system infection
        – Stroke within 6 months before screening
        – History of neuroleptic malignant syndrome or clinically significant tardive dyskinesia
    e. Clinically significant cardiac arrhythmia, cardiomyopathy, or cardiac conduction defect; history of myocardial infarction or unstable angina within the last 3 months before screening; or clinically significant abnormality on screening or baseline electrocardiogram (ECG), including but not limited to:
        – A QT interval corrected using the Fridericia's formula (QTcF) >450 milliseconds for men or >470 milliseconds for women
15. Subject is pregnant, planning to become pregnant, or breastfeeding during the study
16. Subject has participated in a clinical study involving any investigational product (ie, drug, device, or biologic) within the past 3 months or is currently participating in a clinical study involving an investigational product
17. Inadequate muscle mass or excessive subcutaneous fat, as determined by the Investigator, that would interfere with a successful IM injection by either the deltoid or gluteal route

7.2.5. Criteria Based on Laboratory Assessments

18. Subject has any of the following conditions or abnormalities at screening:
    a. Uncontrolled diabetes (HbA1c >7%),
    b. Aspartate aminotransferase or alanine aminotransferase levels ≥3 times the upper limit of the laboratory reference range at screening
    c. Absolute neutrophil count $\leq 1.5 \times 10^3$ per μL
    d. Platelet count $\leq 100 \times 10^3$ per μL
    e. Positive test result for Human Immunodeficiency Virus (HIV) antibody and/or antigen, hepatitis B surface antigen, or anti-hepatitis C virus antibody
    f. Serum creatinine >2.5 mg/dL

7.2.6. General Criteria

19. Subject is employed by Alkermes, the Investigator, the study site (includes permanent or temporary contract workers and designees responsible for the conduct of the study), or a third-party agent of this study or is immediate family[1] of an employee of Alkermes, the Contract Research Organization (CRO), the Investigator, the study site, or other third-party agent
20. If, in the opinion of the Investigator (and/or Sponsor), is unsuitable for enrollment in the study

7.3. Subject Withdrawal

A subject may be discontinued from the study at any time if the subject, Investigator, or Sponsor determines that it is not in the best interest of the subject to continue participation. Reasons for discontinuation include:

- Adverse event
- Lack of efficacy
- Loss to follow-up
- Withdrawal of consent
- Noncompliance with study drug (including missed dose by >2 weeks)
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Other

[1] Immediate family is defined as a spouse, parent, sibling, or child, whether biological or legally adopted.

If a subject withdraws from the study for any reason, any ongoing AEs will be followed until resolution, until deemed stable by the Investigator, or until the subject is deemed by the Investigator to be lost to follow-up. If, in the opinion of the Investigator, it is necessary to monitor a subject beyond the Early Termination (ET)/End of Study (EOS)/End of Treatment (EOT) visit, the Follow-up period may be extended as necessary. In such instances, the Sponsor and the Investigator will agree to an acceptable follow-up schedule.

In the event that a subject chooses to withdraw from the study, the Investigator should make a reasonable effort to ascertain the reason(s) for withdrawal, while fully respecting the subject's rights. Randomized subjects are to be asked to return to the clinic for an ET visit. The ET visit should be scheduled as close as possible to the subject's last dose, and ET assessments and will mimic the assessments scheduled to be conducted at Visit 11/EOT/EOS.

For subjects discontinuing early, any untoward medical condition occurring within 30 days after the last dose should be considered an AE. An unscheduled visit should be captured in the EDC and documented in the source should the subject require a visit to the investigational site.

If the subject fails or refuses to return to the study site, an attempt must be made to contact the subject by telephone in order to assess as many safety and efficacy parameters as possible. All data collected over the telephone must be documented and kept in the subject's record.

The Investigator must maintain a record of all subjects who fail to complete the study. The reason for study discontinuation will be documented and made on the appropriate electronic case report form (eCRF). If a subject is lost to follow-up, a reasonable attempt to contact the subject must be made and documented.

7.4. Replacement of Subjects

Subjects who withdraw from the study after randomization will not be replaced.

8. STUDY DESIGN

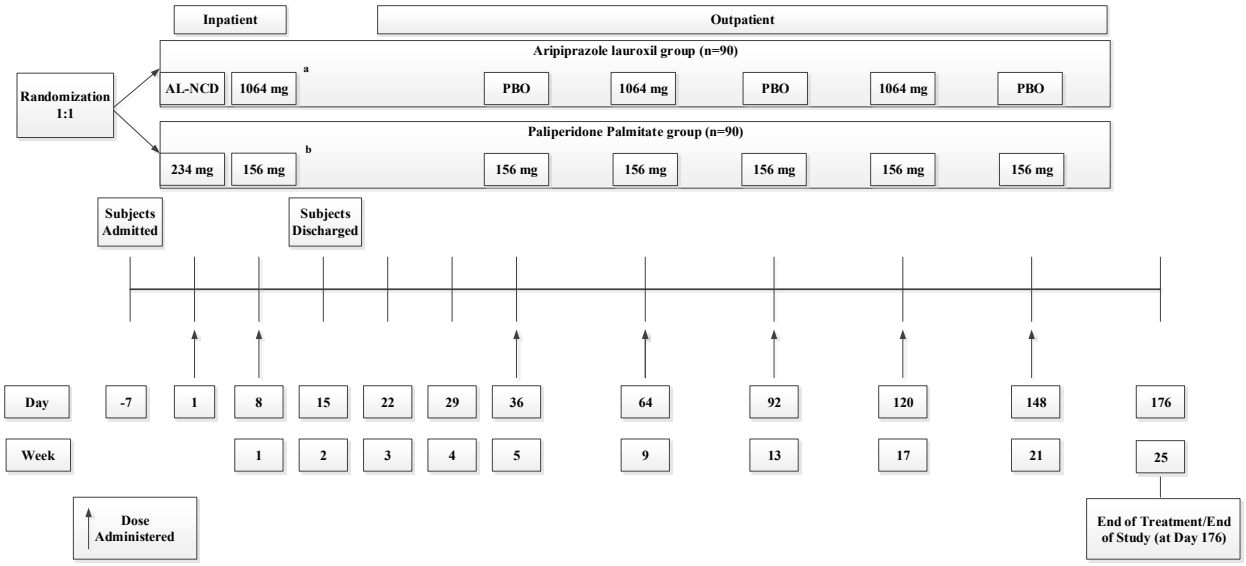
8.1. Overall Study Design and Plan

This is a multicenter, randomized, double-blind study evaluating the efficacy and safety of AL and PP in approximately 180 subjects experiencing an acute exacerbation of schizophrenia. In total, subjects will participate for approximately 26 weeks, including up to 1 week of inpatient screening and 25 weeks of treatment (which includes an initial 2-week inpatient stay). Potential subjects will be evaluated at a Screening visit (up to 7 days) prior to randomization. If a subject does not have historical exposure to aripiprazole and/or risperidone and paliperidone, test doses will be administered during the first 2 days of inpatient stay during the Screening period, prior to randomization, to assess tolerability, as described in Section 9.2.

All subjects should be in an inpatient setting when discontinuing prior antipsychotic medication. The washout of antipsychotics would be at the discretion of the Investigator based on evolving clinical picture. Allowable washout period is 2 to 5 days.

On Day 1, qualified subjects will be randomized to either the AL Treatment Group or the PP Treatment Group and receive dosing with AL or PP as described in Section 9.1. Subjects will remain in the inpatient study unit during the Screening period and for at least 2 weeks after administration of the first dose of study drug on Day 1. Subjects will be discharged from the inpatient unit upon assessment as clinically stable and appropriate for discharge as determined by the Investigator. Subjects will receive their final injection of study drug on Day 148 and will be considered to be on treatment until Day 176. A schematic of the study design is provided in Figure 1.

Figure 1: Study Design Schematic



Abbreviations: AL-NCD=aripiprazole lauroxil NanoCrystal Dispersion; PBO=placebo

[a] Subjects randomized into the AL Treatment Group will receive IM PBO (deltoid) on Days 1 and 8 and 30 mg oral aripiprazole on Day 1

[b] Subjects randomized into the PP Treatment Group will receive IM PBO (gluteal) on Days 1 and 8 and oral PBO on Day 1

Safety and tolerability assessments will include AE monitoring, clinical laboratory testing, vital signs, body weight, 12-lead ECGs, monitoring, abnormal movement scales (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], and Simpson-Angus Scale [SAS]), C-SSRS, injection site reactions (ISRs), the Udvalg for Kliniske Undersøgelser Side Effect Self-Rating Scale - Patient (UKU-SERS-PAT) – Sexual Side Effects Subscale, and Epworth Sleepiness Scale (ESS).

Efficacy assessments will include PANSS, Clinical Global Impression–Severity (CGI-S), and Readiness for Discharge Questionnaire (RDQ).

Subject or caregiver-centered assessments will include Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q-SF), modified Medication Satisfaction Questionnaire (MSQ), the Work Readiness Questionnaire (WoRQ), Handwriting Movement Kinematics, wrist actigraphy, and Resource Utilization Form. Caregivers who meet criteria will also complete the Burden Assessment Scale.

8.2. Schedule of Visits and Assessments

The schedule of assessments is shown in Table 3.

For a missed visit, the study site should attempt to contact the subject to reschedule. A subject who is late for a scheduled injection by more than 2 weeks will be discontinued from treatment.

Premature discontinuation procedures are provided in Section 7.3.

Table 3: Schedule of Assessments

	Screening	Double-blind Treatment Period														
	Required Inpatient Stay[a]								Outpatient Visits							
	V1 Screening[b]	V2 Baseline	V3						V4	V5	V6	V7	V8	V9	V10	V11/EOT/EOS/ ET[c]
									22	29	36	64	92	120	148	176
Procedure/Study Day	-7 to -1	1	2-3	4	5-7	8	9-14	15	±1 day	±3 day window, anchored to the prior injection						
Informed Consent	X															
Clinical-Validation Inventory for Study Admission (C-VISA)[d]	X															
Eligibility Criteria Review	X	X														
Demographics, Medical/Psychiatric History	X															
Caregiver Consent[e]	X															
Caregiver Intake Form[e]	X															
Resource Utilization Form	X										X	X	X	X	X	X
Mini-International Neuropsychiatric Interview 7.0.2 for Schizophrenia and Psychotic Disorder Studies (MINI v 7.0.2)	X															
Physical Examination[f]	X							X								X
Height	X															
Weight	X	X						X		X		X		X		X

Table 3: Schedule of Assessments (Continued)

	Screening	Double-blind Treatment Period														
	Required Inpatient Stay[a]								Outpatient Visits							
	V1 Screening[b]	V2 Baseline	V3						V4	V5	V6	V7	V8	V9	V10	V11/EOT/EOS/ ET[c]
									22	29	36	64	92	120	148	176
Procedure/Study Day	-7 to -1	1	2-3	4	5-7	8	9-14	15	±1 day	±3 day window, anchored to the prior injection						
Urine Drug Screen[g]	X	X														
Pregnancy Test (All Women)	X[h]	X								X	X	X	X	X	X	
Biochemistry, Hematology, and Urinalysis Samples (Including Prolactin)[i]	X	X				X		X			X	X	X	X	X	X
Genotype Sampling		X														
Serology[j]	X															
Vital Signs[k]	X	X				X		X			X	X	X	X	X	X
12-lead Electrocardiogram (ECG)[l]	X	X				X		X			X	X	X	X	X	X
Admission to Inpatient Facility[a]	X															
Administer Test Doses[m]	X															
Randomization		X														
Administer 30 mg Oral Aripiprazole or oral PBO Dose		X[n]														

Table 3: Schedule of Assessments (Continued)

	Screening	Double-blind Treatment Period													
	Required Inpatient Stay[a]								Outpatient Visits						
	V1 Screening[b]	V2 Baseline	V3						V4	V5	V6	V7	V8	V9	V10	V11/EOT/EOS/ ET[c]
									22	29	36	64	92	120	148	176
Procedure/Study Day	-7 to -1	1	2-3	4	5-7	8	9-14	15	±1 day	±3 day window, anchored to the prior injection						
IM Injection of AL-NCD 662 mg or PP 234 mg, and IM PBO Dose		X[n]														
IM Injection of AL 1064 mg or PP 156 mg, and/or PBO Dose						X[n]					X	X	X	X	X	
Injection Site Evaluation[o]		X	X			X	X	X			X	X	X	X	X	
Discharge From the Inpatient Facility[a]								X								
Positive and Negative Syndrome Scale (PANSS)[p]	X	X		X		X		X	X	X	X	X	X	X	X	X
Abnormal Involuntary Movement Scale (AIMS)		X								X						X
Akathisia/Movement Disorder Rating (BARS/SAS)	X	X		X		X		X		X		X				X
Columbia-Suicide Severity Rating Scale (C-SSRS)[q]	X	X				X		X	X	X	X	X	X	X	X	X
Epworth Sleepiness Scale (ESS)								X	X	X		X	X			X
Readiness for Discharge Questionnaire (RDQ)				X	X[r]	X	X[r]	X								

Table 3: Schedule of Assessments (Continued)

	Screening	Double-blind Treatment Period														
		Required Inpatient Stay[a]							Outpatient Visits							
	V1 Screening[b]	V2 Baseline	V3						V4	V5	V6	V7	V8	V9	V10	V11/EOT/EOS/ ET[c]
									22	29	36	64	92	120	148	176
Procedure/Study Day	-7 to -1	1	2-3	4	5-7	8	9-14	15	±1 day	±3 day window, anchored to the prior injection						
Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q-SF)											X		X			X
Modified Medication Satisfaction Questionnaire (MSQ)										X		X		X		X
Work Readiness Questionnaire (WoRQ)								X		X		X		X		X
Udvalg for Kliniske Undersøgelser Side Effect Self-Rating Scale - Patient (UKU-SERS-PAT) – Sexual Side Effects Subscale		X								X		X		X		X
Burden Assessment Scale[s]	X											X				X
Handwriting Movement Kinematics	X							X		X		X		X		
Clinical Global Impression-Severity Scale (CGI-S)	X	X		X		X		X	X	X	X	X	X	X	X	X
Distribute Wrist Actigraph									X			X[t]				

Table 3: Schedule of Assessments (Continued)

	Screening	Double-blind Treatment Period													
	Required Inpatient Stay[a]								Outpatient Visits						
	V1 Screening[b]	V2 Baseline	V3						V4	V5	V6	V7	V8	V9	V10	V11/EOT/EOS/ ET[c]
									22	29	36	64	92	120	148	176
Procedure/Study Day	-7 to -1	1	2-3	4	5-7	8	9-14	15	±1 day	±3 day window, anchored to the prior injection						
Collect Wrist Actigraph											X		X			
Adverse Event Monitoring	X															
Prior and Concomitant Medication Review	X															

Abbreviations: AE=adverse event; AIMS=Abnormal Involuntary Movement Scale; AL=aripiprazole lauroxil; AL-NCD=aripiprazole lauroxil NanoCrystal Dispersion; BARS=Barnes Akathisia Rating Scale; CGI-S=Clinical Global Impression-Severity Scale; C-SSRS=Columbia-Suicide Severity Rating Scale; C-VISA=Clinical-Validation Inventory for Study Admission; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; ESS=Epworth Sleepiness Scale; ET=early termination; HIV=human immunodeficiency virus; IM=intramuscular; ISR=injection site reaction; MINI v 7.0.2=Mini-International Neuropsychiatric Interview 7.0.2 for Schizophrenia and Psychotic Disorder Studies; PANSS=Positive and Negative Syndrome Scale; PBO=placebo; PP=paliperidone palmitate; Q-LES-Q-SF=Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form; RDQ=Readiness for Discharge Questionnaire; SAS=Simpson-Angus Scale; UDS=urine drug screen; UKU-SERS-PAT=Udvalg for Kliniske Undersøgelser Side Effect Self-Rating Scale- Patient; V=visit; WoRQ=Work Readiness Questionnaire

[a] Subjects meeting initial screening eligibility criteria, who are not already inpatient, will be admitted to an inpatient study unit for completion of Screening visit assessments or as soon as possible thereafter. After randomization on Day 1, 2 weeks of inpatient hospitalization is required. Subjects are to be returned to outpatient status when assessed by the Investigator as safe and medically ready for discharge on Day 15. Note: With Medical Monitor approval prior to Day 15, the Investigator may retain the subject in the inpatient unit for up to 1 additional week (to Day 22) if the Investigator deems the subject not safe or medically ready for discharge on Day 15

[b] Screening assessments may be conducted over 2 consecutive days (Inclusion/Exclusion eligibility criteria review must be conducted on the first day of screening); up to 7 days is allowed for screening to ensure availability of safety laboratory assessments, etc; however the shortest Screening period is recommended

[c] The End of Treatment (EOT)/End of Study (EOS) visit is to occur 28 ± 3 days after the previous dose of IM study drug was administered (Visit 10/ Day 148). If a subject terminates early from the study, an Early Termination (ET) visit should occur as close as possible to the subject's last dose, and ET assessments and will mimic the assessments scheduled to be conducted at Visit 11/EOT/EOS. For subjects discontinuing early, any untoward medical condition occurring within 30 days after the last dose and deemed related to study drug should be considered an AE. An unscheduled visit should be captured in the EDC and documented in the source should the subject require a visit to the investigational site

[d] The C-VISA uses audio-digital recordings of key screening assessments as the basis for site-independent eligibility review, which includes study measures such as PANSS, CGI-S, and MINI v 7.0.2

[e] Information about a subject's caregiver will be collected at screening and in the event of a change in a subject's caregiver during the study. Caregiver Consent, and Intake Form can be conducted anytime within the 7 day screening period

[f] Full physical examination is performed at screening and brief examination at all other time points. A symptom-driven physical examination can be completed at other study visits as clinically indicated

[g] At screening, a urine sample for urine drug screen (UDS) will be sent to the central laboratory for analysis (a UDS via dipstick will also be performed). A UDS (via dipstick) will also be performed at V2 predose. At the Investigator's discretion, a UDS (via dipstick) may be performed at any time as an unscheduled assessment

[h] If positive urine pregnancy test (via dipstick) at screening, serum confirmation is required. Urine pregnancy test (via dipstick) at all other applicable visits

[i] Fasting laboratory assessments are performed at screening and on Day 1; all other laboratory sample collections may be performed non-fasting

[j] Serology testing includes anti-human immunodeficiency virus (HIV) antibody and/or antigen, hepatitis B surface antigen, and anti-hepatitis C antibody

[k] Vital signs (ie, blood pressure, pulse, respiratory rate, and body temperature) will be measured at the time points identified in Table 4. During screening, Day 15 , and Visit 11 (EOT/EOS/ET), all vital signs are to be measured anytime during the visit. On Day 1, blood pressure and pulse are to be measured both within 1 hour predose and within 2 to 4 hours postdose and respiratory rate and body temperature are to be measured within 1 hour predose. On days 8, 36, 64, 92, 120, and 148, blood pressure and pulse are to be measured both within 1 hour predose and within 2 to 4 hours postdose, respiratory rate is to be measured within 1 hour predose, and body temperature is to be measured within 2 to 4 hours post. On study days when multiple doses are administered (Day 1 and Day 8), predose assessment timing is relative to the first dose given, and postdose assessment timing is relative to the last dose given

[l] A 12-lead electrocardiogram (ECG) is to be performed at the study visits identified in the schedule of assessments. On days when a subject receives study drug, an ECG will be performed both before and after dosing. Predose ECG should be completed within 1 hour prior to dosing. The postdose ECG should be completed within 2 to 4 hours postdose. On study days when multiple doses are administered (Day 1 and Day 8), predose assessment timing is relative to the first dose given, and postdose assessment timing is relative to the last dose given

[m] Test doses are only distributed if a subject does not have historical exposure to aripiprazole, or if a subject does not have historical exposure to risperidone or paliperidone. For subjects without historical exposure to aripiprazole, oral test doses will consist of 5 mg/day aripiprazole during the first 2 days of inpatient stay to assess tolerability. For subjects without historical exposure to risperidone and paliperidone, oral test doses will consist of 1 mg/day risperidone administered during the first 2 days of inpatient stay to assess tolerability. For subjects who require test doses of both aripiprazole and risperidone, the oral test doses should be administered 8 hours apart on the first 2 days of the inpatient Screening period (eg, administer aripiprazole test dose in the morning and risperidone test dose in the evening, or vice versa).

[n] On study days when multiple doses are administered (Day 1 and Day 8), predose assessment timing is relative to the first dose given, and postdose assessment timing is relative to the last dose given

[o] The injection site(s) and surrounding areas will be inspected for possible ISRs within 2 to 6 hours after last injection. During the inpatient stay, the injection site(s) will also be inspected daily for 2 days post-injection (ie, on Days 2 and 3 and Days 9 and 10) and on Day 15. All ISRs, whether by objective physical finding or subjective report, will also be recorded as AEs and will be followed until resolution

[p] The PANSS assessment should be performed first before any other psychiatric assessment at applicable study visits, with the exception of the Screening visit, where the MINI v 7.0.2 will be conducted first

[q] "Baseline/Screening" version at screening (Visit 1); "Since Last Visit" version at all subsequent visits

[r] Readiness for Discharge scale will be administered daily from Day 4 to Day 15

[s] The Burden Assessment Scale will only be completed by caregivers who are family or friends (ie, nonprofessional caregivers) and the screening Burden Assessment Scale can be conducted anytime within the 7 day screening period

[t] Only two weeks of data will be collected following distribution of actigraph

Notes: For details regarding the timing of the structured interviews and questionnaires, refer to Section 8.3.13. Study drug is administered on Days 1, 8, 36, 64, 92, 120, and 148, as indicated by the gray shading in the column headers.

8.3. Study Procedures Descriptions

Details of the study procedures are described below. The overall schedule of assessments is provided in Table 3.

8.3.1. Informed Consent

The nature of the study and its risks and benefits will be explained to the subject and caregiver by the Principal Investigator or designated study personnel as outlined in Section 18.3.

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

8.3.2. Eligibility Review

An eligibility review using the Clinical-Validation Inventory for Study Admission (C-VISA) will be conducted by the Investigator at the visits specified in Table 3 using the subject inclusion criteria in Section 7.1 and exclusion criteria in Section 7.2. Ratings will be reviewed at screening by raters employed by Bracket, with additional reviews taking place at baseline and on various visits throughout the study according to a prespecified schedule (subject to change based on rater accuracy). Rater review is being carried out for providing an unbiased "second" opinion on critical inclusion/exclusion assessments and efficacy assessments. Additionally, other key eligibility criteria (including medical and psychiatric history) will be reviewed by PPD clinical surveillance team.

8.3.3. Identification of Informant/Caregiver

Each subject enrolled in this study will need a reliable informant/caregiver. The caregiver will be required to sign a caregiver ICF and may withdraw consent at any time, in which case he/she can no longer fill the caregiver role for this study. If a caregiver can no longer fill the caregiver role, he/she should be replaced if possible. If the caregiver cannot be replaced, most subjects will be able to continue in the study. If the subject must also withdraw from the study (eg, the caregiver provided transportation to the site and no other travel arrangements can be made for the subject), the Investigator should make a reasonable effort to ascertain the reason(s) for the caregiver's withdrawal, while fully respecting the caregiver's and subject's rights. The reason for the caregiver's withdrawal and explanation of the subject's discontinuation should be documented in the appropriate eCRF.

Information about a subject's caregiver will be collected at screening and in the event of a change in a subject's caregiver during the study. Please refer to the Caregiver Intake Form located in Section 23.

8.3.4. Demographics and Medical/Psychiatric History

Each subject's demographic data and medical/psychiatric history will be reviewed and documented at the time point(s) specified in Table 3.

8.3.5. Resource Utilization Form

At the time points specified in Table 3, subjects will report resource use, such as emergency room visits and criminal justice involvement, over the time specified. When available, caregiver report and medical records will be used to confirm hospitalizations. This information will be collected in the Resource Utilization Form located in Section 24.

8.3.6. Mini-International Neuropsychiatric Interview 7.0.2 for Schizophrenia and Psychotic Disorder Studies (MINI v 7.0.2)

The MINI v 7.0.2 is a clinician-administered, structured diagnostic interview, with an administration time of approximately 15 minutes (Sheehan et al, 1998). The MINI v 7.0.2 has been validated against the much longer Structured Clinical Interview for DSM Diagnoses that corresponds to the DSM-5. The MINI v 7.0.2 will be used at screening only as indicated in Table 3. The MINI v 7.0.2 is required to be done before any other diagnostic assessments at screening.

8.3.7. Concomitant Medication Review

All medications (prescription and nonprescription, including vitamins and herbal supplements) taken by a given subject within 30 days prior to screening through follow-up will be recorded.

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

8.3.8. Vital Signs

Vital signs (ie, blood pressure, pulse, respiratory rate, and body temperature) will be measured at the time point(s) identified in Table 3 and Table 4 . Blood pressure and pulse and respiratory rate will be measured after the subject has been comfortably seated for at least 5 minutes. Efforts should be made to take all blood pressure and pulse measurements from the same arm (preferably the subject's dominant arm) throughout the study. Automated measurement is preferred. The method of measuring body temperature for a given subject should remain constant throughout the subject's participation in the study.

Table 4: Vital Signs: Assessment Timing from Screening through Visit 11 (EOT/EOS/ET)

Visit	Assessment	Assessment Timing
Screening, Day 15, Visit 11 (EOT/EOS/ET)	Blood pressure Pulse Body temperature Respiratory Rate	Anytime during visit
Day 1[a]	Blood pressure Pulse	Within 1 hour predose and within 2 to 4 hours postdose
	Body temperature Respiratory rate	Within 1 hour predose
Days 8[a], 36, 64, 92, 120, 148	Blood pressure Pulse	Within 1 hour predose and within 2 to 4 hours postdose
	Body temperature	Within 2 to 4 hours postdose
	Respiratory rate	Within 1 hour predose

[a] On study days when multiple doses are administered (Day 1 and Day 8), predose assessment timing is relative to the first dose given and postdose assessment timing is relative to the last dose given.

8.3.9. Physical Examination, Body Height, and Weight

A physical examination will be performed at the time point(s) specified in Table 3. A full physical examination (including a neurological examination) is performed at screening and brief examinations (including HEENT inspection [no otoscopic or fundoscopic examination], chest inspection, percussion and auscultation, abdominal inspection, auscultation, and palpitation) at all other time points. Pelvic and rectal examinations are not required unless clinically needed and then would be referred. A symptom-driven physical examination can be completed at other study visits as clinically indicated.

8.3.10. 12-Lead Electrocardiogram

A 12-lead ECG will be conducted at the time point(s) specified in Table 3. On days when subjects receive injections of IM study drug, an ECG will be performed both before and after dosing. Predose ECG should be completed within 1 hour prior to dosing. The postdose ECG should be completed within 2 to 4 hours postdose. On study days when multiple doses are administered (Day 1 and Day 8), predose assessment timing is relative to the first dose given, and postdose assessment timing is relative to the last dose given. All scheduled ECGs should be performed after the subject has rested quietly for at least 5 minutes in the supine position. QT intervals will be automatically corrected for heart rate by the ECG machine using QTcF. The ECGs will be evaluated by a central facility. Additional details regarding recording and evaluation of ECGs will be described in a manual provided to the study site.

8.3.11. Injection Site Evaluation

The injection site(s) and surrounding areas will be inspected for possible ISRs by the Investigator or designee at the time points identified in Table 3, within 2 to 6 hours after last injection. During the inpatient stay, the injection site(s) will also be inspected daily for 2 days postinjection (on Days 2 and 3 and Days 9 and 10) and on Day 15. All ISRs, whether by objective physical finding or subjective report, will also be recorded as AEs and will be followed until resolution.

8.3.12. Wrist Actigraphy

Investigators or designees will distribute the actigraphy device at the time points identified in Table 3. The device is meant to be worn by each subject on the wrist of the non-dominant arm for around 14 consecutive days after it is distributed. The device will monitor and record the physical activity of each subject. Subjects should be instructed to wear the device at all times. The device should then be collected by sites at the time points identified in Table 3 and returned to the Sponsor/designee for data analysis.

8.3.13. Structured Interviews and Questionnaires

With regard to the structured interviews and questionnaires, when the administration of these rating scales coincide, they should be administered in the following order:

1. MINI v 7.0.2
2. PANSS
3. C-SSRS
4. Abnormal movement scales (AIMS, BARS, and SAS)
5. CGI-S
6. RDQ

It is important that assessments are performed in the proper order. Subject and caregiver reported scales can be collected at any time during the visit, when applicable.

Other assessments that are not structured interviews or questionnaires can be performed as needed.

8.3.13.1. Positive and Negative Syndrome Scale

The PANSS is a scale used to assess positive and negative symptoms in patients with schizophrenia (Kay et al, 1987). Patients are rated on a scale of 1 to 7 on 30 different symptoms. The Investigator or designee will complete the PANSS at time points identified in Table 3. The Structured Clinical Interview for the PANSS will be used to administer the PANSS.

8.3.13.2. Abnormal Movement Scales

Abnormal Movement Scales will include AIMS, BARS, and SAS.

The Investigator or designee will complete the set of abnormal movement rating scales at time points identified in Table 3.

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

8.3.13.3. Columbia-Suicide Severity Rating Scale

The Investigator or designee will administer the C-SSRS according to the schedule in Table 3. At screening, the "Baseline/Screening" version will be administered (Posner et al, 2009a), and at all other visits, the "Since Last Visit" version will be administered. For "Since Last Visit" versions, subjects should be asked to report on ideation and behavior since the last scheduled C-SSRS assessment (Posner et al, 2009b). The C-SSRS should be administered by a clinician trained to assess and manage suicidal ideation and behavior.

8.3.13.4. Epworth Sleepiness Scale

The ESS is a self-reported questionnaire with 8 questions that provides a measure of a person's level of daytime sleepiness (Johns 1991). The ESS assesses, on a 4-point scale (0–3), a person's usual chances of dozing off or falling asleep in 8 different situations or activities. This scale will be completed by the subject at the time points specified in Table 3.

8.3.13.5. Readiness for Discharge Questionnaire

The RDQ is a questionnaire used to assess a patient's readiness for discharge, independent of socio-economic factors (Potkin et al, 2005). The RDQ consists of 6 items assessing suicidality/homicidality, control of aggression/impulsivity, activities of daily living, medication-taking, delusions/hallucinations interfering with functioning and global status. The 6 items ultimately inform a "yes/no" indication of whether the subject is clinically appropriate for discharge. The Investigator or designee will complete the RDQ at time points identified in Table 3. Subjects who are determined to be "ready for discharge" prior to Day 15 are still required to remain inpatient until Day 15.

8.3.13.6. Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form

The Q-LES-Q-SF is a self-reported measure used to assess the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning (Stevanovic 2011). Responses are evaluated on a 5-point scale ("not at all to never" to "frequently or all the time"), with higher scores indicating more enjoyment and satisfaction. Subjects will complete the Q-LES-Q-SF at time points identified in Table 3.

8.3.13.7. Modified Medication Satisfaction Questionnaire

The modified MSQ is a 3-item self-reported patient satisfaction questionnaire which assesses the level of patient satisfaction with medication. Subjects rate their satisfaction with their current medication, their preference for their current medication vs previous medications, and their opinion on the side effects of their current medication vs previous medications. Ratings are on a 5-point Likert scale. The modified MSQ will be collected at the time points identified in Table 3.

8.3.13.8. Work Readiness Questionnaire

The WoRQ is a questionnaire used to assess a patient's ability to engage in socially useful activity, independent of work availability (Potkin et al, 2016). The Investigator or designee will complete the WoRQ at time points identified in Table 3.

8.3.13.9. Udvalg for Kliniske Undersøgelser-Side Effect Self-Rating Scale - Patient, Sexual Side Effects Subscale

The sexual functioning subscale from the UKU-SERS-PAT contains 7 items for males and 9 items for females (Lindstrom et al, 2001; Lingjaerde et al, 1987). Each item is rated on a 4-point scale (0=none or doubtful, 1=present to a mild degree, 2=present to a moderate degree, and 3=present to a severe degree). This scale will be completed by the subject at the time points specified in Table 3.

8.3.13.10. Burden Assessment Scale

The Burden Assessment Scale is a 19-item scale administered to caregivers who are family or friends (ie, nonprofessional caregivers) that focuses on specific subjective and objective consequences of families caring for individuals with severe mental disorders (Reinhard et al, 1994). Respondents are required to indicate whether they have experienced each of the types of burden 'Not at all,' 'A little,' 'Some,' or 'A lot' in the past 4 weeks. These are scored 1, 2, 3, and 4, respectively. A higher score indicates more perceived burden. The Burden Assessment Scale will be administered to the designated caregiver at the time points identified in Table 3.

8.3.13.11. Handwriting Movement Kinematics

A quantitative analysis of handwriting kinematics is used to evaluate effects of antipsychotic medication in patients with schizophrenia (Caligiuri et al, 2009). The Investigator or designee will administer the handwriting tests to the subjects at time points identified in Table 3. Instructions will be provided separately to the site.

8.3.13.12. Clinical Global Impression–Severity

The CGI-S is a 7-point scale used to assess the rate of severity of a patient's illness (Guy 2000). The Investigator or designee will complete the CGI-S scale at time points identified in Table 3.

8.3.14. Laboratory Assessments

8.3.14.1. Drug Testing

Subjects will complete a urine drug test for illicit use of amphetamines, methamphetamines, MDMA, barbiturates, benzodiazepines, cocaine, opioids (including oxycodone, methadone, and buprenorphine), and phencyclidine at screening and baseline. Results must be negative for the subject to be eligible for the study. Use of cannabinoids is not exclusionary but THC levels will be collected as part of the standard urine drug screen. Use of prescribed medications (eg, benzodiazepines or opioids) that account for the positive urine drug test results are not exclusionary. Use of prescribed barbiturates must be stopped 14 days prior to Day 1. Repeat testing may be performed if positive urine drug test results cannot be confirmed by a history of presumed active substance use or use of prescribed medications.

8.3.14.2. Hematology, Biochemistry, and Urinalysis

Blood and urine samples for laboratory assessments will be collected at the time points specified in Table 3. Specific hematology, biochemistry, and urinalysis assessments are listed in Table 5. Samples will be collected in accordance with the study site's usual procedures and analyzed by a central laboratory. Laboratory assessments may be repeated at the Investigator's discretion. The process for the review of prolactin levels is discussed in Section 25.

Table 5: Clinical Laboratory Assessments

Hematology	Biochemistry	Urinalysis
Hematocrit	Sodium	Color and appearance
Hemoglobin	Potassium	pH
Red blood cell count	Glucose	Specific gravity
Total and differential (absolute) white blood cell count	Creatinine	Ketones
Platelets	Total protein	Protein
	Blood urea nitrogen	Glucose
	Albumin	Bilirubin
	Total bilirubin	Nitrite
	Alanine transferase	Urobilinogen
	Aspartate transferase	Occult blood
	Lactic dehydrogenase	Microscopic examination of sediment, *only if urinalysis dipstick results are abnormal*
	Gamma-glutamyl transferase	
	Alkaline phosphatase	
	Creatine phosphokinase	
	HbA1c	
	TSH	
	Free T3[a]	
	Free T4[a]	
	Prolactin	

[a] –Free T3 and free T4 levels will be measured if TSH levels are abnormal.

8.3.14.3. Pregnancy Testing

At the screening visit, results must be negative for the subject to be eligible for the study. If there is a positive urine pregnancy test (via dipstick) at screening, serum confirmation is required. A urine pregnancy test (via dipstick) will be administered at all other applicable visits as specified in Table 3.

Section 14.5 provides guidance on the reporting requirements for pregnancies.

8.3.14.4. Cytochrome P450 Genotype Testing

A blood sample will be collected from each subject for determination of CYP2D6 genotype on Day 1.

8.3.14.5. Serology Testing

A blood sample for a serology panel testing for hepatitis B surface antigen, anti-hepatitis C antibodies, and HIV antibody and/or antigen will be performed at screening only.

8.3.15. Randomization

On Day 1, subjects will be randomized as outlined in Section 9.4.

8.3.16. Drug Dispensation and Reconciliation

Section 9 provides information related to drug dispensing procedures. Study drug will be administered at the time points specified in Table 3.

8.3.17. Adverse Event Monitoring

Adverse events will be monitored continuously from the time a subject signs the informed consent document until the completion of the final study visit (see Table 3). Adverse events and serious adverse events (SAEs) are defined in Section 14.1 and Section 14.2, respectively. Section 14.4 provides guidance on the monitoring and recording requirements for AEs. Section 14.5 provides guidance on the reporting requirements for SAEs.

In the event that a subject experiences an AE of akathisia or seizure during the treatment period, a PK blood sample should be collected at the next visit and shipped frozen to the lab for storage. At the Sponsor's discretion, sites may be instructed to collect PK samples for additional AEs.

8.4. Study Requirements and Restrictions

8.4.1. Contraception and Pregnancy

All male and female subjects must agree to use an acceptable method of contraception for the duration of the study 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 and other hormonal methods (eg, a vaginal ring, contraceptive patch, or contraceptive implant); oral contraceptives should have been initiated at least 30 days prior to screening

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

Subjects 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 are considered surgically sterile. Partner vasectomy is not considered an approved acceptable method of contraception for a female subject.

Women who are postmenopausal are also exempt from the requirement to use contraception. For the purpose of this study, postmenopausal is defined as the permanent cessation of menstruation for at least 12 months prior to screening in women who are 45 years of age or older.

If a subject becomes pregnant while participating in the study, she will be discontinued from study drug immediately. The ET visit will be scheduled and the pregnancy will be reported to Alkermes. Additional follow-up may be required. Pregnancies in female partners of male subjects should also be reported and will be followed in the same manner.

A Pregnancy Report Form must be submitted to Alkermes via PPD Drug Safety (per Section 14.5) immediately within 24 hours of awareness of the pregnancy, irrespective of whether an AE has occurred. The pregnancy will be followed until completion or termination. If the outcome of the pregnancy meets the criteria for classification as a SAE, it should be reported following the SAE procedure (see Section 14.5).

8.4.2. Permitted Therapy

Permissible potential medications to treat EPS may include benzodiazepines, antihistamines, beta-blockers, and anticholinergics. While insomnia may be treated with a variety of agents, short half-life benzodiazepines are preferable to longer half-life benzodiazepines due to the potential for lingering effects on daytime functioning and study assessments. Treatment of agitation and/or anxiety with benzodiazepines is permissible, but the dose should be kept as stable as possible throughout the study as clinically indicated, so as not to interfere with daytime functioning and study assessments. Use of antidepressants other than CYP inhibitors/inducers (Section 21 and Section 22) may be continued during the study if dosage has been stable for 30 days before Day 1 and should be kept as stable as possible throughout the study as clinically indicated.

Therapies based upon the Clinical Investigator's medical judgment to be in the best interest of the patient's safety are permissible after consultation with the Sponsor/CRO Medical Monitor.

8.4.3. Non-medication Therapy

Psychotherapy should not be started or changed during a subject's participation in the study. It is acceptable for a subject already receiving psychotherapy to participate in the study; however, subjects receiving cognitive-behavioral therapy should not be enrolled. While on the inpatient study unit during participation in the study, initiation of augmenting psychotherapies (ie, group therapy) deemed by the Clinical Investigator to be of clinical benefit is discouraged, although standard milieu-related activities are acceptable. Partial hospitalization after discharge from the inpatient study unit is allowed, and the level of care after discharge from the inpatient study unit ultimately should be made based on the Investigator's judgment.

Therapies based upon the Clinical Investigator's medical judgment to be in the best interest of the patient's safety are permissible after consultation with the Sponsor/CRO Medical Monitor.

8.4.4. Prohibited Medications

With the exception of those specifically prohibited, medications are allowed. In this study, the medications listed below are prohibited; the Medical Monitor should be consulted regarding any questions on allowed and prohibited medications:

- Use of potent inducers or inhibitors of CYP3A or inhibitors of CYP2D6, whether as prescription medications, over-the-counter medications, or dietary supplements, within 14 days before dosing and during the course of the study is prohibited
  - A list of common CYP3A inducers or inhibitors and CYP2D6 inhibitors is provided in Section 21 and Section 22, respectively. This list is not exhaustive
- Use of antipsychotic medications during the course of the study is prohibited. Prior antipsychotic medications should be discontinued after screening upon inpatient admission. All subjects should be in an inpatient setting when discontinuing prior antipsychotic medication. The washout of antipsychotics would be at the discretion of the Investigator based on evolving clinical picture. Allowable washout period is 2 to 5 days
  - If administration of a psychotropic medication during a subject's participation in the study is being considered (eg, an antipsychotic as rescue medication during the Treatment period), the Investigator must contact the Medical Monitor to discuss the appropriate course of action
- Monoamine oxidase inhibitors (eg, phenelzine, tranylcypromine, selegiline, moclobemide) are strictly prohibited
- Lithium, valproic acid (divalproex sodium), carbamazepine and lamotrigine are not permitted
- IM medications other than the study drug should be administered contralateral to IM study drug injections to avoid confounding safety assessments of study drug injections sites and surrounding areas

See Section 8.3.7 for details regarding the concomitant medication review.

8.4.5. Dietary Restrictions

Foods and beverages that are inducers or inhibitors of CYP3A or inhibitors of CYP2D6, such as grapefruit, grapefruit juice, Earl Grey tea, etc, are prohibited.

9. TREATMENT OF SUBJECTS

9.1. Study Drug Dose and Administration

Study drug dosing schedule is shown in Table 6.

Subjects randomized to the AL Treatment Group will receive 662 mg AL-NCD (single IM gluteal injection) plus IM placebo (PBO; single IM deltoid injection) plus a 30 mg oral aripiprazole tablet on Day 1. On Day 8, these subjects will receive AL 1064 mg (single IM gluteal injection) plus IM PBO (single IM deltoid injection). On Days 36, 92, and 148,
these subjects will receive IM PBO (single IM gluteal injection), and on Days 64 and 120,
these subjects will receive AL 1064 mg (single IM gluteal injection).

Subjects randomized to the PP Treatment Group will receive PP 234 mg (single IM deltoid injection) plus IM PBO (single IM gluteal injection) plus an oral PBO tablet on Day 1. On Day 8, these subjects will receive PP 156 mg (single IM deltoid injection) plus IM PBO (single IM gluteal injection). On Days 36, 64, 92, 120, and 148, these subjects will receive PP 156 mg (single IM gluteal injection).

Placebo for IM injection is phosphate buffered saline. Placebo will be provided in a single-use prefilled syringe (PFS) with a volume of 2.4 mL. Placebo will be administered via gluteal or deltoid IM injection. It is recommended that all study drugs should be given within 30 minutes.

If a dose is missed by >2 weeks, the subject must discontinue study drug.

Table 6: Dosing Schedule

	Day 1	Day 8 (Week 1)	Day 36 (Week 5)	Day 64 (Week 9)	Day 92 (Week 13)	Day 120 (Week 17)	Day 148 (Week 21)
AL	30 mg oral aripiprazole + AL-NCD 662 mg (gluteal) + IM PBO (deltoid)	AL 1064 mg (gluteal) + IM PBO (deltoid)	IM PBO (gluteal)	AL 1064 mg (gluteal)	IM PBO (gluteal)	AL 1064 mg (gluteal)	IM PBO (gluteal)
PP	Oral placebo + PP 234 mg (deltoid) + IM PBO (gluteal)	PP 156 mg (deltoid) + IM PBO (gluteal)	PP 156 mg (gluteal)	PP 156 mg (gluteal)	PP 156 mg (gluteal)	PP 156 mg (gluteal)	PP 156 mg (gluteal)

Abbreviations: AL=aripiprazole lauroxil; AL-NCD=aripiprazole lauroxil NanoCrystal Dispersion; IM=intramuscular; PBO=placebo; PP=paliperidone palmitate

9.2. Oral Test Doses

If a subject does not have historical exposure to aripiprazole, oral test doses of aripiprazole will be administered during the first 2 days of inpatient stay during the Screening period. If a subject does not have historical exposure to risperidone or paliperidone, oral test doses of risperidone will be administered during the first 2 days of inpatient stay during the Screening period. All test

doses are administered prior to randomization in order to assess tolerability as observed by the study site staff.

For subjects with no history of tolerated exposure to aripiprazole, aripiprazole for use as oral test doses will be commercially available aripiprazole 5 mg tablets, provided in commercial packaging provided to the site by Alkermes. Oral aripiprazole tablets must be kept in a locked storage area before dosing and must be stored in accordance with the full prescribing information for aripiprazole. For all women, a urine pregnancy test will be conducted and the results must be negative prior to administration of aripiprazole test doses. The date and time of test dose administration will be recorded.

For subjects with no history of tolerated exposure to risperidone or paliperidone, risperidone for use as oral test doses will be commercially available risperidone 1.0 mg tablets, provided in commercial packaging provided to the site by Alkermes. Oral risperidone tablets must be kept in a locked storage area before dosing and must be stored in accordance with the full prescribing information for risperidone. For all women, a urine pregnancy test will be conducted and the results must be negative prior to administration of risperidone test doses. The date and time of test dose administration will be recorded.

For subjects who require test doses of both aripiprazole and risperidone, the oral test doses should be administered 8 hours apart on the first 2 days of the inpatient Screening period (eg, administer aripiprazole test dose in the morning and risperidone test dose in the evening, or vice versa).

9.3. Treatment Adherence

All study drug will be directly administered by study site staff.

9.4. Randomization/Method of Assigning Subjects to Treatment

Subjects meeting all eligibility criteria will be randomized to one of two Treatment Groups, as described in Table 7.

Table 7: Treatment Groups

Treatment Group	Aripiprazole lauroxil	Paliperidone palmitate
Day 1	662 mg AL-NCD (IM gluteal) + PBO (IM deltoid) + 30 mg oral aripiprazole	PP 234 mg (IM deltoid) + PBO (IM gluteal) + oral PBO
Day 8	AL 1064 mg (IM gluteal) + PBO (IM deltoid)	PP 156 mg (IM deltoid) + PBO (IM gluteal)
Days 36, 92, and 148	PBO (IM gluteal)	PP 156 mg (IM gluteal)
Days 64 and 120	AL 1064 mg (IM gluteal)	PP 156 mg (IM gluteal)

Abbreviations: AL=aripiprazole lauroxil; AL-NCD=aripiprazole lauroxil NanoCrystal Dispersion; IM=intramuscular; PBO=placebo; PP=paliperidone palmitate

To minimize potential response bias based on antipsychotic medication exposure history, randomization will be stratified by the status of prior exposure to aripiprazole or risperidone/ paliperidone. There are two stratification levels, as described in Table 8. After the stratification level (either Level 1 or Level 2) is determined for the subject, he or she will be randomized to

one of two treatment groups in a 1:1 ratio. Stratification will ensure a balance of the two treatment groups within each stratification level.

Table 8: Stratification Factors

		Prior Risperidone/Paliperidone Exposure	
		Yes	**No**
Prior Aripiprazole Exposure	**Yes**	Level 1	Level 2
	No	Level 2	Level 1

9.5. Blinding

This is a double-blind study; the Investigator and study site staff, subject and caregiver, Sponsor, and CRO will remain blinded throughout the conduct of the study, with two exceptions:

1. All study drugs (IM and Day 1 oral doses) will be administered in a double-blind fashion by a trained unblinded pharmacist (or designee) who is not involved in any efficacy or safety assessments of the subject
2. The CRO unblinded Medical Monitor will monitor postbaseline prolactin values throughout the study (refer to Section 25 for details) and will be a resource to the Investigator/study site staff in the event of the need for emergency unblinding

If the Investigator deems it necessary to break the study blind in the interest of a subject's medical safety, he or she must make every effort to contact the CRO/Sponsor Medical Monitor before the blind is broken. If the site is unable to contact the Medical Monitor prior to breaking the blind, the Medical Monitor must be contacted within 24 hours following disclosure of study drug assignment.

The Investigator is responsible for all study-related medical decisions. When the Investigator deems it necessary, emergency unblinding may be done without contacting a Medical Monitor. Any premature unblinding should be promptly documented and explained to the Medical Monitor.

Breaking the blind for a single subject will not affect the blind for the remaining subjects.

9.6. Study Drug Dose Adjustment and Stopping Rules

Study drug doses cannot be adjusted. Subjects who meet the criteria for study drug discontinuation should be withdrawn from the study as described in Section 7.3.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

The investigational product is a covalent non-ester modification of aripiprazole to form *N*-lauroyloxymethyl aripiprazole. Aripiprazole lauroxil is a white to off-white aqueous extended-release suspension for IM injection provided as single-use PFS in a dose strength of 1064 mg. Aripiprazole lauroxil NanoCrystal Dispersion (AL-NCD) is a white to off-white aqueous extended-release suspension, which is an alternative formulation of AL designed to provide faster dissolution than the AL formulation, provided in single-use PFS containing a dose strength of 662 mg. Additional information is provided in the AL IB.

Oral aripiprazole is a tablet for oral administration in dose strengths of 5 mg (test dose) and 30 mg (oral initiation regimen dose). Additional information is provided in the full prescribing information for aripiprazole.

Paliperidone palmitate (Invega Sustenna) (Invega Sustenna USPI, 2017) is a white to off-white aqueous extended-release injectable suspension for IM injection in dose strengths of 156 mg and 234 mg. Additional information is provided in the paliperidone prescribing information.

Risperidone (Risperdal Consta) (Risperdal Consta USPI, 2017) is a white capsule-shaped tablet provided in a dose strength of 1 mg. Additional information is provided in the risperidone prescribing information.

Placebo for IM injection is phosphate buffered saline. Placebo will be provided in a single-use PFS with a volume of 2.4 mL. Placebo will be administered via gluteal or deltoid IM injection per the Instructions for Use.

The Sponsor will provide all study drugs and PBO to the clinical study sites.

10.2. Packaging and Labeling

Aripiprazole lauroxil and AL-NCD are supplied in a 5 mL PFS. Primary packaging consists of a sterilized, siliconized, cyclo-olefin copolymer plastic syringe barrel with a bromobutyl rubber plunger and bromobutyl rubber tip cap. The clinical kit will contain the PFS, needles, and labeling packaged in a pre-formed tray and carton.

Aripiprazole for oral administration on Day 1 will be provided as 15 count community bottles containing 30 mg aripiprazole or PBO over-encapsulated tablets.

Oral aripiprazole test doses in 5 mg tablet form will be commercially available aripiprazole provided in 30 count community bottles.

Oral risperidone test doses in 1 mg tablet form will be commercially available risperidone provided in 60 count community bottles.

Paliperidone palmitate (Invega Sustenna) will be provided in a PFS (cyclic-olefin-copolymer) with a plunger stopper and tip cap (bromobutyl rubber).

10.3. Storage

Aripiprazole lauroxil, AL-NCD, and PBO 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. Oral aripiprazole tablets must be kept in a locked storage area before dosing and must be stored in accordance with the full prescribing information for aripiprazole.

Paliperidone palmitate (Invega Sustenna) must be stored at room temperature (25°C [77°F]); excursions between 15°C and 30°C (59°F and 86°F) are permitted.

Risperidone (Risperdal) tablets must be stored at controlled room temperature (15°C and 25°C [59°F and 77°F]) and protected from light and moisture.

10.4. Accountability

The study site is required to maintain current drug dispensation and accountability logs throughout the study. All unused supplies will be checked against the drug movement records during the study and/or at the end of the study.

Refer to Section 9 for additional study drug reconciliation procedures.

10.5. Handling and Disposal

Following completion and verification of accountability logs, all unused and used packages must be destroyed. The Sponsor will arrange for destruction with a third-party vendor operating in accordance with GCP and/or Good Manufacturing Practice.

11. ASSESSMENT OF EFFICACY

The primary and secondary efficacy endpoints will be evaluated based on PANSS responses. Additional efficacy endpoints will be evaluated by CGI-S and RDQ.

12. ASSESSMENT OF SUBJECT OR CAREGIVER CENTERED ENDPOINTS

The subject or caregiver centered endpoints will be evaluated by Q-LES-Q-SF, modified MSQ, Burden Assessment Score, WoRQ responses/measurements, Handwriting Movement Kinematics, wrist actigraphy, and resource utilization value.

13. ASSESSMENT OF PHARMACOKINETICS AND PHARMACODYNAMICS

Not applicable.

14. ASSESSMENT OF SAFETY

The following safety and tolerability measures will be assessed throughout the study and summarized:

- AEs
- ISRs (eg, pain, tenderness, induration, pain, ecchymosis, pruritus, redness, swelling, etc)
- Clinical laboratory parameters (chemistry, hematology, and urinalysis)
- Vital signs (blood pressure, pulse, respiratory rate, and body temperature)
- ECGs (heart rate, RR, PR, and QT)
- C-SSRS responses
- Abnormal movement scales scores (AIMS, BARS, and SAS)
- ESS responses
- UKU-SERS-PAT – Sexual Side Effects Subscale responses

14.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject who has been administered a pharmaceutical product. The occurrence, which 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 subject and is considered clinically significant.

Illnesses present prior to the subject signing the ICF are considered to be preexisting conditions and are documented on the medical history eCRF. Pre-existing conditions that worsen during the study are entered on the AE eCRF.

All out-of-range laboratory values will be deemed as clinically significant or not clinically significant by the Investigator. Clinically significant values will be considered AEs and will be recorded as such on the eCRFs. The process for the review of prolactin levels is discussed in Section 25.

Pregnancy is not considered an AE, although a subject will be withdrawn from the study if a pregnancy occurs. As described in Section 8.4.1, the pregnancy, including a partner's pregnancy, must be reported to Alkermes, and additional follow-up may be required.

14.2. Definition of Serious Adverse Events

An SAE is any AE, occurring at any dose and regardless of causality that meets one or more of the following criteria:

- Results in death
- Is life-threatening. The subject 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 or subject 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 (ie, social stay admission) during the study in the absence of untoward medical occurrence will not be considered as an SAE, but will be captured as an AE. Hospitalization due to worsening of behavioral health related issues should be reported as an SAE.

14.3. Relationship to Study Drug

The assessment of study drug relationship to each AE will be reported on the appropriate source document (and SAE form, in the event of an SAE) by the Investigator (or designated subinvestigator) according to his or her best clinical judgment. The criteria listed in Table 9 should be used to guide this assessment. Please note that not all criteria must be present to be indicative of a particular drug relationship. All study drugs are considered "test drugs" for the purposes of the definitions listed in the table.

Table 9: Adverse Event Causality Guidelines

Relationship	Criteria for Assessment
Definitely Related	There is evidence of exposure to the test drug AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable The AE is more likely explained by the test drug than by another cause Dechallenge (if performed) is positive Rechallenge (if feasible) is positive The AE shows a pattern consistent with previous knowledge of the test drug or test drug class
Probably Related	There is evidence of exposure to the test drug AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable The AE is more likely explained by the test drug than by another cause Dechallenge (if performed) is positive
Possibly Related	There is evidence of exposure to the test drug AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable The AE could have been due to another equally likely cause Dechallenge (if performed) is positive
Probably Not Related	There is evidence of exposure to the test drug AND There is another more likely cause of the AE Dechallenge (if performed) is negative or ambiguous Rechallenge (if performed) is negative or ambiguous
Definitely not Related	The subject did not receive the test drug OR Temporal sequence of the AE onset relative to administration of the test drug is not reasonable OR There is another obvious cause of the AE

Abbreviation: AE=adverse event

14.4. Monitoring and Recording of Adverse Events

Adverse event data collection will begin after a subject signs the ICF and will continue until completion of the End of Treatment (EOT)/EOS visit (Visit 11). Any AE or SAE having an onset after the EOT/EOS visit will not be collected or reported unless the Investigator feels that the event may be related to the study drug.

Subjects will be instructed by the Investigator or designee to report the occurrence of any AE. All volunteered, elicited, and observed AEs are to be recorded on the AE eCRFs.

The Investigator will assess all AEs regarding any causal relationship to the study drug (see Section 14.3), the intensity (severity) of the event, action taken, and subject outcome.

The following criteria should be used to guide the assessment of intensity (severity):

- **Mild:** Causes awareness of sign or symptom, but is easily tolerated; does not interfere with usual activities
- **Moderate:** Causes discomfort enough to interfere with usual activities
- **Severe:** Is incapacitating; results in inability to work or perform usual activities

All AEs will be followed until resolution, until deemed stable by the Investigator, or until the subject is deemed by the Investigator to be lost to follow-up.

For clinical study safety reporting purposes, the most recent version of the Investigator's Brochure will be used as the reference document to designate event expectedness.

Withdrawal from the study as a result of an AE and any therapeutic measures that are taken shall be at the discretion of the Investigator. If a subject withdraws from the study for any reason, any ongoing AEs will be followed until resolution, until deemed stable by the Investigator, or until the subject is deemed by the Investigator to be lost to follow-up.

14.5. Reporting of Serious Adverse Events and Pregnancy

All SAEs and pregnancies must be reported to Alkermes via PPD Drug Safety immediately within 24 hours of discovery by emailing or faxing the report to the following:

Attention: PPD Drug Safety

FAX Number: PPD

Phone Number: PPD

Email: PPD

The written report for SAEs should be submitted on the SAE form provided for this purpose. The SAE report must include the Investigator's opinion as to whether the event is study drug-related. If this relationship is determined to be possibly, probably, or definitely related to study drug, evidence to support this assessment must also be provided.

The written report for pregnancies in female subjects and in female partners of male subjects should be submitted on the Pregnancy Report Form provided for this purpose.

15. STATISTICS

15.1. Sample Size Considerations

No formal sample size calculations have been performed. The sample size of 180 subjects is based on practical, clinical considerations.

15.2. General Statistical Methodology

The statistical analysis methods are described below. Additional details will be provided in the Statistical Analysis Plan (SAP) to be finalized before database lock.

In general, summary statistics (n, mean, standard deviation, median, minimum and maximum values for continuous variables and number and percentage of subjects in each category for categorical variables) will be provided for evaluated variables. All individual subject level data will be presented as data listings. All statistical tests and confidence intervals, unless otherwise stated, will be two sided and will be set at alpha=0.05.

15.2.1. Study Populations

15.2.1.1. Safety Population

The Safety population will include all subjects who received at least one dose of study drug (AL injection, AL-NCD injection, 30 mg oral aripiprazole, oral PBO, PBO injection, or PP injection). Safety analyses will be based on the Safety population.

15.2.1.2. Efficacy Population

The Full analysis set (FAS) will include all subjects in the Safety population who have at least one postbaseline assessment of PANSS. Efficacy analyses will be based on the FAS.

15.3. Demographics and Baseline Data

Baseline for each variable will be the last non-missing assessment before the first dosing of randomized study drug on Day 1.

Demographics and baseline characteristics such as gender, age, race, weight, BMI, prior exposure to aripiprazole or risperidone/paliperidone, baseline PANSS, and CGI-S score will be summarized with descriptive statistics to assess the comparability of the study groups. If there are heterogeneities between study groups in any of the subject characteristics that are of clinical importance or could affect the treatment outcome, the impact of the imbalances will be investigated and, if necessary, appropriate adjustments made in the efficacy and safety analyses.

15.4. Efficacy Analyses

15.4.1. Primary Efficacy Endpoint

The change from baseline in the PANSS total score at Week 4 will be tested against no improvement using the one-sample T test for the AL and PP Treatment Groups separately.

15.4.2. Secondary Efficacy Endpoints

The change from baseline in the PANSS total score at Week 9 and Week 25 will be tested against no improvement using the one-sample T test for the AL and PP Treatment Groups separately.

The change from baseline in the PANSS total score at Week 4, at Week 9 or at Week 25 will be compared between the two treatment groups using an analysis of covariance (ANCOVA) with last observation carried forward (LOCF) imputation for missing data. The ANCOVA model will include treatment group, baseline PANSS total score, stratification factor, and the pooled study sites as covariates.

PANSS response based on the observed data or LOCF will also be summarized by treatment group at each visit. A logistic regression model will be used to compare two groups, the model will include the treatment group, baseline PANSS total score, stratification factor, and the pooled study sites as covariates.

Additional imputation approaches will be explored.

15.4.3. Other Efficacy Endpoints

The continuous outcome endpoints (eg, change from baseline in PANSS subscales, CGI-S) will be analyzed using the same ANCOVA with LOCF model. Time from randomization to Readiness for Discharge will be summarized using a Kaplan-Meier plot.

15.5. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

15.6. Safety and Tolerability Analyses

Safety will be evaluated based on the occurrence of AEs, vital signs, results of clinical laboratory tests, and ECG findings, as well as ISRs, AIMS, BARS, SAS, C-SSRS, UKU-SERS-PAT – Sexual Side Effects Subscale, and ESS scores. Reported AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or higher.

Treatment-emergent AEs (TEAEs) are defined as AEs that occur or worsen after the first dose of study drug.

All AEs will be listed. The incidence of TEAEs will be summarized for each study group and overall, by severity and by relationship to study drug. The summary tables will include the number and percentage of subjects with TEAEs overall, by system organ class, and by preferred terms within each system organ class. Similar tables will be prepared for SAEs, TEAEs leading to discontinuation, as well as additional categories of AEs as defined in the SAP.

Concomitant medications will be categorized and presented using the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) drug classification system.

Change from baseline in vital signs measurements, laboratory test results, and ECG parameters will be summarized by treatment group. The number and percentage of subjects with potentially clinically significant values or shift tables will also be summarized by treatment group.

Subjects with suicidal ideation and/or behavior will be summarized.

Injection site reactions reported as AEs and associated information (eg, injection site pain, redness, swelling, etc) will be summarized by treatment group and injection sequence.

The change from baseline in abnormal movement rating scale (ie, AIMS, BARS, and SAS) total scores and subcategory scores will be summarized by treatment group and visit.

Number (percentage) of subjects meeting the criteria treatment-emergent EPS, treatment-emergent akathisia, or treatment-emergent dyskinesia at any postbaseline visits will be summarized.

The UKU-SERS-PAT – Sexual Side Effects Subscale will be summarized by gender and treatment group.

Epworth Sleepiness Scale results will be summarized by treatment group.

Listings will be provided for all safety endpoints. Supporting listings for potentially clinically significant tables will also be provided.

15.7. Analysis of Other Subject or Caregiver Centered Endpoints

The Q-LES-Q-SF total score will be summarized by treatment group.

The Burden Assessment Score and change from baseline will be summarized by treatment group or by caregiver type.

The number and percentage of response for the modified MSQ and WoRQ will be summarized by treatment group.

The number and percentage of subjects who had an ER visit, arrest, or have been incarcerated will be summarized by treatment group.

Handwriting Movement Kinematics and wrist actigraphy results will be summarized by treatment group.

Further analysis details will be specified in the SAP.

16. DIRECT ACCESS TO SOURCE DATA/ DOCUMENTS

16.1. Study Monitoring

Monitoring of the study site (including, but not limited to, reviewing eCRFs for accuracy and completeness) will be performed by an Alkermes Monitor or designee.

16.2. Audits and Inspections

By signing the protocol, the Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of Alkermes, a regulatory authority, and/or an institutional review board (IRB)/independent ethics committee (IEC) may visit the study site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, subject charts and source documents, and other records relative to study conduct. The purpose of an Alkermes audit or inspection is to systematically and independently examine all study-related activities and documents (eg, laboratory reports, x-rays, workbooks, and subjects' medical records) to determine whether these activities were conducted and data recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Council on Harmonisation (ICH), and any applicable regulatory requirements.

The Investigator should contact Alkermes immediately if contacted by a regulatory agency regarding an inspection.

16.3. Institutional Review Board/Independent Ethics Committee

The Investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval, as well as all materials approved by the IRB/IEC for this study, including the subject consent form and recruitment materials, must be maintained by the Investigator and made available for inspection.

17. QUALITY CONTROL AND QUALITY ASSURANCE

This study will be conducted under GCP and all applicable regulatory requirements. To ensure data accuracy, completeness, and compliance, the study site should have processes in place for data review and quality control. Alkermes may also conduct a quality assurance audit. Please see Section 16.2 for details regarding the audit process.

17.1. Case Report Forms

This study will use eCRFs. All eCRF data must be based on source documents or approved to be the original data (ie, data directly reported on the eCRF). All eCRFs will be completed by the clinic staff prior to review by the Alkermes Monitor or designated representative.

The Alkermes Monitor or designated representative will review all source records on site and compare them to the data collected on the eCRF.

17.2. Confidentiality of Data

By signing this protocol, the Investigator affirms to Alkermes that he or she will maintain in confidence information furnished to him or her by Alkermes and will divulge such information to his or her respective IRB or IEC under an appropriate understanding of confidentiality with such board. All data will be considered the sole property of Alkermes. Please refer to the Clinical Study Agreement (CSA) for details.

18. ETHICAL CONSIDERATIONS

18.1. Ethics Review

The study site's IRB/IEC must meet all relevant regulatory requirements. The study protocol and ICF will be reviewed by the IRB/IEC prior to enrolling subjects into the study; written approval from the committee must be received by Alkermes before study drug will be released to the Investigator. The protocol must be reapproved by the IRB/IEC upon receipt of amendments and annually, as local regulatory requirements require.

The Investigator is responsible for submitting all protocol changes and SAE reports to the IRB/IEC according to local procedures. At a minimum, all SAEs requiring an investigational new drug safety report must be immediately reported.

All relevant correspondence from the IRB/IEC will be forwarded by the respective study site to the Sponsor in a timely fashion.

18.2. Ethical Conduct of the Study

This study will be conducted in accordance with the protocol, the ICH Guideline E6, and all applicable local regulatory requirements. Good Clinical Practice is an international ethical and scientific quality standard used for designing, conducting, recording, and reporting studies involving the participation of human subjects. Alkermes is committed to complying with this standard to provide assurance that the rights, safety, and well-being of study subjects will be protected, consistent with the principles having their origin in the Declaration of Helsinki.

18.3. Written Informed Consent

The Investigator (or authorized designee) at each study site will ensure that the subject (or the subject's legal representative) is given full and adequate oral and written information about the nature, purpose, and the potential and possible risks and benefits of the study. Each prospective subject 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 subject and must not include any language that waives the subject's legal rights. Prospective subjects must also be informed of their right to withdraw consent without prejudice at any time during the study. If the subject chooses to participate, he or she must sign the ICF before any study-specific procedures are conducted.

All subjects will be informed of their rights to privacy and will be made aware that the study data will be submitted to Alkermes, the IRB, the CRO, if applicable, and to regulatory authorities for review and evaluation for the duration of the study and until the project has been approved for marketing or is withdrawn from investigation. They will also be informed that the Alkermes Medical Monitor may inspect their medical records to verify the accuracy and completeness of the study records and results.

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 and then signed by all applicable study participants.

The time that informed consent is obtained must be documented. The Investigator must maintain the original signed ICF in the subject's source documents. A copy of the signed ICF must be given to the subject.

19. DATA HANDLING AND RECORDKEEPING

An overview of study data handling and recordkeeping procedures and restrictions is provided in the subsequent sections; please refer to the CSA for further details.

19.1. Data Capture

As stated in Section 17.1, this study will use eCRFs for capturing data. All entries, corrections, and alterations will be made by the Investigator or other authorized study personnel. All data entries will be verified for accuracy and correctness by independent monitors. The electronic data capture system maintains a full audit trail.

A paper copy of all laboratory reports will remain with the source documents at the study site. All electronic source data collected outside of the eCRF, such as e-diaries, and central laboratory, central ECG, or central MRI data, will be transferred directly to electronic data capture or directly to Alkermes for incorporation into the final datasets. All out-of-range laboratory values will be deemed as clinically significant or not clinically significant by the Investigator. Clinically significant values will be considered AEs and will be recorded as such on the eCRFs.

Adverse events will be coded using MedDRA. Concomitant medications will be categorized using the WHO-ATC classification system.

19.2. Inspection of Records

Alkermes or its representative will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the Alkermes Medical Monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and source documents, and other records relative to study conduct.

19.3. Retention of Records

Retention and storage of all essential clinical study documents shall be governed by the terms and conditions of the study site's CSA and in accordance with ICH guidelines/local regulatory requirements as follows:

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by the terms of the CSA. It is the responsibility of the Sponsor to inform the Investigator/ institution as to when these documents no longer need to be retained.

Subjects' medical files should be retained in accordance with the applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution, or private practice.

19.4. Use of Information and Publication Policy

Data generated in this study are proprietary information that are the sole property of Alkermes. Results of the study are to be held in confidence by both the Investigators and the Sponsor.

Please refer to the CSA for details on the procedures for publishing and presenting data.

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21. APPENDIX A: PARTIAL LIST OF PROHIBITED CYP3A INHIBITORS AND INDUCERS

The following is a list of CYP3A inhibitors and inducers that are prohibited 14 days prior to Day 1 and throughout the study. The list is not comprehensive.

Table 10: Partial List of CYP3A Inhibitors and Inducers

Moderate-to-Strong Inhibitors		Moderate-to-Strong Inducers
Aprepitant	Idelalisib	Avasimibe
Boceprevir	Indinavir/Ritonavir[a]	Bosentan
Cimetidine	Itraconazole	Carbamazepine
Ciprofloxacin	Ketoconazole	Efavirenz
Clarithromycin	Lopinavir/Ritonavir[a]	Enzalutamide
Clotrimazole	Mibefradil	Etravirine
Cobicistat	Nefazodone	Mitotane
Conivaptan	Nelfinavir	Modafinil
Crizotinib	Paritaprevir/Ritonavir and (Ombitasvir and/or Dasabuvir)[a]	Phenobarbital
Cyclosporine	Posaconazole	Phenytoin
Danoprevir/Ritonavir[a]	Ritonavir[a]	Rifabutin
Diltiazem	Saquinavir/Ritonavir[a]	Rifampin
Dronedarone	Telaprevir	St. John's Wort
Elvitegravir/Ritonavir[a]	Telithromycin	—
Erythromycin	Tipranavir/Ritonavir[a]	—
Fluconazole	Tofisopam	—
Fluvoxamine	Troleandomycin	—
Grapefruit juice	Verapamil	—
Imatinib	Voriconazole	—

[a] Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.

References: Food and Drug Administration 2016; University of Washington: School of Pharmacy 2017a; University of Washington: School of Pharmacy 2017b

22. APPENDIX B: PARTIAL LIST OF PROHIBITED CYP2D6 INHIBITORS

The following is a list of CYP2D6 inhibitors that are prohibited 14 days prior to Day 1 and throughout the study. The list is not comprehensive.

Table 11: Partial List of CYP2D6 Inhibitors

Moderate-to-Strong Inhibitors	
Bupropion	Fluoxetine
Cimetidine	Mirabegron
Cinacalcet	Paroxetine
Duloxetine	Quinidine
Fluvoxamine	Terbinafine

Reference: Food and Drug Administration 2016

23. APPENDIX C: CAREGIVER INTAKE FORM

Instructions: Collect the following information for each subject's identified caregiver at the Screening visit. In the event a caregiver changes during the study for a given subject, this information should be collected from the newly identified caregiver.

1. Relationship to Subject:
   a. Spouse/Partner/Girlfriend/Boyfriend
   b. Child
   c. Parent/Guardian
   d. Sibling
   e. Friend
   f. Caseworker
   g. Residential Setting Representative
   h. Other, please specify: _____
2. How many hours per week does the caregiver/informant spend with the subject, on average?
   a. < 5 hours per week
   b. 5-9 hours per week
   c. ≥10 hours per week
3. How long has the caregiver/informant known the subject?
   a. < 8 weeks from screening
   b. 8 weeks to 1 year from screening
   c. 1 to 5 years
   d. 5 years or more but less than a lifetime
   e. Lifetime
4.

Can the caregiver/informant comply with the study's obligations?		
a. Complete questionnaires required by the study and follow study site staff's instructions	Yes	No
b. Be available to accompany the subject to required study visits	Yes	No
c. Observe the subject for study related side illness or injury and report them to the study doctor	Yes	No

5.

Did the Investigator meet with the caregiver/informant?	Yes	No

24. APPENDIX D: RESOURCE UTILIZATION FORM

Instructions: Please complete this form with the subject. When possible, confirm information with caregivers. At screening, inquire about the past 3 months. At subsequent visits, the recall period is since the last visit.

1. Since *[date/last visit]*, has the subject visited the ER? (Y/N)
    a. If yes, how many times (__ __)
        i. For each time, what was the date?
            1. Episode 1: (dd MMM yyyy)
            2. Episode 2: (dd MMM yyyy)
            3. Episode 3: (dd MMM yyyy)
        ii. For each time, what was the reason?
            1. Episode 1: (_____)
            2. Episode 2: (_____)
            3. Episode 3: (_____)
2. Since *[date/last visit]*, has the subject been arrested? (Y/N)
    a. If yes, how many times (__ __)
        i. For each time, what was the date?
            1. Episode 1: (dd MMM yyyy)
            2. Episode 2: (dd MMM yyyy)
            3. Episode 3: (dd MMM yyyy)
        ii. For each time, what was the reason?
            1. Episode 1: (_____)
            2. Episode 2: (_____)
            3. Episode 3: (_____)
3. Since *[date/last visit]*, has the subject been incarcerated (in a jail or prison)? (Y/N)
    a. If yes, how many times (__ __)
        i. For each time, what was the date?
            1. Episode 1 Start Date: (dd MMM yyyy)/End Date: (dd MMM yyyy)
            2. Episode 2 Start Date: (dd MMM yyyy)/End Date: (dd MMM yyyy)
            3. Episode 3 Start Date: (dd MMM yyyy)/End Date: (dd MMM yyyy)
        ii. For each time, what was the reason?
            1. Episode 1: (_____)
            2. Episode 2: (_____)
            3. Episode 3: (_____)

4. For recording rater: how did you collect this information? (circle all that apply)
    a. Medical records
    b. Provider report
    c. Subject report
    d. Other (specify): _____

25. APPENDIX E: PROLACTIN BLINDING

To prevent functional unblinding due to the known differential influence on prolactin levels between aripiprazole and paliperidone, postbaseline prolactin levels will be blinded to Investigators and study site staff, Alkermes, and PPD (with the exception of the designated unblinded Medical Monitor).

The unblinded Medical Monitor will remain blinded to treatment assignment, but will receive and monitor prolactin levels for all subjects throughout the study. The unblinded Medical Monitor will contact the Investigator when the pre-defined gender-specific threshold alerts are triggered (see below) to determine if the alert value is clinically significant in the Investigator's opinion.

Alert Thresholds:

- Males: >100 ng/mL
- Females: >150 ng/mL

The alert threshold may be re-evaluated when 50% of subjects have been randomized. Any update to the alert thresholds will not require a protocol amendment, but will be addressed via an administrative change memo.

Investigators may request postbaseline prolactin levels from the unblinded Medical Monitor at their clinical discretion (eg, if a subject has clinical symptoms that may be related to hyperprolactinemia).

Treatment assignments and prolactin levels will be shared with the Investigator at study end when unblinded.