CLINICAL STUDY PROTOCOL

ALK3831-A307

EudraCT 2017-000497-11

Study title:	A Study to Evaluate the Effect of ALKS 3831 Compared to Olanzapine on Body Weight in Young Adults with Schizophrenia, Schizophreniform, or Bipolar I Disorder Who are Early in Their Illness
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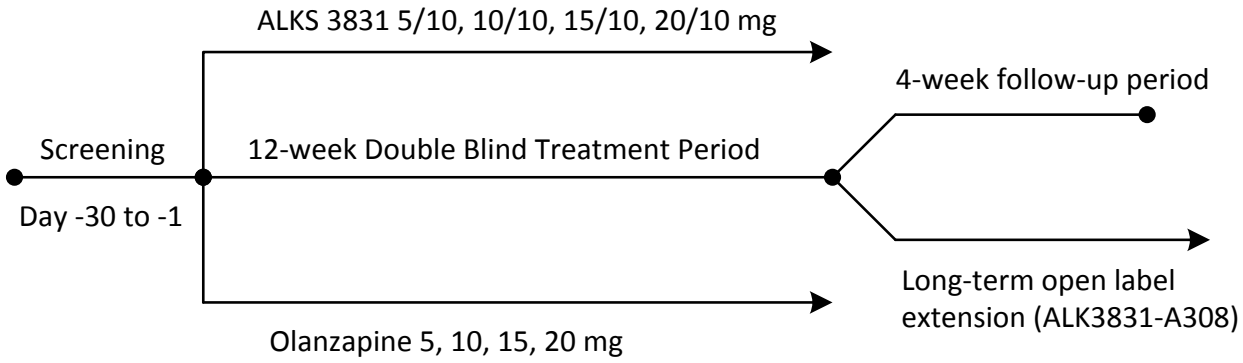
Abbreviations: CRO=contract research organization; SAE=serious adverse event

2. SYNOPSIS

Name of Sponsor/Company: Alkermes, Inc.	
Name of Investigational Product: ALKS 3831	
Name of Active Ingredient: Olanzapine and samidorphan	
Title of Study: A Study to Evaluate the Effect of ALKS 3831 Compared to Olanzapine on Body Weight in Young Adults with Schizophrenia, Schizophreniform, or Bipolar I Disorder Who are Early in Their Illness	
Investigators: This is a multinational multicenter study.	
Study Period: Estimated date of first subject's consent: Q2 2017 Estimated date of last subject's last visit: Q4 2021	**Phase of Development:** 3
Objectives: **Primary:** To evaluate the effect of ALKS 3831, compared to olanzapine, on body weight in young adults with schizophrenia, schizophreniform, or bipolar I disorder who are early in their illness **Secondary:** To evaluate the safety and tolerability of ALKS 3831 in young adults with schizophrenia, schizophreniform, or bipolar I disorder who are early in their illness	
Methodology: This is a Phase 3, multicenter, randomized, double-blind study to evaluate the effect of ALKS 3831 compared to olanzapine on body weight in young adults with schizophrenia, schizophreniform disorder, or bipolar I disorder who are early in their illness. Subjects will be screened at Visit 1, up to 30 days prior to randomization. At Visit 2, eligible subjects will be randomized (1:1) to ALKS 3831 or olanzapine and receive study drug for up to 12 weeks. Randomization will be stratified by diagnosis (schizophrenia/schizophreniform disorder vs bipolar I disorder), region (US vs non-US), and baseline BMI (<25 vs ≥25). Subjects on antipsychotic medications or mood stabilizers (excluding study medication) should be tapered off this medication by the end of Week 2 (Visit 4). Subjects may be inpatient or outpatient at Screening, however in the opinion of the Investigator, all subjects should be appropriate for eventual outpatient treatment. Subjects should be outpatient within 2 weeks post randomization. Cases that require inpatient treatment for longer than 2 weeks will require review and approval by the Medical Monitor on a case by case basis. Starting with Week 2 (Visit 4), subjects will come for biweekly visits for the remaining 10 weeks. Study drug will be provided to subjects as coated bilayer tablets dispensed in blister packs at each visit to be taken at home (one tablet by mouth each day, preferably at bedtime). The doses of olanzapine will be 5, 10, 15, or 20 mg and the doses of ALKS 3831 will be 5, 10, 15, or 20 mg olanzapine combined with 10 mg samidorphan (henceforth will be referred to as 5/10, 10/10, 15/10, or 20/10 mg). For the first week at the discretion of the Investigator, subjects will receive 5 mg, 10 mg, 15 mg, or 20 mg of olanzapine or 5/10 mg, 10/10 mg, 15/10 mg, or 20/10 mg of ALKS 3831. At the end of Week 1, for subjects initiated on 5 mg of olanzapine or 5/10 mg of ALKS 3831, the dose will be increased to 10 mg of olanzapine or 10/10 mg of ALKS 3831. For all other subjects, the dose may also be increased to either 15 or 20 mg of olanzapine or 15/10 or 20/10 mg of ALKS 3831. Following this increase, the dose may be increased or decreased to 5, 10, 15, or 20 mg of olanzapine, or to 5/10, 10/10, 15/10, or 20/10 mg of ALKS 3831 at the Investigator's discretion. Dosing will be flexible throughout the study; however, frequent adjustments are	

discouraged. Dose adjustments can only be performed on-site at the study center. Subjects requiring dose adjustments between scheduled visits should arrange an unscheduled visit.

Body weight, body composition (measured by Bioelectrical Impedance Analysis [BIA]), and metabolic parameters (including fasting triglycerides, cholesterol and glucose) will be measured throughout the 12-week treatment period. Psychiatric symptoms will be evaluated using the Clinical Global Impressions (CGI) scales. Additional assessments will include Impact of Weight on Quality of Life-Lite Questionnaire (IWQOL-Lite). A daily medication adherence monitoring and reminder system (via smartphones) may be used in this study. In addition, subjects will be asked to participate in a supportive clinical care (SCC) program during the 12-week treatment period. Participation in the SCC program will be independent of study visits and based on clinician and subject preference. A schematic summarizing study design is presented below.



Number of Subjects Planned: Approximately 425 subjects will be randomized in order to have 400 subjects in the efficacy population (200 per treatment group).

Main Criteria for Inclusion: For US sites, men and women ≥16 through <40 years of age at Screening. For non-US sites, men and women ≥18 through <40 years of age at Screening. Subjects will have a body-mass index (BMI) of <30.0 kg/m^2 at Screening and Visit 2, with a Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) primary diagnosis of schizophrenia, schizophreniform disorder, or bipolar I disorder and meet Sponsor criteria for previous antipsychotic treatment and duration of illness. Subjects with bipolar I disorder must have experienced an acute episode of mania as defined by DSM-5 within the last 14 days prior to Visit 1.

Main Criteria for Exclusion: Subjects may be excluded based on diagnosis of additional psychiatric conditions, use of prohibited or contraindicated drugs and medications, pre-existing medical conditions, abnormal lab results during Screening, participation in any recent clinical trials or previous clinical trials of ALKS 3831 or samidorphan, pregnancy and relationship to an employee of the study Sponsor, CRO, Investigator, or study site.

Investigational Product, Dosage, Duration, and Mode of Administration: ALKS 3831 refers to the fixed dose combination of olanzapine and samidorphan. ALKS 3831 will be supplied as a coated bilayer tablet containing 5, 10, 15, or 20 mg olanzapine and 10 mg samidorphan. The tablet will be taken by mouth once daily, preferably at bedtime, for up to 12 weeks.

Reference Therapy, Dosage, Duration, and Mode of Administration: Olanzapine will be supplied as an identical bilayer tablet manufactured by Alkermes, Inc., containing 5, 10, 15, or 20 mg of olanzapine only and no additional active ingredients. Olanzapine tablets will be taken by mouth once daily, preferably at bedtime, for up to 12 weeks.

Duration of Study: The total study duration will be approximately 20 weeks including a 4-week Screening Period, a 12-week Treatment Period, and a 4-week Follow-up Period. Subjects completing the treatment period will be eligible to enroll in a long-term safety study (ALK3831-A308) where it is

approved by the local regulatory authority. Subjects not enrolling in the long-term safety study will enter the 4-week safety Follow-up Period.

Criteria for Evaluation:

Primary Endpoint:

- Percent change from baseline in body weight at Week 12

Secondary Endpoints:

- Proportion of subjects with ≥10% weight gain at Week 12
- Proportion of subjects with ≥7% weight gain at Week 12
- Change from baseline in waist circumference at Week 12
- Change from baseline in Clinical Global Impression-Severity (CGI-S) score within the ALKS 3831 Group at Week 12

Other Endpoints:

- Absolute change from baseline in body weight by visit
- Proportion of subjects with ≥5 cm increase in waist circumference from baseline at Week 12
- Body composition endpoints, as assessed by bioimpedance analysis, including:
  - Change from baseline in fat mass by visit
  - Change from baseline in percent body fat by visit
  - Change from baseline in fat mass index by visit
  - Change from baseline in visceral adipose tissue by visit
  - Change from baseline in lean mass by visit
  - Change from baseline in fat free mass index by visit
  - Change from baseline in total skeletal muscle mass by visit
- Percent and absolute change from baseline in fasting lipids (fasting triglycerides, low-density lipoprotein, high-density lipoprotein, total cholesterol), fasting glucose, HbA1c, and fasting insulin by visit
- Percent and absolute change from baseline in additional laboratory parameters including apolipoprotein B (Apo B), apolipoprotein A1 (Apo A1), Apo B/Apo A1, high-sensitivity C-reactive protein, interleukin-6, and tumor necrosis factor α by visit
- Change from baseline in CGI-S score (between and within treatment groups) by visit
- Change from baseline in CGI-S score (between and within treatment groups) by visit and by diagnosis
- CGI-I score by visit
- Change from baseline in IWQOL-Lite score by visit

Statistical Methods: In general, summary statistics (n, mean, standard deviation, median, minimum, and maximum for continuous variables, and number [%] of subjects in each category for categorical variables) will be provided by treatment group for all variables. Source data for the summary tables and statistical analyses will be presented as subject data listings.

Study Populations: The Safety Population will include all randomized subjects who receive at least

one dose of study drug (ALKS 3831 or olanzapine). The efficacy population, ie full analysis set (FAS), will include all subjects in the Safety Population who have at least one post-Baseline weight assessment.

Efficacy Analyses: The efficacy analysis will be carried out using the FAS population. The primary analysis of the primary endpoint will be carried out using an analysis of covariance method (ANCOVA) based on multiple imputation (MI) for missing data using on-treatment weight assessments. The model will include the treatment group and randomization strata as factors and the baseline weight as the covariate. Sensitivity analyses will be carried out to explore the impact of missing data.

For the categorical secondary endpoints of proportion of subjects with ≥10% and ≥7% weight gain at Week 12, the analyses will be carried out using a logistic regression model based on MI for missing data. The model will include the treatment group and randomization strata as factors, and the baseline weight as the covariate. For the change from baseline in waist circumference at Week 12, the analysis will be based on the ANCOVA method with MI for missing data, same as the primary analysis of the primary endpoint. For change from baseline in CGI-S within ALKS 3831 Group at Week 12, the analysis will be based on the mixed model with repeated measurements. The model will include randomization strata, treatment, visit, and treatment-by-visit interaction term as factors; the baseline CGI-S value will be included as a covariate.

To control the overall Type I error rate, hierarchical testing will be performed in the following order: (1) percent change from baseline in body weight at Week 12, (2) proportion of subjects with ≥10% weight gain from baseline at Week 12, (3) proportion of subjects with ≥7% weight gain from baseline at Week 12, (4) change from baseline in waist circumference at Week 12, (5) change from baseline in CGI-S score within the ALKS 3831 Group at Week 12.

Safety Analyses: The safety analysis will be carried out using the Safety Population. All safety assessments will be summarized using descriptive statistics. All safety analyses will be based on observed data only, and no missing values will be imputed. Reported AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by preferred term and system organ class categories.

Observed values and change from baseline in laboratory parameters, vital signs, and ECG parameters will be summarized by treatment group and study visit.

Prior and concomitant medication use will be summarized by World Health Organization Anatomical Therapeutic Chemical (WHO ATC) classification system. Listings will be provided for all concomitant medications.

Pharmacokinetic Analyses: Listings will be provided for concentrations of olanzapine, samidorphan and metabolites of interest. Pharmacokinetic concentrations may be used in a subsequent population PK analysis conducted outside of this study.

Sample Size Considerations: Approximately 425 subjects will be randomized in order to have 400 subjects in the efficacy population (200 per treatment group). Assuming the percent weight gain at week 12 is 5% and 8.5% for ALKS 3831 and olanzapine groups, respectively, a common standard deviation of 8%, and a cumulative dropout rate of 35%, 200 subjects per treatment group (400 subjects in total) will provide at least 90% power to demonstrate a difference of ALKS 3831 relative to olanzapine at a 2-sided significance level of 0.05.

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4. LIST OF ABBREVIATIONS

Table 2: List of Abbreviations and Definition of Terms

Abbreviation or Term	Full Form or Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
Apo A1	Apolipoprotein A1
Apo B	Apolipoprotein B
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical [classification system]
BIA	Bioelectrical Impedance Analysis
BMI	Body-mass index
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CGI	Clinical Global Impressions
CGI-I	Clinical Global Impressions-Improvement
CGI-S	Clinical Global Impressions-Severity
CSA	Clinical Study Agreement
C-SSRS	Columbia-Suicide Severity Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
ET	Early termination
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
hs-CRP	high-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Abbreviation or Term	Full Form or Definition
IEC	Independent Ethics Committee
IL-6	Interleukin 6
IRB	Institutional Review Board
IWQOL-Lite	Impact of Weight on Quality of Life–Lite
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MINI v7.0	Mini International Neuropsychiatric Interview 7.0 for Schizophrenia and Psychotic Disorder Studies
MINI KID v7.0	Mini International Neuropsychiatric Interview for Children and Adolescents 7.0 for Schizophrenia and Psychotic Disorder Studies
MMRM	Mixed model with repeated measurements
OTC	Over-the-counter
PANSS	Positive and Negative Syndrome Scale
PK	Pharmacokinetic
PI	Principal Investigator
PORT	Patient Outcomes Research Team
QTcB	QT interval corrected using the Bazett formula
QTcF	QT interval corrected using the Fridericia formula
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCC	Supportive clinical care
SOP	Standard operating procedures
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment-emergent adverse event
TNFα	Tumor necrosis factor alpha
WHO	World Health Organization

5. INTRODUCTION

5.1. Background

First- and early-episode schizophrenia and bipolar I disorder are critical phases of the diseases where optimal antipsychotic efficacy is crucial. Patients in these early stages are at higher risk for suicide and violence (Hawton et al, 2005; Hayes et al, 2015; Hodgins 2008; Kuo et al, 2005). Additionally, many therapeutic experts consider this time in the course of the disease as the best opportunity for aggressive treatment in order to retain brain function, alter disease trajectory and improve long term treatment outcomes in patients with schizophrenia or bipolar I disorder (Berk et al, 2011; Berk et al, 2009; Lieberman et al, 2006; Tohen et al, 2010).

Olanzapine has been commercially available for over 20 years as a treatment for schizophrenia and bipolar I disorder (see local olanzapine label) and is regarded as a highly effective treatment with demonstrated antipsychotic efficacy and decreased incidence of extrapyramidal symptoms. However, the greater antipsychotic efficacy of olanzapine is undermined by its propensity to cause significant weight gain and increased cardio metabolic risk compared to other atypical antipsychotic drugs (Allison et al, 1999; Leucht et al, 2013; Lieberman et al, 2005; Meyer et al, 2008; Wirshing et al, 1999). Drug-induced weight gain is a major problem in terms of reduced adherence, treatment discontinuation, and exposure to serious long-term obesity-related risks that may shorten life expectancy. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, olanzapine demonstrated robust antipsychotic efficacy with a rapid and significant decrease in Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions-Severity (CGI-S) scores, as well as the least hospitalizations due to exacerbation of schizophrenia compared to other antipsychotics tested, and the lowest all-cause discontinuation rate. However, a larger proportion of subjects in the olanzapine group (9%) discontinued treatment during the 18 month period due to drug-induced weight and metabolic issues compared to the other treatment groups (quetiapine: 4%; risperidone: 2%; perphenazine: 1%; and ziprasidone: 3%; (Lieberman et al, 2005). Furthermore, for subjects in the olanzapine group with Baseline body mass index (BMI) $\leq$30 kg/m^2, weight increased over the study duration (4.7% at 12 weeks, 7.7% at 24 weeks, 9.3% at 48 weeks, and 10.1% at 60 weeks). From a physician's perspective, olanzapine-induced weight gain and metabolic issues, not lack of efficacy, are the primary reasons for discontinuing or not starting treatment with olanzapine.

Olanzapine is recommended as a second-line treatment in patients early in illness according to the Schizophrenia Patient Outcomes Research Team (PORT) treatment guidelines (Buchanan et al, 2010). This is largely due to the fact that olanzapine-induced weight gain and metabolic risk are especially pronounced in patients who are early in illness for both schizophrenia and bipolar disorder (Correll et al, 2014).

Alkermes is developing ALKS 3831 as a fixed-dose combination of olanzapine and samidorphan (a μ-opioid receptor antagonist) to address the serious side effect of weight gain and metabolic consequences associated with olanzapine treatment. The novel combination of olanzapine and samidorphan in ALKS 3831 has the potential to deliver the therapeutic benefits of olanzapine to patients, while avoiding the harmful weight gain and associated metabolic risks. The potential to reduce the weight gain and metabolic effects is even more important in patients who are very

early in their illness of schizophrenia or bipolar disorder. In these patients, the weight gain and metabolic effects associated with olanzapine treatment are even greater than those seen in patients who have been treated with multiple different antipsychotics and who are later in the course of their illness.

A Phase 2 study (Study ALK3831-302) was conducted to evaluate the antipsychotic efficacy and body weight effect of ALKS 3831 in adults with established schizophrenia (first antipsychotic treatment lasted longer than 1 year, symptoms lasting greater than 2 years). In Part A (a 12-week, double-blind, randomized, olanzapine-controlled phase), ALKS 3831 demonstrated similar antipsychotic efficacy compared with olanzapine, based on PANSS total score. ALKS 3831 also led to clinically and statistically significantly less body weight gain compared to olanzapine.

In a 24-week Phase 3 study (ALK3831-A303) comparing ALKS 3831 and olanzapine treatment, ALKS 3831 limited olanzapine-induced weight gain and increases in waist circumference in subjects with schizophrenia. Subjects treated with ALKS 3831 gained less weight across a range of clinically meaningful cutoffs, and had a lower mean percent change in body weight at the end of the treatment period. The inclusion of samidorphan in ALKS 3831 limited olanzapine-induced weight gain and retained similar antipsychotic efficacy.

In a 52-week open-label Phase 3 study (ALK3831-A306) designed to evaluate the long-term safety and tolerability of ALKS 3831 in subjects with schizophrenia, ALKS 3831 was generally well tolerated and continued antipsychotic efficacy was observed.

A Phase 3 study (ALK3831-A305) was conducted to evaluate antipsychotic efficacy and safety in adults with an acute exacerbation of schizophrenia. In the 4-week study ALKS 3831 demonstrated antipsychotic efficacy as evidenced by a statistically significant and clinically meaningful improvement in PANSS and CGI-S scores relative to placebo.

Another open-label Phase 3 study (ALK3831-A304) is ongoing to assess the efficacy, associated weight changes, and long-term safety of ALKS 3831 in adults.

The current Phase 3 study will further evaluate the effect of ALKS 3831 compared to olanzapine on body weight in young adults with schizophrenia, schizophreniform, or bipolar I disorder with a recent onset of symptoms and early in medical treatment.

5.2. Study Drugs

In this study, a fixed-dose combination of olanzapine and samidorphan will be administered in a single bilayer tablet. The following sections provide an overview of samidorphan and olanzapine. Detailed information about the study drugs can be found in the current ALKS 3831 Investigator's Brochure.

5.2.1. Samidorphan

Samidorphan is a new molecular entity in clinical development by Alkermes. Samidorphan is a μ-opioid receptor antagonist. It is currently being investigated in combination with olanzapine for the treatment of schizophrenia (ALKS 3831) and in combination with buprenorphine for the treatment of major depressive disorder (ALKS 5461). Based on its chemical structure, samidorphan is considered a Schedule II controlled substance according to the US Drug Enforcement Agency, and will require proper handling (see Section 10). At least 10 clinical studies of samidorphan have been conducted to date, eight of which included subjects that

received samidorphan alone (not in combination with another product). Overall, over 2000 subjects have been exposed to samidorphan as a single agent, or in combination with olanzapine or buprenorphine in completed and ongoing clinical studies. Commonly reported adverse events (AEs) observed across all studies included nausea, fatigue, and somnolence. Overall, no trends or clinically meaningful changes have been observed in clinical laboratory analytes, vital sign parameters, or electrocardiogram (ECG) data.

5.2.2. Olanzapine

Olanzapine has been commercially available for over 20 years as a treatment for schizophrenia and bipolar I disorder (see local olanzapine label). The safety and tolerability profile of olanzapine is well documented, supported by extensive clinical studies and clinical experience of over 20 years (see local olanzapine label). Commonly reported AEs consistent across all or most dosage forms in short-term, placebo-controlled trials include somnolence, constipation, dry mouth, accidental injury, weight gain, postural hypotension, dizziness, asthenia, fever, and abnormal gait.

5.3. Study Rationale

This study will be the first study to evaluate the effect of ALKS 3831 compared to olanzapine on body weight in subjects who are very early in their course of illness, have bipolar I disorder, or are adolescents. Previous studies of ALKS 3831 have excluded subjects who had less than 1 year since initiating first antipsychotic treatment or since the onset of initial symptoms. The effects of the combination of olanzapine and samidorphan to prevent the weight and metabolic changes seen with olanzapine alone are expected to be independent of the diagnosis of the subjects. Significant weight gain is seen in both schizophrenia and bipolar subjects treated with olanzapine and, thus, it is important to include both diagnoses in a study assessing, in particular, the differences in weight gain seen between olanzapine and ALKS 3831. The onset of schizophrenia is rare before the age of 13, but the rate steadily increases in adolescence, with a peak onset of 15 to 30 years (Sham et al, 1994). The most common age of onset of bipolar disorder is 17 to 21 years (with a mean age of onset of 18 years (Merikangas et al, 2007). As the age of onset of both disorders is frequently around 18 years old or slightly younger, it was decided in this study to permit the inclusion in the US of older adolescent subjects (≥16 years old). Schizophrenia and bipolar I disorder are both characterized by a typical age of onset in the early- to mid-twenties (American Psychiatric Association 2013; Blanco et al, 2016). Gender differences have been described with schizophrenia such that women tend to experience their first episode later than men, showing a peak age of onset in the late twenties, with a second peak in the mid- to late-forties (Hafner 2003; Rabinowitz et al, 2006). Given the range of ages over which patients can be considered early in illness, this study will include young adults and adolescents, ages 16 to 39.

The major focus of this study is to evaluate weight gain on treatment, irrespective of diagnosis, in a particularly sensitive population. Based on ALK3831-302, the addition of samidorphan to olanzapine in ALKS 3831 does not appear to affect the antipsychotic efficacy of olanzapine. Thus, all subjects in this study will be treated with active antipsychotic treatment. It is expected that the antipsychotic efficacy will be similar in both treatment arms. The antipsychotic efficacy of treatment during the study will be assessed by the CGI-S and CGI-Improvement (CGI-I) scales, which quantify clinicians' overall impression of clinical severity and clinical change in

individuals' psychiatric condition (Lepping et al, 2011). The CGI scales have been widely used as a primary outcome measure in clinical trials of medications for depression, schizophrenia, and many other illness conditions (including bipolar disorder; (Spearing et al, 1997). Relapse of schizophrenia, schizophreniform disorder, or bipolar I disorder will be defined by a worsening in a subject's CGI-S score or a hospitalization for worsening of the underlying illness. Additional information regarding nonclinical and clinical studies conducted to date with ALKS 3831 is available in the current version of the Investigator's Brochure.

5.4. Dose Rationale

The selected doses of ALKS 3831 in the current study are supported by the dosing recommendations for olanzapine per the local olanzapine label and the clinical safety, tolerability, and efficacy data from prior studies with ALKS 3831. The 10 mg samidorphan dose was identified as the minimal effective dose in adults based on the efficacy and optimal safety profile observed in Study ALK3831-302. A fixed dose of samidorphan was selected due to the fact that data from Study ALK3831-302 demonstrated no correlation between the ratio of samidorphan/olanzapine dose and percent change from Baseline in body weight after 12 weeks of treatment, indicating that, even with higher olanzapine doses, a fixed dose of samidorphan is sufficient to achieve maximal effect in reducing olanzapine-induced weight gain.

All subjects will be randomized to receive ALKS 3831 or olanzapine. Treatment assignment will be blinded; however, olanzapine dose will be unblinded. The doses of olanzapine will be 5, 10, 15, or 20 mg, and the doses of ALKS 3831 will be 5, 10,15, or 20 mg olanzapine combined with 10 mg samidorphan (henceforth referred to as 5/10, 10/10, 15/10, or 20/10 mg).

5.5. Benefit-Risk Assessment

As stated in the background section, first- and early-episode schizophrenia and bipolar I disorder are critical phases of the diseases, where optimal antipsychotic efficacy is crucial. Treatment with ALKS 3831 combines the advantages of the antipsychotic efficacy of olanzapine in treating both schizophrenia and bipolar disorder, with the potential to mitigate the known effect of olanzapine treatment of excessive weight gain. The antipsychotic efficacy seen in stable subjects treated in study ALK3831-302 was similar between ALKS 3831 and olanzapine as measured by Total PANSS and CGI scores. Based on the available data from the completed studies in healthy volunteers (ALK33-301) and in subjects with schizophrenia (ALK3831-302), subjects treated with ALKS 3831 have been shown to gain less weight compared to subjects treated with olanzapine alone. In ALK3831-302, the prevention of weight gain persisted during the 3-month ALKS 3831 treatment period.

The important identified risks associated with the use of olanzapine include weight gain, glucose dysregulation, and dyslipidemia. For additional information on the known risks of olanzapine, see the local label. The safety profile of ALKS 3831 is consistent with that of olanzapine (see local label). In study ALK3831-302, the only adverse events reported with ALKS 3831 treatment occurring in ≥5% of subjects and at ≥2 times the rate of olanzapine alone were somnolence, sedation, dizziness, and constipation. Notably, these are all labeled events for olanzapine. The most common adverse events noted in clinical studies in >2% of subjects with ALKS 3831 to date have been somnolence, dizziness, weight increased, sedation, increased appetite, headache, orthostatic hypotension, and liver function test abnormal (see current ALKS 3831 Investigator's

Brochure). In summary, data from the completed ALKS 3831 studies have demonstrated a favorable benefit-risk profile for further investigating ALKS 3831 in subjects with schizophrenia, schizophreniform disorder, or bipolar I disorder.

6. OBJECTIVES

6.1. Primary Objective

The primary objective of this study is to evaluate the effect of ALKS 3831, compared to olanzapine, on body weight in young adults with schizophrenia, schizophreniform, or bipolar I disorder who are early in their illness.

6.2. Secondary Objective

The secondary objective of this study is to evaluate the safety and tolerability of ALKS 3831 in young adults with schizophrenia, schizophreniform, or bipolar I disorder who are early in their illness.

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 qualify for participation in this study.

1. Subject is willing and able to give informed consent/assent, as per local requirements
2. Subject meets the following antipsychotic treatment and duration of illness eligibility requirements:
   - Subject has less than 24 weeks previous treatment with antipsychotics (cumulative; lifetime)
     - Subject treated with aripiprazole can receive an additional 1 year of treatment at ≤5 mg/day, and this treatment will not be considered as part of the 24 weeks of previous treatment with antipsychotics
   - Subject has less than 4 years elapse since the initial onset of active phase of symptoms
   - For subjects currently taking antipsychotic medication, the subject and the treating physician feel that a switch in medication is needed (ie, unsatisfactory clinical response, AEs, or nonadherence to current medication)
3. For US sites, subject is ≥16 and <40 years of age at Screening. For subjects ≥16 and <18 years of age, must have had previous antipsychotic exposure. For non-US sites, subject is ≥18 and <40 years of age at Screening
4. Subject has a BMI <30.0 kg/m^2 at Screening
5. Subject agrees to use an acceptable method of contraception for the duration of the study and for 30 days after any study drug administration, unless surgically sterile or postmenopausal (please refer to Section 8.4.1 for additional details regarding contraception)
6. Subject meets the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) criteria for a primary diagnosis of schizophrenia, schizophreniform disorder, or bipolar I disorder, confirmed with the Mini International Neuropsychiatric Interview 7.0 for Schizophrenia and Psychotic Disorder Studies (MINI v7.0) for subjects ≥18 years of age, or with the Mini International Neuropsychiatric Interview for Children and Adolescents 7.0 for Schizophrenia and Psychotic Disorder Studies (MINI KID v7.0) for subjects 16 to <18 years of age at Visit 1
7. For subjects with bipolar I disorder, they must have been experiencing an episode of acute mania as defined by DSM-5 within the last 14 days prior to Visit 1

8. Subject is suitable for eventual outpatient treatment based on the opinion of the Investigator and review of medical and clinical history by the Sponsor (or designee)

7.2. Subject Exclusion Criteria

Each subject must not have any of the following conditions to qualify for participation in this study.

7.2.1. Psychiatric Exclusion Criteria

1. Subject has any of the following psychiatric conditions per DSM-5 criteria, as assessed by the MINI v7.0 or MINI KID v7.0. Conditions not assessable by the MINI v7.0 or MINI KID v7.0 should be assessed by clinical judgment:
   - Diagnosis of schizoaffective disorder, bipolar II disorder or current, untreated, or unstable major depressive disorder
   - Clinically significant cognitive difficulties, including dementia, delirium, or amnestic syndromes, or any other cognitive disorder, except for cognitive impairment associated with schizophrenia and bipolar I disorder present within the past 2 years that could interfere with participation in the study
   - Drug-induced or toxic psychosis
   - Alcohol or drug use (with the exception of nicotine) disorder, moderate or severe, currently or at any time during the 3 months prior to Visit 1
   - Any other psychiatric condition that could interfere with participation in the study
2. Subject poses a current suicide risk at Visit 1 or Visit 2, in the opinion of the Investigator, and as confirmed by the following:
   - Answers "Yes" on items 4 or 5 from the Columbia-Suicide Severity Rating Scale (C-SSRS) with ideation or suicidal behavior occurring within the past year

7.2.2. Exclusion Criteria based on Treatment History

3. Subjects on medications that are prohibited (see Section 8.4.2)
4. Subject has a history of using olanzapine >14 days (cumulative) during the 6 months prior to Visit 1, or a has a lifetime history of using olanzapine for >3 weeks (cumulative), or has a history of poor or inadequate response to treatment with olanzapine
5. Subject has been treated with long-acting injectable antipsychotic medication within the 2 months prior to screening, or has >6 months cumulative lifetime use; subject has received treatment with electroconvulsive therapy in their lifetime
6. Current treatment with mood stabilizers (eg, lithium, valproate, etc.) that exceeds 2 months prior to Visit 1

7.2.3. Exclusion Criteria based on Drug/Alcohol Use and Concomitant Medications

7. Subject has a positive drug screen for opioids, phencyclidine, amphetamine, methamphetamine, or cocaine at Visit 1 or Visit 2
8. Subject has taken opioid agonists (eg, codeine, oxycodone, tramadol, or morphine) within the 14 days prior to Visit 1 and/or anticipates a need to take opioid medication during the

study period (eg, planned surgery), or has taken opioid antagonists including naltrexone (any formulations) and naloxone within 60 days prior to Visit 1

9. Subject is taking any weight loss agents or hypoglycemic agents at Visit 1

7.2.4. Exclusion Criteria based on Medical Conditions/Medical History

10. Subject has a known or suspected intolerance, allergy, or hypersensitivity to olanzapine, opioid antagonists, or any of the ingredients of the study drug (see Section 10.1) at Visit 1
11. Subject has a clinically significant or unstable medical illness, condition, or disorder that would be anticipated to potentially compromise subject safety or adversely affect the evaluation of efficacy
12. Subject has a personal or family history of neuroleptic malignant syndrome, or has had clinically significant tardive dyskinesia
13. Subjects with a history of or current neurologic conditions, including seizures (excluding febrile seizures), head trauma, or brain injury, should be discussed with the Sponsor prior to study entry
14. Subjects with a history of any illness or procedures (including inflammatory bowel disease, GI surgery, liposuction, or eating disorders) that could change weight should be discussed with the Sponsor prior to study entry
15. Subject has joined a weight management program or had significant changes in diet or exercise regimen within the 6 weeks prior to Visit 1 or plans to join a weight management program during the study
16. Subject has started a smoking cessation program within the 6 months prior to Visit 1 or anticipates quitting smoking during the study
17. Subject has a history of diabetes
18. Subject has had a significant blood loss (>500 mL) or blood product donation (including platelets or plasma) within 60 days of Visit 1, or anticipated blood or blood product donation at any time during the study period
19. Subject has known risk of narrow-angle glaucoma

7.2.5. Exclusion Criteria Based on Laboratory Assessments

20. Subject has a laboratory abnormality that would compromise the well-being of the subject, or has any of the following specific laboratory results at Visit 1:
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) value ≥2 times the upper limit of the laboratory normal reference range
    - Absolute neutrophil count (ANC) $<1.2 \times 10^3$ per μL
    - Platelet count $\leq 75 \times 10^3$ per μL
    - Serum creatinine >2.0 mg/dL for males and >1.5 mg/dL for females

21. Subject has a positive serology test for hepatitis B surface antigen, hepatitis C antibody confirmed by ribonucleic acid (RNA) testing, or human immunodeficiency virus (HIV) antibody at Visit 1
22. Subject has dyslipidemia, defined for this study as total fasting cholesterol >280 mg/dL or fasting triglycerides >500 mg/dL, at Visit 1
23. Subject has a Hemoglobin A1c (HbA1c) ≥6.0% at Visit 1
24. Subject has a fasting plasma glucose ≥126 mg/dL (7.0 mmol/L) at Visit 1
25. Subject has a clinically significant ECG abnormality at Visit 1
    - Subject has a QT interval >450 msec for men and >470 msec for women, as corrected by the Fridericia formula (QTcF), observed at Visit 1

7.2.6. General Exclusion Criteria

26. Subjects with an electronic implant of any kind (eg, pacemaker) or any active prostheses
27. Subject is currently pregnant or breastfeeding, or is planning to become pregnant during the study or within 30 days of the last study drug administration
28. Subject has any finding that, in the view of the Investigator or Medical Monitor, would compromise the subject's ability to fulfill the protocol visit schedule or study requirements
29. Subject has participated in another clinical trial in which the subject received an experimental or investigational drug or agent within 3 months before Visit 1 by self-report or through confirmation using a clinical trial subject registry
30. Subject has participated in a prior clinical study of ALKS 3831 or samidorphan
31. Subject is employed by the Sponsor, contract research organization (CRO), Investigator, or study site (permanent, temporary contract worker, or designee responsible for the conduct of the study), or is immediate family[1] of the Sponsor, Investigator, or study site employee

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. If a subject has an ANC $<1.0 \times 10^3$ per μL or HbA1c ≥6.5% at any time, the Principal Investigator (PI; or designee) should discontinue the subject from participation immediately. Reasons for discontinuation include:

- AE
- Lack of efficacy

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

- Lost to follow-up
- Withdrawal by subject
- Protocol deviation (including noncompliance with study drug or study procedures)
- Pregnancy
- Study terminated by Sponsor
- Other

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 Safety Follow-up 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 who terminate the treatment early (prior to Visit 9) will be asked to complete an Early Termination (ET) Visit and the Safety Follow-up Period (Visits 10 and 11). The ET Visit should be scheduled as close as possible to the subject's last dose and will mimic the assessments scheduled to be conducted at Visit 9. Subjects will then be asked to return to the study center for biweekly visits until the end of planned treatment, to collect the following information: weight, waist circumference, body composition, AEs, and concomitant medications. If the subject fails or refuses to return to the study center, 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 Phase 3, multicenter, randomized, double-blind study to evaluate the effect of ALKS 3831 compared to olanzapine on body weight in young adults with schizophrenia, schizophreniform disorder, or bipolar I disorder who are early in their illness.

Subjects will be screened at Visit 1, up to 30 days prior to randomization. At Visit 2, eligible subjects will be randomized 1:1 to ALKS 3831 or olanzapine, and receive study drug for up to 12 weeks. Randomization will be stratified by diagnosis (schizophrenia/schizophreniform disorder vs bipolar I disorder), region (US vs non-US), and baseline BMI (<25 vs ≥25). Subjects on antipsychotic medications or mood stabilizers (excluding study medication) should be tapered off this medication by the end of Week 2 (Visit 4). Subjects may be inpatient or outpatient at Screening; however, in the opinion of the Investigator, all subjects should be appropriate for eventual outpatient treatment. Subjects should be outpatient within 2 weeks postrandomization. Cases that require inpatient treatment for longer than 2 weeks will require review and approval by the Medical Monitor on a case by case basis.

Starting with Week 2 (Visit 4), subjects will come for biweekly visits for the remaining 10 weeks. Study drug will be provided to subjects as coated bilayer tablets dispensed in blister packs at each visit to be taken at home (one tablet by mouth each day, preferably at bedtime). For the first week, at the discretion of the Investigator, subjects will receive 5, 10, 15, or 20 mg of olanzapine, or 5/10, 10/10, 15/10, or 20/10 mg of ALKS 3831. At the end of Week 1, for subjects initiated on 5 mg of olanzapine or 5/10 mg of ALKS 3831, the dose will be increased to 10 mg of olanzapine or 10/10 mg of ALKS 3831. For all other subjects, the dose may also be increased to either 15 or 20 mg of olanzapine, or 15/10 or 20/10 mg of ALKS 3831. Following this increase, the dose may be increased or decreased to 5, 10, 15, or 20 mg of olanzapine, or to 5/10, 10/10, 15/10, or 20/10 mg of ALKS 3831 at the Investigator's discretion. Dosing will be flexible throughout the study; however, frequent adjustments are discouraged. Dose adjustments can only be performed on-site at the study center. Subjects requiring dose adjustments between scheduled visits should arrange an unscheduled visit for the following procedures: study drug return and dispensation, adherence review, AE, and concomitant medication monitoring.

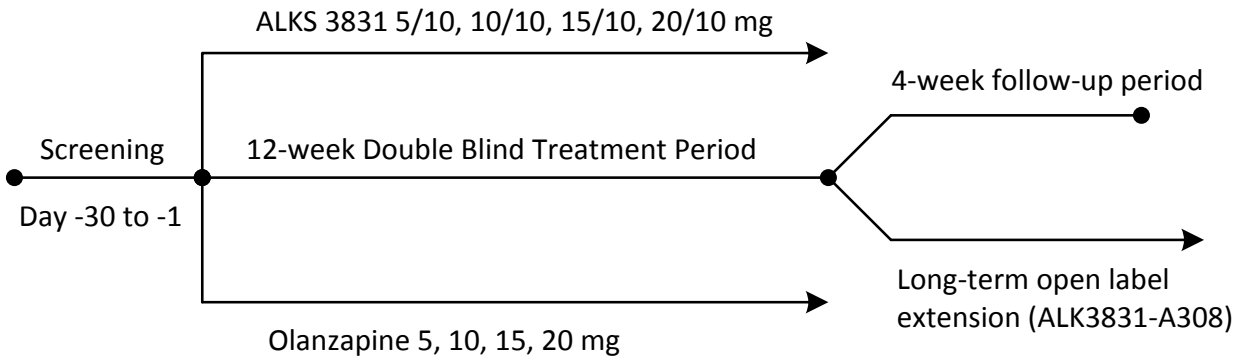
Body weight, body composition (measured by Bioelectrical Impedance Analysis [BIA] using a Body Composition Analyzer), and metabolic parameters (including fasting triglycerides, cholesterol, and glucose) will be measured throughout the 12-week treatment period. Psychiatric symptoms will be evaluated using the CGI scales. Additional assessments will include Impact of Weight on Quality of Life – Lite Questionnaire (IWQOL-Lite). A daily medication adherence monitoring and reminder system (via smartphones) may be used in this study. In addition, subjects will be asked to participate in a supportive clinical care (SCC) program during the 12-week treatment period. Participation in the SCC program will be independent of study visits and based on clinician and subject preference.

The total study duration will be approximately 20 weeks, including a 4-week Screening Period, a 12-week Treatment Period, and a 4-week Follow-up Period. Subjects completing this study will be eligible to enroll in a long-term safety study (ALK3831-A308), where it is approved by the

local regulatory authority. Subjects not enrolling in the long-term safety study will enter the 4-week Safety Follow-up Period and return to their normal standard of care once their participation has ended. A schematic of the study design is provided in Figure 1.

The end of trial is defined as the date of the last subject's last visit.

Figure 1: Study Design



8.2. Schedule of Visits and Assessments

The schedule of assessments is shown in Table 3.

For a missed visit, the site should attempt to contact the subject to reschedule.

Premature discontinuation procedures are provided in Section 7.3.

Table 3: Schedule of Assessments

	SCN Day -30 to -1	12-Week Double-Blind Treatment								Safety Follow-up[a]		Bi-Weekly Visits[b]
Visit Number	**1**	**2[c]**	**3**	**4**	**5**	**6**	**7**	**8**	**9/ET**	**10**	**11**	**12-15[b]**
Study Week (Visit Window of ±2 Days for Visits 3-15)			**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	
Qualification/Diagnostic Assessments												
Informed Consent	X											
Eligibility Review	X	X										
Demographics and Medical/ Psychiatric History	X											
MINI v7.0/MINI KID v7.0	X								X[d]			
Height	X											
Qualification Safety Assessments												
Serology Testing	X											
Urine Pregnancy Testing (all women)	X	X			X		X		X		X	
Urine Drug Screen	X	X										
Physical Examination	X	X							X			
Biochemistry, Hematology, and Urinalysis Samples	X	X		X					X			
Pharmacokinetic Samples[e]				X					X			
Vital Signs	X	X		X		X			X		X	
12-Lead ECG	X								X			
Weight[f], Waist Circumference[g], and Body Composition[f]	X	X	X	X	X	X	X	X	X	X	X	X

Table 3: Schedule of Assessments (Continued)

	SCN Day -30 to -1	12-Week Double-Blind Treatment							Safety Follow-up		Bi-Weekly Visits[b]
Visit Number	**1**	**2[c]**	**3**	**4**	**5**	**6**	**7**	**8**	**9/ET**	**10**	**11**	**12-15[b]**
Study Week (Visit Window of ±2 Days for Visits 3-15)			**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	
AE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS[h]	X	X	X	X	X	X	X	X	X	X	X	
Psychiatric Efficacy/Quality of Life Assessments												
CGI-S		X	X	X	X	X	X	X	X			
CGI-I			X	X	X	X	X	X	X			
IWQOL-Lite		X			X				X			
Other/General Procedures												
Randomization		X										
Genotype Sample	X											
Study Drug Dispensation		X	X	X	X	X	X	X				
Study Drug Return			X	X	X	X	X	X	X			

Abbreviations: AE=adverse event; BIA=Bioelectrical Impedance Analysis; CGI-I=Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions-Severity; C-SSRS=Columbia-Suicide Severity Scale; d=day; ECG=electrocardiogram; ET=early termination; IWQOL-Lite=Impact of Weight on Quality of Life–Lite; MINI v7.0=Mini International Neuropsychiatric Interview 7.0 for Schizophrenia and Psychotic Disorder Studies; MINI KID v7.0=Mini International Neuropsychiatric Interview for Children and Adolescents 7.0 for Schizophrenia and Psychotic Disorder Studies; PK=pharmacokinetic; SCN=screening

[a] Subjects who consent for the open label safety extension study (ALK3831-A308) will continue to Visit 1 in that study and will not complete the Safety Follow-up Visits

[b] Only for subjects who terminate the study early: subjects who terminate the study early will be asked to schedule an ET Visit as close as possible to the subject's last dose, and then to return for the Safety Follow-up visits. Subjects will then return for up to 4 biweekly assessments. Assessments at the biweekly visits include weight, body composition, waist circumference, adverse event monitoring, and concomitant medication review.

[c] All assessments will be conducted predose

[d] This assessment will only be completed at Visit 9 for subjects diagnosed with schizophreniform disorder at Visit 1

[e] One PK draw to occur during each indicated visit. When PK and safety blood samples are scheduled to be collected on the same day, efforts should be made to collect during the same draw
[f] Will be collected by Body Composition Analyzer
[g] Waist circumference to be measured in triplicate at all indicated visits
[h] "Baseline/Screening" version to be completed at Screening. "Since Last Visit" version to be completed at subsequent timepoints

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 by the Principal Investigator or designated study personnel, as outlined in Section 17.3.

Prior to the administration of any study-specific procedures, authorized study personnel will obtain written informed consent/assent, as per local requirements, from each potential subject.

8.3.2. Eligibility Review

An eligibility review 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. Eligibility criteria will be reviewed by the Medical Monitor or designee prior to subject randomization.

8.3.3. Demographics and Medical / Psychiatric History

Subject's demographic data and medical/psychiatric history will be reviewed and documented at the timepoint specified in Table 3.

8.3.4. Concomitant Medication Review

All medications (prescription and nonprescription, including vitamins and herbal supplements) taken by a given subject within 60 days of Screening through Follow-up will be recorded. This includes review and recording of all psychotropic and antipsychotic medications.

At each study visit (see Table 3), the Investigator or designee 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.

8.3.5. Vital Signs

Vital signs (ie, blood pressure, heart rate, respiratory rate, and oral body temperature) will be assessed at the timepoints specified in Table 3. An effort will be made to consistently use the same arm (preferably the subject's dominant arm) to measure blood pressure and heart rate throughout the study. The blood pressure cuff will be calibrated per study site standard operating procedures (SOP). Automated measurement is preferred, but if performed manually, heart rate will be measured in the brachial artery for at least 30 seconds.

Blood pressure, heart rate, and respiratory rate will be measured after the subject has been in the supine position for at least 5 minutes. Vital signs may be collected at any time during a scheduled visit, unless otherwise noted.

8.3.6. Physical Examination

A physical examination will be performed at the timepoints specified in Table 3. Full physical examination at Screening (Visit 1); brief physical examination at all other indicated visits.

8.3.7. Height, Body Weight, Body Composition Analysis, and Waist Circumference

Height will be measured at Screening only. Waist circumference will be measured at all the timepoints specified in Table 3, and will be measured 3 consecutive times at each time point. The Body Composition Analyzer will collect multiple measures related to body composition using BIA, including, but not limited to, weight, fat mass, lean mass, and percentage body fat, at all the timepoints specified in Table 3.

For the Body Composition Analyzer measurements, subjects should be asked to void immediately prior to measurement and should be dressed in a hospital gown with consistent under-attire for each measurement. Subjects should remove all personal items (including shoes, watches, and jewelry) and they should be weighed on a study-approved and calibrated scale for each measurement under the same conditions. The body composition analysis should not be performed when the subject is attached to any portable electronic equipment (eg, a portable ECG machine).

8.3.8. 12-Lead Electrocardiogram

A 12-lead ECG will be conducted at the timepoints specified in Table 3. All scheduled ECGs must be performed after the subject has rested quietly for at least 5 minutes in the supine position.

A qualified clinician will conduct ECGs and assess ECG results using equipment that has been calibrated according to the site's SOP. The following ECG parameters will be collected: pulse, RR, PR, QRS, QT, QTcF, and QT interval corrected using the Bazett formula (QTcB).

All ECGs will be evaluated by a central reader.

8.3.9. Structured Interviews and Questionnaires

Brief descriptions of each of the interviews and questionnaires to be distributed are available below. All interviews and questionnaires will be administered by trained and qualified study personnel.

For assessments performed at multiple visits, every effort should be made to pair the same clinician/rater with the same subject across visits.

Table 3 provides information on the timepoints at which each assessment should be administered.

8.3.9.1. Rater Review

Rater (ie, study staff) accuracy for the MINI interview at Screening will be reviewed by central raters. Rater review is necessary for mitigating inaccurate inclusion/exclusion assessments.

Rater assessments require subject interviews to be audio recorded. The audio recording will be disclosed and explained to the subject by study staff and will be disclosed in the ICF during the informed consent process. No subject will be recorded without the knowledge that a recording is being made.

8.3.9.2. Diagnostic Assessments

8.3.9.2.1. Mini International Neuropsychiatric Interview/Mini International Neuropsychiatric Interview for Children and Adolescents

The Mini International Neuropsychiatric Interview 7.0 for Schizophrenia and Psychotic Disorder Studies (MINI v7.0) and the Mini International Neuropsychiatric Interview for Children and Adolescents 7.0 for Schizophrenia and Psychotic Disorder Studies (MINI KID v7.0) are short, clinician-administered, structured diagnostic interviews, with an administration time of approximately 15 minutes (Sheehan et al, 1998). The MINI v7.0 and MINI KID v7.0 have been validated against the much longer Structured Clinical Interview for DSM Diagnoses. The MINI v7.0 and MINI KID v7.0 will be administered by the PI or designee at the timepoints in Table 3.

The MINI v7.0 will be conducted with subjects ≥18 years of age and the MINI KID v7.0 will be conducted with subjects <18 years of age.

8.3.9.3. Safety Assessments

8.3.9.3.1. Columbia-Suicide Severity Rating Scale

The PI or designee will administer the C-SSRS according to the timepoints in Table 3. The "Baseline/Screening" version of the C-SSRS will be completed at Screening (Posner et al, 2009a). The "Since Last Visit" version will be completed at all other scheduled timepoints (Posner et al, 2009b). The C-SSRS should be administered by a qualified clinician trained in assessing and managing suicidal ideation and behavior.

8.3.9.4. Antipsychotic Efficacy Assessments

For assessments performed at multiple timepoints, every effort should be made to pair the same clinician/rater with the same subject across timepoints.

8.3.9.4.1. Clinical Global Impressions-Severity

The PI or designee will complete the CGI-S scale at the timepoints specified in Table 3. The CGI-S measures mental illness severity. Clinicians are asked to rate subjects based on their prior experience working with individuals in a similar patient population (Guy 1976).

8.3.9.4.2. Clinical Global Impressions-Improvement

The PI or designee will complete the CGI-I scale at the timepoints specified in Table 3. The CGI-I measures mental illness improvement. Clinicians are asked to rate subjects based on their prior experience working with individuals in a similar patient population (Guy 1976).

8.3.9.5. Other Assessments

8.3.9.5.1. Impact of Weight on Quality of Life-Lite

Subjects will complete the IWQOL-Lite questionnaire (Kolotkin et al, 2001) at the timepoints specified in Table 3.

8.3.10. Supportive Clinical Care

Subjects will be offered SCC during the 12-week Treatment Period. Participation in the SCC program will be independent of study visits and based on clinical and subject preference. The SCC component modules may include individual psychotherapy, supported education services, and family education and support. Investigators and subjects will be able to select the modules to be used based on their judgment of appropriateness. The use of any or all modules will not be mandatory for each subject.

8.3.11. Laboratory Assessments

8.3.11.1. Drug Testing

A urine drug test for opioids and drugs of abuse, including amphetamine/methamphetamine, phencyclidine, and cocaine, will be performed at the timepoints specified in Table 3. Results must be negative at Screening (Visit 1) and Baseline (Visit 2) for the subject to be eligible for the study. Centralized drug testing will be performed at Screening (Visit 1) and local drug testing (via dipstick) at other timepoints, as specified in Table 3. The urine drug screen may be repeated at any point during the study based on the Investigator's discretion.

8.3.11.2. Hematology, Biochemistry, and Urinalysis

Fasting blood and urine samples for laboratory assessments will be collected at the timepoints specified in Table 3 for specific hematology, biochemistry, and urinalysis assessments listed in Table 4. Subjects will be instructed not to eat or drink anything (except water) for 8 hours before each visit where blood samples for biochemistry and hematology assessments will be collected. Samples will be collected in accordance with the site's usual procedures and analyzed by a central laboratory. Laboratory assessments may be repeated at the Investigator's discretion.

Table 4: Clinical Laboratory Assessments

Hematology	Biochemistry	Urinalysis
Hematocrit	**General Chemistry**	Bilirubin
Hemoglobin	Albumin	Color and appearance
Platelets	Bicarbonate	Glucose
Red blood cell count	Calcium	Ketones
Total and differential (absolute) white blood cell count[a]	Chloride	Leukocytes
	Creatine phosphokinase	Nitrite
	Glucose	Occult blood
	hs-CRP	pH
	Interleukin 6	Protein
	Lactic dehydrogenase	Specific gravity
	Potassium	Urobilinogen
	Sodium	Cotinine
	Total protein	Microscopic examination of sediment, *only if urinalysis dipstick results are abnormal*
	Tumor necrosis factor α	
	Uric acid	
	Endocrine Function Test	
	Thyroid-stimulating hormone[b]	
	HbA1c[c]	
	Prolactin	
	Insulin	
	Liver Function Tests	
	Alanine aminotransferase	
	Alkaline phosphatase	
	Aspartate aminotransferase	
	Gamma-glutamyl transferase	
	Total bilirubin	
	Renal Function Tests	
	Blood urea nitrogen	
	Creatinine	
	Lipid Panel	
	High-density lipoprotein	
	Low-density lipoprotein	
	Total cholesterol	
	Triglycerides	
	Apolipoprotein B	
	Apolipoprotein A1	

Abbreviations: ANC=absolute neutrophil count; HbA1c=Hemoglobin A1c; hs-CRP=high-sensitivity C-reactive protein; PI=Principal Investigator

[a] At screening, if a subject has an ANC $<1.2 \times 10^3$ per µL, a repeat will be allowed. However, if a subject has an ANC $<1.0 \times 10^3$ per µL at any time, the PI (or designee) should discontinue the subject from participation immediately, as indicated in Section 7.3

[b] At Screening only; if the thyroid-stimulating hormone results indicate the value is outside of normal limits, the central lab will automatically test the same Screening visit sample and provide a free T4 and T3 analysis
[c] No repeats will be allowed. If a subject has HbA1c ≥6.5% at any time, the PI (or designee) should discontinue the subject from participation immediately, as indicated in Section 7.3

8.3.11.3. Urine Pregnancy Testing

A urine pregnancy test will be administered to all women at the timepoints specified in Table 3. Results must be negative for the subject to be eligible for the study at Screening (Visit 1) and Baseline (Visit 2). As highlighted in Section 7.3, a positive pregnancy test result at any time will necessitate the subject's immediate withdrawal from the study. Additional follow-up may be necessary, as indicated in Section 8.4.1.

8.3.12. Serology Testing

A blood sample for a serology panel testing for hepatitis B surface antigen, anti-hepatitis C antibodies, and HIV will be performed at Screening only, as specified in Table 3. A positive hepatitis C antibody test must be confirmed by RNA testing to be exclusionary.

8.3.13. Genotype Sampling

A blood sample may be collected (at the timepoint indicated in Table 3) for evaluation of genotypes that are potentially related to response and to explore potential genetic associations with efficacy, adverse effects, symptoms, or outcomes. No other tests will be performed with these samples.

8.3.14. Pharmacokinetic Assessments

Concentrations of olanzapine, samidorphan, and metabolites of interest will be determined from plasma samples collected according to the schedule in Table 3. The time of last study drug administration (when applicable) and the time of each pharmacokinetic (PK) blood draw must be documented in the subject's source documents. Samples for PK analysis will be stored at -20°C ±10°C. Pharmacokinetic data from these samples may be included in a subsequent population PK analysis or other post-hoc analyses conducted outside of this study.

8.3.15. Randomization

At the timepoints specified in Table 3, subjects will be randomized, as outlined in Section 9.3.

8.3.16. Drug Dispensation and Reconciliation

Section 9 provides information related to drug dispensing procedures. Study drug will be dispensed/administered at the timepoints specified in Table 3. The study drug use and storage information will be explained to/reviewed with the subject.

8.3.16.1. Medication Adherence and Reminder System

A daily medication adherence monitoring and reminder system (via smartphones) may be used in this study to automatically confirm medication ingestion. After confirmation, all collected data and video recordings will be encrypted and may be transmitted to a secure centralized location, in accordance with local regulations, for further analysis, including testing for duplicate

enrollment. The captured data and video are reviewable only through a roles- and rules-restricted system ensuring privacy of the information. The system is compliant with the Health Insurance Portability and Accountability Act (HIPAA), which protects the privacy and security of healthcare information. In addition, built-in reminders and a communication system will allow real-time intervention in case of drug interruptions. Phone numbers of the patients may also be collected and stored in an encrypted manner. At no time is the phone number visible to healthcare providers or monitoring personnel. Use of this system will in no way supersede or replace the physician- and/or trial-prescribed medication protocol of the patients.

8.3.17. Emergency Treatment Card

An emergency treatment card will be distributed to each subject at Screening (Visit 1) and collected at Visit 9. The card will indicate that the subject is receiving an opioid antagonist and/or olanzapine, and will include the PI's contact information, a suggested pain management plan, and information regarding opiate blockade. Subjects will be instructed to keep the card with them at all times. Study personnel will confirm that subjects have the card in their possession at each study visit.

8.3.18. Adverse Event Monitoring

All AEs 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 AEs (SAEs) are defined in Section 13.1 and 13.2, respectively. Section 13.4 provides guidance on the monitoring and recording requirements for AEs. Section 13.5 provides guidance on the reporting requirements for SAEs.

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. All female subjects must agree to use an acceptable method for 30 days after the last dose of study drug, unless they are surgically sterile or postmenopausal (see below). The following are considered acceptable methods of contraception:

1. Intrauterine device
2. Oral contraceptive pills and other hormonal methods (eg, a vaginal ring, contraceptive patch, contraceptive implant)
3. Double-barrier protection (eg, a condom with spermicide or a diaphragm with spermicide)
4. Abstinence (see below)

Subjects who are abstinent are eligible, provided they agree to use an acceptable contraceptive method should they become sexually active. Abstinence is defined as "true abstinence" in which subjects must refrain from heterosexual intercourse for the full duration of the study and must be in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to the study drug, and withdrawal are not acceptable methods of contraception.

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 and Safety Follow-up Visits 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. If a female partner of a male subject becomes pregnant, she may be required to sign an informed consent form to obtain pregnancy follow-up information, per local requirements.

A Pregnancy Report Form must be submitted to Alkermes via Premier Research Group Limited (per Section 13.5) 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 an SAE, it should be reported following the SAE procedure (see Section 13.5).

8.4.2. Prohibited Medications

The use of any antipsychotic other than study drug is prohibited, except when subjects are tapering off of current medication (see Section 8.1). The following medications will be prohibited for the duration of the study, unless otherwise indicated:

- The following psychotropic medications, other than study drug:
  - Antipsychotics (subjects must be tapered off any previous antipsychotic medications within 14 days after randomization)
  - Antidepressants for bipolar I disorder subjects at Visit 1 and Visit 2 (subjects may be initiated on antidepressants after Visit 2, as described in Section 8.4.3)
  - Mood stabilizers (subjects must be tapered off any mood stabilizer medications within 14 days after randomization)
- Chantix® (varenicline; however, nicotine replacement therapy, including nicotine replacement patch and oral nicotine gum, is permitted)
- All prescription or over-the-counter (OTC) agents taken for the purpose of weight reduction
- Systemic steroids administered by oral, intravenous, or intramuscular route
- Topiramate (Topamax®) and combination products containing topiramate; calcitonin (eg, Miacalcin®)
- Diabetes treatments and hypoglycemic agents, including metformin and insulin

- Moderate-to-strong inducers or inhibitors of cytochrome P450 (CYP) 3A (prescription medications, OTC medications, or dietary supplements) within 30 days before randomization through Follow-up (refer to Appendix A for a list of CYP3A inhibitors and inducers)

The CRO Medical Monitor should be consulted for any questions about use of any psychotropic medications during a subject's participation in this study.

8.4.3. Permitted Medications

- Medications that exhibit drug interaction potential with olanzapine, including known inhibitors and inducers of CYP1A2 (Appendix B), may affect olanzapine concentrations. Hence, investigators must use caution with inhibitors and inducers of CYP1A2 and monitor for need for study drug dose adjustment
- Medicinal products known to be associated with increase in QTc interval should be used with caution given the increased risk of torsade de pointes (Appendix C)
- Oral contraceptive pills and other hormonal methods (eg, a vaginal ring, contraceptive patch, contraceptive implant) will be permitted
- Antidepressants
  - Bipolar I disorder: Antidepressants are not permitted at Visit 1 and Visit 2. However, a selective serotonin reuptake inhibitor (SSRI) antidepressant may be initiated during the Treatment Period, if clinically indicated. Treatment with SSRIs that may cause significant weight gain should be avoided (eg, paroxetine).
  - Schizophrenia and schizophreniform disorder: May remain on the medication if stable on antidepressants for greater than 30 days prior to study entry. However, an SSRI antidepressant may be initiated during the Treatment Period, if clinically indicated. Treatment with SSRIs that may cause significant weight gain should be avoided (eg, paroxetine).

8.4.4. Pain Management

Because ALKS 3831 contains samidorphan, a μ-opioid antagonist, subjects may experience reduced or ineffective analgesia when taking an opioid analgesic agent concurrently with ALKS 3831, including several days after last dosing of ALKS 3831.

In the event of an emergency, pain management of the subject should include the following:

- Regional analgesia or use of non-opioid analgesics
- If opiate anesthesia or analgesia is required, the subject should be continuously monitored, in an anesthesia care setting, by persons not involved in the conduct of the surgical or diagnostic procedure. The opioid therapy must be provided by individuals specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, specifically the establishment and the maintenance of a patent airway and assisted ventilation

- Close monitoring by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation

For subjects requiring emergency opioid analgesics prior to dosing, the study drug should not be administered. If opioid analgesics are required after the study drug has been dosed, it may take several days for opiate sensitivity to be restored, since samidorphan functions as a μ-opioid antagonist and could interfere with opioid-mediated pain management.

8.4.5. Fasting

Subjects are required to fast for at least 8 hours (no food or drink, except water) prior to laboratory blood draws.

8.4.6. Other Restrictions and Requirements

Additional restrictions and requirements include:

- Prohibited substances include opioids, amphetamines (including methamphetamine), cocaine, and phencyclidine
- Subjects will be required to abstain from blood or blood product donation during the study and for 30 days following the Follow-up Visit
- Subjects will be instructed to maintain their normal caffeine intake and/or tobacco use, as well as normal activity/exercise, throughout the study. Subjects will be asked to abstain from strenuous physical activity for 48 hours prior to each study visit
- Subjects are prohibited from participating in a weight management program (including weight loss surgery) or from entering a smoking cessation program for the duration of the study
- Subjects will be asked to refrain from driving, operating machinery, or engaging in hazardous activities until they and the Investigator are sure the study drug is not impairing their judgment and/or ability to perform skilled tasks

See Section 8.3.4 for details regarding the concomitant medication review.

9. TREATMENT OF SUBJECTS

9.1. Study Drug Dose and Administration

Study drugs include:

- ALKS 3831 5/10, 10/10, 15/10, or 20/10 mg, administered as a coated bilayer tablet
- Olanzapine 5, 10, 15, or 20 mg, administered as a coated bilayer tablet

For the first week, at the discretion of the Investigator, subjects will receive 5, 10, 15, or 20 mg of olanzapine or 5/10, 10/10, 15/10, or 20/10 mg of ALKS 3831. At the end of Week 1, for subjects initiated on 5 mg of olanzapine or 5/10 mg of ALKS 3831, the dose will be increased to 10 mg of olanzapine or 10/10 mg of ALKS 3831. For all other subjects, the dose may also be increased to either 15 or 20 mg of olanzapine, or 15/10 or 20/10 mg of ALKS 3831. Following this increase, the dose may be increased or decreased to 5, 10, 15, or 20 mg of olanzapine, or to 5/10, 10/10, 15/10, or 20/10 mg of ALKS 3831, at the Investigator's discretion. Dosing will be flexible throughout the study; however, frequent adjustments are discouraged. Dose adjustments can only be performed on-site at the study center.

For subjects requiring initial inpatient care, study drug will be administered orally, once daily, preferably at bedtime. Following discharge, subjects will be given study drug to take home and will be instructed to take one tablet orally, preferably at bedtime. If there are tolerability problems, dosing may be switched to another time, based on the judgment of the Investigator; frequent switching is discouraged.

Subjects will be instructed to keep all unused tablets in their blister card and to return unused tablets to the study site at their next visit. If dosing is to occur at that visit, the dose should be taken from the subject's next blister card, not from the card they are returning.

If a dose is missed or forgotten, subjects will be instructed to resume regular dosing the following night. Subjects will be instructed not to take a double dose to try to "make up" for the missed dose.

9.2. Treatment Adherence

A daily medication adherence monitoring and reminder system (via smartphones) may be used in this study (as described in Section 8.3.16.1). Subjects will be instructed to keep all unused tablets in their original containers and to return the original containers with any unused study drug at each visit following dispensation. Study drug accountability will be documented as the number of tablets dispensed, dosed, lost/missing, or remaining. If applicable, the site will discuss nonadherence with the subject.

9.3. Randomization/Method of Assigning Subjects to Treatment

Subjects meeting eligibility criteria at baseline (Visit 2) will be randomized in a (1:1) ratio to ALKS 3831 or olanzapine. The randomization will be stratified by diagnosis (schizophrenia/schizophreniform disorder vs bipolar I disorder) , region (US vs non-US), and baseline BMI (<25 vs ≥25).

Randomization will be performed centrally through an Interactive Web Response System (IWRS). A unique randomization number will be assigned by the IWRS once eligibility has been determined. Once a randomization number has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. Codes will be prepared by an independent biostatistician who is not otherwise involved in this study.

9.4. Blinding

All Alkermes staff, CRO staff, clinical staff, subjects, and caregivers will be blinded to treatment assignment until database lock.

The PI is responsible for all trial-related medical decisions. If the Investigator deems it necessary to break the study blind in the interest of a subject's medical safety, he or she is encouraged to contact the CRO/Sponsor Medical Monitor to discuss their rationale for unblinding. However, to prevent delays to the Investigator or medical personnel responding to a potentially emergent situation, unblinding of study drug will not be dependent upon the Investigator receiving approval from the Sponsor/CRO Medical Monitor (ie, the Investigator will be able to obtain the code break information independent of the Sponsor/CRO Medical Monitor). 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. 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.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

The ALKS 3831 drug product will be supplied as a coated bilayer tablet in four fixed-dose combinations:

- ALKS 3831 5/10 (5 mg olanzapine/10 mg samidorphan)
- ALKS 3831 10/10 (10 mg olanzapine/10 mg samidorphan)
- ALKS 3831 15/10 (15 mg olanzapine/10 mg samidorphan)
- ALKS 3831 20/10 (20 mg olanzapine/10 mg samidorphan)

The tablets contain olanzapine and samidorphan L-malate (RDC-0313-02), and the following excipients commonly used in pharmaceutical drug products: microcrystalline cellulose, lactose monohydrate, crospovidone, colloidal silica dioxide, and magnesium stearate.

The tablet coating contains hydroxypropyl methylcellulose 2910 (HPMC 2910), titanium dioxide, lactose monohydrate, and triacetin as well as one or more of the following dye components; iron oxide yellow, iron oxide red, and/or FD&C blue #2/indigo carmine AL.

Matching olanzapine-only drug will be manufactured by Alkermes, Inc and will be supplied as a coated bilayer tablet in four dose strengths:

- OLZ 5 (5 mg olanzapine)
- OLZ 10 (10 mg olanzapine)
- OLZ 15 (15 mg olanzapine)
- OLZ 20 (20 mg olanzapine)

The tablets contain olanzapine and the following excipients commonly used in pharmaceutical drug products: microcrystalline cellulose, lactose monohydrate, crospovidone, colloidal silica dioxide, and magnesium stearate.

The tablet coating contains hydroxypropyl methylcellulose 2910 (HPMC 2910), titanium dioxide, lactose monohydrate, and triacetin as well as one or more of the following dye components; iron oxide yellow, iron oxide red, and/or FD&C blue #2/indigo carmine AL.

10.2. Packaging and Labeling

ALKS 3831 and olanzapine will be supplied in blister packs. Blister cards will be in weekly and biweekly configurations. Weekly blister cards will contain 9 tablets, enough for 1 week of dosing, plus sufficient overage for two additional once daily doses. Biweekly blister cards will contain 16 tablets, enough for 2 weeks of dosing, plus sufficient overage for two additional once daily doses.

10.3. Storage

Product should be stored at no more than 25°C.

Under the US Controlled Substances Act, samidorphan is considered a Schedule II substance because it is derived from opium alkaloids. Therefore, samidorphan and/or blinded study drug must be stored in accordance with restrictions related to Schedule II substances. The site will take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance.

10.4. Accountability

The clinical 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 8.3.16 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. Packages may be destroyed on site according to Good Clinical Practice (GCP) and site practice. Alternatively, the sponsor may arrange for destruction with a third party vendor operating in accordance with GCP and/or Good Manufacturing Practice (GMP), as applicable.

11. ASSESSMENT OF EFFICACY

11.1. Primary Efficacy Endpoint

- Percent change from baseline in body weight at Week 12

11.2. Secondary Efficacy Endpoints

- Proportion of subjects with ≥10% weight gain at Week 12
- Proportion of subjects with ≥7% weight gain at Week 12
- Change from baseline in waist circumference at Week 12
- Change from baseline in CGI-S score within the ALKS 3831 Group at Week 12

11.3. Other Endpoints

- Absolute change from baseline in body weight by visit
- Proportion of subjects with ≥5 cm increase from baseline in waist circumference at Week 12
- Body composition endpoints, as assessed by bioimpedance analysis, including
  - Change from baseline in fat mass by visit
  - Change from baseline in percent body fat by visit
  - Change from baseline in fat mass index by visit
  - Change from baseline in visceral adipose tissue by visit
  - Change from baseline in lean mass by visit
  - Change from baseline in fat free mass index by visit
  - Change from baseline in total skeletal muscle mass by visit
- Percent and absolute change from baseline in fasting lipids (fasting triglycerides, low-density lipoprotein [LDL], high-density lipoprotein [HDL], total cholesterol), fasting glucose, HbA1c, and fasting insulin by visit
- Percent and absolute change from baseline in additional laboratory parameters including apolipoprotein B (Apo B), apolipoprotein A1 (Apo A1), Apo B/Apo A1, high-sensitivity-C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor α (TNFα) by visit
- Change from baseline in CGI-S score (between and within treatment groups) by visit
- Change from baseline in CGI-S score (between and within treatment groups) by visit and by diagnosis
- CGI-I score by visit

- Change from baseline in IWQOL-Lite score by visit

12. ASSESSMENT OF PHARMACOKINETICS

Concentrations of olanzapine, samidorphan, and metabolites of interest will be determined from plasma samples collected according to the schedule in Table 3. Data from these PK samples may be included in a subsequent population PK analysis conducted outside of this study. By-subject listings of plasma concentrations will be provided.

13. ASSESSMENT OF SAFETY

Safety will be assessed on the basis of:

- AEs
- Vital signs (ie, oral temperature, respiratory rate, blood pressure, and heart rate)
- Clinical laboratory parameters, including chemistry, hematology, and urinalysis
- ECG results
- C-SSRS

13.1. 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 pre-existing 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.

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.

Transition from schizophreniform to schizophrenia is not considered an AE, unless deemed so by the Investigator.

13.2. Definition of Serious Adverse Event

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

- Results in death
- Is life-threatening. The subject is at immediate risk of death from the reaction as it occurs. This does not include a 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 and 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, they 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 nonmedical reason (ie, social stay admission) during the study, in the absence of an untoward medical occurrence, will not be considered an SAE, but will be reported as an AE. Hospitalization due to worsening of behavioral health-related issues should be reported as an SAE.

13.3. 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/her best clinical judgment. The criteria listed in Table 5 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 5: 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

13.4. 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 Safety Follow-up Visit (Visit 11). Any AE or SAE having an onset after the Safety Follow-up 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 13.3), 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.

13.5. Reporting of Serious Adverse Events and Pregnancy

All SAEs and pregnancies must be reported to Alkermes via Premier Research Group Limited immediately, within 24 hours of discovery, by emailing or faxing the report to the following:

Attention: Safety Premier Medical Monitor

US Email: GlobalPV-US@premier-research.com

EU/Rest of the world (ROW) Email: PVDS-ROW@premier-research.com

US Fax Number: + 1 (215) 972-8765

EU/ROW Fax Number: + 421 2 6820 3713

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.

14. STATISTICS

14.1. Sample Size Considerations

Approximately 425 subjects will be randomized in order to have 400 subjects (200 per treatment group) in the efficacy population. Assuming the percent weight gain at Week 12 is 5% and 8.5% for ALKS 3831 and olanzapine groups, respectively, a common standard deviation of 8%, and a cumulative dropout rate of 35%, 200 subjects per treatment group (400 subjects in total) will provide at least 90% power to demonstrate a difference of ALKS 3831 relative to olanzapine at a two-sided significance level of 0.05.

14.2. General Statistical Methodology

The statistical analysis methods are described below. Additional details are provided in the Statistical Analysis Plan (SAP).

Baseline is defined as the last nonmissing values on or before the first dose of study drug in the double-blind Treatment Period.

In general, summary statistics (n, mean, standard deviation, median, minimum and maximum for continuous variables, and number [%] of subjects in each category for categorical variables) will be provided by treatment group for all variables.

Source data for the summary tables and statistical analyses will be presented as subject data listings.

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

14.2.1. Study Populations

14.2.1.1. Safety Population

The Safety Population, defined as all randomized subjects who receive at least one dose of study drug (ALKS 3831 or olanzapine), will be used in the safety analyses.

14.2.1.2. Efficacy Population

The Efficacy Population (ie, full analysis set [FAS]), defined as all subjects in the Safety Population who have at least one postbaseline weight assessment, will be used in the efficacy analyses.

14.3. Demographics and Baseline Data

Demographics and baseline characteristics, such as gender, age, race, weight, BMI, and psychiatric history, will be summarized with descriptive statistics. 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 will be made in the efficacy and safety analyses.

14.4. Efficacy Analyses

All efficacy analyses will be based on the FAS Population.

Primary Endpoint

The primary endpoint is:

- Percent change from baseline in body weight at Week 12

The primary analysis will be carried out using an analysis of covariance (ANCOVA) method based multiple imputation (MI) for missing data. The model will include the treatment group and randomization strata as factors, and the baseline weight as the covariate. Sensitivity analyses will be carried out to explore the impact of missing data.

Secondary Endpoints

The secondary endpoints are:

- Proportion of subjects with ≥10% weight gain at Week 12
- Proportion of subjects with ≥7% weight gain at Week 12
- Change from baseline in waist circumference at Week 12
- Change from baseline in CGI-S score within the ALKS 3831 Group at Week 12

For the categorical secondary endpoints of proportion of subjects with ≥10% and ≥7% weight gain at Week 12, the analyses will be carried out using a logistic regression model based on MI for missing data. The model will include the treatment group and randomization strata as factors, and the baseline weight as the covariate. For the change from baseline in waist circumference at Week 12, the analysis will be based on the ANCOVA method with MI for missing data, same as the primary analysis of the primary endpoint. For change from baseline in CGI-S within ALKS 3831 Group at Week 12, the analysis will be based on the mixed model with repeated measurements (MMRM). The model will include randomization strata, treatment, visit, and treatment-by-visit interaction term as factors; the baseline CGI-S value will be included as a covariate.

To control the overall Type I error rate, hierarchical testing will be performed in the following order: (1) percent change from baseline in body weight at Week 12, (2) proportion of subjects with ≥10% weight gain from baseline at Week 12, (3) proportion of subjects with ≥7% weight gain from baseline at Week 12, (4) change from baseline in waist circumference at Week 12, (5) change from baseline in CGI-S score within the ALKS 3831 Group at Week 12.

Other Endpoints

Other endpoints are:

- Absolute change from baseline in body weight by visit
- Proportion of subjects with ≥5 cm increase from baseline in waist circumference at Week 12
- Body composition endpoints, as assessed by bioimpedance analysis, including

  - Change from baseline in fat mass by visit
  - Change from baseline in percent body fat by visit
  - Change from baseline in fat mass index by visit
  - Change from baseline in visceral adipose tissue by visit
  - Change from baseline in lean mass by visit
  - Change from baseline in fat free mass index by visit
  - Change from baseline in total skeletal muscle mass by visit
- Percent and absolute change from baseline in fasting lipids (fasting triglycerides, LDL, HDL, total cholesterol), fasting glucose, HbA1c, and fasting insulin by visit
- Percent and absolute change from baseline in additional laboratory parameters including Apo B, Apo A1, Apo B/Apo A1, hs-CRP, IL-6, and TNFα by visit
- Change from baseline in CGI-S score (between and within treatment groups) by visit
- Change from baseline in CGI-S score (between and within treatment groups) by visit and by diagnosis
- CGI-I score by visit
- Change from baseline in IWQOL-Lite score by visit

Absolute change from baseline in body weight and all body composition endpoints will be analyzed using ANCOVA method with MI for missing data, same as the primary analysis of the primary endpoint.

The proportion of subjects with ≥5 cm increase from baseline in waist circumference at Week 12 will be analyzed by logistic regression model based on MI for missing data, in a similar fashion as the proportion of subjects with ≥10% weight gain.

The percent and absolute change from baseline in the laboratory parameters will be analyzed by MMRM model. The model will include randomization strata, treatment, visit, and treatment-by-visit interaction term as factors; the corresponding baseline value will be included as a covariate.

Change from baseline in CGI-S score between and within ALKS 3831 and olanzapine treatment groups (by visit, and by visit and by diagnosis) and change from baseline in IWQOL-Lite will be analyzed similarly by MMRM model.

CGI-I score, and CGI-I responder status (≤2 versus >2) at each visit will be summarized by descriptive statistics.

Details of statistical methods will be listed in SAP.

14.5. Pharmacokinetic Analyses

Listings will be provided for concentrations of olanzapine, samidorphan, and metabolites of interest. Pharmacokinetic concentrations may be used in a subsequent population PK analysis conducted outside of this study.

14.6. Safety and Tolerability Analyses

All safety assessments will be summarized using descriptive statistics. All safety analyses will be based on observed data only, and no missing values will be imputed. Safety will be evaluated based on the occurrence of AEs, vital signs, results of clinical laboratory tests, and ECG findings. Reported AE terms will be coded using the MedDRA and will be summarized by preferred terms and system organ class categories.

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

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

Observed values and change from Baseline in laboratory parameters, vital signs, and ECG parameters will be summarized by treatment group and study visit.

The number and percentage of subjects who have met potentially clinically significant (PCS) criteria at any post-Baseline visit will be summarized by treatment group for laboratory parameters, vital signs, and ECG parameters. Supporting listings will be provided.

The number and percentage of subjects with C-SSRS assessments of suicidal ideation and behavior will also be summarized.

Prior and concomitant medications will be summarized using the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) classification system. Listings will be provided for all concomitant medications.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. 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.

15.2. 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 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, subject medical records) to determine whether these activities were conducted, and whether data were recorded, analyzed, and accurately reported, according to the protocol, GCP guidelines of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and any applicable regulatory requirements.

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

15.3. 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.

16. 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 15.2 for details regarding the audit process.

16.1. 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.

16.2. 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.

17. ETHICAL CONSIDERATIONS

17.1. Ethics Review

The clinical 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 drug will be released to the Investigator. The protocol must be re-approved 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.

17.2. 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.

17.3. Written Informed Consent

The Investigator (or authorized designee) at each center will ensure that the subject and parent/caregiver (as per local requirements) or the subject's legal representative is given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the study. Each prospective subject and parent/caregiver (as per local requirements) will receive an IRB/IEC-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/she must sign the ICF and, if required, the parent/caregiver must sign the parent/caregiver 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/IEC, 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 Study 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/IEC, 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.

18. 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.

18.1. Data Capture

As stated in Section 16.1, 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, central laboratory, central ECG, or central MRI data, will be transferred directly to the electronic data capture system 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 the MedDRA. Concomitant medications will be categorized using the WHO-ATC classification system.

18.2. 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 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.

18.3. Retention of Records

Retention and storage of all essential clinical study documents shall be governed by the terms and conditions of the 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 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.

Subject 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.

18.4. 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.

19. REFERENCES

Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry.* 1999;156(11):1686-1696.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5).* 5th ed. Washington, DC. American Psychiatric Association; 2013.

Berk M, Brnabic A, Dodd S, et al. Does stage of illness impact treatment response in bipolar disorder? Empirical treatment data and their implication for the staging model and early intervention. *Bipolar disorders.* 2011;13(1):87-98. doi: 10.1111/j.1399-5618.2011.00889.x.

Berk M, Malhi GS, Hallam K, et al. Early intervention in bipolar disorders: clinical, biochemical and neuroimaging imperatives. *J Affect Disord.* 2009;114(1-3):1-13. doi: 10.1016/j.jad.2008.08.011.

Blanco C, Compton Wilson M, Saha Tulshi D, et al. Epidemiology of DSM-5 bipolar I disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions – III. *J Psychiatr Res.* 2016. doi: 10.1016/j.jpsychires.2016.10.003.

Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull.* 2010;36(1):71-93. doi: 10.1093/schbul/sbp116.

Correll CU, Robinson DG, Schooler NR, et al. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. *JAMA Psychiatry.* 2014;71(12):1350-1363. doi: 10.1001/jamapsychiatry.2014.1314.

Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. 2016; http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

Guy W. *ECDEU Assessment Manual for Psychopharmacology.* Rockville, MD: Department of Health, Education, and Welfare; 1976.

Hafner H. Gender differences in schizophrenia. *Psychoneuroendocrinology.* 2003;28 Suppl 2:17-54.

Hawton K, Sutton L, Haw C, Sinclair J, Harriss L. Suicide and attempted suicide in bipolar disorder: a systematic review of risk factors. *J Clin Psychiatry.* 2005;66(6):693-704.

Hayes JF, Miles J, Walters K, King M, Osborn DP. A systematic review and meta-analysis of premature mortality in bipolar affective disorder. *Acta Psychiatr Scand.* 2015;131(6):417-425. doi: 10.1111/acps.12408.

Hodgins S. Violent behaviour among people with schizophrenia: a framework for investigations of causes, and effective treatment, and prevention. *Philos Trans R Soc Lond B Biol Sci.* 2008;363(1503):2505-2518. doi: 10.1098/rstb.2008.0034.

Kolotkin RL, Crosby RD, Kosloski KD, Williams GR. Development of a brief measure to assess quality of life in obesity. *Obes Res.* 2001;9(2):102-111. doi: 10.1038/oby.2001.13.

Kuo CJ, Tsai SY, Lo CH, Wang YP, Chen CC. Risk factors for completed suicide in schizophrenia. *J Clin Psychiatry.* 2005;66(5):579-585.

Lepping P, Sambhi RS, Whittington R, Lane S, Poole R. Clinical relevance of findings in trials of antipsychotics: systematic review. *Br J Psychiatry.* 2011;198(5):341-345. doi: 10.1192/bjp.bp.109.075366.

Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet.* 2013;382(9896):951-962. doi: 10.1016/S0140-6736(13)60733-3.

Lieberman JA, Malaspina D, Jarskog LF. Preventing clinical deterioration in the course of schizophrenia: the potential for neuroprotection. *CNS Spectr.* 2006;11(4):13.

Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med.* 2005;353(12):1209-1223.

Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry.* 2007;64(5):543-552. doi: 10.1001/archpsyc.64.5.543.

Meyer JM, Davis VG, McEvoy JP, et al. Impact of antipsychotic treatment on nonfasting triglycerides in the CATIE Schizophrenia Trial phase 1. *Schizophr Res.* 2008;103(1-3):104-109. doi: 10.1016/j.schres.2008.04.023.

Posner K, Brent D, Lucas C, et al. *Columbia-Suicide Severity Rating Scale (C-SSRS): Baseline/Screening Version.* New York, NY: New York State Psychiatric Institute; 2009a.

Posner K, Brent D, Lucas C, et al. *Columbia-Suicide Severity Rating Scale (C-SSRS): Since last visit.* New York, NY: New York State Psychiatric Institute; 2009b.

Rabinowitz J, Levine SZ, Hafner H. A population based elaboration of the role of age of onset on the course of schizophrenia. *Schizophr Res.* 2006;88(1-3):96-101. doi: 10.1016/j.schres.2006.07.007.

Sham PC, MacLean CJ, Kendler KS. A typological model of schizophrenia based on age at onset, sex and familial morbidity. *Acta Psychiatr Scand.* 1994;89(2):135-141.

Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry.* 1998;59 Suppl 20:22-33.

Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res.* 1997;73(3):159-171.

Tohen M, Vieta E, Gonzalez-Pinto A, Reed C, Lin D. Baseline characteristics and outcomes in patients with first episode or multiple episodes of acute mania. *J Clin Psychiatry.* 2010;71(3):255-261. doi: 10.4088/JCP.08m04580.

University of Washington: School of Pharmacy. In Vivo CYP3A Inducers. Seattle, WA: M and T Drug Interaction Database; 2017a.

University of Washington: School of Pharmacy. In Vivo Inhibitors of CYP3A Probes. Seattle, WA: M and T Drug Interaction Database; 2017b.

Wirshing DA, Wirshing WC, Kysar L, et al. Novel Antipsychotics: Comparison of Weight Gain Liabilities. *J Clin Psychiatry.* 1999;60(6):358-363.

20. APPENDIX A: PARTIAL LIST OF PROHIBITED CYTOCHROME P450 (CYP) 3A INHIBITORS AND INDUCERS

The following is a list of CYP3A inhibitors and inducers that subjects are to avoid within 30 days of Screening and throughout the study. This list is not comprehensive.

Table 6: 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

Source: (Food and Drug Administration 2016; University of Washington: School of Pharmacy 2017a; University of Washington: School of Pharmacy 2017b)

21. APPENDIX B: PARTIAL LIST OF CYP1A2 MODERATE-TO-STRONG INHIBITORS AND MODERATE INDUCERS

Table 7: Partial List of CYP1A2 Inhibitors and Inducers

Moderate-to-Strong CYP1A2 Inhibitors		Moderate CYP1A2 Inducers
Ciprofloxacin[a]	Oral Contraceptives	Phenytoin[a]
Enoxacin	Zafirlukast	Rifampin[a]
Fluvoxamine[a]	—	Ritonavir[a]
Methoxsalen	—	Teriflunomide
Mexiletine	—	Tobacco

[a] These drugs are also known to be CYP3A inhibitors or inducers and are prohibited, as shown in Appendix A
Source: (Food and Drug Administration 2016)

22. APPENDIX C: PARTIAL LIST OF MEDICATIONS KNOWN TO BE ASSOCIATED WITH PROLONGED QTc INTERVAL AND TORSADE DE POINTES

The following is a list of medications known to be associated with prolonged QTc interval and torsade de pointes. This list is not comprehensive.

Table 8: Partial List of Medications Known to Be Associated with Prolonged QTc Interval and Torsade de Pointes

Generic Name		
Amiodarone	Domperidone	Oxaliplatin
Anagrelide	Donepezil	Papaverine HCl (Intra-coronary)
Arsenic trioxide	Dronedarone[a]	Pentamidine
Azithromycin	Droperidol[b]	Pimozide[b]
Chloroquine	Erythromycin[a]	Procainamide
Chlorpromazine[b]	Escitalopram	Propofol
Cilostazol	Flecainide	Quinidine
Ciprofloxacin[a]	Fluconazole[a]	Sevoflurane
Citalopram	Haloperidol[b]	Sotalol
Clarithromycin[a]	Ibutilide	Thioridazine[b]
Cocaine[b]	Levofloxacin	Vandetanib
Disopyramide	Methadone[b]	—
Dofetilide	Ondansetron	—

[a] These drugs are also known to be CYP3A inhibitors or inducers and are prohibited, as shown in Appendix A
[b] Antipsychotics (other than the study drug), drugs of abuse, and prescribed opioids are prohibited in the study