CLINICAL STUDY PROTOCOL

ALK3831-A308

EudraCT 2017-000918-36

Study Title:	A Phase 3 Study to Assess the Long-Term Safety, Tolerability, and Durability of Treatment Effect of ALKS 3831 in Subjects with Schizophrenia, Schizophreniform Disorder, or Bipolar I Disorder
Document Date:	Amendment 3.0: 09 May 2019 Amendment 2.0: 10 Jan 2018 Amendment 1.0: 12 Sep 2017 Original Protocol: 01 Feb 2017
Sponsor:	Alkermes, Inc. 852 Winter Street Waltham, MA 02451 USA

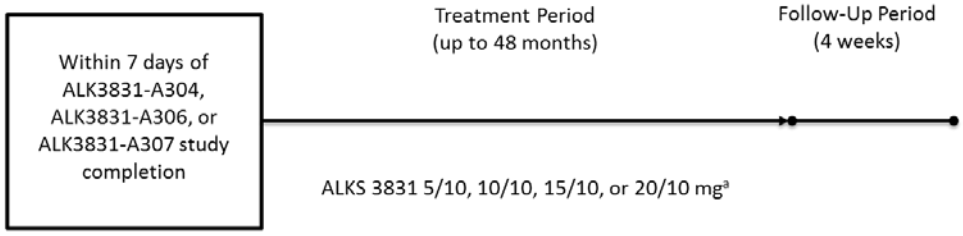
CONTACT INFORMATION

Table 1: Study Contact Information

Role in Study	Name	Address and Telephone
Coordinating Principal Investigator	PPD	PPD
Alkermes Medical Monitor	PPD	PPD
Alkermes Global Safety Officer	PPD	PPD
CRO Medical Monitor and 24-Hour Emergency Contact	PPD	PPD
SAE and Pregnancy Reporting	PPD	PPD

Abbreviation: 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 Phase 3 Study to Assess the Long-Term Safety, Tolerability, and Durability of Treatment Effect of ALKS 3831 in Subjects with Schizophrenia, Schizophreniform Disorder, or Bipolar I Disorder	
Investigator(s): 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 2022	**Phase of Development:** 3
Objective: The primary objective of this study is to evaluate the long-term safety, tolerability, and durability of treatment effect of ALKS 3831 in subjects with schizophrenia, schizophreniform disorder, or bipolar I disorder.	
Methodology: This is a multicenter, open-label study to evaluate the long-term safety, tolerability, and durability of treatment effect of ALKS 3831 in subjects with schizophrenia, schizophreniform disorder, or bipolar I disorder. Subjects that have completed the antecedent studies (ALK3831-A304, ALK3831-A306, or ALK3831-A307) within the past 7 days will be eligible to enroll in this study. Subjects enrolled in the study will be started on the same olanzapine dose that they had maintained at the end of the antecedent study. Available doses of ALKS 3831 will be 5, 10, 15, and 20 mg olanzapine combined with 10 mg samidorphan (henceforth to be referred to as 5/10, 10/10, 15/10, and 20/10 mg). Subjects may be titrated to a different dose after the start of the study at the Investigator's discretion. Dosing will be flexible throughout the study; however, frequent adjustments are discouraged. Dose adjustments will only be performed on-site at the study center. Subjects requiring dose adjustments between scheduled visits will need to arrange an unscheduled visit. Safety assessments will include adverse event (AE) monitoring, clinical laboratory testing, vital signs, body weight, electrocardiograms (ECGs), and the Columbia-Suicide Severity Rating Scale (C-SSRS). Psychiatric symptoms will be evaluated using the Clinical Global Impressions-Severity (CGI-S) scale. Additional assessments will include Impact of Weight on Quality of Life-Lite Questionnaire (IWQOL-Lite). A schematic summarizing study design is presented below. **Study Design Schematic:**  [a]Visits will occur monthly throughout the 48-month Treatment period. Subjects will start the study on the equivalent olanzapine dose to what they maintained at the end of the antecedent study. The dose may be adjusted to either 5/10, 10/10, 15/10, or 20/10mg throughout the study period based on investigator discretion, and such dose adjustments will require subjects to visit the study site.	

Number of Subjects Planned: Approximately 500 subjects
Main Criteria for Inclusion: Subjects will have completed the treatment period in one of the following antecedent studies within 7 days: ALK3831-A304, ALK3831-A306, or ALK3831-A307. Subjects will have potential to benefit from ALKS 3831 in the opinion of the investigator, and agree to use an acceptable method of contraception during the study and until 30 days after any study drug administration, unless surgically sterile or post-menopausal. **Main Criteria for Exclusion:** Subjects may be excluded based on positive tests for drugs of abuse at study entry, any finding that would compromise the subject's safety or their ability to fulfill the study requirements, pregnancy or breastfeeding, or employment by (or relationship to an employee of) the study sponsor, clinical research organization, 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 at least 24 but not more than 48 months. The study is planned to be open until approximately the 4th quarter 2022 or until regulatory action. Therefore, depending on when a subject is enrolled, the duration of participation in this study will vary.
Reference Therapy, Dosage, Duration, and Mode of Administration: None
Duration of Study: The total study duration will be up to 49 months, including a treatment period of 24 to 48 months and a 4-week safety Follow-up period.
Criteria for Evaluation: **Safety and Tolerability:** The following parameters will be collected to measure safety and tolerability throughout the study: • AEs (including clinically significant abnormal ECG findings) • Vital signs (oral temperature, respiratory rate, blood pressure, and heart rate) • Weight and waist circumference • Clinical laboratory parameters (biochemistry, hematology, and urinalysis) • C-SSRS **Efficacy:** Throughout the study, CGI-S scores will be collected to measure the durability of treatment effect. **Other:** Throughout the study, IWQOL-Lite scores will be collected to obtain information regarding subject experience. **Endpoints:** **Safety and Tolerability Endpoints:** • Incidence of AEs • Percent change from baseline in body weight by visit • Absolute change from baseline in body weight by visit • Change from baseline in waist circumference by visit **Efficacy Endpoints:** • Change from baseline in CGI-S by visit • Time to discontinuation • 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 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 enrolled subjects who receive at least 1 dose of study drug. All analyses will be conducted using the Safety Population.

Efficacy Analyses: Changes from baseline in CGI-S and IWQOL-Lite scores will be summarized using descriptive statistics. The time to discontinuation will be estimated using the Kaplan-Meier (KM) method and the KM plot will be provided.

Safety 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. Reported AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by preferred term and system organ class categories. Serious adverse events (SAEs) and AEs leading to study discontinuation will also be summarized.

Observed values and change from baseline in laboratory parameters and vital signs will be summarized by study visit. The number and percentage of subjects who have met potentially clinically significant criteria at any post baseline visit will be summarized for laboratory and vital signs. The number and percentage of subjects with shifts in laboratory parameters will be summarized. Supporting listings will be provided. The number and percentage of subjects with C-SSRS assessments of suicidal ideation and behavior will also be summarized.

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.

Sample Size Considerations: No formal sample size calculation will be performed for this extension study. A sample size of approximately 500 is based on the estimated number of subjects who are expected to roll over from the antecedent Phase 3 studies (ALK3831-A304, ALK3831-A306, and ALK3831-A307).

3. TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS

Table 2: List of Abbreviations and Definition of Terms

Abbreviation or Term	Full Form or Definition
AE	Adverse event
ANC	Absolute neutrophil count
ATC	Anatomical Therapeutic Chemical [classification system]
CGI-S	Clinical Global Impressions-Severity
CRO	Clinical Research Organization
CSA	Clinical Study Agreement
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
ECG	Electrocardiogram
eCRF	Electronic case report form
ET	Early termination
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
ICF	Informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IWQOL-Lite	Impact of Weight on Quality of Life-Lite
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
SAE	Serious adverse event
SAP	Statistical Analysis Plan
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

5. INTRODUCTION

5.1. Background

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). Olanzapine is also 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 is 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), for the treatment of schizophrenia designed to combine the antipsychotic efficacy of olanzapine with a reduced risk of weight gain and associated metabolic deficits. 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.

Development of ALKS 3831 as a fixed-dose combination of olanzapine and samidorphan has the potential to improve upon the benefit/risk profile of olanzapine alone and address a significant clinical need for patients that are currently forced to choose between treatment efficacy and safety. Four Phase 3 studies (ALK3831-A303, ALK3831-A304, ALK3831-A305, and ALK3831-A306) are ongoing to assess the efficacy, associated weight changes, and safety of ALKS 3831 in subjects with schizophrenia. One Phase 3 study (ALK3831-A307) is planned to begin enrollment in 2017 and will 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 10.5). 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, and AE labeling is supported by an extensive safety database with over 20 years of post-marketing experience (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 Phase 3 study is an extension study (for antecedent studies ALK3831-A304, ALK3831-A306, and ALK3831-A307) that will evaluate the long-term safety, tolerability, and durability of treatment effect of ALKS 3831 in subjects with schizophrenia, schizophreniform disorder, or bipolar I disorder. This study will extend subject exposure by up to 4 years, and provide valuable safety and tolerability data over the longest treatment durations evaluated so far (up to 5.5 years). Information regarding non-clinical and clinical studies completed to date with ALKS 3831 is available in the current version of the Investigator's Brochure.

5.4. Dose Rationale

All subjects will receive ALKS 3831. The doses of ALKS 3831 will be 5, 10, 15, and 20 mg olanzapine combined with 10 mg samidorphan (henceforth to be referred to as 5/10, 10/10, 15/10, and 20/10 mg). These doses represent the intended therapeutic doses of ALKS 3831 and include the full range of doses used in all antecedent studies. The 10 mg samidorphan dose was identified as the minimal effective dose 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.

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 long term safety, tolerability, and durability of treatment effect of ALKS 3831 in subjects with schizophrenia, schizophreniform disorder, or bipolar I disorder.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

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

7.1. Subject Inclusion Criteria

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

1. Subject is willing and able to give informed consent/assent as per local requirements
2. Subject agrees to use an acceptable method of contraception during the study and until 30 days after any study drug administration, unless surgically sterile or post-menopausal
3. Subject has the potential to benefit from the administration of ALKS 3831, in the opinion of the Investigator
4. Subject met the eligibility criteria of the antecedent study at the time of enrollment in the antecedent study and completed the treatment period in one of the following antecedent studies within 7 days: ALK3831-A304, ALK3831-A306, or ALK3831-A307

7.2. Subject Exclusion Criteria

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

1. Subject has any finding that in the view of the investigator or medical monitor would compromise the safety of the subject or affect his/her ability to fulfill the protocol visit schedule or visit requirements
2. Subject has a positive test for drugs of abuse (see Section 8.3.9.1) at study entry
3. Subject is currently pregnant. breastfeeding or is planning to become pregnant during the study or within 30 days of the last study drug administration
4. Subject is employed by Alkermes, the Investigator or study site (permanent, temporary contract worker, or designee responsible for the conduct of the study) or is immediate family[1] of an Alkermes, clinical research organization, or study site employee
5. If in the opinion of the Investigator (and/or Sponsor) is unsuitable for enrollment in the study

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

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 absolute neutrophil count (ANC) < 1.0×10^3 per µL or Hemoglobin A1c (HbA1c) ≥6.5% at any time, the PI (or designee) should discontinue the subject from participation immediately. Reasons for discontinuation include:

- Adverse Event
- Lack of Efficacy
- Lost to Follow-up
- Withdrawal by Subject
- Protocol Deviation (including non-compliance 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 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. Subjects who terminate the treatment early (prior to Visit 25) will complete an early termination (ET) visit and the 4-week Safety Follow-up period. 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 the EOT Visit. 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 will not be replaced.

8. STUDY DESIGN

8.1. Overall Study Design and Plan

This is a multicenter, open-label study to evaluate the long term safety, tolerability, and durability of treatment effect of ALKS 3831 in subjects with schizophrenia, schizophreniform disorder, or bipolar I disorder. Subjects that have completed the antecedent studies (ALK3831-A304, ALK3831-A306, or ALK3831-A307) within the past 7 days will be eligible to enroll in this study.

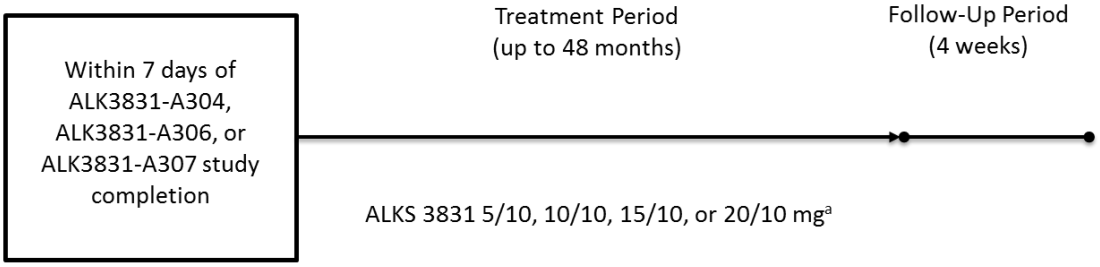
Subjects enrolled in the study will be started on the same olanzapine dose that they had maintained at the end of the antecedent study. Available doses of ALKS 3831 will be 5/10, 10/10, 15/10, and 20/10 mg. Subjects may be titrated to a different dose after the start of the study at the Investigator's discretion. Dosing will be flexible throughout the study; however, frequent adjustments are discouraged. Dose adjustments will only be performed on-site at the study center. Subjects requiring dose adjustments between scheduled visits will need to arrange an unscheduled visit.

Safety assessments will include AE monitoring, clinical laboratory testing, vital signs, body weight, ECGs, and the Columbia-Suicide Severity Rating Scale (C-SSRS). Psychiatric symptoms will be evaluated using the CGI-S scale. Additional assessments will include Impact of Weight on Quality of Life-Lite Questionnaire (IWQOL-Lite).

The duration of the treatment period will vary by subject, between 24 and 48 months, or until regulatory action; duration will vary by subject. The study completion is targeted for the 4th quarter of 2022. After the last subject is enrolled, the end date of the study will be set to occur 24 months later (approximately the 4th quarter of 2022), and subjects will be informed of the target completion date. The total study duration will be up to 49 months including a treatment period of 24 to 48 months and a 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 Schematic



[a]Visits will occur monthly throughout the 48-month Treatment period. Subjects will start the study on the equivalent olanzapine dose to what they maintained at the end of the antecedent study. The dose may be adjusted to either 5/10, 10/10, 15/10, or 20/10mg throughout the study period based on investigator discretion, and such dose adjustments will require subjects to visit the study site.

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

Visits 1-25[b]	Treatment Period[a]				Follow-up Period[a]
	Transition from Previous Study[c]	**Monthly Visits[d]**	**Quarterly Visits**	**EOT/ ET**	**Safety Follow-up Visit[e]**
	1	**2, 3, 5, 6, 8, 9, 11, 12, 14, 15, 17, 18, 20, 21, 23, 24**	**4, 7, 10, 13, 16, 19, 22, 25**	**No later than Visit 49**	**No later than Visit 50**
Visits 26-50[b]	—	**26, 27, 29, 30, 32, 33, 35, 36, 38, 39, 41, 42, 44, 45, 47, 48**	**28, 31, 34, 37, 40, 43, 46**		
Qualification/ Safety Assessments					
Informed Consent	X				
Eligibility Review	X				
Urine Pregnancy Testing (all women)	X	X	X	X	X
Urine Drug Screen	X[f]		X		
Physical Examination and ECG			X	X	
Vital Signs			X	X	
Biochemistry, Hematology, and Urinalysis Samples			X	X	
Weight and Waist Circumference		X	X	X	X
Adverse Event Monitoring		X	X	X	X
Concomitant Medication Review		X	X	X	X
C-SSRS[g]		X	X	X	X
Psychiatric/ Quality of Life Assessments					
CGI-S		X	X	X	X
IWQOL-Lite			X	X	
Other/ General Procedures					
Study Drug Dispensation	X	X	X		
Study Drug Return Review		X	X	X	

Abbreviations: CGI-S=Clinical Global Impressions-Severity; C-SSRS=Columbia-Suicide Severity Scale; ECG=electrocardiogram; EOT=end of treatment; ET=early termination; IWQOL-Lite=Impact of Weight on Quality of Life-Lite

[a] A visit window of ±4 days is allowed throughout the treatment period and the Follow-up period.

[b] Subjects may be treated with study drug for 24 to 48 months, or until regulatory action; duration will vary by subject.
[c] Visit 1 must occur within 7 days of the EOT visit of the antecedent studies (ALK3831-A304, ALK3831-A306, or ALK3831-A307) and may occur on the same day. Subsequent visits are to be conducted every month (every 28 days [±4 days]).
[d] Except for every 3rd visit from Visit 1 (Quarterly Visits).
[e] To be performed one month (28 days [±4 days]) after the EOT/ET visit.
[f] The urine drug screen will be performed at Visit 1; however if Visit 1 is the same as EOT visit of the antecedent study and a urine drug screen was already performed during that visit, it doesn't need to be repeated.
[g] 'Since Last Visit' version to be used at all indicated visits.

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 (PI) 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 as specified in Table 3.

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.

8.3.3. Demographics and Medical / Psychiatric History

Subject's demographic data and medical / psychiatric history (including primary psychiatric diagnosis) will be carried over from the antecedent studies (ALK3831-A304, ALK3831-A306, or ALK3831-A307).

8.3.4. Concomitant Medication Review

At the timepoints specified in Table 3, subjects will be asked about the medications they have taken since their last visit, including prescription and nonprescription medications, vitamins, and supplements.

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

8.3.5. Vital Signs

Vital signs (ie, blood pressure, pulse, 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. 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, 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 brief physical examination and an ECG (local) will be performed at the timepoints specified in Table 3.

8.3.7. Weight and Waist Circumference

Weight and waist circumference will be measured at all the timepoints specified in Table 3.

For weight 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 the same scale for each measurement under the same conditions.

Both weight and waist circumference will be measured three consecutive times at each assessment and all measurements will be recorded in the eCRF.

8.3.8. 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.

8.3.8.1. Safety Assessments

8.3.8.1.1. Columbia-Suicide Severity Rating Scale

The PI or designee will administer C-SSRS according to the timepoints in Table 3. The "Since Last Visit" version of the C-SSRS will be used at all indicated visits. The C-SSRS should be administered by a qualified clinician trained in assessing and managing suicidal ideation and behavior (Posner et al, 2011).

8.3.8.2. Psychiatric/Quality of Life Assessments

8.3.8.2.1. 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).

8.3.8.2.2. 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.

8.3.9. Laboratory Assessments

8.3.9.1. 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 for the subject to be eligible for the study. The urine drug screen will be

performed at Visit 1; however if Visit 1 is the same as the end of treatment visit of the antecedent study and a urine drug screen was already performed during that visit, it doesn't need to be repeated. The urine drug screen may be repeated at any point during the study based on the investigator's discretion.

8.3.9.2. Hematology, Biochemistry, and Urinalysis

Blood and urine samples for laboratory assessments will be collected at the timepoints specified in Table 3. Specific hematology, biochemistry, and urinalysis assessments are 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 Hemoglobin Platelets Red blood cell count Total and differential (absolute) white blood cell count	<u>General Chemistry</u> Albumin Bicarbonate Calcium Chloride Creatine phosphokinase Glucose Lactic dehydrogenase Potassium Sodium Total protein Uric acid <u>Endocrine Function Test</u> HbA1c Prolactin Insulin <u>Liver Function Tests</u> Alanine aminotransferase Alkaline phosphatase Aspartate aminotransferase Gamma-glutamyl transferase Total bilirubin <u>Renal Function Tests</u> Blood urea nitrogen Creatinine <u>Lipid Panel</u> High-density lipoprotein Low-density lipoprotein Total cholesterol Triglycerides	Bilirubin Color and appearance Glucose Ketones Leukocytes Nitrite Occult blood pH Protein Specific gravity Urobilinogen Cotinine Microscopic examination of sediment, *only if urinalysis dipstick results are abnormal*

8.3.9.3. Urine Pregnancy Testing

A urine pregnancy test will be administered to all women at the timepoints specified in Table 3. At Visit 1, results must be negative for the subject to be eligible for the study. 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.

8.3.10. 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.

8.3.11. Emergency Treatment Card

An emergency treatment card will be distributed to each subject at Visit 1 and collected at the EOT/ET Visit. The card will indicate that the subject is receiving an opioid antagonist and 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.

8.3.12. 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). All AEs ongoing at the end of trial or concomitant medications continuing from the antecedent study will be carried over and followed until resolution. All AEs and serious adverse events (SAEs) are defined in Section 13.2 and Section 13.3, respectively. Section 13.5 provides guidance on the monitoring and recording requirements for AEs. Section 13.6 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 male subject has a partner who becomes pregnant, the partner may need to provide written informed consent to obtain pregnancy follow-up information, as per local requirements.

A Pregnancy Report Form must be submitted to Alkermes via [redacted] (per Section 13.6) 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 13.6).

8.4.2. Prohibited Medications

In this study, the medications listed below are prohibited:

- Antipsychotic medications for any indication
- Diabetes treatments and hypoglycemic agents including Metformin and Insulin
- Moderate to strong inhibitors or inducers of cytochrome P450 (CYP) 3A (prescription medications, OTC medications, or dietary supplements) within 30 days before enrollment through Follow-up (refer to Section 20 for a list of CYP3A inhibitors and inducers)
- Use of opioid antagonists, including naltrexone (any formulations) and naloxone
- Opioid agonists should be avoided as they may be rendered ineffective by samidorphan

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

In this study, the medications listed below are permitted:

- Medications that exhibit drug interaction potential with olanzapine, including known inhibitors and inducers of CYP1A2 (Section 21), 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 (Section 22)

- Oral contraceptive pills and other hormonal methods (eg, a vaginal ring, contraceptive patch, contraceptive implant) will be permitted
- Permissible medications to treat extrapyramidal symptoms may include benzodiazepines, antihistamines, and anticholinergics. Benzodiazepines should be utilized for treatment-emergent akathisia
- Treatment of agitation and/or anxiety with benzodiazepines is permissible

8.4.4. Pain Management

Because ALKS 3831 contains samidorphan, a μ-opioid antagonist, patients 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 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

9. TREATMENT OF SUBJECTS

9.1. Study Drug Dose and Administration

The study drug, ALKS 3831 will be available in the following doses:

- ALKS 3831 5/10, 10/10, 15/10, and 20/10 administered as a coated bilayer tablet

Subjects enrolled in the study will be started on the same olanzapine dose that they had maintained at the end of the antecedent study. Subjects may be titrated to a different dose after the start of the study at the Investigator's discretion. Dosing will be flexible throughout the study; however, frequent adjustments are discouraged. Dose adjustments will only be performed on-site at the study center.

Subjects will be given study drug to take home and 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

Subjects will undergo a study drug adherence review at the timepoints indicated in Table 3. 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 non-adherence with the subject.

9.3. Randomization/Method of Assigning Subjects to Treatment

Not applicable.

9.4. Blinding

Not applicable.

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.

10.2. Packaging and Labeling

ALKS 3831 will be supplied in blister packs. Blister cards will be in biweekly configurations. Biweekly blister cards will contain 16 tablets, enough for 2 weeks of dosing plus sufficient overage for 2 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, ALKS 3831 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 8.3.10 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

Throughout the study, CGI-S scores will be collected to measure the durability of treatment effect. Time to discontinuation will also be estimated. Throughout the study, IWQOL-Lite scores will be collected to obtain information regarding subject experience.

11.1. Efficacy Endpoints

- Change from baseline in CGI-S by visit
- Time to discontinuation
- Change from baseline in IWQOL-Lite score by visit

12. ASSESSMENT OF PHARMACOKINETICS

Not applicable.

13. ASSESSMENT OF SAFETY

Safety will be assessed on the basis of:

- AEs (including clinically significant abnormal ECG findings)
- Vital signs (oral temperature, respiratory rate, blood pressure, and heart rate)
- Weight and waist circumference
- Clinical laboratory parameters (biochemistry, hematology, and urinalysis)
- C-SSRS results

13.1. Safety Endpoints

- Incidence of AEs
- Percent change from baseline in body weight by visit
- Absolute change from baseline in body weight by visit
- Change from baseline in waist circumference by visit

13.2. 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 informed consent form (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.

13.3. 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 reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (eg, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be immediately life threatening, or require hospitalization may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require intervention to prevent one of the other outcomes listed above. Admission to an inpatient unit or hospital for a nonmedical or nonbehavioral reason (ie, social stay admission) during the study in the absence of 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.

13.4. 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 Sub-Investigator) 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.

Abbreviations: AE=adverse event

13.5. Monitoring and Recording of Adverse Events

All AE data collection will begin after a subject signs the ICF and will continue until completion of the safety follow-up visit. 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 13.4), 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.

13.6. Reporting of Serious Adverse Events and Pregnancy

All SAEs and pregnancies must be reported to PPD [redacted] immediately, within 24 hours of discovery, by emailing or faxing the report to the following:

Attention: PPD [redacted] Medical Monitor
US Email: [redacted]
ROW Email: [redacted]
US Fax Number: [redacted]
ROW Fax Number: [redacted]

The written report should be submitted on the SAE form provided for this purpose. The 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

No formal sample size calculation will be performed for this extension study. A sample size of approximately 500 subjects is based on the estimated number of subjects who are expected to roll over from the antecedent Phase 3 studies within 7 days (ALK3831-A304, ALK3831-A306, and ALK3831-A307).

14.2. General Statistical Methodology

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

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

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

14.2.1. Study Population

14.2.1.1. Safety Population

The safety population will include all enrolled subjects who receive at least one dose of study drug. All analyses will be conducted using the safety population.

14.3. Demographics and Baseline Data

Demographics and baseline characteristics such as gender, age, race, weight, and body mass index will be summarized.

14.4. Efficacy Analyses

Changes from baseline in CGI-S and IWQOL-Lite scores will be summarized using descriptive statistics. The time to discontinuation will be estimated using the Kaplan-Meier (KM) method and the KM plot will be provided.

14.5. Pharmacokinetic Analyses

Not applicable.

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 (including clinically significant abnormal ECG findings), vital signs, and results of clinical laboratory tests. Reported AE terms will be coded using the MedDRA preferred terms and system organ classes.

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 percent of subjects with TEAEs by system organ class, and by preferred terms 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 by severity and by relationship to the study drug.

Observed values and change from baseline in laboratory parameters and vital signs will be summarized by visit.

The number and percentage of subjects who have met potentially clinically significant criteria at any postbaseline visit will be summarized for laboratory and vital signs. Supporting listings will be provided.

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

Concomitant medications will be summarized by World Health Organization (WHO) Anatomical Therapeutic Chemical (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, 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, subjects' medical records) to determine whether these activities were conducted, and data recorded, analyzed and accurately reported, according to the protocol, GCP guidelines of the International Council on Harmonisation (ICH), and any applicable regulatory requirements.

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

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 (GCP) 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-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/assent form (as per local requirements) 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, the contract research organization (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/assent form, which must be reviewed and approved by the IRB, and then signed by all applicable study participants.

The time that informed consent is obtained must be documented. The Investigator must maintain the original, signed ICF/assent form in the subject's source documents. A copy of the signed ICF/assent form 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, or central MRI data, will be transferred directly to EDC 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.

All AEs will be coded using 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.

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

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.

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. Accessed on 08 Sep 2017.

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

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.

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

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, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry.* 2011;168(12):1266-1277. doi: 10.1176/appi.ajp.2011.10111704.

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 enrollment and through follow-up. 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 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