A Phase 3, Multicenter Study to Assess the Long Term Safety and Tolerability of ALKS 3831 in Subjects with Schizophrenia

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STATISTICAL ANALYSIS PLAN

ALK3831-A306

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ABBREVIATIONS

Abbreviation or Term	Explanation or Definition
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ATC	Anatomical Therapeutic Chemical [classification system]
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CI	Confidence interval
C-SSRS	Columbia Suicide Severity Rating Scale
EC	Excited Component
ECG	Electrocardiogram
eCRF	Electronic case report form
EOT	End of treatment
EPS	Extra pyramidal symptoms
EQ-5D	EuroQOL-5D
ET	Early termination
FAS	Full analysis set
HbA1C	Hemoglobin A1c
IWQOL	Impact of Weight on Quality of Life
MedDRA	Medical Dictionary for Regulatory Activities
OLZ	Olanzapine
PANSS	Positive and Negative Syndrome Scale
PCS	Potentially clinically significant
PK	Pharmacokinetic
PT	Preferred term
KM	Kaplan-Meier
QTcB	QT corrected with Bazett formula

Abbreviation or Term	Explanation or Definition
QTcF	QT corrected with Fridericia formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Simpson-Angus Scale
SD	Standard deviation
SMQ	Standardized MedDRA queries
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
VAS	Visual analogue scale
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used for analyses and presentation of safety and efficacy data for the study ALK3831-A306. This document has been prepared based on Alkermes ALK3831-A306 Study Protocol Amendment 2.0 (dated 25 Apr 2017)[1].

1.1. Study Objectives

1.1.1. Primary objective

The primary objective of this study is to evaluate the long term safety and tolerability of ALKS 3831 in subjects with schizophrenia.

1.2 Summary of the Study Design

Subjects that have completed the 4-week Treatment Period of the antecedent study, ALK3831-A305, within the past 7 days are eligible to be enrolled in the study. Subjects completing the 4-week Treatment Period of the antecedent study, ALK3831-A305, as inpatients may continue as inpatients for up to 1 week in this extension study. These subjects may be discharged from the inpatient unit at any time during this week based on Investigator's judgment.

Subjects enrolled in the study will be started on ALKS 3831 10/10 (10 mg olanzapine/10 mg samidorphan). The ALKS 3831 dose may be increased to 15/10 (15 mg olanzapine/10 mg samidorphan) or 20/10 (20 mg olanzapine/10 mg samidorphan) during the first week of treatment or thereafter, based on Investigator discretion. For subjects entering this study as outpatients, study staff will check in with them by phone on Day 3 to assess tolerability and determine if a dose increase to ALKS 3831 15/10 or 20/10 is needed. An Unscheduled Visit will be arranged mid-Week 1 for subjects requiring a dose increase. Following a dose increase, the dose may be decreased back to 15/10 or 10/10 if there are tolerability issues. Thus, dosing is flexible and subjects will receive ALKS 3831 10/10, 15/10, or 20/10 throughout the duration of the study, based on Investigator discretion. 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, adherence review, and study drug dispensation.

Safety assessments will include AE monitoring, clinical laboratory testing, vital signs, weight and waist circumference assessments, 12-lead ECGs, movement disorder assessments, including the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), Simpson Angus Scale (SAS), and the Columbia-Suicide Severity Rating Scale (C-SSRS).

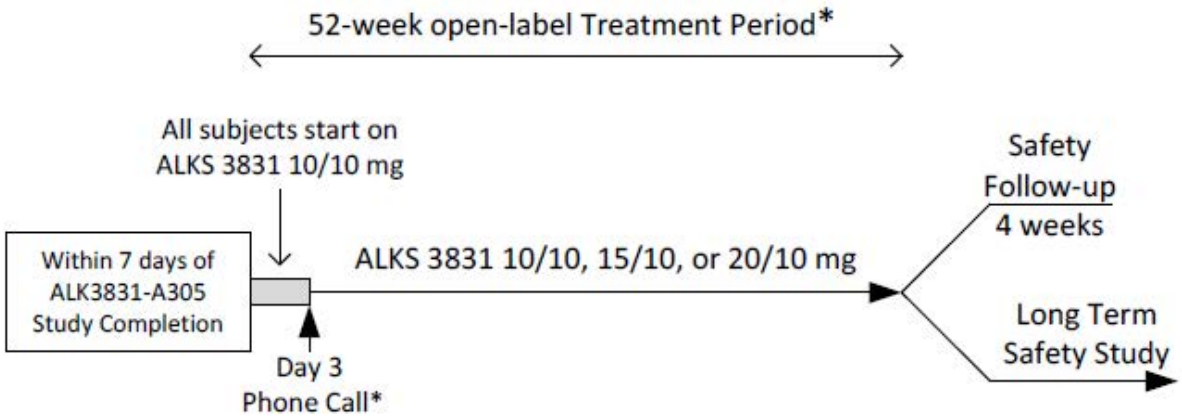
Efficacy assessments to evaluate the durability of treatment effect will include Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions-Severity (CGI-S).

Additional assessments include Impact of Weight on Quality of Life–Lite Questionnaire (IWQOL-Lite), Cigarette Use, and EuroQOL-5D (EQ-5D).

Subjects completing 52 weeks of treatment with study drug will be eligible to continue in the open-label, long-term safety study (ALK3831-A308) and will continue to receive ALKS 3831. Subjects not continuing in the ALK3831-A308 long-term safety study will enter a 4-week Safety Follow-up Period.

A schematic of the study design is provided in Figure 1.

Figure 1: Study Design Schematic



*Visits will occur weekly for the first 2 weeks, then biweekly thereafter. Outpatient subjects will be contacted by phone on Day 3 to determine if a dose increase is needed, and, if so, an unscheduled visit will be arranged mid-Week 1. The dose may be adjusted to either 10/10, 15/10, or 20/10 mg throughout the study period, based on Investigator discretion, and such dose adjustments will require subjects to visit the study site

2. SAMPLE SIZE CONSIDERATION

No formal sample size calculation is performed for this extension study. A sample size of approximately 390 is based on the estimated maximum number of subjects who might be expected to continue from the ALK3831-A305 study.

3. DATA ANALYSIS

3.1. General Statistical Methodology

Baseline for efficacy or safety analysis is defined as the last non-missing assessment before the first dose of ALKS 3831 in ALK3831-A306 study, and it will be used for all efficacy and safety analysis unless specified otherwise.

Antecedent study baseline, defined as the last non-missing assessment on or before the first dose of study drug during double-blind treatment period in ALK3831-A305 study, may be explored as applicable.

Treatment sequence is defined according to the treatment assignment in antecedent and current studies as ALKS 3831/ALKS 3831 (ALKS 3831 in both ALK3831-A305 study and ALK3831-A306 study), OLZ/ALKS 3831 (olanzapine in ALK3831-A305 study and ALKS 3831 in ALK3831-A306 study), or PBO/ALKS 3831 (placebo in ALK3831-A305 study and ALKS 3831 in ALK3831-A306 study).

In general, descriptive statistics: n, mean (±standard deviation [SD]), median, minimum, and maximum, for continuous variables and number and percentage of subjects in each category for categorical variables will be provided.

All statistical tests and confidence intervals (CIs), unless stated otherwise, will be 2-sided and will be set at an alpha level of 0.05.

All source data will be presented as subject data listings.

3.2. Definitions of Analysis Populations

3.2.1. Safety Population

The Safety Population will include all subjects who enrolled and received at least 1 dose of study drug during the treatment period. The Safety Population will be used for the safety analyses.

3.2.2. Efficacy Population

The Full Analysis Set (FAS) will include all subjects in the Safety Population who have at least one postbaseline PANSS assessment.

3.3. Disposition

The number and percentage of subjects completing or prematurely discontinuing the study including reasons for discontinuation will be summarized by treatment sequence and overall for the following:

- Subjects who enrolled in the study
- Subjects in the Safety Population
- Subjects in the FAS Population

- Subjects who completed the treatment period
- Subjects who discontinued treatment along with reasons for discontinuation

3.4. Protocol Deviation

Subjects with major protocol deviations in the following categories will be summarized by treatment sequence and oveall. A supportive listing will be provided as well.

- Did not meet the inclusion/exclusion criteria
- Received prohibited medications
- Lack of adherence with study medication, as defined by subjects taking less than 70% of protocol specified amount of study medication
- Dosing error

3.5. Demographics and Baseline Characteristics

Demographics and baseline characteristics such as gender, age, race, ethnicity, weight, and BMI will be summarized by treatment sequence and overall for the Safety and FAS population.

3.6. Prior and Concomitant Medication

Prior medications are defined as medications taken prior to the first dose of study drug in ALK3831-A306 study. Concomitant medications are defined as medications taken on or after the first dose of study drug in ALK3831-A306 study. All medications will be coded using the World Health Organization WHO-DD Enhanced + Herbal (version: March 2016) or higher.

Concomitant medications are defined as medications taken during the treatment period and will be summarized by the preferred drug name for the Safety population. All reported medications (including those initiated after the last dose of study medication) will be included in listing. For the summary table, if a subject has taken a concomitant medication more than once, the subject will be counted only once for that medication.

3.7. Treatment Adherence Rate and Duration of Study Drug Administration

3.7.1. Treatment Adherence Rate

Treatment adherence to the daily dosing schedule during treatment period will be summarized by treatment sequence for Safety Population. Treatment adherence will be calculated as follows:

$$100 \times \frac{\text{Total tablets dispensed} - \text{total tablets returned} - \text{total tablets lost}}{\text{Total tablets scheduled to be taken}}$$

3.7.2. Duration of Study Drug Administration

Duration of study drug administration (ALKS 3831) is defined as the number of days from the date of the first dose of study drug to the date of the last dose of study drug, inclusive (ie, last dose date – first dose date + 1 day). Duration of study drug administration will be summarized for the Safety Population by treatment sequence and overall.

The overall mean and modal dose of olanzapine will be summarized by treatment sequence and overall. Number and percentage of subjects will be summarized by their final dose level by treatment sequence and overall.

3.8. Efficacy Analyses

3.8.1. General Considerations

All statistical analysis will be performed at the 5% significance level. All confidence intervals (CI) will be 2-sided 95% confidence intervals. Efficacy analysis will be carried out using the FAS population. PANSS total and subscale scores, CGI-S, PANSS response analyses and body weight will be based on both observed data and the LOCF (last observation carried forward) imputation, that is, the last observed non-missing postbaseline value will be carried forward for missing postbaseline assessments.

3.8.2. Efficacy Analysis

The following endpoints will be used to evaluate durability of treatment effect and summarized by treatment sequence and overall for FAS population:

- Change from baseline in PANSS total score, and subscale scores (positive, negative, and general psychopathology subscales) by visit
- Change from baseline in PANSS Excited Component (EC) score (comprised of 5 items, P4. excitement, G4. tension, P7. hostility, G8. uncooperativeness, and G14. poor impulse control) by visit
- Change from baseline in PANSS Marder factor scores by visit
- Change from baseline in CGI-S by visit
- Proportion of Subjects with PANSS response ($\geq$ 30% improvement from baseline in PANSS total score)
- Time to first relapse
- Time to first remission
- Time to discontinuation

In general, continuous and categorical endpoints will be summarized using descriptive statistics by treatment sequence and overall. Change from baseline within the treatment sequence and overall may also be tested using an one-sample t-test.

The PANSS Marder factor model[2] consisted of the following 5 factors:

- Negative symptoms
  - N1. blunted affect
  - N2. emotional withdrawal
  - N3. poor rapport
  - N4. passive social withdrawal
  - N6. lack of spontaneity
  - G7. motor retardation
  - G16. active social avoidance
- Positive symptoms
  - P1. delusions
  - P3. hallucinatory behavior
  - P5. grandiosity
  - P6. suspiciousness
  - N7. stereotyped thinking
  - G1. somatic concern
  - G9. unusual thought content
  - G12. lack of judgment and insight
- Disorganized thought
  - P2. conceptual disorganization
  - N5. difficulty in abstract thinking
  - G5. mannerisms and posturing
  - G10. disorientation
  - G11. poor attention
  - G13. disturbance of volition
  - G15. preoccupation
- Uncontrolled hostility/excitement
  - P4. excitement
  - P7. hostility

  - G8. uncooperativeness
  - G14. poor impulse control
- Anxiety/depression
  - G2. anxiety
  - G3. guilt
  - G4. tension
  - G6. depression

Stabilization is defined as meeting all of the following stablization criteria:

- PANSS total score ≤ 80
- PANSS score ≤ 4 on each of the following items:
  - P2: conceptual disorganization
  - P3: hallucinatory behavior
  - P6: suspiciousness
  - G9: unusual thought content

After a subject achieves stabilization, relapse and remission are defined as following:

- Relapse: ≥ 30% increase in PANSS total score or re-hospitalization for psychotic symptoms.
- Remission: PANSS score ≤3 (mild or less) on each of the following items in two consecutive efficacy assessments
  - P1: delusions
  - G9: unusual thought content
  - P3: hallucinatory behavior
  - P2: conceptual disorganization
  - G5: mannerisms/posturing
  - N1: blunted affect
  - N4: social withdrawal
  - N6: lack of spontaneity

Time to first relapse will be estimated using the Kaplan-Meier method by treatment sequence and overall. It is defined as the time from the date of stabilization to the date of first relapse. Subjects who completed the treatment without relapse will be censored at the date of last dose. Time to first remission will be analyzed similarly.

Time to treatment discontinuation will be analyzed similarly using the Kaplan-Meier method by treatment sequence and overall. Both all cause dicontinuation and discontinuation due to AE will be summarized. For prematurely discontinued subjects (all cause or due to AE), time to event is defined as time from the date of first dose of study drug to the date of last dose of study drug. Other subjects will be censored at the last dose of the study drug.

3.8.3. Other Assessments

- Change from baseline in IWQOL-Lite scales (total score, physical function, self-esteem, sexual life, public distress, and work) by visit
- Change from baseline in EQ-5D-5L index value and VAS score by visit
- Cigarette use

The IWQOL-Lite scale is a 31-item self-report measure of obesity-specific quality of life. IWQOL-Lite provides an overall total score as well as scores on five domains: (1) physical function, (2) self-esteem, (3) sexual life, (4) public distress, and (5) work. The raw scores will be transformed as follows (Tessier et al, 2012)[3]: the transformed scores range from 0 to 100, with 100 representing the best, and 0 representing the most impaired quality of life.

$$Transformed\ Score = \frac{maximum\ theoretical\ score - actual\ score}{test\ score\ range} X100$$

The EQ-5D-5L is a validated quality of life questionnaire developed by the EuroQol Group in order to provide a simple, generic utility measure for characterizing current health states of patients. EQ-5D-5L is designed for self-completion by subjects. It consists of 2 parts – the EQ-5D-5L descriptive system and the visual analogue scale (VAS).

The EQ-5D-5L descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels.

The 5 dimensional 5-level systems are converted into an index value. Values for theoretically possible health states are calculated using a regression model and weighted according to the social preferences of the U.S. population (Van Hout et al, 2012)[4]. The VAS records the respondent's self-rated health on a vertical visual analogue scale. The VAS has 100 (Best health you can imagine) at the top, and 0 (Worst health you can imagine) at the bottom. This information can be used as a quantitative measure of health outcomes as judged by the individual respondents. EQ-5D-5L self-reported VAS data generates information on the self-perceived overall health-related quality of life. Change from baseline in EQ-5D-5L index value and VAS score will be analyzed.

Number of cigarettes used will be summarized at each visit by treatment sequence and overall.

3.8.3.1. Examination of Subgroups

Subgroup analysis by region (US vs non-US) will be performed for selected endpoints, including but not limited to, change from baseline in PANSS total and subscale scores, and PANSS response.

3.8.4. Multiple Comparison / Multiplicity

Not applicable.

3.9. Safety Analysis

All safety endpints will be summarized by treatment sequence and overall for the Safety Population.

3.9.1. Adverse Events

Incidence of treatment emergent AEs will be analyzed as a safety endpoint. Adverse events will be coded by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 19.0 or higher. The verbatim term will be included in the AE listings.

An AE (coded by preferred term) will be considered as treatment emergent AE (TEAE) if the event is newly occurring or worsening on or after the date of first dose of study drug in this study.

The number and percentage of subjects reporting TEAEs during the treatment period will be presented by treatment sequence and overall for the following categories:

- System organ class and preferred term
- Preferred term, and including the following subset:
  - TEAEs experienced by ≥5% of subjects (in any group) System organ class, preferred term, and severity
  - System organ class, preferred term for serious TEAEs
  - System organ class, preferred term, and relationship
  - System organ class, preferred term for study drug related TEAEs
  - System organ class, preferred term , and severity for study drug related TEAEs

If the same preferred term occurred more than once for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug.

In addition, the number and percentage of subjects reporting AEs during the safety follow-up period will be tabulated by the system organ class, preferred term and treatment sequence and overall.

The number and percentage of subjects who have serious adverse events (SAE) and AEs leading to premature discontinuation from the treatment will be summarized by system organ class, preferred term, and treatment sequence and overall.

3.9.1.1. Other significant AEs

In addition, incidence of a selected subset of relevant AEs in this class of drugs (eg, Extrapyramidal symptoms (EPS) TEAEs, AEs associated with abuse potential, drug withdrawal, and suicide related events, etc.) will be summarized by preferred term and treatment sequence and overall. The selection of AEs per subset will be based on the preferred terms and customized or Standardized MedDRA queries (SMQs).

3.9.2. Clinical Laboratory Parameters

Laboratory parameters will be presented in conventional (ie, US) units. Only scheduled laboratory parameters will be included in the summaries, unless specified otherwise. All laboratory data, including those collected at unscheduled visits, will be included in the listings.

Laboratory results including baseline and change from baseline for the Safety Population during the treatment period for chemistry and hematology parameters will be summarized by treatment sequence, overall, and by visit.

Clinical laboratory test values, scheduled or unscheduled, will be considered potentially clinically significant (PCS) if they meet PCS criteria listed in Table 1. The number and percentage of subjects who have postbaseline PCS clinical laboratory values will be summarized by treatment sequence and overall. The percentages will be calculated based on the number of subjects with non-PCS baseline value and have at least 1 postbaseline assessment. All PCS values including baseline PCS values will be included in supportive listings.

Shift tables for selected metabolic parameters (glucose, total cholesterol, LDL, HDL, tryglyceride, and HbA1c) and liver function tests will be presented. The criteria are summarized in Table 2, Table 3 and Table 4.

Table 1: Criteria of Potentially Clinically Significant (PCS) Abnormality for Selected Analytes

Parameters	Criteria
Chemistry	
Albumin	<2.5 g/dL
Alkaline Phosphatase (U/L)	≥3 × ULN
Alanine Aminotransferase (U/L)	≥3 × ULN
Aspartate Aminotransferase (U/L)	≥3 × ULN
Bilirubin, Total	≥2.0 mg/dL
Blood Urea Nitrogen	>30 mg/dL
Cholesterol, Random	>300 mg/dL
Cholesterol, Fasting	≥240 mg/dL
Cholesterol, HDL Fasting	≤30 mg/dL
Cholesterol, LDL Fasting	≥160 mg/dL
Creatine Kinase (U/L)	≥3 × ULN
Creatinine	≥2.0 mg/dL
Glucose, Random	<50 mg/dL or ≥200 mg/dL
Glucose, Fasting	<50 mg/dL or ≥126 mg/dL
Potassium	<3 mmol/L or >5.5 mmol/L
Lactate Dehydrogenase (U/L)	>3 × ULN
Prolactin (Female)	>30 ng/mL
Prolactin (Male)	>20 ng/mL
Sodium	<130 mmol/L or >150 mmol/L
Triglycerides, Fasting (Female)	≥120 mg/dL
Triglycerides, Fasting (Male)	≥160 mg/dL

Table 1: Criteria of Potentially Clinically Significant (PCS) Abnormality for Selected Analytes (Continued)

Parameters	Criteria
Hematology	
Eosinophils	$>1.0 \times 10^3/\mu L$
Hematocrit (Female)	≤32%
Hematocrit (Male)	≤37%
Neutrophils, Absolute	$<1.5 \times 10^3/\mu L$
Platelets	$<75.0 \times 10^3$ cells/μL or $\geq 700.0 \times 10^3$ cells/μL
Leukocytes	$\leq 2.8 \times 10^3/\mu L$ or $\geq 16.0 \times 10^3/\mu L$

Table 2: Shifts Category from Baseline to Any Postbaseline for Selected Lipid Parameters

Total cholesterol (fasting) mg/dL
Normal (<200) to High (≥240)
Borderline (≥200 and < 240) to High (≥240)
Normal/Borderline (<240) to High (≥240)
Normal (<200) to borderline/High (≥200)
Increase ≥40 mg/dL
LDL Cholesterol (fasting) mg/dL
Normal (<100) to high (≥160)
Borderline (≥100 and <160) to high (≥160)
Normal/borderline (<160) to high (≥160)
Normal (<100) to borderline/high (≥100)
Increase ≥30 mg/dL
HDL Cholesterol (fasting) mg/dL
Normal (≥40) to low (<40)
Decrease ≥20 mg/dL
Triglycerides (fasting) mg/dL

Normal (<150) to high (≥200)
Normal (<150) to very high (≥500)
Borderline (≥150 and <200) to high (≥200)
Borderline (≥150 and <200) to very high (≥500)
Normal/borderline (<200) to high (≥200)
Normal/borderline (<200) to very high (≥500)
Normal (<150) to borderline/high/very high (≥150)
Increase ≥50 mg/dL

Table 3: Shift Category from Baseline to Any Postbaseline in Glucose and HbA1c

Serum glucose (fasting) mg/dL
Normal (<100) to High (≥126)
Impaired (≥100 and <126) to High (≥126)
Normal/Impaired (<126) to High (≥126)
Increase ≥10 mg/dL
HbA1c %
Shift from baseline (<5.7%) to postbaseline ≥5.7%
Shift from baseline (<5.7%) to postbaseline ≥5.7% and <6.5%
Shift from baseline (<5.7%) to postbaseline ≥6.5%

Table 4: Shift Category from Baseline to Any Postbaseline in Liver Function Test

Alanine Aminotransferase (ALT) (U/L)
Shift from Normal to ≥3 x ULN
Shift from Normal to ≥5 x ULN
Shift from Normal to ≥10 x ULN
Aspartate Aminotransferase (AST) (U/L)
Shift from Normal to ≥3 x ULN
Shift from Normal to ≥5 x ULN
Shift from Normal to ≥10 x ULN
Bilirubin, Total (mg/dL)

Shift from Normal to >1 x ULN
Shift from Normal to ≥2 x ULN

3.9.3. Vital Signs, Body Weight, and ECG

3.9.3.1. Vital Signs

Descriptive statistics for vital signs and changes from baseline values at each scheduled time point will be presented by treatment sequence for the treatment period.

Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline criteria listed in Table 5. The number and percentage of subjects with PCS postbaseline values will be tabulated by treatment sequence. The percentages will be calculated based on the number of subjects with non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the number of subjects with non-PCS baseline values and at least 1 postbaseline PCS value. A supportive listing of subjects with PCS postbaseline values will be provided.

All vital signs will be presented in the subject data listing.

Orthostatic hypotension (20/10 mmHg) is defined as a fall in systolic blood pressure of at least 20 mmHg and a fall in the diastolic blood pressure of at least 10 mmHg upon standing from supine. Orthostatic hypotension (30 mmHg) is defined as a fall in systolic blood pressure of at least 30 mmHg upon standing from supine.

Orthostatic tachycardia is defined as a heart rate increase of 30 beats per minute (bpm) or more upon standing from supine, or over 120 bpm upon standing.

The number and percentage of subjects with orthostatic hypotension or orthostatic tachycardia occurring at any postbaseline visit will be summarized for by treatment sequence.

Table 5: Criteria for Potentially Clinically Significant (PCS) Blood Pressure or Pulse Rate

Parameter	Criteria
Supine Systolic Blood Pressure	≤90 and decrease ≥20 mm Hg ≥180 and increase ≥20 mm Hg
Supine Diastolic Blood Pressure	≤50 and decrease ≥15 mm Hg ≥105 and increase ≥15 mm Hg
Supine Heart Rate	≤50 and decrease ≥15 bpm ≥120 and increase ≥15 bpm

3.9.3.2. Weight and Body Mass Index

Weight (kg), BMI (kg/m^2) and waist circumferences (cm) (baseline and change from baseline) will be summarized using both observed data and LOCF imputation for missing data. Absolute

and percent change from baseline in body weight will be summarized by treatment sequence and overall.

Number and percentage of subjects with ≥7% or ≥10% weight gain from baseline based on the observed data and LOCF will be summarized by treatment sequence and overall and by visit.

Subgroup analysis by region (US vs non-US) will be performed.

In addition, number and percentage of subjects with weight change values considered as PCS occurring at any post-baseline visit will be summarized by treatment sequence and overall. Criteria for PCS are presented below. The percentages will be calculated relative to the number of subjects in the Safety Population with at least one post-baseline value. A supportive listing will be provided for subjects with PCS values.

Table 6: Criteria for Potentially Clinically Significant (PCS) Changes from Baseline in Body Weight

Parameter	Criteria
Body Weight	Decrease from Baseline ≥7% Increase from Baseline ≥7%

3.9.3.3. Electrocardiograms

Descriptive statistics for ECG parameters (heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval) at baseline and change from baseline values at each scheduled assessment timepoint and at the end of the treatment period will be presented by treatment sequence for the treatment period. QTc interval will be calculated using both Bazett ($QTcB = QT/(RR)^{1/2}$) and Fridericia ($QTcF = QT/(RR)^{1/3}$) corrections; if RR is not available, it will be replaced with 60/HR in the correction formula.

Electrocardiogram parameter values are considered PCS if they meet or exceed the higher-limit PCS criteria listed in Table 7 . The number and percentage of subjects with PCS postbaseline ECG values will be tabulated by treatment sequence. The percentages will be calculated based on the number of subjects with non-PCS baseline values and at least 1 postbaseline assessment. The numerator is the number of subjects with non-PCS baseline values and at least 1 postbaseline PCS value. A supportive listing of subjects with PCS values will be provided.

Table 7: Criteria for Potentially Clinically Significant (PCS) QTcB and QTcF

Parameter	Criteria
QTcB and QTcF	>450 to ≤480 msec
	>480 to ≤500 msec
	>500 msec
	Change from baseline >30 to ≤60 msec

Parameter	Criteria
	Change from baseline >60 msec

3.9.4. Abnormal Movement Scales

Extra pyramidal symptoms (EPS) will be evaluated as AEs and also as assessed by abnormal movement scales. Abnormal movement scales will include the following: Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson-Angus Scale (SAS).

For all abnormal movement scales, total scores and subscale scores will be summarized by treatment sequence at each visit for the absolute value and for changes from baseline.

Number and percentage of subjects meeting the criteria for treatment emergent Parkinsonism (SAS total score>3), for treatment emergent akathisia (BARS global clinical assessment of akathisia score ≥2), for treatment emergent dyskinesia (AIMS score ≥3 on any of the first 7 items, or a score ≥2 on two or more of any of the first 7 items) at any postbaseline visit will be summarized by treatment sequence.

A listing will be provided for every abnormal movement scale. Listing for treatment emergent EPS will be provided.

3.9.5. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire used to measure the presence and intensity of suicidal ideation and behavior.

Suicidal behavior and suicidal ideation will be summarized for the Safety Population. The number of subjects with suicidal ideation and suicidal behavior will be summarized by treatment sequence when applicable.

Supportive tabular display of subjects with all values will be provided.

Table 8: C-SSRS Categories for Analysis

Category	C-SSRS Item response is "YES"
Suicidal behavior	Preparatory acts or behavior Aborted attempt Interrupted attempt Actual attempt Complete suicide

Suicidal ideation	Wish to be dead Non-specific active suicidal thoughts Active suicidal ideation with any methods (not plan) without intent to act Active suicidal ideation with some intent to act, without specific plan Active suicidal ideation with specific plan and intent
Non-suicidal Self-Injurious Behavior	Non-suicidal Self-Injurious Behavior

3.10. Pharmacokinetic/ Pharmacodynamic Data Analysis

Not applicable.

4. INTERIM ANALYSES

No interim analysis is planned for this study.

5. CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

There are no major deviations from the protocol specified analysis.

6. DEFINITIONS AND CONVENTIONS FOR HANDLING OF THE DATA

Dataset specifications will be provided in a separate document.

6.1. Analysis Visit Windows

Scheduled analysis visits are visits at scheduled timepoints as specified in the protocol (Table 1 Schedule of Visits and Assessments).

Scheduled analysis visits during the study period will be the same as the nominal visits collected in eCRF. There will be one valid value of assessment kept for each scheduled analysis visit in summary/analysis statistics.

Unscheduled visits are visits with data not collected on the scheduled time point. Unscheduled visits will not be used for by-visit summary/analysis statistics, unless specified otherwise.

All unscheduled visits as collected in eCRF will be included in listings.

Visit Day is calculated as date of visit – date of the first dose of study drug + 1 day.

Last postbaseline values are defined as the last valid postbaseline values collected for each subject during the treatment period.

6.2. Handling of Partial Dates of Concomitant Medication

Partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. In the case of completely missing stop date, medication will be assumed to be ongoing.

6.3. Handling of Safety Data

All efforts should be made to obtain the missing information from the investigator. For C-SSRS, vital signs, laboratory testing (chemistry, hematology, urinalysis), and 12-lead ECGs, only observed data will be used for analyses, and missing data will not be imputed.

7. GENERAL STATISTICAL METHODOLOGY

In general, summary statistics (n, mean, SD, median, minimum, and maximum for continuous variables, and number and percentage of subjects in each category for categorical variables) will be provided by treatment sequence. All summary tables will be based on observed data, and missing values will not be imputed, unless otherwise indicated. Measurements collected from unscheduled visits or repeated assessments will not be included in the by-visit summary tables or figures, but will be included in the analyses for the PCS postbaseline values, and subject listings. Source data for the summary tables will be presented as subject data listings.

7.1. Reporting Precision

Summary statistics will be presented to the following degree of precision, unless otherwise specified:

Table 9: Degree of Precision

Statistics	**Degree of Precision**
Mean, Median, Confidence limit boundaries	One more than the raw data, up to 3 decimal places.
Standard deviation, Standard error	One more than the mean, up to 3 decimal places
Minimum, Maximum	The same as the raw data, up to 2 decimal places
P-value	Rounded to 3 decimal places and therefore presented as 0.xxx; *P*-values smaller than 0.001 as ‘<0.001’; P-values greater than 0.999 as ‘>0.999’.
Percentage	One decimal place. A percentage of 100% will be reported as 100%. Percentages of zero will be reported as 0.

Fractional numeric values will be presented with a zero to the left of the decimal point (for example, 0.12 – 0.30).

For weight, height, and body mass index (BMI), one decimal place will be used for summary statistics, unless otherwise specified.

8. PROGRAMMING SPECIFICATIONS

Programming specifications will be provided in a separate document.

9. MOCK TABLES, LISTINGS AND FIGURES (TLFS)

Mock-up tables and listings will be provided in a separate document.

10. REFERENCES

1. Alkermes ALK3831-A306 Study Protocol Amendment 2.0 Date: 25 Apr 2017
2. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry*. 1997; 58(12): 538-546.
3. Tessier A et al. Understanding the Determinants of Weight-Related Quality of Life among Bariatric Surgery Candidates. *Journal of Obesity* 2012; 2012: 713426
4. Van Hout B, Janssen MF, et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value in Health* 2012 Jul-Aug;15(5):708-15