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-A304

NCT02873208

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

Abbreviation or Term	Explanation or Definition
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
CGI-S	Clinical Global Impression - Severity
C-SSRS	Columbia Suicide Severity Rating Scale
CMQ	Customized MedDRA queries
ECG	Electrocardiogram
eCRF	Electronic case report form
EPS	Extra pyramidal symptoms
EQ-5D	EuroQOL-5D
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	Pharmacokinetics
PT	Preferred term
KM	Kaplan-Meier
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

Abbreviation or Term	Explanation or Definition
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-A304. ALK3831-A304 is a 52-week, open-label safety extension study of ALK3831-A303. This document has been prepared based on Alkermes ALK3831-A304 Study Protocol Amendment 3.0 (dated 26 April 2018)[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 are eligible to be enrolled in the study within 7 days after completing the 24-week treatment period of the antecedent study, ALK3831-A303.

Subjects enrolled in the study will be started on the same olanzapine dose that they had maintained at the end of ALK3831-A303. Subjects taking 20 mg olanzapine (either as OLZ 20 or ALKS 3831 20/10 [20 mg olanzapine/10 mg samidorphan]) will start on ALKS 3831 20/10 in this study and subjects taking 10 mg olanzapine (either as OLZ 10 or ALKS 3831 10/10 [10 mg olanzapine/10 mg samidorphan) will start on ALKS 3831 10/10 in this study. An intermediate dose, ALKS 3831 15/10 (15 mg olanzapine/10 mg samidorphan), will also be available, and subjects may be titrated to this dose any time after the start of the study at the investigator's discretion. Dosing is flexible throughout the study; however, frequent adjustments are discouraged. Dose adjustments can only be performed on-site at the study center. Subjects requiring dose adjustments between scheduled visits should arrange an unscheduled visit for the following procedures: study drug return, adherence review, adverse event monitoring, 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).

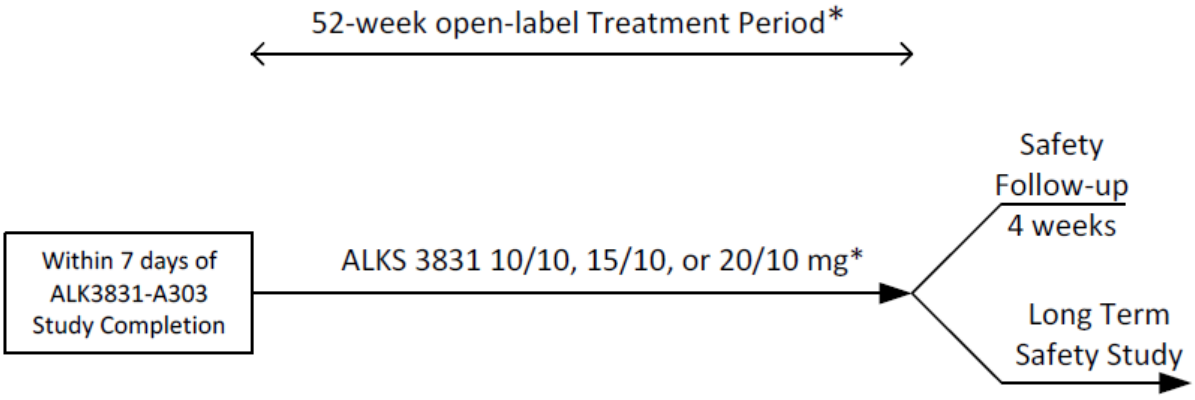
Efficacy assessments to evaluate the durability of treatment effect will include Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions-Severity (CGI-S).

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 another 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 biweekly throughout the 52-week Treatment Period. Subjects will start the study on the equivalent olanzapine dose to what they maintained at the end of ALK3831-A303. 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 540 is based on the estimated maximum number of subjects who might be expected to continue from the ALK3831-A303 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 the ALK3831-A304 study, and it will be used for all efficacy and safety analysis, unless specified otherwise.

Baseline of precedent study (A303) is defined as the last non-missing assessment before the first dose of study drug in the ALK3831-A303 study. It will be used for the summary of the PANSS total score and subscales and body weight results.

Treatment sequence is defined according to the treatment assignment in antecedent and current studies as ALKS 3831/ALKS 3831 (ALKS 3831 in both ALK3831-A303 study and ALK3831-A304 study) and OLZ/ALKS 3831 (olanzapine in ALK3831-A303 study and ALKS 3831 in

ALK3831-A304 study). All efficacy and safety analysis will be presented by treatment sequence and overall.

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 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 one dose of ALKS 3831 in the ALK3831-A304 study. All analyses will be conducted using the Safety Population except for AEs in the safety follow-up period and AE to evaluate the potential for drug withdrawal and dependence. The populations used for the analyses of these events are specified below.

3.2.2. Follow-up Safety Population

Follow-up Safety Population will be defined with respect to the 5 half-lives of the product as subjects in the Safety Population and met any of the following criteria:

- Completed at least one follow-up visit after >7 days of the last dose of ALKS 3831
- Reported at least one AE reported after >7 days of the last dose of ALKS 3831

This population will be used to analyze the AEs in the safety follow-up period.

3.2.3. Post-discontinuation Safety Population

Post-discontinuation Safety Population will be defined as subjects in the Safety Population and met any of the following criteria:

- Completed at least one follow-up visit after >2 day within 16 days of the last dose of ALKS 3831
- Reported at least one AE reported after >2 day after the last dose of ALKS 3831

AE to evaluate potential for drug withdrawal and dependence emerging following discontinuation of ALKS 3831 will be assessed for this population, during the period of >2 days to 16 days after the last dose of drug for subjects with at least 4 weeks study drug exposure.

3.3. Disposition

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

- Subjects who enrolled in the study

- Subjects in the Safety Population
- Subjects who completed the treatment period
- Subjects who discontinued treatment along with reason for discontinuation (as indicated in case report form)

3.4. Protocol Deviation

Subjects with major protocol deviations in the following categories will be summarized. A supportive listing will be provided as well.

- Did not meet the study entry 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 sex, age, race, ethnicity, weight, and body mass index (BMI) will be summarized for the Safety Population and for the subset of subjects who participated in the patient voice substudy.

3.6. Prior and Concomitant Medication

Prior medications will be defined as medications taken prior to the first dose of study drug in ALK3831-A304 study. Concomitant medications will be defined as medications taken on or after the first dose of study drug in ALK3831-A304 study. All medications will be coded using the World Health Organization WHO-DD Enhanced + Herbal (version: March 2016) or higher.

Concomitant medications taken during the treatment period will be summarized by the preferred drug name. All reported medications (including those initiated after the last dose of study medication) will be included in the 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 Extent of Exposure to Study Drug

3.7.1. Treatment Adherence Rate

Treatment adherence to the daily dosing schedule during treatment period will be summarized. 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. Extent of Exposure to Study Drug

Duration of exposure to study drug (ALKS 3831) is defined as the number of days from the date of the first dose of study drug of this study (ALK3831-A304) 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.

The overall mean and modal dose of olanzapine will be summarized

3.8. Efficacy Analyses

3.8.1. General Considerations

In general, continuous and categorical endpoints will be summarized using descriptive statistics based on observed data.

3.8.2. Efficacy Analysis

The following endpoints will be used to evaluate durability of treatment effect:

- Change from baseline in PANSS total score, and subscales (positive, negative, and general psychopathology subscales) by visit
- Change from baseline in CGI-S by visit
- Shift analysis in CGI-S
- Time to treatment discontinuation

Summary statistics will be provided for all continuous endpoints based on observed data.

Change from current (A304) and precedent (A303) study baseline in PANSS total score and subscales will be summarized for the subset of subjects who participated in the patient voice substudy.

CGI-S response will be categorized into the categories summarized in Table 1. The number and percentage of subjects in each category and with shifts from baseline will be summarized based on the observed data by descriptive statistics at 4, 12, 24 and 52 weeks. The shift categories are summarized in Table 2.

Time to treatment discontinuation will be analyzed using the Kaplan-Meier method. Both all-cause discontinuation and discontinuation due to AE will be summarized. For prematurely discontinued subjects (all-cause or due to AE), time to discontinuation 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.

Table 1: Definition of CGI-S Categories

Response Category	CGI-S Score
Markedly to Extremely Ill	≥5

Response Category	CGI-S Score
Moderately Ill	4
Normal to Mildly Ill	≤3

Table 2: Shift Categories for CGI-S response

Shift from Baseline Category for CGI-S Response Baseline Category Shift Category
Markedly to Extremely Ill No change ≥1 level improvement 2 level improvement
Moderately Ill No change 1 level improvement 1 level worsening
Normal to Mildly Ill No change ≥1 level worsening 2 level worsening

3.8.3. Other Endpoints

- 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 visual analogue scale (VAS) score by visit

Descriptive statistics of IWQOL-Lite scales and EQ-5D-5L, including n, mean, SD, median, minimum, and maximum, will be summarized by visit based on observed data.

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 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 VAS. 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.

3.8.4. Multiple Comparison / Multiplicity

Not applicable.

3.9. Safety Analysis

3.9.1. Adverse Events

Incidence of treatment emergent AEs (TEAEs) 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 21.0 or higher. The verbatim term will be included in the AE listings.

An AE (coded by preferred term) will be considered as a TEAE if the event is newly occurring or worsening on or after the date of first dose of study drug and within 7 days after the last dose of study drug in this study.

An overview table, including number of subjects with TEAEs, AEs leading to treatment discontinuation, study drug related TEAEs, and SAEs will be provided.

The incidence (number and percentage) of subjects reporting TEAEs during the treatment period will be presented for the following categories:

- System organ class and preferred term
- Preferred term, and including the following subset:
  - TEAEs experienced by ≥2% of subjects (in any group)
- System organ class, preferred term, and severity
- System organ class, preferred term for severe TEAEs

- System organ class, preferred term, and relationship
- System organ class, preferred term 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 and preferred term.

Subgroup analysis by age (<40 years vs ≥40 years), sex (Female vs Male) and race (Black or African American, White, and Other) will be performed for TEAEs during the treatment period by preferred term.

3.9.1.1. Deaths, Serious and Other Significant AEs

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

By-subject listings will be provided for SAEs, AEs leading to treatment discontinuation and AEs leading to death.

3.9.1.2. Other Significant AEs

In addition, incidence of a selected subset of relevant AEs in this class of drugs (e.g., Extrapyramidal symptoms [EPS) TEAEs, TEAE to evaluate potential of suicidal ideation and behavior, etc.) will be summarized by preferred term. The selection of AEs per subset will be based on the preferred terms from Standardized MedDRA queries (SMQs) or Customized MedDRA queries (CMQ's).

3.9.1.3. Analysis of Abuse Potential, Withdrawal, and Dependence

3.9.1.3.1. Analysis of Abuse Potential

Number and percentage subjects with TEAEs to evaluate abuse potential will be summarized by category (abuse behavior, euphoria related, and non-specific) and preferred term. The selection of AEs per subset will be based on the preferred terms from Customized MedDRA queries (CMQs).

3.9.1.3.2. Analysis of Withdrawal and Dependence

Adverse events with an onset date within 2 weeks (>2 to ≤16 days) after the last dose of the study drug in those subjects who have received at least 4 weeks of study drug will be included in the evaluation of the potential for withdrawal and dependence. The selection of AEs per subset will be based on the preferred terms from Customized MedDRA queries (CMQs).

The number and percentage of subjects with such AEs will be summarized in the Post-discontinuation Safety Populations by preferred term for subjects with a duration of study drug exposure ≥4 weeks.

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 during the treatment period for chemistry and hematology parameters will be summarized by visit.

Clinical laboratory test values, scheduled or unscheduled, will be considered potentially clinically significant (PCS) if they meet PCS criteria listed in Table 3. The number and percentage of subjects who have postbaseline PCS clinical laboratory values will be summarized. The percentages will be calculated based on the number of subjects with non-PCS baseline value and have at least one postbaseline assessment. All PCS values including baseline PCS values will be included in supportive listings.

For selected metabolic parameters (fasting total cholesterol, fasting high density lipoprotein[HDL], fasting low density lipoprotein[LDL], fasting triglycerides, fasting glucose, and hemoglobin A1c[HbA1c]), an analysis of sustained PCS values will also be conducted. The percentage of subjects with sustained PCS values through the treatment period will be summarized. The denominator is all subjects with non-PCS at baseline and at least two postbaseline assessments, and the numerator is the number of subjects who met PCS criteria at the last 2 assessments within the treatment period.

Shift tables for selected fasting metabolic parameters (total cholesterol, LDL, HDL, triglycerides, glucose and HbA1c) and liver function tests will be presented. The criteria are summarized in Table 4, Table 5 and Table 6.

Table 3: Criteria of Potentially Clinically Significant (PCS) Abnormality for Selected Analytes

Parameter	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[a]	≥240 mg/dL
Cholesterol, Fasting	Increase ≥40 mg/dL
Cholesterol, HDL Fasting	<40 mg/dL
Cholesterol, HDL Fasting	Decrease ≥20 mg/dL
Cholesterol, LDL Fasting	≥160 mg/dL
Cholesterol, LDL Fasting	Increase ≥30 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
Glucose, Fasting	Increase ≥10 mg/dL
HbA1c	≥ 5.7%
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

Table 3: Criteria of Potentially Clinically Significant (PCS) Abnormality for Selected Analytes (Continued)

Triglycerides, Fasting	≥200 mg/dL
Triglycerides, Fasting	Increase ≥50 mg/dL
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 $\geq 16.0 \times 10^3/\mu L$

[a] reported fasting.

Table 4: Shifts Categories 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 (<200) to Borderline (≥200 and <240)
LDL Cholesterol (fasting) mg/dL
Normal (<100) to High (≥160)
Borderline (≥100 and <160) to High (≥160)
Normal (<100) to Borderline (≥100 and <160)
HDL Cholesterol (fasting) mg/dL
Normal (≥40) to Low (<40)
Triglycerides (fasting) mg/dL
Normal (<150) to High (≥200)
Borderline (≥150 and <200) to High (≥200)
Normal (<150) to Borderline (≥150 and <200)

Table 5: Shift Categories from Baseline to Any Postbaseline in Glucose and HbA1c

Glucose (fasting) mg/dL
Normal (<100) to Impaired (≥100 and <126)
Normal (<100) to High (≥126)
Impaired (≥100 and <126) to High (≥126)
HbA1c %
Normal (<5.7%) to Borderline (≥5.7% and <6.5%)
Borderline (≥5.7% and <6.5%) to High (≥6.5%)
Normal (<5.7%) to High (≥6.5%)

Table 6: Shift Categories 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.

Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline criteria listed in Table 7. The number and percentage of subjects with PCS postbaseline values will be tabulated. The percentages will be calculated based on the number of subjects with non-PCS baseline values and at least one postbaseline assessment. The numerator

will be the number of subjects with non-PCS baseline values and at least one 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.

Table 7: 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

Body weight (kg), BMI (kg/m^2) and waist circumferences (cm) (baseline and change from baseline) will be summarized using observed data. Absolute (kg) and percent change from baseline in body weight will be summarized by visit.

Absolute and percent change from current (A304) and precedent (A303) study baseline in body weight will also be summarized for the subset of subjects who participated in the patient voice substudy.

Number and percentage of subjects with ≥7% or ≥10% weight gain from baseline based on the observed data will be summarized by visit. In addition, number and percentage of subjects with weight change values considered as PCS occurring at any postbaseline visit will be summarized. 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 postbaseline value. A supportive listing will be provided for subjects with PCS values.

Table 8: 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. QTc interval will be calculated using 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 9. The number and percentage of subjects with PCS postbaseline ECG values will be tabulated. The percentages will be calculated based on the number of subjects with non-PCS baseline values and at least one postbaseline assessment. The numerator is the number of subjects with non-PCS baseline values and at least one postbaseline PCS value. A supportive listing of subjects with PCS values will be provided.

Table 9: Criteria for Potentially Clinically Significant (PCS) QTcF

Parameter	Criteria
QTcF	>450 to ≤480 msec
	>480 to ≤500 msec
	>500 msec
	Change from baseline >30 to ≤60 msec
	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).

Change from baseline in all abnormal movement scales, total scores and subscale scores will be summarized by visit.

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.

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 descriptively (Table 10). The number of subjects with suicidal ideation and suicidal behavior will be summarized.

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

Table 10: C-SSRS Categories for Analysis

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

[a] Derived based on responses to individual items listed within the category

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

To further assess the long-term durability, the following analysis was added in SAP but were not specified in protocol.

- Shift analysis in CGI-S

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 3 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.

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

An early termination (ET) visit during the on-treatment period can be mapped to a scheduled visit, if there is no valid value already at that visit. Visit windows are defined in Table 11 and Table 12. An ET visit that is not mapped will not be summarized in the tables or figures, but will be included in the listing.

Table 11: Visit Window for All Efficacy and Safety Assessments Excluding PANSS

Analysis Visit to be Mapped to	Target Study Week	Target Visit Day[a]	Visit Window
Visit 1	Week 0	Day 1	1
Visit 2	Week 2	Day 15	[2, 21]
Visit 3	Week 4	Day 29	[22, 35]
Visit 4	Week 6	Day 43	[36, 49]
Visit 5	Week 8	Day 57	[50, 70]
Visit 7	Week 12	Day 85	[71, 98]

Analysis Visit to be Mapped to	Target Study Week	Target Visit Day[a]	Visit Window
Visit 9	Week 16	Day 113	[99, 126]
Visit 11	Week 20	Day 141	[127, 154]
Visit 13	Week 24	Day 169	[155, 182]
Visit 15	Week 28	Day 197	[183, 210]
Visit 17	Week 32	Day 225	[211, 238]
Visit 19	Week 36	Day 253	[239, 266]
Visit 21	Week 40	Day 281	[267, 294]
Visit 23	Week 44	Day 309	[295, 322]
Visit 25	Week 48	Day 337	[323, 350]
Visit 27	Week 52	Day 365	[351, 371]

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

Table 12: Visit Window for PANSS Assessments

Analysis Visit to be Mapped to	Target Study Week	Target Visit Day	Visit Window
Visit 2	Week 2	Day 15	[2, 21]
Visit 3	Week 4	Day 29	[22, 42]
Visit 5	Week 8	Day 57	[43, 70]
Visit 7	Week 12	Day 85	[71, 126]
Visit 13	Week 24	Day 169	[127, 210]
Visit 19	Week 36	Day 253	[211, 308]
Visit 27	Week 52	Day 365	[309, 371]

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 and overall. All summary tables will be based on observed data, and missing values will not be imputed. 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 13: 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 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-A304 Study Protocol Amendment 3.0 Date: 26 April 2018
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

APPENDIX 1. AESI - MOVEMENT DISORDERS (INCLUDING EXTRAPYRAMIDAL SYNDROME AND TARDIVE DYSKINESIA; STANDARDIZED MEDDRA QUERY)

Preferred Term (SMQ [#20000095] of Extrapyramidal syndrome)	PT Code
Abnormal involuntary movement scale	10075002
Action tremor	10072413
Akathisia	10001540
Akinesia	10001541
Athetosis	10003620
Ballismus	10058504
Blepharospasm	10005159
Bradykinesia	10006100
Bradyphrenia	10050012
Buccoglossal syndrome	10006532
Chorea	10008748
Choreoathetosis	10008754
Chronic tic disorder	10076661
Cogwheel rigidity	10009848
Complex tic	10076663
Dopamine dysregulation syndrome	10067468
Dopa-responsive dystonia	10080034
Drooling	10013642
Dyskinesia	10013916
Dyskinesia neonatal	10013922
Dyskinesia oesophageal	10013924
Dysphonia	10013952
Dystonia	10013983
Dystonic tremor	10073210
Early onset primary dystonia	10076668
Emprosthotonus	10014566
Extrapyramidal disorder	10015832

Preferred Term (SMQ [#20000095] of Extrapyramidal syndrome)	PT Code
Facial spasm	10063006
Fine motor skill dysfunction	10076288
Freezing phenomenon	10060904
Gait disturbance	10017577
Gait inability	10017581
Grimacing	10061991
Hyperkinesia	10020651
Hyperkinesia neonatal	10020652
Hypertonia	10020852
Hypertonia neonatal	10048615
Hypokinesia	10021021
Hypokinesia neonatal	10021022
Laryngeal tremor	10078751
Laryngospasm	10023891
Meige's syndrome	10027138
Micrographia	10057333
Mobility decreased	10048334
Motor dysfunction	10061296
Movement disorder	10028035
Muscle contractions involuntary	10028293
Muscle rigidity	10028330
Muscle spasms	10028334
Muscle spasticity	10028335
Muscle tightness	10049816
Muscle tone disorder	10072889
Muscle twitching	10028347
Musculoskeletal stiffness	10052904
Oculogyric crisis	10030071
Oesophageal spasm	10030184
On and off phenomenon	10030312

Preferred Term (SMQ [#20000095] of Extrapyramidal syndrome)	PT Code
Opisthotonus	10030899
Oromandibular dystonia	10067954
Oropharyngeal spasm	10031111
Parkinsonian crisis	10048868
Parkinsonian gait	10056242
Parkinsonian rest tremor	10056437
Parkinsonism	10034010
Parkinsonism hyperpyrexia syndrome	10071243
Parkinson's disease	10061536
Parkinson's disease psychosis	10074835
Pharyngeal dyskinesia	10070912
Pleurothotonus	10035628
Postural reflex impairment	10067206
Postural tremor	10073211
Posture abnormal	10036436
Posturing	10036437
Protrusion tongue	10037076
Provisional tic disorder	10076694
Psychomotor hyperactivity	10037211
Rabbit syndrome	10068395
Reduced facial expression	10078576
Respiratory dyskinesia	10057570
Resting tremor	10071390
Restlessness	10038743
Risus sardonicus	10039198
Secondary tic	10076702
Spasmodic dysphonia	10067672
Tardive dyskinesia	10043118
Tic	10043833
Tongue spasm	10043981

Preferred Term (SMQ [#20000095] of Extrapyramidal syndrome)	**PT Code**
Torticollis	10044074
Torticollis psychogenic	10044076
Tremor	10044565
Tremor neonatal	10044575
Trismus	10044684
Uvular spasm	10050908
Walking disability	10053204
Writer's cramp	10072249

APPENDIX 2. AESI - SUICIDAL IDEATION AND BEHAVIOR (CUSTOM MedDRA QUERY)

Preferred Term	PT Code
Columbia suicide severity rating scale abnormal	10075616
Completed suicide	10010144
Depression suicidal	10012397
Intentional overdose	10022523
Intentional self-injury	10022524
Overdose	10033295
Poisoning deliberate	10036000
Self-injurious ideation	10051154
Suicidal behaviour	10065604
Suicidal ideation	10042458
Suicide attempt	10042464
Suicide threat	10077417

APPENDIX 3. AE TERMS - ABUSE POTENTIAL (CUSTOM MedDRA QUERY)

Category	Preferred Term	PT Code
Abuse behavior	Accidental overdose	10000381
	Drug abuse	10013654
	Drug abuser	10061111
	Drug detoxification	10052237
	Drug diversion	10066053
	Drug level above therapeutic	10061132
	Drug level increased	10013722
	Drug screen	10050837
	Drug screen positive	10049177
	Drug use disorder	10079381
	Drug use disorder, antepartum	10079382
	Drug use disorder, postpartum	10079383
	Intentional overdose	10022523
	Intentional product misuse	10074903
	Intentional product use issue	10076308
	Maternal use of illicit drugs	10026938
	Needle track marks	10028896
	Neonatal complications of substance abuse	10061862
	Overdose	10033295
	Prescription drug used without a prescription	10076639
	Prescription form tampering	10067669
	Product tampering	10069330
	Reversal of opiate activity	10039004
	Substance abuse	10066169
	Substance abuser	10067688
	Substance use	10070964
	Substance use disorder	10079384
	Substance-induced mood disorder	10072387

Category	Preferred Term	PT Code
	Substance-induced psychotic disorder	10072388
	Toxicity to various agents	10070863
Euphoria related	Euphoric mood	10015535
	Feeling abnormal	10016322
	Feeling drunk	10016330
	Feeling of relaxation	10016352
	Hallucination	10019063
	Hallucination, auditory	10019070
	Hallucination, gustatory	10019071
	Hallucination, olfactory	10019072
	Hallucination, synaesthetic	10062824
	Hallucination, tactile	10019074
	Hallucination, visual	10019075
	Hallucinations, mixed	10019079
	Inappropriate affect	10021588
	Mood altered	10027940
	Mood swings	10027951
	Thinking abnormal	10043431
Non-specific	Acute psychosis	10001022
	Aggression	10001488
	Cognitive disorder	10057668
	Confusional state	10010305
	Delirium	10012218
	Delusional disorder, unspecified type	10012255
	Depersonalisation/derealisation disorder	10077805
	Disorientation	10013395
	Dissociation	10013457
	Disturbance in attention	10013496
	Disturbance in social behaviour	10061108
	Dizziness	10013573

Category	Preferred Term	PT Code
	Dopamine dysregulation syndrome	10067468
	Emotional disorder	10014551
	Flight of ideas	10016777
	Medication overuse headache	10072720
	Mental impairment	10027374
	Narcotic bowel syndrome	10072286
	Paranoia	10033864
	Psychotic behaviour	10037249
	Psychotic disorder	10061920
	Sedation	10039897
	Somnolence	10041349
	Stupor	10042264

APPENDIX 4. AE TERMS – DEPENDENCE (CUSTOM MedDRA QUERY)

Preferred Term	PT Code
Dependence	10012335
Drug dependence	10013663
Drug dependence, antepartum	10013675
Drug dependence, postpartum	10013676
Drug tolerance	10052804
Drug tolerance decreased	10052805
Drug tolerance increased	10052806
Substance dependence	10076595

APPENDIX 5. AE TERMS – WITHDRAWAL (CUSTOM MedRA QUERY)

Preferred Term	PT Code
Abdominal pain	10000081
Agitation	10001497
Anhedonia	10002511
Anxiety	10002855
Arthralgia	10003239
Chills	10008531
Depressed mood	10012374
Depression	10012378
Diarrhoea	10012735
Drug detoxification	10052237
Drug rehabilitation	10064773
Drug withdrawal convulsions	10013752
Drug withdrawal headache	10013753
Drug withdrawal maintenance therapy	10052970
Drug withdrawal syndrome	10013754
Drug withdrawal syndrome neonatal	10013756
Dysphoria	10013954
Dyssomnia	10061827
Feeling of despair	10016344
Headache	10019211
Hyperhidrosis	10020642
Insomnia	10022437
Irritability	10022998
Morose	10027977
Mydriasis	10028521
Nausea	10028813
Negative thoughts	10058672
Nervousness	10029216

Preferred Term	PT Code
Obsessive thoughts	10029897
Pain	10033371
Persistent depressive disorder	10077804
Piloerection	10035039
Poor quality sleep	10062519
Rebound effect	10038001
Restlessness	10038743
Reversal of opiate activity	10039004
Rhinorrhoea	10039101
Steroid withdrawal syndrome	10042028
Syncope	10042772
Tachycardia	10043071
Terminal insomnia	10068932
Tremor	10044565
Vomiting	10047700
Withdrawal arrhythmia	10047997
Withdrawal syndrome	10048010
Yawning	10048232