FINAL STATISTICAL ANALYSIS PLAN

ALKS 3831-A308

NCT03201757

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 Status:	Version 1.0
Document Date:	13 Jun 2023
Based on:	ALKS 3831-A308 Protocol Amendment 3.0 Date: 09 May 2019 and ALKS 3831-A308 Interim Statistical Analysis Plan 1.0 Date: 06 Jun 2019
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ABBREVIATIONS

Abbreviation or Term	Explanation or Definition
AE	Adverse event
BMI	Body mass index
CGI-S	Clinical Global Impression - Severity
CI	Confidence interval
C-SSRS	Columbia Suicide Severity Rating Scale
CMQ	Customized MedDRA queries
eCRF	Electronic case report form
EPS	Extra pyramidal symptoms
HbA1C	Hemoglobin A1c
SAP	statistical analysis plan
IWQOL	Impact of Weight on Quality of Life
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
OLZ	Olanzapine
PCS	Potentially clinically significant
PK	Pharmacokinetic
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SMQ	Standardized MedDRA queries
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
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 study ALK3831-A308 to support the clinical study report (CSR) development. This document has been prepared based on Alkermes ALKS 3831-A308 Study Protocol Amendment 3.0 (dated 09 May 2019) and Alkermes ALKS 3831-A308 Interim Statistical Analysis Plan to Support New Drug Application (NDA) Submission (dated 09 Jun 2019).

Subjects who have completed or prematurely discontinued ALKS 3831 will be included in the analysis described in this document.

1.1. Study Objectives

1.1.1. 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.

1.2. Summary of the Study Design

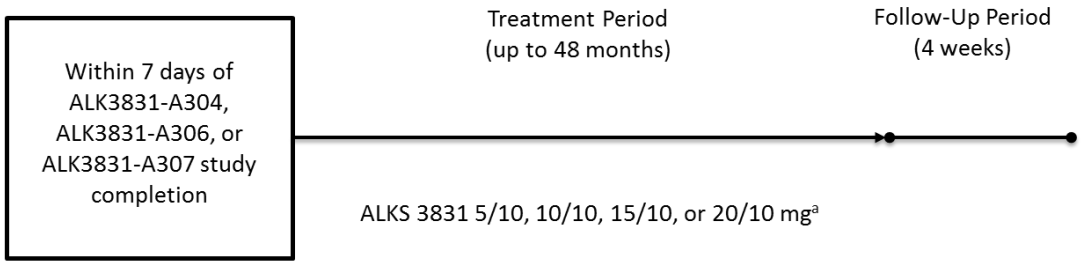
Subjects are eligible to be enrolled in the study within 7 days after completing the antecedent studies (ALK3831-A304, ALK3831-A306, or ALK3831-A307).

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 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 of the study design is provided in Figure 1.

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.

2. SAMPLE SIZE CONSIDERATION

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

3. DATA ANALYSIS

3.1. General Statistical Methodology

Baseline for efficacy or safety analyses is defined as the last non-missing assessment before the first dose of ALKS 3831 in the ALK3831-A308 study, and it will be used for all efficacy and safety analyses, unless specified otherwise.

All results from this analysis will be presented for the overall group, ie all subjects as a single group, and not by previous treatment sequence in antecedent studies of ALK3831-A303 and ALK3831-A305.

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-A308 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 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 after >7 days of the last dose of ALKS 3831
- Follow-up Safety 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 >2 days after the last dose of ALKS 3831
- Reported at least one AE >2 days after the last dose of ALKS 3831

AEs 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 ALKS 3831 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
- Subjects who are ongoing in the treatment period

3.4. 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.

3.5. Prior and Concomitant Medication

Prior medications will be defined as medications taken prior to the first dose of study drug in ALK3831-A308 study. Concomitant medications will be defined as medications taken on or after the first dose of study drug in ALK3831-A308 study. All medications will be coded using the World Health Organization WHO-DD Enhanced + Herbal (version: March 2016).

Concomitant medications taken during the treatment period will be summarized by the preferred name, for the Safety Population. 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.

3.6. Treatment Adherence Rate and Extent of Exposure to Study Drug

3.6.1. Treatment Adherence Rate

Treatment adherence to the daily dosing schedule during treatment period will be summarized. Treatment adherence will be calculated as follows:

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

3.6.2. 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 in this study (ALK3831-A308) to the date of the last dose of study drug, inclusive (ie, last dose date – first dose date + 1 day). Duration of exposure to study drug will be summarized for the Safety Population.

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

extent of exposure will also be presented by demographic subgroups: Age, Sex, Race, Region, weight, and body mass index (BMI). Dose level will be summarized by visit at 12 months, 18 months, 24 months, and 48 months.

Dose level at12 months, 18 months 24 months, and 48 months will be summarized by antecedent study.

3.7. Efficacy Analyses

3.7.1. Efficacy Analysis

The following efficacy endpoints will be analyzed:

- Change from baseline in CGI-S score by visit
- Shift analysis in CGI-S
- Change from baseline in IWQOL-Lite scales (total score, physical function, self-esteem, sexual life, public distress, and work) by visit
- Time to treatment discontinuation

Value and change from baseline in CGI-S and IWQOL-Lite scores by visit will be summarized using descriptive statistics.

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): the transformed scores range from 0 to 100, with 100 representing the best, and 0 representing the most impaired quality of life.

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

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 1, 3, 6, and 12 months. The shift categories are summarized in Table 2.

Table 1: Definition of Shift CGI-S Categories

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

Time to treatment discontinuation will be analyzed using the Kaplan-Meier method and the KM plot will be provided. Both all-cause discontinuation 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 in study ALK3831-A308 to the date of last dose of study drug. Other subjects will be censored at the last dose of the study drug.

3.7.2. Multiple Comparison / Multiplicity

Not applicable.

3.7.3. Subgroup Analysis

Subgroup analyses of efficacy endpoints will be performed for each of the

following categories:

- Bipolar disorder
  - Change from baseline in IWQOL-Lite score by visit
  - Weight, metabolic responses, waist circumference, safety AEs and shift in CGI score in 2 points or 5 compared to those hospitalized due to AEs will be presented by visit.
- Sex (male, female)
- Age (<18 years, ≥18 years)
- Age (<30 years, ≥30 years)
- Race (Black or African American, Non-Black or Non-African American)

- Baseline BMI (<25 kg/m2, ≥25 kg/m2)
- Region (US, Non-US)
- Among those who completed study at 24 months, 36 months, and 48 months, change in weight, waist circumference and metabolic responses will be summarized.
- For those who switched from ALKS3831-A307 to ALKS3831-A308 change from baseline in CGI, weight, waist circumference and lipid levels by visit will be summarized.

Descriptive statistics will be provided for the subgroups listed above.

3.7.4. Other Endpoints

Other endpoints include:

- Absolute change from baseline in fasting lipids (triglycerides, LDL, HDL, total cholesterol, fasting glucose, hemoglobin A1c (HbA1c), insulin) by subgroups
- Absolute change from baseline in fasting lipids (triglycerides, LDL, HDL, total cholesterol, fasting glucose, hemoglobin A1c (HbA1c), insulin) by antecedent study at End of the treatment
- Absolute change from baseline in BMI by visit
- BMI shift:
  - Proportion of subjects shifting from BMI <25 kg/m2 at baseline to BMI ≥25 kg/m2 by visit
  - Proportion of subjects shifting from BMI <30 kg/m2 at baseline to BMI ≥30 by visit

3.8. Safety Analysis

All safety endpoints will be summarized for the Safety Population.

3.8.1. 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 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 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
- 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.

3.8.1.1. Deaths, Serious and Other Significant AEs

The number and percentage of subjects who have serious adverse events (SAE) and AEs leading to discontinuation from the treatment will be summarized by system organ class and preferred term. And the number and percentage of subjects reporting SAEs will be summarized by system organ class, preferred term, and relationship to study drug.

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

3.8.1.2. AEs of Special Interest

In addition, incidence of a selected subset of relevant AEs in this class of drugs (eg, TEAE to evaluate potential of movement disorders, 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 (CMQs).

3.8.2. 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 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 abnormal baseline value and have at least one postbaseline assessment. All PCS values including baseline PCS values will be included in supportive listings.

Shift tables for selected fasting metabolic parameters (glucose, total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL], triglycerides, and hemoglobin A1c [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 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	>400 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	<40 mg/dL or ≥250 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

Parameter	Criteria
Prolactin (Female)	≥ 1 X ULN[b]
Prolactin (Male)	≥ 1 X ULN[b]
Prolactin (Female)	≥ 3 X ULN[b]
Prolactin (Male)	≥ 3 X ULN[b]
Sodium	<130 mmol/L or >150 mmol/L
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
[b] ULN is 30 ng/mL for females and 20 ng/mL for males

Table 4: 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 (<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 Category 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 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

3.8.3. Vital Signs and Body Weight

3.8.3.1. Vital Signs

Descriptive statistics for vital signs and changes from baseline values at each scheduled time point will be presented 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 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 abnormal baseline values and at least one postbaseline assessment. The numerator will be the number of subjects with abnormal 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.

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

3.8.3.2. Weight and Body Mass Index

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

Number and percentage of subjects with ≥7% or ≥10% weight gain from baseline based on the observed data will be summarized 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. Criteria for PCS are presented below in Table 8. 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 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%

3.8.4. 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 (Table 9).

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 when applicable.

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

Table 9: 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

3.9. Pharmacokinetic/ Pharmacodynamic Data Analysis

Not applicable.

4. INTERIM ANALYSES

As described in Section 1, this SAP document is an update of the interim analysis that was conducted to support the ALKS 3831 New Drug Application (NDA). The full study population will be analyzed once the study is completed.

5. CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

To further assess the long-term durability, the following analysis was added in ISAP but was 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 1).

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 window as defined in Table 10 for weight, waist circumference and CGI-S data and Table 11 for vital signs, lab and IWQOL-Lite data will be used to map the assessments collected after premature discontinuation of the study drug. An ET visit that is not mapped will not be summarized in the tables or figures but will be included in the listing.

Table 10: Visit Window Definition for Weight, Waist Circumference and CGI-S Data

Analysis Visit to be Mapped to	Target Study Month	Target Visit Date	Visit Window
Visit 2	Month 1	Day 29	[2, 42]
Visit 3	Month 2	Day 57	[43, 70]
Visit 4	Month 3	Day 85	[71, 98]
Visit 5	Month 4	Day 113	[99, 126]
Visit 6	Month 5	Day 141	[127, 154]
Visit 7	Month 6	Day 169	[155, 182]
Visit 8	Month 7	Day 197	[183, 210]
Visit 9	Month 8	Day 225	[211, 238]
Visit 10	Month 9	Day 253	[239, 266]
Visit 11	Month 10	Day 281	[267, 294]
Visit 12	Month 11	Day 309	[295, 322]
Visit 13	Month 12	Day 337	[323, 350]
Visit 14	Month 13	Day 365	[351, 378]
Visit 15	Month 14	Day 393	[379, 406]
Visit 16	Month 15	Day 421	[407, 434]
Visit 17	Month 16	Day 449	[435, 462]

Analysis Visit to be Mapped to	Target Study Month	Target Visit Date	Visit Window
Visit 18	Month 17	Day 477	[463, 490]
Visit 19	Month 18	Day 505	[491, 518]
Visit 20	Month 19	Day 533	[519, 546]
Visit 21	Month 20	Day 561	[547, 574]
Visit 22	Month 21	Day 589	[575, 602]
Visit 23	Month 22	Day 617	[603, 630]
Visit 24	Month 23	Day 645	[631, 658]
Visit 25	Month 24	Day 673	[659, 686]
Visit 26	Month 25	Day 701	[687, 714]
Visit 27	Month 26	Day 729	[715, 742]
Visit 28	Month 27	Day 757	[743, 770]
Visit 29	Month 28	Day 785	[771, 798]
Visit 30	Month 29	Day 813	[799, 826]
Visit 31	Month 30	Day 841	[827, 854]
Visit 32	Month 31	Day 869	[855, 882]
Visit 33	Month 32	Day 897	[883, 910]
Visit 34	Month 33	Day 925	[911, 938]
Visit 35	Month 34	Day 953	[939, 966]
Visit 36	Month 35	Day 981	[967, 994]
Visit 37	Month 36	Day 1009	[995, 1022]
Visit 38	Month 37	Day 1037	[1023, 1050]
Visit 39	Month 38	Day 1065	[1051, 1078]
Visit 40	Month 39	Day 1093	[1079, 1106]
Visit 41	Month 40	Day 1121	[1107, 1134]
Visit 42	Month 41	Day 1149	[1135, 1162]
Visit 43	Month 42	Day 1177	[1163, 1190]
Visit 44	Month 43	Day 1205	[1191, 1218]
Visit 45	Month 44	Day 1233	[1219, 1246]
Visit 46	Month 45	Day 1261	[1247, 1274]
Visit 47	Month 46	Day 1289	[1275, 1302]
Visit 48	Month 47	Day 1317	[1303, 1330]

Analysis Visit to be Mapped to	Target Study Month	Target Visit Date	Visit Window
Visit 49	Month 48	Day 1345	[1331, 1351]

Visit Day is calculated as visit date – date of the first dose of study drug + 1. 1 month=28 days

Table 11: Visit Window Definition for Vital Signs, Lab and IWQOL-Lite Data

Analysis Visit to be Mapped to	Target Study Month	Target Visit Day	Visit Window
Visit 4	Month 3	Day 85	[2, 126]
Visit 7	Month 6	Day 169	[127, 210]
Visit 10	Month 9	Day 253	[211, 294]
Visit 13	Month 12	Day 337	[295, 378]
Visit 16	Month 15	Day 421	[379, 462]
Visit 19	Month 18	Day 505	[463, 546]
Visit 22	Month 21	Day 589	[547,630]
Visit 25	Month 24	Day 673	[631,714]
Visit 28	Month 27	Day 757	[715,798]
Visit 31	Month 30	Day 841	[799, 882]
Visit 34	Month 33	Day 925	[883,966]
Visit 37	Month 36	Day 1009	[967,1050]
Visit 40	Month 39	Day 1093	[1051,1134]
Visit 43	Month 42	Day 1177	[1135,1218]
Visit 46	Month 45	Day 1261	[1219,1302]
Visit 49	Month 48	Day 1345	[1303,1351]

Visit Day is calculated as visit date – date of the first dose of study drug + 1. 1 month=28 days

6.2. Handling of Partial Dates of Concomitant Medication and Adverse Events

Partial start dates of prior, concomitant medications, and adverse events will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior, concomitant medications, and adverse events 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 and laboratory testing (chemistry, hematology, urinalysis), only observed data will be used for analyses, and missing data will not be imputed.

7. GENERAL STATISTICAL METHODOLOGY (AND REPORTING OF RESULTS)

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. 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 (Table 12), unless otherwise specified:

Table 12: 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

Tessier A, Zavorsky GS, Kim dJ, Carli F, Christou N, Mayo NE. Understanding the Determinants of Weight-Related Quality of Life among Bariatric Surgery Candidates. *J Obes.* 2012;2012:713426. doi: 10.1155/2012/713426.

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
Drooling	10013642
Dyskinesia	10013916
Dyskinesia hyperpyrexia syndrome	10071302
Dyskinesia neonatal	10013922
Dyskinesia oesophageal	10013924
Dysphonia	10013952
Dystonia	10013983
Dystonic tremor	10073210
Emprosthotonus	10014566
Extrapyramidal disorder	10015832
Facial spasm	10063006
Fine motor skill dysfunction	10076288
Freezing phenomenon	10060904

Preferred Term (SMQ [#20000095] of Extrapyramidal syndrome)	**PT Code**
Gait disturbance	10017577
Gait inability	10017581
Grimacing	10061991
Hyperkinesia	10020651
Hyperkinesia neonatal	10020652
Hypertonia	10020852
Hypertonia neonatal	10048615
Hypokinesia	10021021
Hypokinesia neonatal	10021022
Hypokinetic dysarthria	10082243
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
Opisthotonus	10030899
Oromandibular dystonia	10067954
Oropharyngeal spasm	10031111
Parkinsonian crisis	10048868

Preferred Term (SMQ [#20000095] of Extrapyramidal syndrome)	PT Code
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
Pharyngeal dystonia	10081226
Pleurothotonus	10035628
Postural reflex impairment	10067206
Postural tremor	10073211
Posture abnormal	10036436
Posturing	10036437
Propulsive gait	10082328
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
Status dystonicus	10088053
Tardive dyskinesia	10043118
Tic	10043833
Tongue spasm	10043981
Torticollis	10044074
Torticollis psychogenic	10044076
Tremor	10044565

Preferred Term (SMQ [#20000095] of Extrapyramidal syndrome)	**PT Code**
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
Assisted suicide	10079105
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
Suspected suicide	10082458
Suspected suicide attempt	10081704

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
	Substance-induced psychotic disorder	10072388
	Toxicity to various agents	10070863

Category	Preferred Term	PT Code
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
	Dopamine dysregulation syndrome	10067468
	Emotional disorder	10014551
	Flight of ideas	10016777
	Medication overuse headache	10072720

Category	Preferred Term	PT Code
	Mental impairment	10027374
	Narcotic bowel syndrome	10072286
	Paranoia	10033864
	Psychotic behaviour	10037249
	Psychotic disorder	10061920
	Sedation	10039897
	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 MedDRA 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
Obsessive thoughts	10029897
Pain	10033371

Preferred Term	**PT Code**
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

APPENDIX 6. COVID-19 ANALYSIS

Pandemic has resulted in certain disruptions in the study conduct since early 2020, including site closure, delayed study drug supply, subjects discontinuation and missing assessments. These impacts were limited in scope upon review of the protocol deviations, and also confounded by the initiation of new regions. Sites in Ukraine and Russia were first initiated in March 2020 and July 2020. Therefore, only descriptive statistics will be provided to explore the potential impact of the pandemic on the primary and secondary objectives of the study. The following subgroup analysis (before vs during pandemic) will be conducted:

- Disposition
- Demographics and Baseline Characteristics
- Protocol Deviation
- Primary Efficacy Endpoint
- Key Secondary Endpoints
- TEAE
- SAE

Subjects enrolled before 01 Mar 2020 will be grouped as before pandemic, and subjects enrolled after this date will be grouped as during pandemic. While the pandemic has started in various regions a few weeks apart, a single cutoff date will be applied.

Signature Page for CLIN_ALK3831-A308-sap

Approved	Name: PPD Capacity: Other Date: 04-Dec-2023 19:59:22 GMT+0000

Approved	Name: PPD Capacity: Clinical Date: 04-Dec-2023 23:33:04 GMT+0000

Approved	Name: PPD Capacity: Clinical Date: 07-Dec-2023 12:34:29 GMT+0000

Approved	Name: PPD Capacity: Other Date: 07-Dec-2023 13:00:52 GMT+0000