A Phase 2, Randomized, Multicenter, Safety, Tolerability, and Dose-Ranging Study of Samidorphan, a Component of ALKS 3831, in Adults with Schizophrenia Treated with Olanzapine

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SIGNATURE PAGE

Author:

PPD
PPD
PPD

Date

PPD
PPD
Alkermes, Inc.

Date

Approved by:

PPD
PPD
PPD

Date

PPD
PPD
Alkermes, Inc.

Date

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ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
CDT	Carbohydrate Deficient Transferrin
CGI-S	Clinical Global Impression–Severity
CI	Confidence Interval
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
C-VISA	Clinical Validation Inventory for Study Admission
DSMB	Data Safety Monitoring Board
ET	Early Termination
ECG	Electrocardiogram
FAS	Full Analysis Set
FCI	Food Craving Inventory
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
HbA1c	Hemoglobin A1c
HDL	High Density Lipoprotein
HR	Heart Rate
ICH	International Conference on Harmonization
IWQOL-Lite	Impact of Weight on Quality of Life-Lite
IWRS	Interactive Web Response Systems
LDL	Low Density Lipoprotein
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
PANSS	Positive and Negative Syndrome Scale
PBO	Placebo
PD	Pharmacodynamic
PK	Pharmacokinetics
PSP	Personal and Social Performance
PT	Preferred Term
QOL	Quality of Life
QTcB	QTcB – Bazett's correction formula
QTcF	QTcF – Friderica's correction formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TLF	Table, Listing, and Figure
TLFB	Timeline Follow-Back
TEAE	Treatment-Emergent Adverse Event

WHO-ATC	World Health Organization Anatomical Therapeutic Chemical

1 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used for analyses and data presentation for reporting efficacy and safety results for study ALK3831-302. This document has been prepared based on Alkermes ALK3831-302 Study Protocol Amendment 2 (dated 16 February 2014) [1].

1.1 STUDY OBJECTIVES

The objectives of this study are to evaluate 3 doses of samidorphan co-administered with olanzapine (ALKS 3831) in subjects with schizophrenia to (1) evaluate ALKS 3831 as a treatment for schizophrenia, (2) assess the safety and tolerability of ALKS 3831, and (3) characterize the impact of samidorphan component of ALKS 3831 on weight and other metabolic factors.

1.2 SUMMARY OF THE STUDY DESIGN

This is a Phase 2, randomized, placebo-controlled multicenter study that is divided into 2 parts: Part A and Part B.

Part A will begin with screening followed by a 1-week olanzapine lead-in period where subjects will receive olanzapine daily and a 12-week double-blind, placebo-controlled treatment period where subjects will receive samidorphan or placebo (in addition to the olanzapine prescribed on Study Day 1) daily. Olanzapine dosing will be selected and titrated by the investigator based upon individual subject needs and consistent with current clinical practice. Subjects will be randomized in a 1:1:1:1 ratio to receive either samidorphan (5, 10, or 20 mg) or placebo.

Part B will include an additional 12-week treatment period where all subjects will receive active olanzapine + samidorphan (ie, ALKS 3831). Subjects randomized to samidorphan during Part A will continue receiving the same dose of samidorphan during Part B. Subjects randomized to placebo during Part A will receive the highest dose of samidorphan during Part B. Dose level during Part B will be double-blind. For all subjects, samidorphan dosing will stop at the end of Part B, but olanzapine dosing will continue uninterrupted through a 4-week follow-up period, which includes 2 safety visits.

This study will use an independent Data Safety Monitoring Board (DSMB) to monitor subject safety data. After at least one week of safety data has been collected for 40 randomized subjects, the DSMB will review the accumulated safety data for all subjects. After at least one week of safety data has been collected for 150 randomized subjects, the DSMB will review the accumulated safety data for all subjects. Additional reviews of the data may occur at the discretion of the DSMB. Complete details of the data review procedures of the DSMB are available in the DSMB charter.

This is the first study of ALKS 3831 in a population of adults with schizophrenia. Subjects will be monitored in an inpatient setting for 2 nights following randomization (Visit 3) and during the transition from Part A to Part B (Visit 13). These are the two periods where samidorphan treatment may be initiated. Subjects will be monitored in an inpatient setting whether or not samidorphan treatment is being initiated in order to maintain double-blind dosing and a consistent subject experience consistent across treatment groups.

2 SAMPLE SIZE CONSIDERATIONS

Sample size calculations are based on the primary endpoint of absolute change in PANSS total score. These calculations assume an equivalence margin of 10 points, a standard deviation of 20 points, and a true difference of 0 points. With these assumptions, 280 randomized subjects provide 95% power to demonstrate equivalence on the primary endpoint (absolute PANSS total score change from randomization to the end of Part A) with a 2-sided test at an alpha level of 0.05. These 280 subjects represent 70 subjects for each treatment arm (ALKS 3831 5 mg, ALKS 3831 10 mg, ALKS 3831 20 mg, and placebo) in a 1:1:1:1 ratio. For the primary analysis, subjects in the 3 ALKS 3831 treatment groups will be pooled for comparison with placebo. If this analysis shows equivalence, follow-up analyses on individual dose levels will be performed. Assuming a 20% discontinuation rate prior to randomization, an estimated 350 subjects will be enrolled in this study.

3 DATA ANALYSIS

3.1 GENERAL STATISTICAL METHODOLOGY

In general, descriptive 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 group for all variables.

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.

Body weight will be measured 3 times at every visit. The median weight will be used in summary tables or figures.

3.1.1 Baseline Definition

Baseline for Part A is defined as the last non-missing observation on or before the first dose of study drug following randomization at Visit 3 (Day 8).

Baseline for Part B is defined as the last non-missing observation on or before the date of the first dose of study drug at Visit 13 (Day 92).

3.2 DEFINITIONS OF ANALYSIS SETS (POPULATIONS)

3.2.1 Enrolled Population

Enrolled population is defined as all subjects who enrolled in the study and received at least one dose of olanzapine before randomization.

3.2.2 Efficacy Populations

The efficacy analysis will be conducted on 2 analysis populations:

- FAS 1 Population is defined as all randomized subjects who received at least one dose of study drug and have at least one post-baseline assessment of PANSS total score.

- FAS 2 Population is defined as all FAS 1 subjects who gained weight during the first week of olanzapine treatment prior to randomization and have at least one post-baseline weight assessment.

FAS 1 population will be the primary efficacy population for analyses on all efficacy variables.

3.2.3 Safety Population

- Safety Population is defined as all randomized subjects who received at least 1 dose of study drug.

- Safety Population for Part B is defined as all randomized subjects who enrolled in Part B and received at least 1 dose of study drug in Part B.

3.3 DISPOSITION

The subject disposition will be summarized for the enrolled population by treatment group and overall and will include the following

- Subjects who were randomized
- Subjects in Safety Population
- Subjects in the FAS 1 Population
- Subjects in the FAS 2 Population
- Subjects who completed the olanzapine lead-in period and continued into Part A
- Subjects who discontinued the study during the olanzapine lead-in period along with reasons for discontinuation
- Subjects who completed the Part A placebo-controlled period and continued into Part B
- Subjects who discontinued the study during Part A placebo-controlled period along with reasons for discontinuation

- Subjects in Safety Population for Part B
- Subjects who completed Part B ALKS 3831 treatment period
- Subjects who discontinued the study during Part B ALKS 3831 treatment period along with reasons for discontinuation
- Subjects entering the safety follow-up period will include
    - Subjects who completed the safety follow-up after discontinuation in the olanzapine lead-in period
    - Subjects who discontinued the safety follow-up after discontinuation in the olanzapine lead-in period
    - Subjects who completed the safety follow-up after discontinuation in Part A placebo-controlled period
    - Subjects who discontinued during the safety follow-up period after discontinuation in Part A placebo-controlled period
    - Subjects who completed the safety follow-up after Part B ALKS 3831 treatment period
    - Subjects who discontinued during the safety follow-up period after Part B ALKS 3831 period

3.4 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics such as gender, age, race, ethnicity, weight, BMI, PANSS, and CGI-S will be summarized by treatment group and overall for FAS 1 Population, FAS 2 Population, and Safety Population.

If there are heterogeneities between treatment groups in any of the subject characteristics that are of clinical importance or could affect the treatment outcome, the impact of the imbalances will be investigated and, if necessary, appropriate adjustments will be considered in the efficacy and safety analyses.

Medical and psychiatric history will be summarized by treatment group and overall using the number and percentage of subjects by category for the Safety Population.

3.5 TREATMENT ADHERENCE RATE AND EXTENT OF EXPOSURE

Treatment adherence refers to a subject's adherence to the daily dosing schedule as assessed by the number of tablets of samidorphan or placebo dispensed, returned and lost. Treatment

adherence of samidorphan or placebo will be calculated as a percentage for the treatment periods as follows:

$$Adherence = 100 \times \frac{(Total\ Tablets\ Dispensed - Total\ Tablets\ Returned - Total\ Tables\ Lost)}{Total\ Tablets\ Scheduled\ to\ be\ Taken}$$

Treatment adherence of samidorphan/placebo will be summarized for Part A using the Safety Population and for Part B using the Safety population for Part B.

Exposure to study drug will be summarized separately for olanzapine and samidorphan/placebo. It will be summarized for Part A using Safety Population and for Part B using the Safety Population for Part B. The exposure is defined as follows.

$$Exposure\ (days) = Date\ of\ last\ dose\ of\ study\ drug - date\ of\ first\ dose\ of\ study\ drug + 1$$

In addition, the time-weighted average olanzapine dose level will be summarized for Part A placebo-controlled period and Part B ALKS 3831 treatment period using the FAS 1 population. Average olanzapine dose level in a treatment period is defined as follows.

$$Average\ olanzapine\ dose\ level = \frac{Sum(olanzapine\ dose\ level * days\ on\ such\ dose\ level)}{exposure}$$

3.6 EFFICACY ANALYSIS

3.6.1 Change in PANSS total Score

The primary endpoint is the change in PANSS total score from randomization to Day 92 and will be evaluated by treatment group (ALKS 3831 pooled vs. the placebo group [olanzapine alone]) using a 2-sided mixed-model for repeated measures (MMRM) to test for equivalence at an alpha level of 0.05. The primary analysis will be conducted in the FAS 1 population.

The null hypothesis is that the PANSS total score change from randomization to Day 92 of ALKS 3831 treatment group will be different to that of the placebo group [olanzapine alone]. The bound of the 2-sided 95% CIs of the difference between the changes of ALKS 3831 – Placebo [olanzapine alone] will be outside the equivalence interval of -10 and 10.

If this analysis shows equivalence, similar analyses on individual dose levels will be performed.

Change in PANSS total score from baseline to Day 92 will be analyzed using MMRM model. The MMRM model will include variables for weight change strata in the olanzapine lead-in period, treatment group, visit, and treatment group-by-visit interaction term as categorical fixed effect, baseline value will be included as a covariate. An AR(1) covariance structure will be

applied for the MMRM. The Kenward-Roger approximation [2] will be used to adjust the denominator degree of freedom. The analysis will be performed on all observed post-randomization scores without imputation of missing data.

A sample of SAS implementation code for analyzing change from randomization to Day 92 using an MMRM is given below.

```
proc mixed data=datain;
class strata usubjid trt visit;
    model change = strata trt visit trt*visit base
    / DDFM=KENWARDROGER;
repeated visit/ type=AR(1) subject=usubjid;
lsmeans trt*visit / diff cl;
run;
```

The least squares (LS) mean, standard error (SE), and LS mean difference between pooled ALKS 3831 treatment group and placebo [olanzapine alone], as well as between each ALKS 3831 treatment group and the placebo [olanzapine alone] at Day 92, along with the 95% CI, will be summarized.

3.6.1.1 Sensitivity Analysis

ANCOVA (analysis of covariance) model will be conducted with the olanzapine lead-in period weight change strata and treatment group as factor and the baseline weight as the covariate for FAS 1. The ANCOVA model will be based on the LOCF (last observation carried forward) imputation, that is, if a subject misses a post-baseline scheduled visit, a record for the scheduled visit will be imputed using the value from the most recent post-baseline visit.

For both FAS 1 and FAS 2 populations, summary of change from baseline in PANSS total score and subscales at each visit will also be presented using descriptive statistics. Change from Part B baseline will also be summarized at each visit in Part B.

3.6.2 Percent Change in Body Weight

The secondary endpoint, percent change in weight from randomization to Day 92, will be evaluated by treatment group using an MMRM approach similar to that of the primary endpoint. Pooled and individual ALKS 3831 treatment group will be compared to the placebo [olanzapine alone] group with a 2-sided hypothesis test to test for superiority at an alpha level of 0.05. The secondary efficacy analysis will be conducted in both FAS 1 and FAS 2 population. The MMRM model includes variables for the weight change strata in olanzapine lead-in period, treatment group, visit, and treatment group-by-visit interaction term as categorical fixed effect; baseline weight value will be included as a covariate.

3.6.2.1 Sensitivity Analysis

To assess the robustness of the MMRM results on the percent weight change, ANCOVA and LOCF analysis will be conducted with the olanzapine lead-in period weight change strata and treatment group as factor and the baseline weight as the covariate (similar as Section 3.6.1.1).

In addition, the MMRM model will include treatment group, visit, and treatment group-by-visit interaction term as categorical fixed effect; baseline BMI value and continuous weight change value in the olanzapine lead-in period will be included as covariates.

Percent weight change will also be analyzed by a linear mixed effects model with treatment as fixed effect, visit and treatment by visit interaction as random effect, and with adjustment for the olanzapine lead-in period weight change strata as factor and baseline weight as covariates. In this model, visit will be treated as a continuous variable and will be the number of days from Day 8. Denominator degrees of freedom will be estimated using the Kenward–Roger approximation. Change from baseline at Day 92 will be obtained from the model.

For both FAS 1 and FAS 2 populations, summary of weight change from baseline at each visit will also be presented using descriptive statistics for both Part A and Part B. Change from Part B baseline will also be summarized at each visit in Part B.

Waterfall plots will be produced for the percent change from baseline to Day 92 by the treatment group.

3.6.3 Absolute Change in Body Weight

The statistical analysis for absolute change in weight will be similar to the analysis for percent change in body weight (Section 3.6.2).

3.6.4 Proportion of Subjects Exhibiting Significant Weight Gain

A subject will be considered as exhibiting significant weight gain if he or she has a body weight change of ≥5%, ≥7% or ≥10% from baseline.

The proportion of subjects with significant weight gain will be estimated at each visit by the treatment group. Pooled and individual ALKS 3831 treatment group will be compared with placebo [olanzapine alone] group, and the difference with 95% CI will be reported for each comparison. It will be based on the observed values. A Cochran-Mantel-Haenszel (CMH) option will be used to make adjustment for the olanzapine lead-in period weight change strata. A sample of SAS implementation code is provided below (assuming ≥7% weight gain is coded 1 and <7% weight gain is coded 2 for the responder variable).

```
proc freq data=datain;
      tables strata*trt01p*responder/CMH;
      where trt01p in ('ALKS3831' 'Placebo')
      and avisit='Week 12';
run;
```

The proportion of subjects with significant weight gain based on observed cases without imputation will also be summarized at each visit by treatment group for Part A and Part B.

3.6.5 Examination of Subgroups

For percent change in body weight and proportion of subjects exhibiting significant weight gain, the following subgroup analysis will be performed with similar analysis methods as described in Sections 3.6.2 and 3.6.4 when appropriate:

- Weight gain category during the olanzapine lead-in period (change ≤0 kg, increase >0 to <1 kg, increase ≥ 1 kg)
- BMI (<25, ≥25)
- BMI (<27, ≥27)
- Gender (male, female)
- Age (≥18-<=39,≥ 40-<=50)
- Region (US, non-US)

3.6.6 Change in Clinical Global Impression - Severity

The CGI-S is a 7-point scale ranging from 1=normal to 7=extremely ill. .

The change from baseline to Day 92 in CGI-S will be carried out using the MMRM model including the weight change strata in olanzapine lead-in period, treatment group, visit, and a treatment group-by-visit interaction term as categorical fixed effects; baseline CGI-S value will be included as a covariate.

A summary of CGI-S at each visit will be presented using descriptive statistics for Part A and Part B.

3.6.7 Efficacy Analysis for the Additional Endpoints

Unless otherwise specified, exploratory efficacy endpoints will be summarized in descriptive statistics by visit and treatment groups. They include change in waist circumference, change in IWQOL-Lite scales (total score, physical function, self-esteem, sexual life, public distress, and work), change in PSP, change in FCI (total score, high fat, sweets, carbohydrates/starches, fast-food fats), and change in alcohol and drug use.

For change in waist circumference, MMRM will also be conducted, including the weight change strata in olanzapine lead-in period, treatment group, visit, and treatment group-by-visit interaction term as categorical fixed effects; baseline value will be included as a covariate.

For IWQOL-Lite scale is a 31-item self-report measure of obesity-specific quality of life. The

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 [4]. The transformed scores range from 0 to 100, with 100 representing the best and 0 the most impaired quality of life.

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

For FCI, total scores and subscores for high fat, sweets, carbohydrates/starches and fast-food fats will be calculated as following:

FCI Total score = average response for items 1 to 28. Possible range is 1-5.

High fat subscore=average response for items 3, 4, 6, 10, 15, 19, 26 and 27. Possible range is 1-5.

Sweets subscore=average response for items 1, 8, 13, 16, 17, 23, 24 and 25. Possible range is 1-5.

Carbohydrates/starches subscore=average response for items 5, 9, 12, 14, 18, 21, 22 and 28. Possible range is 1-5.

Fast-food fats subscore=average response for items 2, 7, 11 and 20. Possible range is 1-5.

For alcohol use as assessed by TLFB, percent of drinking days for the prior 30 days will be summarized at each visit.

Number and percentage of subjects with any drug use at each scheduled time point will be summarized by treatment group. It will also be summarized for individual drugs.

3.7 SAFETY ANALYSIS

3.7.1 General Considerations

Safety analyses will be primarily based on Safety Populations and include AEs, clinical laboratory assessments (hematology, blood clinical biochemistry, and urinalysis), vital signs, ECG parameters, and data from C-SSRS surveys in Part A and Part B treatment periods.

Safety analyses will be performed on observed data, and no missing values will be imputed.

3.7.2 Adverse Events

Reported AE terms will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA®) version 15.0. The verbatim term will be included in the AE listings.

3.7.2.1 Treatment-Emergent Adverse Event

An AE will be considered as treatment-emergent AE (TEAE) if the event is newly occurring or after the first dose of study drug. AEs will be identified as emerging in the following periods:

- TEAEs during the olanzapine lead-in period
- TEAEs for the Part A placebo-controlled period
- TEAEs for the Part B ALKS 3831 treatment period
- TEAEs for the Part A placebo-controlled period and Part B ALKS 3831 treatment period combined
- TEAEs during the follow-up period:
    - after discontinuation in the olanzapine lead-in period
    - after discontinuation in Part A placebo-controlled period
    - after discontinuation or completion of Part B ALKS 3831 treatment period

All AEs will be listed by subject, but only TEAEs will be included in the summary tables. Summary tables will be produced for the specified periods above.

An overall summary of TEAEs such as all TEAEs, treatment-related TEAEs, TEAEs leading to study discontinuation, serious TEAEs, serious and treatment-related TEAEs, and TEAEs resulting in death will be summarized for each treatment group.

In addition, the following summary tables will be produced:

- TEAEs experienced by ≥2% of subjects in any treatment group for Part A placebo-controlled period, Part B ALKS 3831 treatment period, and combined period
- Treatment-related TEAEs experienced by ≥2% of subjects in any treatment group for Part A placebo-controlled period, Part B ALKS 3831 treatment period, and combined period

- The number and percentage of subjects with TEAEs by treatment group, SOC, PT, and severity for Part A placebo-controlled period, Part B ALKS 3831 treatment period, and combined period

A subject with the same AE more than once will be counted once in the number and percentage of subjects calculation for that AE. Similarly, if a subject has more than one AE in an SOC, the subject will be counted only once in the total number of subjects with an AE for that SOC. If a subject has the same AE on multiple occasions, the highest severity (severe>moderate>mild) or drug relationship (definitely related>probably related>possibly related>probably not related>definitely not related) recorded for the event will be presented.

An AE that occurs after a subject provides informed consent but before the first dose of study drug will be considered as a pre-treatment AE.

3.7.2.2 Deaths, Serious and Other Significant AEs

The number and percentage of subjects with at least one treatment emergent SAE will be summarized by System Organ Class, and Preferred Term for each treatment group for Part A placebo-controlled period, Part B ALKS 3831 treatment period, and combined period. Subjects with AEs leading to study discontinuation will be summarized similarly. Subjects who died during the study will be listed.

3.7.2.2.1 Other significant AEs

The following categories for adverse events were selected based on effects that have been observed with olanzapine. The PTs to be included in each category were based on Standardized MedDRA queries (SMQs) or custom searches if the SMQs did not exist or were inadequate. These significant AEs will be summarized by the AE category, PT and treatment group.

- Extrapyramidal symptoms (list of PTs provided in Appendix)
- Nausea or vomiting (include these 2 PTs)
- Sedation (including sedation, somnolence, lethargy or hypersomnia)

3.7.3 Clinical Laboratory Parameters

Laboratory parameters will be presented in conventional units. Only laboratory results at the scheduled visits will be included in the summary tables. All lab data will be included in the listings.

Results will be summarized for hematology and chemistry by visit and the treatment group for Part A and Part B.

Additionally, for select parameters, number and percentage of subjects with values considered potentially clinically significant (PCS) occuring at any time post-baseline will be summarized

by treatment group. Criteria for PCS are presented in Table 1 and Table 2. Criteria for shift in lipids, glucose and HbA1c are presented in Table 3 and Table 4.

Table 1: Potentially Clinically Significant Results Criteria for Chemistry

Parameters	Criteria
Albumin	<2.5 g/dL
Alkaline phosphatase (U/L)	≥3 x ULN
Alanine Aminotransferase (U/L)	≥3 x ULN
Aspartate Aminotransferase (U/L)	≥3 x ULN
Alanine Aminotransferase (U/L)	≥3 x 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 x ULN
Creatinine	≥2.0 mg/dL
Glucose, Random	<50 mg/dL or ≥200 mg/dL
Potassium	<3 mmol/L or >5.5 mmol/L
Lactate Dehydrogenase (U/L)	>3 x ULN
Phosphate	<2 mg/dl or >5 mg/dl
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 2: Potentially Clinically Significant Results Criteria for Hematology

Parameters	Criteria
Eosinophils	>1.0 x 10^3/uL
Hematocrit (Female)	<=32%
Hematocrit (Male)	<=37%
Neutrophils, Absolute	<1.5 x 10^3/uL
Platelets	<75.0 x 10^3 cells/uL or ≥ 700.0 x 10^3 cells/uL
Leukocytes	≤ 2.8 x 10^3/uL or ≥ 16.0 x10^3/uL

Table 3: Shifts Category in Lipid Parameters from Baseline to Any Post-Baseline.

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 4: Shift Category in Glucose and HbA1c from baseline to any post-baseline

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 (fasting) %
Shift from baseline (<6.1%) to: Post-baseline ≥6.1%
Post-baseline ≥8%
Post-baseline ≥10%
Post-baseline ≥12%

3.7.4 Vital Signs

Descriptive statistics for vital signs and changes from baseline values at each scheduled time point will be presented by treatment group. Additionally, number and percentage of subjects with values considered PCS occurring at any time post-baseline will be summarized by treatment group. Criteria for PCS are presented in Table 5.

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

Parameter	PCS Criterion
Systolic blood pressure, supine	Low:≤ 90mm Hg and decrease ≥20 mm Hg
	High: ≥180 mm Hg and increase ≥20 mm Hg
Diastolic blood pressure, supine	Low: ≤ 50mm Hg and decrease ≥15 mm Hg
	High: ≥105 mm Hg and increase ≥15 mm Hg
Pulse, supine	Low: ≤ 50 bpm and decrease ≥15 bpm
	High: ≥120 bpm and increase ≥15 bpm

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

Orthostatic hypotension (20/10) 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) 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 post-baseline timepoint will also be summarized by treatment group.

3.7.5 Electrocardiograms

Descriptive statistics for ECG parameters (heart rate, RR interval, PR interval, QRS interval, QT interval, QTcB [QT interval corrected using Bazett's method], QTcF [QT interval corrected using Fridericia's method]) and changes from baseline values at each scheduled time point will be presented by treatment group. Any other ECG parameters that are collected will be presented in the listings only.

In addition, the number and percentages of subjects with any post-baseline results meeting supra-threshold QTc criteria, as defined in Table 6, based on ICH (International Conference on Harmonization) Guidance E14[3] will be presented by treatment for QTcB and QTcF. A listing will present all values for a subject and parameter for cases where at least one value for that parameter was potentially significant.

Table 6: Abnormal results for Electrocardiogram

Parameter	Abnormal ECG Results Criteria

QTcB, QTcF	• >500 milliseconds
	  o >60 millisecond change from baseline
	  o >30 - <=60 millisecond change from baseline
	• >480 and ≤500 milliseconds
	  o >60 millisecond change from baseline
	  o >30 - <=60 millisecond change from baseline
	• >450 and ≤ 480 milliseconds
	  o >60 millisecond change from baseline
	  o >30 - <=60 millisecond change from baseline
	• >60 millisecond change from baseline
	• >30 - <=60 millisecond change from baseline

3.7.6 Prior and Concomitant Medications

Prior medications are defined as medications taken prior to the first dose of the randomized study medication. Concomitant medications are defined as medications taken during the treatment period. Concomitant medications for Part A placebo-controlled period are defined as medications taken between the first dose of the randomized medication to the end of Part A treatment period (inclusive). Concomitant medications for Part B ALKS 3831 treatment period are defined as medications taken between the first dose of the samidorphan to the end of Part B treatment period (inclusive).

All medications as documented by the investigator will be coded using the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) drug dictionary, version March 2012.

Prior and concomitant medications will be summarized by the Preferred Term and by treatment group. Medication taken only during the follow-up period will be presented in the subject data listing only. For the summary tables, if a subject has taken a prior or concomitant medication more than once, the subject will be counted only once for the medication. Partial date imputation for medications is described in Section 3.11.5. All reported medications will be presented in the subject data listing.

3.7.7 Columbia Suicide Severity Rating Scale

Response to individual items of C-SSRS as well as the presence (yes or no) of any completed suicide, suicide attempt, preparatory actions towards imminent suicidal behavior, suicidal ideation, and non-suicidal self-injurious behavior at any post-baseline visit will be summarized using number and percentage of subjects for each category.

Table 7. C-SSRS category mapping.

Category	**Definition** **("Yes" answer to any one of the following)**
Completed suicide	Completed Suicide
Suicide attempt	Actual attempt
Preparatory actions towards imminent suicidal behavior	• Interrupted attempt • Aborted attempt • Preparatory acts or behavior
Suicide 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

3.8 PHARMACOKINETIC/PHARMACODYNAMIC DATA ANALYSIS

Subject listings for the concentrations, PK sampling time, and the prior drug dosing time of samidorphan, RDC-9986 (primary metabolite of samidorphan), and olanzapine will be provided.

3.9 INTERIM ANALYSES AND DATA SAFETY MONITORING BOARD

An independent Data Safety Monitoring Board (DSMB) will monitor for tolerability of study drug. Complete details of can be found in DSMB SAP.

3.10 DEVIATIONS FROM THE PROTOCOL AND SPECIFIED ANALYSES

There are no deviations from the protocol specified analyses.

3.11 DEFINITIONS AND CONVENTIONS FOR HANDLING OF DATA

3.11.1 Analysis Visit

Unless otherwise specified, this provides general rules across datasets in ADaMs.

3.11.1.1 Scheduled analysis visit

Scheduled analysis visits are visits upon scheduled time points 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 would be one valid value of assessment kept for each scheduled analysis visit in summary/analysis statistics.

The scheduled repeat measurements at the same visit will be handled as described in SAP Section 3.1.

3.11.1.2 Unscheduled visit

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 will be included as collected in eCRF in listings.

3.11.1.3 Early termination (ET) visit

An early termination (ET) visit can be mapped to a scheduled visit and be used for analysis and summaries only if there is no valid value already at the mapped visit.

A mapped ET visit will be treated as a scheduled visit to be included in table summaries. Otherwise, it will be treated as an unscheduled visit.

Two rules will be used to map an ET visit.

First, a 7-day (inclusive) window (≤last dose date + 7) will be used to determine if the assessment at the ET visit is considered to be an on-treatment result. If an ET visit is within 7 days after the last dose of samidorphan/placebo, it will be considered as a valid on-treatment

visit.

Second, visit windows (inpatient stay is excluded) will be applied to determine to which visit an ET valid on-treatment assessment can be mapped to. Visit windows are defined in Table 8 below.

If a subject didn't complete the Part A, his/her ET assessment will not be mapped to Part B visits, i.e. Visit 14 to 23.

Table 8: Visit Window Definition

Analysis Visit to be Mapped to	Target Study Day	Visit Window
Visit 6	15	[9, 18]
Visit 7	22	[19, 25]
Visit 8	29	[26, 32]
Visit 9	36	[33, 43]
Visit 10	50	[44, 57]
Visit 11	64	[58, 71]
Visit 12	78	[72, 85]
Visit 13	92	[86, 98]
Visit 16	99	[99, 102]
Visit 17	106	[103, 109]
Visit 18	113	[110, 116]
Visit 19	120	[117, 127]
Visit 20	134	[128, 141]
Visit 21	148	[142, 155]
Visit 22	162	[156, 169]
Visit 23	176	[170, 183]

3.11.1.4 Follow-up Visits

Follow-up visits for ET subjects will be reported after the lead-in period, Part A placebo-controlled period and Part B ALKS 3831 treatment period respectively.

For Part B, the follow-up visit after ET and that after completion of treatment in Part B will be reported without distinction.

3.11.2 Last Post-baseline Values

Last post-baseline values are defined as the last valid post-baseline values collected for each subject during the treatment period or a specified reporting period. Values collected at unscheduled visits can be used to derive the last post-baseline values.

3.11.3 Any Post-baseline Values

Any post-baseline values are defined as any valid values collected from scheduled or unscheduled visits, if applicable.

3.11.4 Missing Safety Data

Missing data from safety assessment or evaluation will not be imputed. However, they will be reviewed for possible data issues.

3.11.5 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.

4 MOCK TABLES, LISTINGS AND GRAPHS

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

5 REFERENCES

1. Alkermes ALK3831-302 Study Protocol Amendment 2 (dated 26 February 2014)

2. Kenward MG and Roger JH (1977) Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997; 53: 983–997

3. ICH Guidance "E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs”

4. Tessier A et al. (2012) Understanding the Determinants of Weight-Related Quality of Life among Bariatric Surgery Candidates. Journal of Obesity 2012; 2012: 713426

6 APPENDIX A STANDARDIZED MEDICAL QUERY PREFERRED TERMS FOR EXTRAPYRAMIDAL SYMPTOM (EPS)-RELATED SMQS

Akathisia
SMQ Level: 2 SMQ Code: 20000096

Preferred Terms:
- Akathisia
- **With and without;**
  - Restlessness
  - Psychomotor hyperactivity
  - Hyperkinisia

Dyskinisia
SMQ Level: 2 SMQ Code: 20000097

Preferred Terms:
- Athetosis
- Ballismus
- Buccoglossal syndrome
- Chorea
- Choreoathetosis
- Dopamine dysregulation syndrome
- Dyskinesia
- Dyskinesia oesophageal
- Grimacing
- Pharyngeal dyskinesia
- Protrusion tongue
- Rabbit syndrome
- Respiratory dyskinesia
- Tardive dyskinesia
- Muscle twitching
- Tic

Dystonia
SMQ Level: 2 SMQ Code: 20000098

Preferred Terms:
- Dystonia
- Dystonic tremor
- Emprosthotonus
- Meige's syndrome

- Oculogyric crisis
- Opisthotonus
- Oromandibular dystonia
- Pleurothotonus
- Spasmodic dysphonia
- Torticollis
- Trismus
- Writer's cramp
- Abasia
- Blepharospasm
- Facial spasm
- Laryngospasm
- Muscle contractions involuntary
- Muscle spasms
- Muscle spasticity
- Muscle tightness
- Oesophageal spasm
- Oropharyngeal spasm
- Posture abnormal
- Posturing
- Risus sardonicus
- Tongue spasm
- Uvular spasm

Parkinson-like events
SMQ Level: 2 SMQ Code: 20000099

Preferred Terms:
- Akinesia
- Bradykinesia
- Cogwheel rigidity
- Freezing phenomenon
- Hypertonia
- Masked facies
- Muscle rigidity
- On and off phenomenon
- Parkinson's disease
- Parkinsonian crisis
- Parkinsonian gait
- Parkinsonian rest tremor
- Parkinsonism

- Parkinsonism hyperpyrexia syndrome
- Resting tremor
- Action tremor
- Bradyphrenia
- Drooling
- Dysphonia
- Extrapyramidal disorder
- Gait disturbance
- Hypokinesia
- Micrographia
- Mobility decreased
- Motor dysfunction
- Movement disorder
- Muscle tone disorder
- Musculoskeletal stiffness
- Postural reflex impairment
- Postural tremor
- Tremor
- Walking disability