A Phase 3b Extension Study of Adjunctive ALKS 5461 in the Treatment of Refractory Major Depressive Disorder

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STATISTICAL ANALYSIS PLAN

ALK5461-218

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LIST OF ABBREVIATIONS

The following abbreviations are used in the statistical analysis plan.

Abbreviation	Definition
ADT	Antidepressant Therapy
AE	Adverse Event
BUP	Buprenorphine
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
EOT	End of Treatment
EOS	End of Study
ET	Early Termination
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
PDEAE	Post-discontinuation Emergent Adverse Event
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods and data presentation to be used at study completion for analyzing and reporting ALKS 5461 data for Study ALK5461-218, A Phase 3b Extension Study of Adjunctive ALKS 5461 in the Treatment of Refractory Major Depressive Disorder (MDD). This document has been prepared based on Alkermes ALK5461-218 study protocol v3.0 (dated 19 November 2019) [1].

1.1. Study Objectives

The objective of this study is to evaluate the long-term safety and tolerability of adjunctive ALKS 5461 in adults who have treatment-refractory MDD.

1.2. Summary of the Study Design and Schedule of Assessments

This is an open-label, Phase 3b, multicenter extension study to evaluate the long-term safety and tolerability of ALKS 5461 administration for use as an adjunctive therapy to antidepressants for the treatment of refractory MDD. Subjects who complete participation in the ALK5461-217 study will be eligible for enrollment into the study.

At Visit 1 (day 1), all eligible, consenting subjects will begin the treatment period. One tablet will be taken sublingual on each dosing day. From Day 1 onward, all participating subjects will take ALKS 5461 2/2 mg and an approved antidepressant therapy (ADT).

Study staff will administer the first dose of ALKS 5461 on Day 1. From that point on during the treatment period, the staff will dispense ALKS 5461 for subjects' self-administration. Subjects will be advised to take the study drug at bedtime.

During the treatment period, subjects will return to the clinic for periodic scheduled visits, at which time safety and tolerability will be assessed, as well as a 2-week post-discontinuation Follow-up visit.

For a missed visit, the study site should attempt to contact the subject to reschedule. Subjects who discontinue from the study prematurely will be encouraged to return for an Early Termination visit and a 2-week post-discontinuation Follow-up visit.

Subjects' demographic data will be carried over from the ALK5461-217 study. If ≥30 days have elapsed since end-of-treatment in ALK5461-217, medical and psychiatric history for the intervening period will be queried and updated in the ALK5461-218 database as necessary.

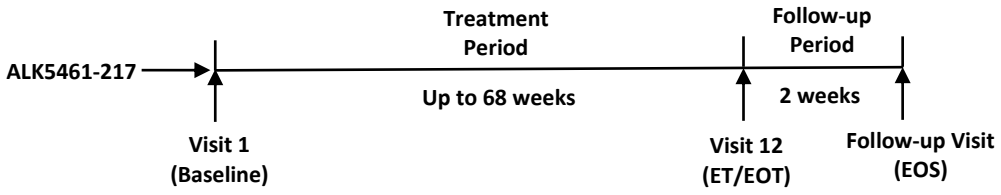
At each visit, subjects will be asked about the medications they have taken since the last visit.

Drug adherence for ALKS 5461 will be reviewed with subjects at each visit.

Please refer to the protocol for a detailed schedule of assessments. A brief schematic of study design is provided in Figure 1. A summary of the schedule of safety assessments is presented in

Table 1.

Figure 1: Study Design Schematic



Abbreviations: EOS=end of study; EOT=end of treatment; ET=early termination

Table 1: Schedule of Safety Assessments

Procedure or Assessment	Schedule
Dispensation of study drug	All scheduled visits prior to End of Treatment or Early Termination Visit (i.e., Screening [Day 1], weeks 1, 2, 6, 12, 20, 28, 36, 44, 52, 60)
• Adverse Event • C-SSRS (since last visit) • Drug Adherence • Concomitant Medications • Urine Pregnancy Test	Screening (Day 1), weeks 1, 2, 6, 12, 20, 28, 36, 44, 52, 60, 68 (ET/EOT), 14 days after last dose (Follow-up visit)
Urine Drug Screen	Screening (Day 1), at subsequent visits as needed based on the investigator's judgment

Abbreviations: C-SSRS=Columbia-Suicide Severity Rating Scale; EOT=end of treatment; ET=early termination

1.3. Criteria for Evaluation

Safety and Tolerability:

The following assessments will be collected to measure safety and tolerability throughout the study:

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Columbia Suicide Severity Rating Scale (C-SSRS)

2. SAMPLE SIZE CONSIDERATION

No formal sample size calculation has been performed. A sample size of up to 250 subjects is based on an estimated number of subjects who may wish to continue from Study ALK5461-217.

3. DATA ANALYSIS

3.1. General Statistical Methodology

Summary 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 for subjects receiving one or more doses on ALKS 5461. Summary statistics will be based on observed data. In general, only data collected during the ALK5461-218 study will be summarized even though baseline demographic data may have been assessed in study ALK5461-217.

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

3.2. Study Population

3.2.1. Definitions of Analysis Populations

Safety Population will consist of all enrolled subjects who received at least 1 dose of study drug in the ALK5461-218 study.

Post-discontinuation Safety Population will consist of subjects who received at least 1 dose of study drug in the ALK5461-218 study, and met one of the following criteria:

- Subjects who entered the Post-discontinuation Period and had a Post-discontinuation Follow-up Visit
- Subjects who did not enter the Post-discontinuation Period (i.e., final visit was last visit in treatment period), but had at least 1 PDEAE reported
- Subjects who died after either completing the treatment or having an Early Termination (ET) Visit

3.2.2. Definitions of Baseline and Analysis Periods

Baseline

For demographics and baseline disease characteristics, baseline will be defined as assessments recorded at Visit 1. Note that the actual assessment for some variables was made in the antecedent study, ALK5461-217. For adverse events, baseline will be defined as prior to Visit 1 (i.e., the period from completion of ALK5461-217 to first dose received in ALK5461-218). For the Columbia-Suicide Severity Rating Scale (C-SSRS) baseline will be defined as the assessment made during Visit 1.

Treatment Period

The treatment exposure period (i.e., Treatment Period) will be defined as the interval between Visit 1 and the last dose date plus 1 day, inclusive.

Visit 1 is the first scheduled visit during the scheduled treatment period and Visit 12 is the last scheduled visit including ET visit during treatment.

Post-Discontinuation Period

Post-discontinuation Safety Period will be defined as the interval starting from the last dose date plus 2 days to the end of study date, inclusive.

3.2.3. Disposition

Subject disposition will be summarized for all subjects. The number and percentage of subjects will be summarized for the following:

- Subjects who enrolled in the study
- Subjects in the Safety Population
- Subject who completed treatment (as indicated on the case report form (CRF))
- Subjects who completed the study (as indicated on the CRF)
- Subjects who discontinued from the study

For subjects who prematurely discontinue from the study, the reasons for discontinuation as recorded on the disposition CRF will be presented. Percentage will be calculated based on Safety Population.

A listing of disposition for all subjects will be provided.

3.2.4. Protocol Deviations

Subjects with major protocol deviations will be summarized along with supportive listings for each of the following categories:

- Did not meet the inclusion / exclusion criteria
- Received prohibited medications
- Dosing error
- Other major protocol deviation

3.3. Demographic Characteristics

Demographic characteristics data (i.e., age, gender, primary race, ethnicity and region (United States [US], non-US)) will be summarized for the Safety Population. Categories for missing data will be provided as necessary.

Medical history collected since the completion of the antecedent study will be summarized using the number of observations and percentage of subjects reporting each category for the Safety Population.

Demographic and baseline listings will be provided for all subjects.

3.4. Prior and Concomitant Medications

Prior medications are defined as medications taken between the completion of study ALK5461-217 and the first dose of ALKS 5461 in this study. Concomitant medications are defined as medications taken during the treatment period (defined as first dose date and the last dose date of study drug plus 1 day, inclusive). All medications as documented by the investigator will be coded using the WHODrug Format C, Version March 2017, WHO DDE + Herbal.

Prior medications and concomitant medications will be summarized by Preferred Term (PT) for the Safety Population. 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.

Listings will be provided for all prior and concomitant medications.

3.5. Treatment Adherence Rate and Extent of Exposure

Treatment adherence to the daily dosing schedule of study drug is measured as the rate of actual compared to intended number of doses to be taken during the ALK5461-218 study. Percentage of treatment adherence will be calculated during the treatment period for the Safety Population as follows:

$$100 \times \frac{\text{Total tablets taken}}{\text{Total tablets subject should have taken from the first dose date to the last dose date, inclusive}}$$

Duration of exposure to study drug is defined as the number of days from the first dose date of study drug taken to the date of the last dose taken during the ALK5461-218 study, inclusive.

Treatment adherence and exposure of study drug will be summarized for the Safety Population. Treatment adherence will be summarized as a continuous measure and as a categorical measure for each adherence rate category (rounded to the whole number): <70%; ≥70% to 80%; >80% to 90%; >90% to 100%; >100% to 110%; >110% to 120%; and >120%.

The number of subjects exposed to study drug and the extent of exposure (i.e., days of treatment) will be summarized as a continuous measure using descriptive statistics.

3.6. Safety Analysis

3.6.1. General Considerations

All safety endpoints will be summarized based on observed data for the Safety Population during the Treatment Period / during the Post-discontinuation Safety Period.

3.6.2. Adverse Events

Adverse events will be coded by System Organ Class (SOC) and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA, version 20.0). The verbatim term will be included in the AE listings.

An AE will be considered as a treatment-emergent adverse event (TEAE) if it starts or worsens (if present during baseline period) on or after first dose date during the treatment period (defined as the period between the first dose date and last dose date +1). An AE will be considered as a PDEAE if it starts during the Post-discontinuation Safety Period (defined as after the period after last dose date plus 2 days, inclusive, and include AEs with preferred terms that may have also

been TEAEs during the Treatment Period. For the determination of TEAEs during the treatment period, AEs with the greatest severity before the baseline will be used as the benchmark for the comparison of the AEs occurring during the treatment period. For PDEAEs, all AEs starting during the Post-discontinuation Safety Period will be summarized.

All AEs will be listed by subject. TEAEs / PDEAEs, deaths, serious adverse events (SAEs), and AEs leading to study discontinuation will be included in the summary tables. For AEs leading to study discontinuation or deaths, the AEs will be summarized in the period in which the discontinuation or death occurred. Drug-related TEAEs include those scored as definitely related, probably related, and possibly related by the investigator.

The following summary tables will be produced for the treatment period / Post-discontinuation Safety Period for the Safety Population:

- Overview AE summary tables (TEAEs / PDEAEs)
- TEAEs / PDEAEs by System Organ Class and Preferred Term
- TEAEs / PDEAEs by Preferred Term
- TEAEs / PDEAEs experienced by ≥5% of subjects by Preferred Term
- TEAEs / PDEAEs by System Organ Class, Preferred Term, and Severity
- Drug-related TEAEs by Preferred Term
- SAEs (fatal and non-fatal) by Preferred Term
- AEs leading to study discontinuation by System Organ Class and Preferred Term
- AEs leading to study discontinuation by Preferred Term

A subject having the same AE (as determined by the coded MedDRA preferred term) more than once will be counted only once in the calculation of the number and percentage of subjects for that AE. Similarly, if a subject has more than one AE in a System Organ Class, the subject will be counted only once in the number of subjects with an AE for that System Organ Class. If a subject has the same AE on multiple occasions, the highest severity (severe > moderate > mild) recorded for the event will be presented in the AE by severity summary. Similarly, if a subject has the same AE on multiple occasions, the closest relationship (related > not related, where related includes definitely related, probably related, and possibly related; and not related includes probably not related and definitely not related) recorded for the event will be presented in the AE by relationship summary.

Subgroup analyses are planned for TEAEs only. Subgroups to include:

- Demographics (age [<55 years, ≥55 years], race [white, all other races], gender [female, male])
- Region (US, non-US)

Subject listings for AEs will be included.

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

Columbia Suicide Severity Rating Scale items of suicidal behavior and suicidal ideation will be summarized at baseline (Visit 1) and post-baseline for the Safety Population. The proportion of subjects who meet the criterion for each of these four categories (suicidal behavior, suicidal ideation, suicidal behavior or ideation, and self-injurious behavior without suicidal intent) as described in Table 2: will be summarized. In addition, each item will be presented separately within each category. Data will be presented for baseline, any post-baseline during the treatment period, at last post-baseline visit during the treatment period, and any post-discontinuation values.

Any behaviors experienced will be listed with a brief narrative. Any completed suicides will be presented with full narrative.

Table 2: C-SSRS Summary Categories for Analysis

Category	**C-SSRS item response is "YES"**
Suicidal ideation	1) Wish to be dead 2) Non-specific active suicidal thoughts 3) Active suicidal ideation with any methods (not plan) without intent to act 4) Active suicidal ideation with some intent to act, without specific plan 5) Active suicidal ideation with specific plan and intent
Suicidal behavior	6) Preparatory acts or behavior 7) Aborted attempt 8) Interrupted attempt 9) Actual attempt 10) Completed suicide
Suicidal behavior or ideation	Including 10 items above
Self-injurious behavior without suicidal intent	Purely for other reasons / without any intention of killing yourself

3.6.4. Other Safety Assessments

Listings for urine pregnancy test and urine drug screen will be provided.

4. INTERIM ANALYSES

No interim analysis is planned.

5. CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

Not applicable.

6. DEFINITIONS AND CONVENTIONS FOR HANDLING OF THE DATA

Dataset specifications will be provided in a separate document.

6.1. Analysis Visit Windows

Not applicable. Longitudinal analysis is not planned.

6.2. Handling of Partial Dates of Prior and Concomitant Medications

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.

7. GENERAL STATISTICAL METHODOLOGY

7.1. Statistical Conventions

In general, summary 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 summary tables will be based on observed data, and missing values will not be imputed. Source data for the summary tables and statistical analyses will be presented as subject data listings.

7.2. Reporting Precision

Summary statistics will be presented to the degree of precision in 5, unless otherwise specified.

Table 3: Degree of Precision

Statistics	Degree of Precision
Mean, Median, Quartiles	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.
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).

7.3. PROGRAMMING SPECIFICATIONS

Programming specifications will be provided in a separate document.

8. MOCK TABLES, LISTINGS AND FIGURES (TLFS)

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

9. REFERENCES