A Phase 3b Efficacy and Safety Study of Adjunctive ALKS 5461 in Treatment Refractory Major Depressive Disorder

Unique Protocol ID:	ALK5461-217
NCT Number:	NCT03188185
Date of Statistical Analysis Plan:	02 Oct 2019

STATISTICAL ANALYSIS PLAN

ALK5461-217

Study Title:	A Phase 3b Efficacy and Safety Study of Adjunctive ALKS 5461 in Treatment Refractory Major Depressive Disorder
Document Status:	Final, Version 2.0
Document Date:	02 Oct 2019
Based on:	ALK5461-217 Study Protocol Versions: v4.0 (incorporates Amendment 3 [02 Oct 2019] and Administrative Change Memo 2 [10 Apr 2019]) v3.0 (incorporates Amendment 2 [25 Jan 2018] and Administrative Change Memo 1 [10 Jul 2017]) v2.0 (incorporates Amendment 1): 18 Apr 2017 Original Protocol v1.0: 11 Jan 2017
Sponsor:	Alkermes, Inc. 852 Winter Street Waltham, MA 02451 USA

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LIST OF ABBREVIATIONS

The following abbreviations are used in the statistical analysis plan (SAP).

Abbreviation	Definition
ADT	Antidepressant Therapy
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical (classification system)
BLOQ	Below Lower Limit of Quantification
BMI	Body Mass Index
BUP	Buprenorphine
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CNS	Central Nervous System
COWS	Clinical Opiate Withdrawal Scale
C-SSRS	Columbia-Suicide Severity Rating Scale
CI	Confidence Interval
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ET	Early Termination
FAS	Full Analysis Set
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D	17 Item Hamilton Rating Scale for Depression
HIR	Historical Inadequate Response
HR	Heart Rate
IxRS	Interactive Voice or Web Response System
LOCF	Last Observation Carried Forward
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MMRM	Mixed Model for Repeated Measures
nBUP	nor-buprenorphine
PDEAE	Post-discontinuation Emergent Adverse Event
NR	Non-responder
PIR	Prospective Inadequate Response
PK	Pharmacokinetic
PLI	Prospective Lead-in
PMM	Pattern Mixture Model
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form
QTcB	QTcB – Bazett's correction formula
QTcF	QTcF – Fridericia's correction formula
SAE	Serious Adverse Event
SAM	Samidorphan
SAP	Statistical analysis plan
SD	Standard Deviation
SHAPS	Snaith-Hamilton Pleasure Scale
SIGH-D	Structured Interview Guide for the HAM-D
SIGMA	Structured Interview Guide for the MADRS
SL	Sublingual
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SPCD	Sequential Parallel Comparison Design
SSRI	Selective Serotonin Reuptake Inhibitor
TEAE	Treatment Emergent Adverse Events
ULN	Upper limit of normal
WHO-ATC	World Health Organization Anatomical Therapeutic Chemical

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods and data presentation to be used for analyzing and reporting efficacy and safety data for study ALK5461-217. This document has been prepared based on Alkermes ALK5461-217 Study Protocol Amendment 3.0 (dated 02 Oct 2019) and the associated Unmasked Addendum Amendment 2.0 (dated 25 Jan 2018).

1.1. Study Objectives

The objectives of this study are:

- To evaluate the efficacy of adjunctive ALKS 5461 for treatment refractory major depressive disorder (MDD) in adults
- To evaluate the safety and tolerability of adjunctive ALKS 5461 in adults who have treatment refractory MDD

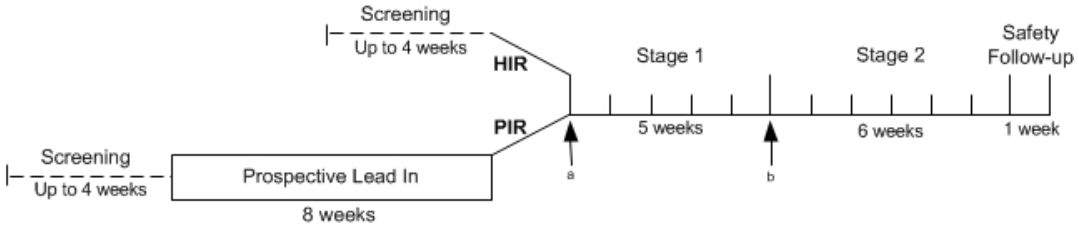
1.2. Summary of the Study Design

This is a Phase 3b multicenter study of adjunctive ALKS 5461 2/2 (2 mg buprenorphine [BUP]/2 mg samidorphan [SAM], hereafter referred to as ALKS 5461 2/2) that will utilize a randomized, double-blind, two-stage, placebo-controlled, sequential parallel comparison design (SPCD). The purpose of this study is to evaluate the efficacy, safety, and tolerability of adjunctive ALKS 5461 2/2 taken sublingually (SL) once a day in male and female subjects with treatment refractory MDD (defined as having at least 2 inadequate responses to antidepressant therapies [ADT] in the current major depressive episode [MDE]).

ALKS 5461 2/2 (plus current, approved ADT) or placebo (plus current, approved ADT) will be administered to subjects for 5 weeks in Stage 1 and for 6 weeks in Stage 2. During Stages 1 and 2, subjects will return to the clinic every week for assessments. Subjects will return to the clinic for a Safety Follow-up Visit (Visit 14), 1 week after Visit 13. The total study duration for a given subject will be up to approximately 24 weeks, which includes a Screening Period of up to 4 weeks, an 8-week Prospective Lead-in (PLI) period (if required as determined during Screening), two treatment periods of 5- and 6-weeks duration (Stages 1 and 2, respectively) and a 1-week Follow-up period.

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

Figure 1: Study Design Schematic



Abbreviations: HIR=historic inadequate responder; PIR=prospective inadequate responder
[a] Stage 1 treatment initiation
[b] Stage 2 treatment initiation

1.3. Screening and Prospective Lead-in Period

Potential subjects will be evaluated during a Screening Period (Visit 1) lasting up to 4 weeks. Screening will include an assessment of each subject's history of inadequate response to ADT. Based on this assessment at Screening, qualifying subjects will either participate in an 8-week PLI Period (prospective inadequate responders [PIRs]) or will be eligible to bypass the PLI Period and proceed directly to Stage 1 (historic inadequate responders [HIRs]).

Throughout the PLI Period, subjects will return to the clinic for brief assessments (Visits 1a-1f) that will occur weekly for the first 4 weeks and biweekly for the remainder of the PLI Period. At Visit 1f, subjects will be assessed for eligibility in an automated interactive voice or web response system (IxRS) using masked criteria. Based on this assessment, subjects will be classified as either being eligible to continue in the study or screen failures.

1.4. Double-Blind Treatment Period

The 11-week treatment period (Visits 2-13) will be divided into Stage 1 (Visits 2–7, 5 weeks) and Stage 2 (Visits 7-13, 6 weeks). At Visit 2, PIR and HIR subjects who meet all the entry criteria will be randomized in a 2:5 ratio to receive either ALKS 5461 2/2 or placebo for 5 weeks, in addition to background ADT.

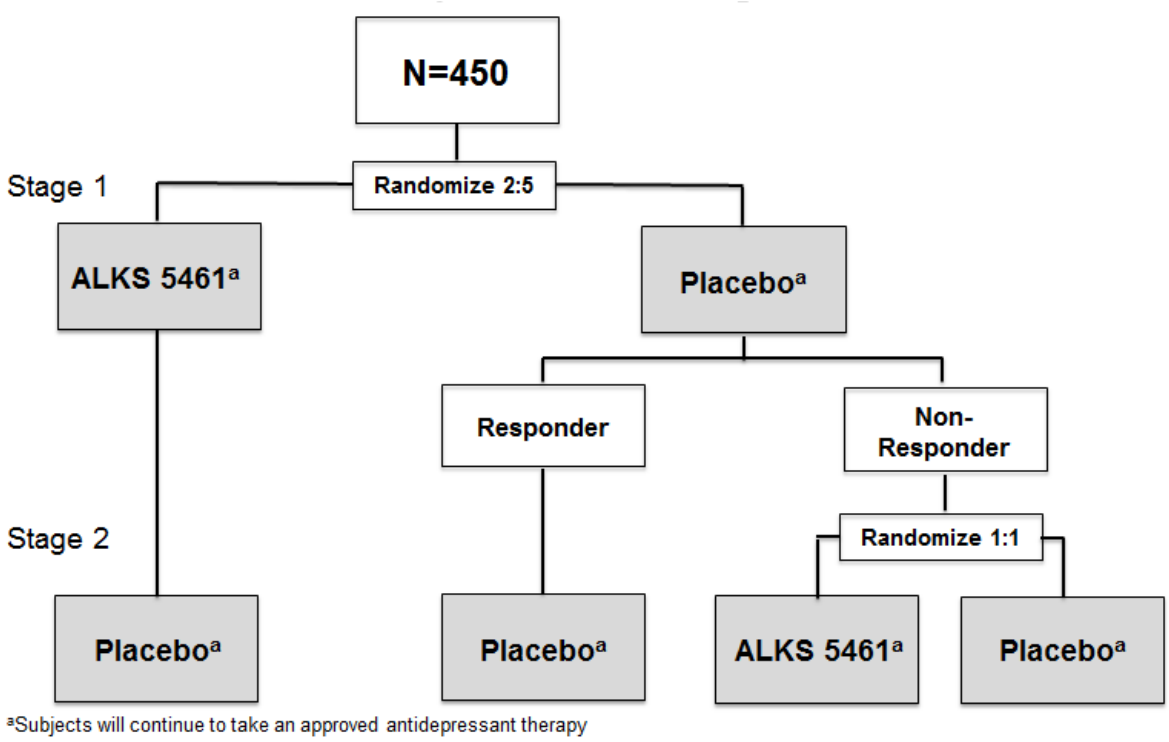
At Visit 7, response to treatment will be calculated electronically based on Montgomery Åsberg Depression Rating Scale (MADRS) score change from baseline (Visit 2) to the end of Stage 1 (Visit 7). Subjects in the Stage 1 placebo group will be categorized as either placebo responders or placebo nonresponders. The criteria for placebo nonresponders is defined in Unmasked Addendum Amendment 2.0.

Subjects who fail to meet nonresponder criteria will be categorized as placebo responders.

Subjects categorized as placebo nonresponders will be rerandomized in a 1:1 ratio to ALKS 5461 2/2 or placebo for 6 weeks in Stage 2. Subjects categorized as placebo responders will not be rerandomized and will remain on placebo for 6 weeks in Stage 2. Subjects who received ALKS 5461 2/2 in Stage 1 will be switched to placebo for 6 weeks in Stage 2. All subjects will continue on the same background ADT as Stage 1.

A study flow diagram is provided in Figure 2.

Figure 2: Study Flow Diagram



1.5. Safety Follow-up Period

Subjects who complete Stage 2 (Visit 13) or who prematurely discontinue during either Stage 1 or 2 should return to the clinic 1 week later for a Safety Follow-up Visit (Visit 14).

1.6. Criteria for Evaluation

Efficacy:

Primary Efficacy Endpoint:

- MADRS-10 score change from baseline to the end of treatment period

Secondary Efficacy Endpoints:

- Average of the differences in change from baseline at each Week from Week 3 through the end of treatment period between ALKS 5461 vs placebo in MADRS-10
- MADRS response, defined as a ≥50% reduction in MADRS-10 score from baseline to the end of treatment period
- MADRS remission, defined as MADRS-10 score ≤10 at the end of treatment period

Exploratory Endpoints:

- Change over time in Clinical Global Impression-Severity (CGI-S) scores
- Absolute Clinical Global Impression-Improvement (CGI-I) scores over time

- Change over time in Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) scores
- Change over time in Brief Pain Inventory-Short Form (BPI-SF) scores
- Change over time in Snaith-Hamilton Pleasure Scale (SHAPS) scores
- Change over time in Connor-Davidson Resilience Scale (CD-RISC-25) scores

Safety and Tolerability:

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

- Adverse events (AEs)
- Clinical laboratory parameters (chemistry, hematology, and urinalysis)
- Vital signs
- Weight
- Electrocardiogram (ECG) parameters
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Clinical Opiate Withdrawal Scale (COWS)

2. SAMPLE SIZE AND STATISTICAL POWER CONSIDERATION

Approximately 450 subjects are planned to be randomized in Stage 1 to have approximately 200 subjects rerandomized to treatment in Stage 2. This will provide at least 80% power to show superiority for ALKS 5461 2/2 compared to placebo at the two-sided alpha level 0.05, for the primary endpoint, assuming an effect size of at least 0.20 in Stage 1, 0.44 in Stage 2 and 0.32 overall (average of Stage 1 and Stage 2); and a standard deviation (SD) of 8.5 for MADRS-10 scores.

3. DATA ANALYSIS

3.1. Study Population

3.1.1. Definition of Analysis Populations (Analysis Sets)

3.1.1.1. Safety Populations

The primary safety populations for evaluation of safety of ALKS 5461 2/2 compared to placebo will be defined as follows and are illustrated in Figure 3.

Stage 1 Safety Population will consist of all randomized subjects who received at least one dose of study drug (placebo or ALKS 5461 2/2) during Stage 1.

Stage 2 Safety Population 1 will consist of Stage 1 placebo nonresponders who entered Stage 2 and received at least one dose of study drug (placebo or ALKS 5461 2/2) during Stage 2.

Subjects in the above safety populations will be analyzed by the treatment group defined by the actual treatment received.

Other safety populations will be defined as follows:

Stage 2 Safety Population 2 will include Stage 1 placebo responders who continued on placebo in Stage 2, and subjects randomized to ALKS 5461 2/2 in Stage 1 and switched to placebo during Stage 2. Summary of disposition will be presented for this population. Safety data will not be summarized for this population separately, but will be included in data listings.

Stage 2 Entire Safety Population will consist of subjects who received at least one dose of study drug (placebo or ALKS 5461 2/2) during Stage 2. This population comprises subjects in Stage 2 Safety Population 1 and subjects in Stage 2 Safety Population 2.

Subjects in Stage 2 Safety Population 2 will be summarized by the treatment group defined by the actual treatment received. Subjects in the Stage 2 Entire Safety Population will be summarized by the treatment sequence defined by the actual treatment received in each stage:

- Placebo nonresponder - ALKS 5461 2/2
- Placebo nonresponder - placebo
- Placebo responder - placebo
- ALKS 5461 2/2 - placebo

Post-discontinuation Safety Population will consist of subjects in the Stage 1 Safety Population who have at least one post-discontinuation measurement.

There will be three post-discontinuation safety populations, two will be used to analyze post-discontinuation emergent adverse events (PDEAEs, defined as AEs that started or worsened after last dose date plus 1 day), and the other will be to analyze COWS scores, grouped by the last treatment received in the study.

Stage 1 Post-discontinuation Safety Population for PDEAEs consists of subjects who were randomized and received at least one dose of study drug in Stage 1, grouped by the treatment received in Stage 1.

Stage 2 Post-discontinuation Safety Population for PDEAEs consists of subjects who were Stage 1 placebo nonresponders, grouped by the last treatment received in Stage 2, and met any of the following criteria:

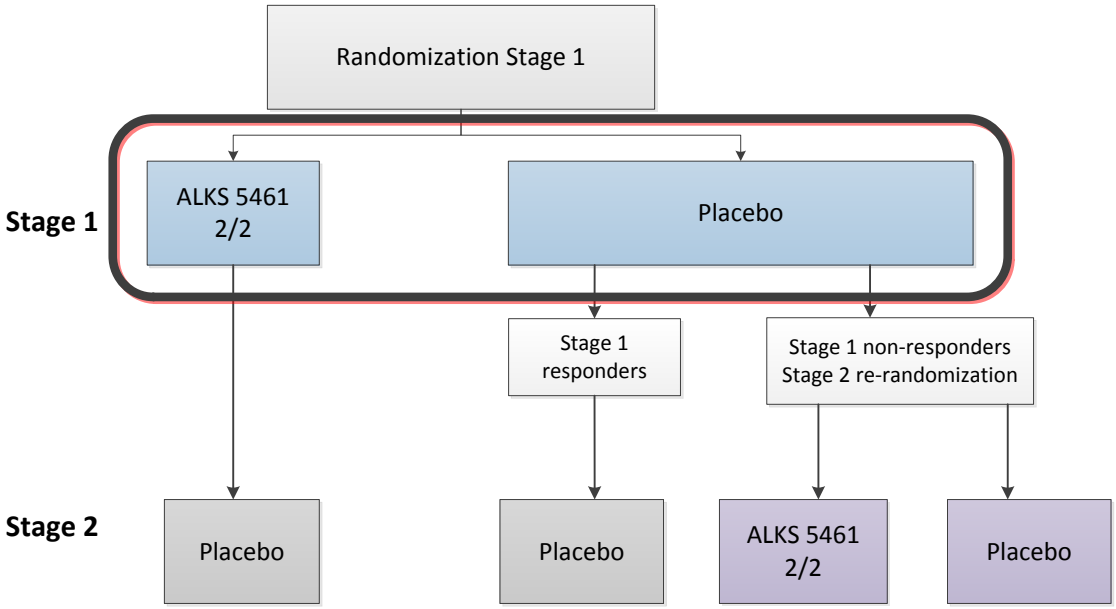
- Subjects who entered the Post-discontinuation period and had a Post-discontinuation Visit 14
- Subjects who did not enter the Post-discontinuation period, but had at least one PDEAE reported
- Subjects who died after either completing the treatment or having an Early Termination (ET) Visit

Stage 2 Post-discontinuation Safety Population for COWS consists of subjects who were Stage 1 placebo nonresponders, grouped by the last treatment received in Stage 2, and had at least one postbaseline COWS assessment (Visit 14) that occurred from >2 to 16 days post last dose of study drug.

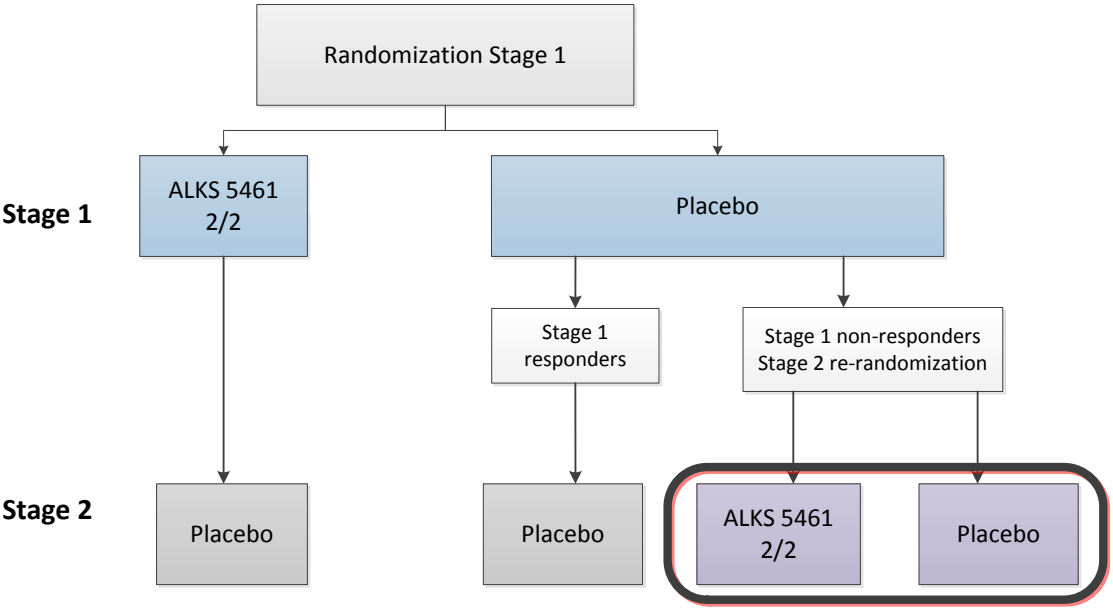
Prospective Lead-in Period Safety Population will consist of all PIR subjects who received at least one dose of ADT during the PLI Period.

Figure 3: Primary Safety Populations

Stage 1 Safety Population



Stage 2 Safety Population 1



3.1.1.2. Full Analysis Set Populations

The FAS populations defined by stage are illustrated in Figure 4.

Stage 1 FAS will consist of subjects who received at least one dose of study drug (placebo or ALKS 5461 2/2) during Stage 1 and had at least one postbaseline assessment of MADRS-10 score in Stage 1.

Stage 2 FAS will consist of all subjects who were randomized and entered Stage 2 and received at least one dose of study drug (placebo or ALKS 5461 2/2) during Stage 2 and had at least one postbaseline assessment of MADRS-10 score in Stage 2.

Subjects in the above populations will be analyzed by the treatment group into which they were randomized.

Subjects identified as duplicate subjects (see Section 3.1.3) will not be included in the FAS Populations.

Figure 4: Efficacy Populations

Stage 1 Full Analysis Set

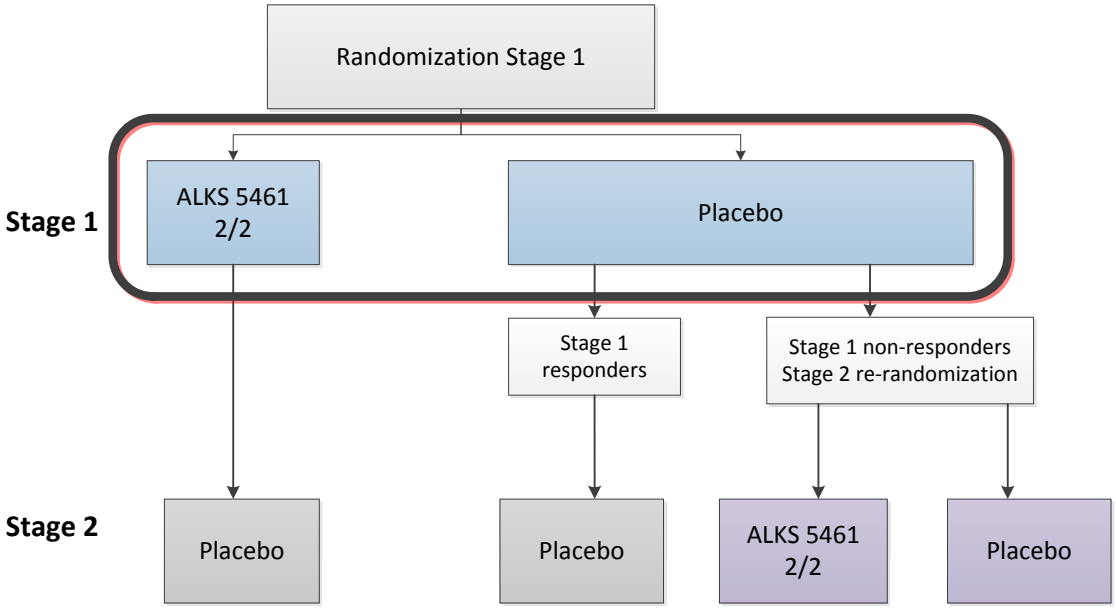
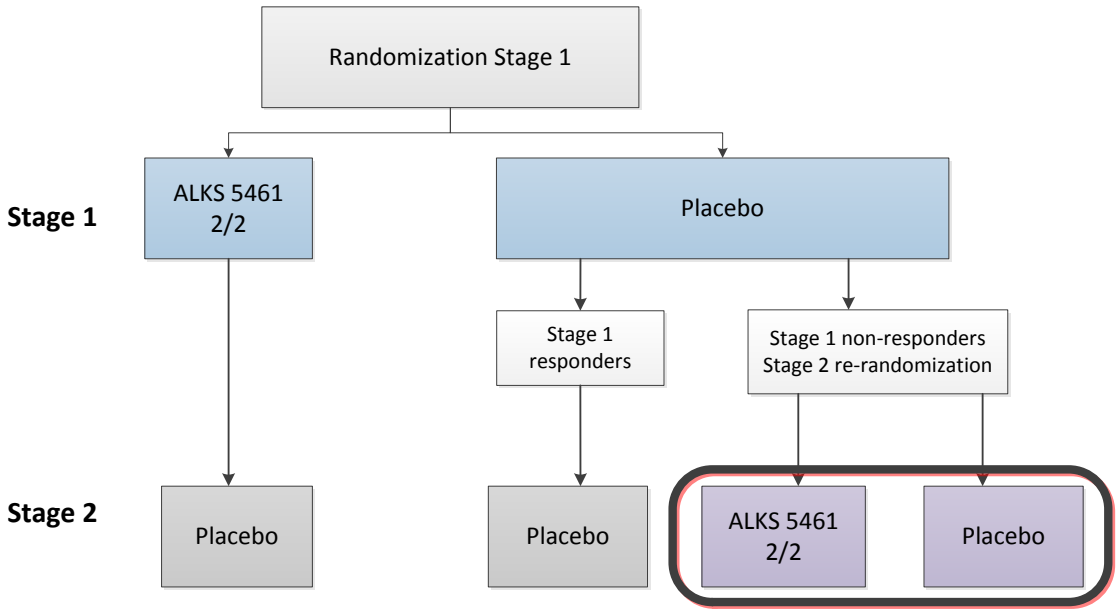


Figure 4: Efficacy Populations (Continued)

Stage 2 Full Analysis Set



3.1.1.3. Pharmacokinetic Population

Stage 1 Pharmacokinetic Population will consist of all subjects who had at least one measurable plasma concentration of any analyte in Stage 1.

Stage 2 Pharmacokinetic Population will consist of all subjects who had at least one measurable plasma concentration of any analyte in Stage 2.

3.1.2. Disposition

Subject disposition will be summarized for the following:

For Stage 1, based on randomized subjects:

- Subjects randomized
- Subjects in the Stage 1 Safety Population
- Subjects in the Stage 1 FAS Population
- Subjects who completed Stage 1 treatment period
- Subjects who discontinued the study during Stage 1
- Subjects in the Post-discontinuation Safety Population
- Subjects who entered Stage 2

For Stage 2, based on Stage 2 Safety Population 1:

- Subjects in the Stage 2 Safety Population 1

- Subjects in the Stage 2 FAS Population
- Subjects who completed treatment
- Subjects who completed study
- Subjects who discontinued the study during Stage 2
- Subjects in the Post-discontinuation Safety Population

For Stage 2, based on the Stage 2 Entire Safety Population (summarized by treatment sequence):

- Subjects in the Stage 2 Entire Safety Population
- Subjects who completed the Stage 2 treatment period
- Subjects who completed the study
- Subjects who discontinued the study during Stage 2
- Subjects in the Post-discontinuation Safety Population

Disposition will be summarized by Stage 1 treatment group in Stage 1, and by Stage 2 treatment group in Stage 2. For subjects who prematurely discontinue from study, the reasons for discontinuation, as recorded on disposition page, will be presented.

Subjects completing Stage 1 treatment period are defined as those who have assessments at Visit 7. Subjects completing the treatment or completing the study are those with completion indicated on the disposition page in the case report form.

In addition, disposition over the entire study will be summarized based on the treatment group subjects were assigned to when the disposition event occurred. Furthermore, disposition over the PLI period, based on the PLI Period Safety Population, will also be provided.

Cumulative discontinuation rates will be provided by stage, by visit and by treatment arm.

Supporting listings will be provided for subjects who enrolled in the PLI period, as well as for all randomized subjects.

3.1.3. Protocol Deviations

Subjects with major protocol deviations who fall into the following categories will be summarized by treatment group for each stage, along with supportive listings for each category:

- Informed Consent - Informed consent not obtained prior to assessments
- Violation of Enrollment Criteria - Subjects entered into the study even though they did not meet the eligibility criteria, including previous participation in the current study or another study in the FORWARD program and receipt of investigational drug, etc.
- Prohibited Concomitant Medications - Use of a prohibited concomitant medication that may affect either efficacy or safety, including changes in ADT prescription or dosing during the treatment period

- Nonadherence with Study Treatment - Lack of adherence defined as taking less than 70% or more than 130% of the protocol-specified amount of study drug during the subject's study participation
- Randomization or Dosing Errors – Includes randomization errors and significant dosing errors
- Improper Collection of Primary Efficacy Assessment - MADRS assessment conducted by a rater not certified for the ALK5461-217 study or other improper collection of MADRS
- Other - GCP violations or other unanticipated deviations not included in the categories above that could potentially affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects

Duplicate subjects include subjects who enrolled in multiple studies or multiple times in the same study, or other concurrent studies, despite clear instruction that prior participation is exclusionary per Study Protocol. These subjects put themselves at greater safety risk with inaccurate medical information misrepresenting disease symptoms and medical history to enroll more than once. These subjects violate the consent letter and spirit of the protocol regarding multiple participations (exclusion criteria 23 and 24). The data collected on these subjects are unreliable and are likely to misinform and adversely influence the interpretation of study results.

During the conduct of this study, data (eCRF and other sources) will be reviewed to identify duplicate subjects and sites will be contacted to investigate and confirm duplicate enrollment. Upon confirmation, duplicate subjects will be prohibited from further participation in the study and will be discontinued from the study for exclusion criterion 2. Details of the procedure to be followed are summarized in ALKS 5461 Protocol Deviation Process.

Data from these subjects will be included in the safety analyses, but excluded from the efficacy analyses.

3.2. Demographic and Baseline Characteristics

Demographics and other baseline characteristics (eg, age, gender, race, primary race, ethnicity, region [United States (US), non-US], HIR or PIR, duration of current MDE, current ADT, lifetime number of MDEs, lifetime number of antidepressants, number of ADT failures within the current MDE, total lifetime ADTs failed, ADT Class for current MDE, benzodiazepines (BDZ) use, opioid use, H1 antagonist use, weight, height, and body mass index [BMI]) at randomization (Stage 1 baseline Visit 2) will be summarized for the following populations:

- Stage 1 Safety Population by Stage 1 treatment group
- Stage 2 Safety Population 1 by Stage 2 treatment group

Medical and psychiatric history (coded by MedDRA) will be summarized by Stage 1 treatment group using the number and percentage of subjects who reported each category for the Stage 1 Safety Population as following:

- By System Organ Class and Preferred Term
- By Preferred Term in decreasing frequency

Baseline efficacy variables (MADRS-10, CGI-S, HAM-A, Q-LES-Q-SF, BPI-SF, SHAPS, and CD-RISC-25) will be summarized by Stage 1 treatment group for the Stage 1 FAS at randomization baseline at Visit 2, and summarized by Stage 2 treatment group for the Stage 2 FAS at rerandomization baseline at Visit 7 to assess the comparability of the treatment groups.

Continuous variables will be summarized by number of subjects, mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects in each category. Categories for missing data will be provided as necessary.

Demographic and baseline characteristic listings will be provided for all subjects.

3.3. Prior and Concomitant Medications

Prior medications are defined as medications taken prior to the first dose of study drug. Concomitant medications are defined as medications taken during the period between the first dose date to the last dose date of study drug, inclusive. All medications, as documented by the Investigator, will be coded using the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) drug dictionary version WHODRUG_C / 171E+H/ CMCODE.

Prior medications and concomitant medications will be summarized by ATC code and preferred term, by preferred term, and by corresponding treatment group and overall for the Safety Population. Prior medications will be summarized by Stage 1 treatment group for the Stage 1 Safety Population. Concomitant medications will be summarized by treatment group in each stage as follows: concomitant medications that were taken during the period between the first dose date to the last dose date in Stage 1, inclusive, will be summarized by Stage 1 treatment group based on the Stage 1 Safety Population; concomitant medications that were taken during the period between the first dose date to the last dose date in Stage 2, inclusive, will be summarized by Stage 2 treatment group based on Stage 2 Safety Population 1.

In addition, the concomitant ADTs by ADT class (selective serotonin reuptake inhibitor [SSRI], and serotonin-norepinephrine reuptake inhibitor [SNRI) and preferred term will be summarized similarly.

Summary tables for benzodiazepine use, opioid use, and sedating H1 antagonist use (prior medication/concomitant medication) by preferred term will be summarized, respectively.

All reported medications will be listed. A list of subjects taking ADTs, benzodiazepines (BDZ) and BDZ-like drugs, opioids, and sedating H1 antagonists will be provided.

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 6.4.

3.4. Treatment Adherence Rate and Extent of Exposure

Treatment adherence to the daily dosing schedule of the study drug is measured as the rate of actual number of doses taken compared to intended number of doses to be taken. Percentage of treatment adherence will be calculated for study drug during the 5-week treatment period in Stage 1 and during the 6-week treatment period in Stage 2 as follows:

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

Duration of treatment of study drug is defined as the number of days from the date of the first dose of study drug taken to the date of the last dose taken, inclusive, for the relevant period.

Treatment adherence and exposure will be summarized as follows:

- During Stage 1 for Stage 1 Safety Population
- During Stage 2 for Stage 2 Safety Population 1

Treatment adherence and exposure to study drug will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). In addition, treatment adherence rate (rounded to the nearest whole number) will be categorized as <70%, ≥70 to 79%, ≥80 to 89%, ≥90% to 100%, >100% to 110%, >110% to 120%, and >120%.

The exposure to ADT will be summarized by ADT class (SSRI, SNRI, and other) and preferred term using descriptive statistics in a similar fashion. In addition, descriptive statistics of mean daily dose of ADT will be summarized by ADT class and preferred term for each stage.

3.5. Efficacy Analyses

3.5.1. Primary Efficacy Endpoints

The primary efficacy endpoint is:

- MADRS-10 score change from baseline to the end of treatment period (Week 5 for Stage 1, Week 6 for Stage 2)

The MADRS-10 score is the sum of all 10 items and ranges from 0 to 60.

Analysis for the primary efficacy endpoint will be performed using a mixed model for repeated measures (MMRM) to evaluate changes from baseline in each stage. The primary efficacy analysis will be based on the combined estimates from Stage 1 and Stage 2 using MMRM.

The estimate for Stage 1 will be the change from the baseline to end of Week 5 and the estimate for Stage 2 will be the change from baseline to the end of Week 6.

3.5.2. General Consideration

Efficacy endpoints will be evaluated during the defined treatment period. The entire 11 week treatment period is divided into two stage-specific treatment periods. The treatment period for Stage 1 is defined as the period spanning from the Stage 1 baseline (Visit 2) to the Stage 1 Week 5 (Visit 7). The treatment period for Stage 2 is defined as the period spanning from the Stage 2 baseline (Visit 7) to the Stage 2 Week 6 (Visit 13).

Baseline for Stage 1 will be defined as the last nonmissing observation on or before the date of Visit 2. Baseline for Stage 2 will be defined as the last non-missing observation on or before the date of Visit 7.

For continuous endpoints with repeated postbaseline measurements, a MMRM will be used for the analysis of changes from baseline for each stage.

Sensitivity analyses using the delta-adjusted pattern mixture model (PMM), analysis of covariance (ANCOVA) with last observation carried forward (LOCF) approach, and alternative stage-specific weights for combined MMRM analysis will be conducted for the primary efficacy endpoint (see Section 3.5.3).

Using LOCF, a missing value at a visit will be imputed using the value from the most recent postbaseline visit within each stage, and the baseline value will not be carried forward to any postbaseline visit. The LOCF method will be used for efficacy endpoint total score or subscale score only; individual item scores will not be carried forward. For efficacy endpoints with a total score or subscale score derived from individual items, the postbaseline total or subscale will be imputed using the value from the most recent postbaseline visit; individual item score will not be carried forward. The derivation of the total score and subscale score are provided in Section 6.2.

The overall treatment effect and associated standard error will be obtained from the stage-specific treatment effect estimates and standard errors, and the Wald test will be used to test the overall treatment effect. Stage-specific MMRM estimates and standard errors will be combined using equal weights to obtain the overall estimates and associated standard error across the two stages.

For derived binary endpoints (ie, MADRS response and remission), normal approximation to binomial distributions will be used to obtain the difference in rates between active group and placebo by visit for each stage. The LOCF method will be used for imputation prior to the categorization of the treatment responder or remission status. The stage-specific rate differences and standard errors will be combined using equal weights to obtain the overall difference in responder or remission rate and corresponding standard error across the two stages.

In addition, descriptive statistics will be provided for all efficacy variables by visit and Stage 1 and Stage 2 treatment sequence throughout the entire study based on the Combined Stage FAS.

Unless stated otherwise, all statistical hypothesis tests will be two-sided with α=0.05 and 95% confidence intervals (CIs), will be two-sided, and will be set at an alpha of 0.05. Source data used for the summary tables and statistical analyses will also be listed on the subject level.

3.5.2.1. Pooling of Centers

A five level variable for geographic region will be included in the statistical model. The five level categorical region variable representing geographic region will include 1 category for non-US and 4 categories for US site region (Table 1). The definition of the 4 US categories is based on the United States (US) Census Bureau regions with the inclusion of Puerto Rico in the Northeast category. Although Puerto Rico is not included in one of the US Census Bureau Regions, inclusion in the Northeast category is consistent with another established geographical classification system, the standard federal regions established by US Office of Management and Budget.

Table 1: The United States Census Bureau Regions

Category Used in MMRM Model	Census Bureau Regions	Definition
1	Northeast	Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, Pennsylvania, Puerto Rico
2	Midwest	Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota
3	South	Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, District of Columbia, West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma, Texas
4	West	Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming, Alaska, California, Hawaii, Oregon, Washington
5	Non-US	Australia

3.5.2.2. Examination of Subgroups

The following subgroups will be examined for the primary efficacy endpoints:

- Sex (male, female)
- Age (<55 years, ≥55 years)
- Race (White, all other races)
- Duration of current MDE (≤6 months, >6 months)
- Number of ADT failures in the current MDE at randomization (2, >2)
- ADT type (SSRI, SNRI, other)
- Region (US [including Puerto Rico], Non-US)
- MADRS-10 at randomization (<30, ≥30)
- Subject type (HIR, PIR)

The primary analysis for the primary efficacy endpoint will be repeated by subgroup. In addition, forest plots of the least squares mean difference, along with 95% CIs, from primary analysis (as described in Section 3.5.3.1) of the change from baseline to the end of treatment period in MADRS-10 score, as well as combined across stages, between ALKS 5461 and placebo, will be provided by the subgroup factors listed above. No p-values will be provided as the study is not powered to detect treatment effects within subgroups.

3.5.3. Efficacy Analysis for Primary Efficacy Endpoint

3.5.3.1. Primary Efficacy Analysis

Analysis for the primary efficacy endpoint will be performed using a MMRM to evaluate changes from baseline in each stage. The model will include variables for treatment group, visit, treatment group-by-visit interaction, and region as categorical fixed effects. Baseline value and baseline-by-visit interaction will be included as covariates in the model. The comparison (ALKS 5461 2/2 vs placebo) will be made using the combined weighted least squares mean difference from Stage 1 and Stage 2. These estimates, along with the corresponding 95% CIs, will be reported.

An unstructured covariance matrix will be used to model the within-subject variability. The Kenward-Roger approximation will be used to adjust the denominator degrees of freedom (Kenward and Roger 1997). The analysis will be performed based on all observed postbaseline scores without any imputation of missing data. In the case when the MMRM fails to converge using an unstructured covariance matrix in any stage, a less stringent covariance matrix (eg, autoregressive 1) will be used. The same covariance matrix structure will be used across all treatment stages.

The primary efficacy endpoint will be analyzed for each stage separately. The comparison of treatment effects between the ALKS 5461 2/2 and the placebo treatment group for each of the three primary endpoints in the two stages will be combined using the prespecified equal weights of 0.5 and 0.5 for Stage 1 and Stage 2. Specifically, let $\theta^{(1)}$ and $\theta^{(2)}$denote the treatment effects between the ALKS 5461 2/2 and placebo treatment group in Stage 1 and Stage 2, respectively, and $\hat{\theta}^{(1)}$and $\hat{\theta}^{(2)}$denote the corresponding point estimates based on the MMRM analyses.

These comparisons will be made through the following hypothesis of no treatment effect in both stages:

$$H_0: w\theta^{(1)} + (1-w)\theta^{(2)} = 0 \quad \text{vs} \quad H_a: w\theta^{(1)} + (1-w)\theta^{(2)} > 0.$$

The weighted test statistic for testing the above hypothesis is

$$\frac{w\hat{\theta}^{(1)} + (1-w)\hat{\theta}^{(2)}}{\sqrt{w^2\mathrm{Var}\left(\hat{\theta}^{(1)}\right) + (1-w)^2\mathrm{Var}\left(\hat{\theta}^{(2)}\right)}}, \text{where } w = 0.5.$$

The SPCD analysis *P*-value is obtained by referring the above weighted test statistic to the standard normal distribution under the null hypothesis of no treatment effect in both stages. The validity of the weighted test statistic has been established (Chen et al, 2011).

The hypothesis of no treatment effect in both stages, for an endpoint will be rejected if the SPCD analysis two-sided *P*-value is <0.05.

In addition, descriptive statistics of MADRS-10 and individual item scores, and changes from baseline in MADRS-10 and individual item scores at each visit by treatment group for each stage will be presented based on observed data.

The least squares mean change from baseline in MADRS-10 total score (± standard error) over time will be provided graphically by Stage 1 treatment group based on the Stage 1 FAS, and Stage 2 treatment group based on Stage 2 FAS.

Graphical subject profiles of MADRS-10 change from baseline by stage, by visit and treatment arm will be provided for all randomized subjects by stage to evaluate whether there is evidence of a trend in the profile for those who discontinued vs. those who completed the study across both treatment arms.

3.5.3.2. Effect Size

The effect size is defined as the difference in the reduction from baseline between active and placebo treatment groups divided by the SD, and is expressed as *Hedges' g* of all three primary efficacy endpoints using the following formula:

$$Hedges'g = \frac{M_1 - M_2}{SD_{pooled}}$$

Where M_1 denotes the mean reduction from baseline of the active treatment group, M_2 denotes the mean reduction from baseline of the placebo group, and SD_{pooled} denotes the pooled SD. Standard deviation will be calculated from model standard error with the following formula:

$$SD = se * \sqrt{n}$$

Where *n* is the sample size in Stage 1 and Stage 2 for the given treatment group and *se* is the model derived standard error associated with the least-squares mean derived from the MMRM model.

The pooled SD will then be derived with the following formula:

$$SD_{pooled} = \sqrt{\frac{(n_1 - 1) * SD_1^2 + (n_2 - 1) * SD_2^2}{n_1 + n_2 - 2}},$$

where n_1 and n_2 are the sample size from each treatment group (active vs placebo) and SD_1 and SD_2 are the associated SDs.

Hedges' g will be estimated for each stage of the treatment period first, assuming *Hedges' g* is asymptotically independent between the two stages. The combined-stage effect size is defined as the average of the stage-specific effect sizes, and the combined-stage effect size is derived using the following formula

$$\text{Combined - stage effect size} = \frac{w\hat{\theta}^{(1)} + (1-w)\hat{\theta}^{(2)}}{\sqrt{w^2 \text{Var}(\hat{\theta}^{(1)}) + (1-w)^2 \text{Var}(\hat{\theta}^{(2)})}},$$

where w=0.5, and $\hat{\theta}^{(1)}$ and $\hat{\theta}^{(2)}$ refer to the effect sizes for the two stages.

3.5.3.3. Sensitivity Analysis

To assess the robustness of the primary MMRM results with equal weights for the primary efficacy endpoint, sensitivity analyses will be conducted using three approaches, the delta adjusted PMM, ANCOVA with LOCF, and alternative stage-specific weights for combined MMRM analysis approach, as described below. Additional sensitivity analysis may be performed to further explore the data.

Since the MMRM is valid only under the missing at random assumption, the PMM approach, which assumes missing not at random will be used as a sensitivity analysis. In particular, the delta-adjusted PMM, which incorporates the clinical assumption that subjects who discontinue at a given time point would have, on average, their unobserved efficacy score worsen by some amount (δ) compared with the observed efficacy score of subjects on the same treatment arm who continue to the next time point will be used. A sequential regression-based multiple imputation (MI) procedure will be used to incorporate the assumption and to allow uncertainty in the imputations to be reflected appropriately in the analysis.

The imputation model will include the measurement at the current time point as the response variable, and the measurements at the previous time points and the baseline as covariates. The imputation will be performed separately for each treatment group. Twenty imputations will be carried out. For each imputed data set, an ANCOVA model will be fitted to the change from baseline to the end of the treatment period in MADRS-10 scores with treatment as a factor and baseline value as a covariate to obtain the treatment effect estimate and standard error.

The imputation and ANCOVA model fitting will be done for each stage and an overall weighted estimate of treatment effect and associated standard error will be obtained from the stage-specific treatment effect estimates and standard errors with equal weights for the two stages. Rubin's rule will be used to combine the treatment effect estimates and standard errors across imputations. The shift parameters in the two stages to be used in the sensitivity analysis are (0, 0), (0.6, 0.2), (1.5, 0.5), and (2, 1). In particular, the shift of (0, 0) corresponds to multiple imputation under the missing at random assumption.

The ANCOVA using LOCF will also be conducted as a sensitivity analysis. The ANCOVA model will include the change from baseline to the end of the treatment period in MADRS-10 scores as a dependent variable, treatment group as a factor, and baseline value as a covariate. The overall weighted estimate of treatment effect and associated standard error will be obtained from the stage-specific estimates and standard errors with equal weights for the two stages.

Descriptive statistics for MADRS-10 score and change from baseline in MADRS-10 scores at each visit by treatment group will also be presented based on the LOCF approach.

In addition, the treatment effect estimates based on the MMRM analyses in the two stages will be combined using weights proportional to the inverse of the associated variance estimates. Specifically, the weight for the Stage 1 treatment effect estimate is

$$w = \frac{1/\mathrm{Var}(\hat{\theta}^{(1)})}{1/\mathrm{Var}\left(\hat{\theta}^{(1)}\right) + 1/\mathrm{Var}(\hat{\theta}^{(2)})} = \frac{\mathrm{Var}(\hat{\theta}^{(2)})}{\mathrm{Var}(\hat{\theta}^{(1)}) + \mathrm{Var}(\hat{\theta}^{(2)})},$$

and the weight for the Stage 2 treatment effect estimate is

$$1 - w = \frac{\mathrm{Var}\left(\hat{\theta}^{(1)}\right)}{\mathrm{Var}(\hat{\theta}^{(1)}) + \mathrm{Var}\left(\hat{\theta}^{(2)}\right)}.$$

The resulting linear combination test statistic is asymptotically normal due to the independence between the treatment effect estimate and the associated variance estimate within each stage.

An additional sensitivity analysis will employ bootstrap methodology for empirical estimation and inference of ALKS 5461 vs. placebo difference in MADRS-10 change from baseline. Results obtained from this approach (mean, standard error, empirical 95% CI and associated p-value using 10,000 replicates) will be compared to those obtained from normal-based approach used in the primary analysis. In additional to the density plots of bootstrap treatment effects will be provided displaying ALKS 5461 vs. Placebo difference (x-axis) by density (y-axis).

3.5.3.4. Supportive Analysis for Primary Endpoints

As a supportive analysis, additional MMRM analyses will be conducted for the primary efficacy endpoint by including a more restricted nonresponder criterion of MADRS-10 score >15 at Visit 7 and <40% reduction in MADRS-10 score from Visit 2 to Visit 7.

To evaluate the assumption of homogeneous variances across treatment arms two approaches will be used: (1) density plots will display change from baseline in MADRS-10 score by stage and treatment arm (x and y-axes will be change from baseline and density, respectively, where the sum of the area under the density plot for both treatment groups will equal one); and (2) a tabular display will present correlation (measured using the Pearson correlation coefficient) by visit and treatment arm within each stage for MADRS-10 scores.

3.5.4. Efficacy Analysis for the Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Average of the differences in change from baseline at each Week from Week 3 through the end of treatment period between ALKS 5461 vs placebo in MADRS-10
- Proportion of subject who demonstrated MADRS treatment response, defined as a ≥50% reduction in MADRS-10 score from randomization baseline to the end of treatment
- Proportion of subjects who achieved remission, defined as MADRS-10 score ≤10 at the end of treatment

The statistical testing of the three secondary endpoints will be done using a hierarchical testing approach, with the order of testing being the rank order in which the secondary endpoints are listed, only if the primary efficacy endpoint is significant at two sided α=0.05.

The secondary hypotheses will be evaluated using a fixed sequence approach to adjust for multiple comparisons.

Step 1: Testing ALKS 5461 2/2 relative to placebo using average of the differences in change from baseline at each Week from Week 3 to the end of treatment in MADRS-10. The average of the differences in change from baseline at each Week from Week 3 to the end of treatment in MADRS-10 will be tested using the combined effect of Stage 1 and Stage 2. Proceed to Step 2, only if significant at two-sided α=0.05.

Step 2: Testing ALKS 5461 2/2 relative to placebo using MADRS treatment response. The MADRS treatment response will be tested using combined effect of Stage 1 and Stage 2. Proceed to Step 3, only if significant at two-sided α=0.05.

Step 3: Testing ALKS 5461 2/2 relative to placebo using remission. The remission will be tested using the combined effect of Stage 1 and Stage 2.

3.5.4.1. Average of the Differences in Change from Vaseline at Each Week from Week 3 to the End of Treatment Period in MADRS-10

For this secondary endpoint, the estimate for Stage 1 will be the average of three time points (ie, the average of the change from baseline to Week 3, change from baseline to Week 4, and change from baseline to Week 5). The estimate for Stage 2 will be the average of four time points (ie, the average of the change from Baseline to Week 3, change from baseline to Week 4, change from baseline to Week 5 and change from baseline to Week 6).

Analysis for this secondary efficacy endpoint will be performed using the same method as described for the primary efficacy analysis.

3.5.4.2. Proportion of MADRS Treatment Responders at the End of Treatment Period

A MADRS treatment responder is defined as a subject with a ≥50% reduction in MADRS score from baseline.

The proportion of responders in each treatment group will be estimated using subject response (observed or imputed using LOCF if missing) at the end of the treatment period in each stage. A comparison between ALKS 5461 2/2 vs placebo will be conducted at the end of the treatment period in each stage, and the estimated difference in rates with 95% CIs and *P*-value will be reported for the comparison based on normal approximation to binomial distribution.

Specifically, let

$$p_1 = \Pr(\text{drug response in Stage 1}), q_1 = \Pr(\text{placebo response in Stage 1}),$$

$$p_2 = \Pr(\text{drug response in Stage 2} \mid \text{placebo non-responder in Stage 1}), \text{ and}$$

$$q_2 = \Pr(\text{placebo response in Stage 2} \mid \text{placebo non-responder in Stage 1}).$$

The treatment effect in Stage 1 is, $\Delta_1 = p_1 - q_1$,

and the treatment effect in Stage 2 is $\Delta_2 = p_2 - q_2$.

Let $\hat{p}_j = \frac{x_j}{n_j}$ *and* $\hat{q}_j = \frac{y_j}{m_j}$ denote the estimated proportions of responders for the drug and placebo groups in stage *j* (*j* = 1, 2) respectively. The estimated rate difference in stage *j* is $\hat{\Delta}_j = \hat{p}_j - \hat{q}_j$ and the associated variance estimate is:

$$\text{Var}(\hat{\Delta}_j) = \frac{\hat{p}_j(1-\hat{p}_j)}{\hat{n}_j} + \frac{\hat{q}_j(1-\hat{q}_j)}{\hat{m}_j}.$$

Based on normal approximation to binomial distribution, the 95% CI for $\hat{\Delta}_j$ is:

$$\hat{\Delta}_j \pm 1.96\sqrt{\text{Var}(\hat{\Delta}_j)},$$

and the *P*-value is obtained be referring the test statistic,

$$\frac{\hat{\Delta}_j}{\sqrt{\text{Var}\,(\hat{\Delta}_j)}},$$

to the standard normal distribution under the null hypothesis of no treatment effect in stage j for $j = 1, 2$.

The comparison of treatment effect between the ALKS 5461 2/2 and placebo treatment groups in the two stages will be combined using the prespecified equal weights of 0.5 and 0.5 for Stage 1 and Stage 2. Specifically, let Δ_1 and Δ_2 denote the treatment effects between ALKS 5461 2/2 and placebo in Stage 1 and Stage 2, respectively, and $\hat{\Delta}_1$ and $\hat{\Delta}_2$ denote the corresponding point estimates. The weighted test statistic is:

$$\frac{w\hat{\Delta}_1+(1-w)\hat{\Delta}_2}{\sqrt{w^2\text{Var}(\hat{\Delta}_1)+(1-w^2)\text{Var}(\hat{\Delta}_2)}}, \text{ where } w = 0.5.$$

The *P*-value will be obtained by referring the above weighted test statistic to the standard normal distribution under the null hypothesis of no treatment effect in both stages. For binary efficacy endpoints of MADRS responder and remission for this study, the validity of the above weighted test statistic relies on the independence of treatment effect estimates in the two stages, which is shown in Appendix 1.

The proportion of MADRS treatment responders will be summarized at each visit by treatment group for each stage based on data with LOCF imputation. In addition, the bar graphs of the proportion of MADRS treatment responders will be provided by treatment group over time for each stage. The bar graphs for placebo-adjusted responder rate (ie, difference in responder rate between ALKS 5461 2/2 and placebo) during the treatment period will also be provided for each stage, as well as combined across stages.

3.5.4.3. Proportion of Subjects Achieving Remission at the End of Treatment Period

Remission is defined as a subject with a MADRS score ≤10. The remission analysis method will be the same as described for the MADRS responder analysis.

3.5.5. Efficacy Analysis for the Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

- Change from randomization baseline to the end of the treatment period in CGI-S scores
- Absolute CGI-I scores from randomization baseline to the end of the treatment period
- Change from randomization baseline to the end of the treatment period in the following efficacy measurements:
  - Q-LES-Q-SF scores
  - BPI-SF scores
  - SHAPS scores
  - CD-RISC-25 scores

For the efficacy endpoints listed above, analysis methods will be same as those describe for the primary analysis of the primary efficacy endpoints. In addition, descriptive statistics based on observed data will be provided by stage, by visit, and by treatment group for the the Stage 1 FAS and the Stage 2 FAS.

3.6. Safety Analysis

3.6.1. General Consideration

Safety and tolerability of ALKS 5461 will be assessed throughout the study based on AEs, vital signs, weight, laboratory test results (chemistry, hematology, and urinalysis), ECG results, COWS scores, and C-SSRS scores. Criteria for evaluation will include incidence of treatment-emergent AEs (TEAEs), AEs of special interest (AESIs), the change from baseline in continuous variables, categorical analysis of potentially clinically significant (PCS) values of laboratory results, weight, vital sign, and ECG parameters, and the rate of suicidal ideation and behavior based on the C-SSRS. Subjects will be included in the C-SSRS analysis if they have at least one postbaseline assessment. Subjects will be included in the COWS analysis if they have an adequate baseline, at least one postbaseline assessment, and at least 4 weeks of study drug exposure.

All safety analyses will be based on the safety populations defined in Section 3.1.1.1.

Safety periods to be evaluated and associated definitions of baseline are described below:

Stage 1 Treatment Period

The Stage 1 treatment period for AEs includes the interval between the date of Visit 2 and the last dose date plus 1 day, inclusive, for subjects who did not enter Stage 2; or the interval between the date of Visit 2 and the date of Visit 7 minus 1 day, inclusive, for subjects who entered Stage 2. The baseline for AEs is defined as all data collected prior to the date of Visit 2.

The Stage 1 treatment period for other safety endpoints covers the values collected at the baseline visit and the postbaseline visits throughout the Stage 1 treatment period starting from Visit 2 in Stage 1 to the last assessment visit date in Stage 1. The baseline for these other safety endpoints is defined as the last nonmissing value on or before the date of Visit 2.

Stage 2 Treatment Period

The Stage 2 treatment period for AEs includes the interval between the date of Visit 7 and the last dose date plus 1 day, inclusive. The baseline for AEs is defined as all data collected prior to Visit 7 for Stage 2 Safety Population 1.

The Stage 2 treatment period for other safety endpoints covers the values collected at the Stage 2 baseline visit and the postbaseline visits throughout the Stage 2 treatment period starting from Visit 7 in Stage 2 to the last assessment visit date in Stage 2. The Stage 2 treatment period will only be summarized for Stage 2 Population 1 and the baseline for these other safety endpoints is defined as the last nonmissing value on or before the date of Visit 7.

Post-discontinuation Safety Period

Only AEs and COWS scores will be summarized for the Post-discontinuation Safety population. Post-discontinuation labs, vital signs and ECGs will be included in the descriptive summaries for the Stage 1 and Stage 2 treatment periods.

For AEs, the Stage 1 Post-discontinuation Safety period is defined as the interval starting from the last dose date plus 2 days to the last study visit, inclusive, for early termination (ET) subjects during Stage 1, or starting from the date of Visit 7 to the last study visit, inclusive, for subjects who entered Stage 2.

For AEs, the Stage 2 Post-discontinuation Safety period is defined as the interval starting from the last dose date plus 2 days to the last study visit, inclusive.

For COWS scores, the Stage 2 post-discontinuation Safety period covers the values collected at Visit 13 through the post-discontinuation visit. The baseline for COWS assessments is the measurement at Visit 13.

The general approach to summarize safety endpoints is illustrated in Table 2. Details are described in the relevant sections.

All safety analyses will be based on observed data only; no missing values will be imputed. For the by-visit summary tables, the last assessment during the treatment period, defined as the value from the last scheduled postbaseline visit for the relevant treatment period, will also be included.

Table 2: Summary Approach for Safety Endpoints

Safety Population	Safety Period	Treatment to Summarize	Safety Endpoint
Stage 1 Safety Population	Stage 1 Treatment Period	Stage 1 Treatment	AE (including AESI)
Stage 1 Safety Population	Stage 1 Treatment Period and Post-discontinuation Safety Period Combined	Stage 1 Treatment	Lab/VS/ECG, PCS, C-SSRS
Stage 2 Safety Population 1	Stage 2 Treatment Period	Stage 2 Treatment	AE (including AESI)
Stage 2 Safety Population 1	Stage 2 Treatment Period and Post-discontinuation Safety Period Combined	Stage 2 Treatment	Lab/VS/ECG, PCS, C-SSRS
Stage 2 Entire Safety Population	Entire Study	Stage 1/Stage 2 Treatment Sequence	Lab/VS/ECG
Post-discontinuation Population	Post-discontinuation Safety Period	Last treatment[a]	PDEAE (including AESI), COWS (Stage 2 re-randomized)
Stage 1 Safety Population who were not re-randomized in Stage 2	Stage 2 Treatment Period	Last treatment in Stage 1	PDEAE (including AESI)

[a] Last treatment is the last treatment subjects received. That is, Stage 1 treatment group for subjects who did not enter Stage 2; or Stage 2 treatment group for subjects who entered Stage 2.

Abbreviations: ECG = electrocardiogram; Lab=laboratory results; VS=vital signs; PCS=potentially clinically significant; PDEAE=post-discontinuation emergent adverse events; AESI=adverse event of special interest; AE=adverse event; COWS= Clinical Opiate Withdrawal Scale; C-SSRS= Columbia-Suicide Severity Rating Scale

3.6.2. Adverse Events

Adverse events will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 20. The verbatim term will be included in the AE listings.

An AE will be considered a TEAE if it starts or worsens (if present at baseline) on or after baseline during the relevant safety period. Adverse events will be identified as emerging in the Stage 1 treatment period, Stage 2 treatment period, or Post-discontinuation Safety period. For the determination of the TEAEs during the Stage 1 treatment period and Stage 2 treatment period, AEs with the greatest severity before the baseline of the respective safety period will be used as the benchmark for comparison with the AEs occurring during the respective safety period. In addition, PDEAEs, defined as AEs that start or worsen after the last dose date plus 1 day, will also be summarized. For PDEAEs, the greatest severity before or on the last dose date plus 1 day will be used as the benchmark for the comparison of the AEs occurring during the Post-discontinuation Safety period.

All AEs will be listed by subject, but only TEAEs, serious AEs (SAEs), AEs leading to study discontinuation, and PDEAEs will be included in the summary tables. Summary tables will be produced for the Stage 1 treatment period and Stage 2 treatment period. For AEs leading to study discontinuation, the AEs will be summarized in the safety period by the treatment group the subjects were in when the discontinuation occurred.

An overview table, including the numbers of subjects with TEAEs, AEs leading to study discontinuation, SAEs, and study drug-related TEAEs will be provided for the Stage 1 treatment period and the Stage 2 treatment period.

The following summary tables will be produced for the Stage 1 treatment period and the Stage 2 treatment period:

- TEAEs by System Organ Class and Preferred Term
- TEAEs by Preferred Terms in decreasing frequency
- TEAEs by System Organ Class, Preferred Term, and severity
- TEAEs by System Organ Class, Preferred Term for drug-related TEAEs

In addition, an AE overview table and AEs by system organ class and preferred term will be summarized for PDEAEs based on the Stage 1/Stage 2 Post-discontinuation Safety population, by the last treatment group in which subjects were included for their respective stages.

An AE overview table and AEs by system organ class and preferred term will also be provided for AEs that started during the PLI period for the PLI Period Safety population. Furthermore, an AE overview table and TEAEs by system organ class and preferred term during the entire treatment period, defined as date of first dose up to the date of the last dose, will be summarized for the Stage 2 Safety population.

All AE tables will be sorted by System Organ Class in alphabetical order and then Preferred Term in decreasing frequency of the number and percentage of subjects in the ALKS 5461 2/2 treatment group.

A subject having the same AE (as determined by the coded MedDRA Preferred Term) more than once in a stage will be counted only once in the total number of subjects with that AE during the stage. Similarly, if a subject had more than one AE in a System Organ Class in a stage, the subject will be counted only once in the total number of subjects with the AE for that system organ class during the stage. 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.

All AEs will be included in the listings.

3.6.3. Deaths, Serious and Other Significant Adverse Events

The number and percentage of subjects with at least one SAE will be summarized by treatment group, System Organ Class, and Preferred Term for the Stage 1 treatment period and the Stage 2 treatment period. Adverse events leading to discontinuation will be summarized similarly and will be based on the the treatment group subjects were in when the discontinuation occurred. Supporting listings of SAEs and AEs leading to study discontinuations will be provided. Subjects who died during the study will also be listed.

3.6.4. Adverse Events of Special Interest

Adverse events of special interest (AESIs) will be summarized by Preferred Term and treatment group during the Stage 1 treatment period and the Stage 2 treatment period for the Safety population/Follow-up Safety population for any TEAEs or PDEAEs of special interest. The following summaries will be created for AESIs:

- TEAEs associated with abuse potential
- TEAEs potentially associated with dependence
- PDEAEs potentially associated with withdrawal
- TEAEs potentially associated with suicidal ideation and behavior
- TEAEs potentially associated with hypomania/mania
- TEAEs potentially associated with central nervous system (CNS) depression and sedation
- TEAEs potentially associated with respiratory depression
- TEAEs potentially associated with orthostasis/hypotension
- TEAEs potentially associated with hypersensitivity
- TEAEs potentially associated with hepatic effects

Treatment-emergent AEs potentially associated with abuse potential will be presented by *ad hoc* system organ class and preferred term, where *ad hoc* system organ class is manually classified by the Alkermes Medical Director as three categories: abuse behavior, euphoria-related, and non-specific.

Treatment-emergent AEs associated with dependence will be presented for subjects with any exposure, ≥4 weeks exposure, and <4 weeks exposure, respectively.

Post-discontinuation emergent AEs associated with withdrawal will be presented for subjects with any exposure, ≥4 weeks exposure, and <4 weeks exposure, respectively. Adverse events of special interest associated with withdrawal are PDEAEs that occur from >2 to 16 days post last dose, as this is the period during which physiological opioid withdrawal would be expected to present, based on the half-lives of both BUP and SAM.

Supportive listings will be provided for each AESI group. Narratives will be provided for clinically meaningful events within each AESI group.

3.6.5. Clinical Laboratory Parameters

Laboratory parameters will be presented in conventional (ie, US) units. Only scheduled laboratory parameters will be included in the summaries. All laboratory data, including unscheduled assessments, will be included in the listings.

Laboratory results (baseline and change from baseline) for chemistry and hematology parameters for each visit will be summarized by treatment group for the following populations and safety periods: the Stage 1 Safety population over the Stage 1 treatment period, Visit 8 (if any), and Post-discontinuation Safety period combined; Stage 2 Safety Population 1 over the Stage 2 treatment period and Post-discontinuation Safety period combined; and the Stage 1 and Stage 2 treatment sequence for the Stage 2 Entire Safety population over the entire study. For urinalysis, rate of abnormalities at any postbaseline visit will be summarized. In addition, the number and percentage of subjects with values considered PCS occurring at any postbaseline visit for select parameters will be summarized. The rate of abnormality of urinalysis and PCS summaries will be provided by treatment group for the Stage 1 Safety Population over the Stage 1 treatment period and Follow-up Safety period combined; and for Stage 2 Safety Population 1 over the Stage 2 treatment period and Post-discontinuation Safety period combined. For PCS, the summary will also be provided for the Stage 2 Safety population over the entire study.

Potentially clinically significant criteria for hematology, chemistry, and urinalysis parameters are presented in Table 3. The percentages will be calculated relative to the number of subjects with available non-PCS baseline values with respect to the specific criterion and at least one postbaseline assessment. The numerator is the total number of subjects with non-PCS baseline values and at least one postbaseline PCS value with respect to the specific criterion. Parameter order for summary tables and listings will be alphabetical. Supportive listings will present all values for a parameter for subjects with at least one PCS value for that parameter. Numbers and percentage of subjects with PCS values occurring at any postbaseline visit will be summarized by treatment group for the Stage 1 Safety population over the Stage 1 treatment period, for Stage 2 Safety Population 1 over the Stage 2 treatment period, and for the Stage 2 Safety population over the entire study period by the Stage 1 and Stage 2 treatment sequence.

In addition, the listing of subjects meeting Hy's Law, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3× ULN, along with total bilirubin ≥2× ULN and a nonelevated alkaline phosphatase (ALP) <2× ULN, with all values of relevant laboratory parameters will be provided.

Pregnancy and drug screening data will be listed.

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

Category	Parameter	Criteria
Hematology	Eosinophils	>1.0×10^3/μL
	Hematocrit	≤32% and 3 point decrease from baseline (Female) ≤37% and 3 point decrease from baseline (Male)
	Hemoglobin	≤9.5 g/dL (Female) ≤11.5 g/dL (Male)
	Leukocytes	≤2.8×10^3/μL ≥16×10^3/μL
	Neutrophils, Absolute	<1.5×10^3/μL
	Platelets	<75.1×10^3/μL ≥700×10^3/μL
Chemistry	Alanine Aminotransferase	≥3×ULN
	Albumin	<2.5 g/dL
	Alkaline Phosphatase	≥3×ULN
	Aspartate Aminotransferase	≥3×ULN
	Bicarbonate	<15 mmol/L >31 mmol/L
	Blood Urea Nitrogen (BUN)	>30 mg/dL
	Calcium	<8.2 mg/dL >12 mg/dL
	Chloride	≤90 mmol/L ≥118 mmol/L
	Creatine Phosphokinase	>3×ULN
	Creatinine	≥2 mg/dL
	Gamma Glutamyltransferase	≥3×ULN
	Glucose	<50 mg/dL >200 mg/dL
	HDL Cholesterol	≤30 mg/dL
	Lactate Dehydrogenase	>3×ULN
	LDL Cholesterol	≥160 mg/dL
	Phosphate	<2 mg/dL >5 mg/dL
	Potassium	<3 mmol/L >5.5 mmol/L
	Prolactin	>1×ULN

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

Category	Parameter	Criteria
Chemistry	Sodium	<130 mmol/L >150 mmol/L
	Total Bilirubin	≥2 mg/dL
	Total Cholesterol	>300 mg/dL
	Triglycerides	≥120 mg/dL (Female) ≥160 mg/dL (Male)
	Uric Acid	>9 mg/dL >8 mg/dL (Female) >10 mg/dL (Male)
Urinalysis	Glucose	at least 2+
	Protein	at least 2+

Abbreviations: BUN=blood urea nitrogen; HDL=high density lipoproteins; LDL=low density lipoprotein; ULN=upper limit of normal reference range

3.6.6. Vital Signs and Electrocardiogram

3.6.6.1. Vital Signs

Vital signs (supine systolic and supine diastolic blood pressure, heart rate, respiratory rate, oral temperature, weight, and BMI) and weight will be summarized (baseline and change from baseline) by treatment group for the following populations and safety periods: the Stage 1 Safety population over the Stage 1 treatment period, Visit 8 (if any), and Post-discontinuation Safety period combined; Stage 2 Safety Population 1 over the Stage 2 treatment period and Post-discontinuation Safety period combined; and the Stage 1 and Stage 2 treatment sequence for the Stage 2 Entire Safety population over the entire study. All vital sign data will be presented in the subject data listings.

Numbers and percentage of subjects with PCS values occurring at any postbaseline visit will be summarized by treatment group for the Stage 1 Safety population over the Stage 1 treatment period, for Stage 2 Safety Population 1 over the Stage 2 treatment period, and for the Stage 2 Safety population over the entire study period by the Stage 1 and Stage 2 treatment sequence. Criteria for PCS are presented in Table 4 and will be presented for each criterion. The percentages will be calculated relative to the number of subjects with non-PCS baseline values with respect to the specific criterion and at least one postbaseline assessment in the relevant safety population. A supportive listing will present all values for a parameter for subjects with at least one PCS value for that parameter.

Table 4: Criteria for Potentially Clinically Significant Abnormal Vital Sign Values

Parameter	PCS Criteria
Temperature	Hyperthermia: ≥38.1°C
	Hypothermia: ≤35.0°C
Supine Systolic Blood pressure	Low: ≤90 mm Hg and decrease ≥20 mm Hg
	High: ≥140 mm Hg and increase ≥20 mm Hg
Supine Diastolic Blood pressure	Low: ≤50 mm Hg and decrease ≥10 mm Hg
	High: ≥90 mm Hg and increase ≥10 mm Hg
Heart Rate	Low: ≤50 bpm and decrease ≥15 bpm
	High: ≥100 bpm and increase ≥15 bpm
Respiratory Rate	Low: <12 breaths per minute
	High: >25 breaths per minute
Body Weight	Decrease from baseline ≥7%
	Increase from baseline ≥7%

3.6.6.2. Electrocardiograms

Electrocardiogram parameters (heart rate, RR interval, PR interval, QRS interval, QT interval, QTcB [QT interval corrected using Bazett's method], and QTcF [QT interval corrected using Fridericia's method]) will be summarized (baseline and change from baseline) by treatment group for the following populations and safety periods: the Stage 1 Safety population over the Stage 1 treatment period, Visit 8 (if any), and Post-discontinuation Safety period combined; Stage 2 Safety Population 1 over the Stage 2 treatment period and Post-discontinuation Safety period combined; and the Stage 1 and Stage 2 treatment sequence for the Stage 2 Entire Safety population over the entire study.

Numbers and percentage of subjects with PCS values occurring at any postbaseline visit will be summarized by treatment group for the Stage 1 Safety population over the Stage 1 treatment period, for Stage 2 Safety Population 1 over the Stage 2 treatment period, and for the Stage 2 Safety population over the entire study period by the Stage 1 and Stage 2 treatment sequence. Potentially clinically significant criteria are presented in Table 5. A subject will be counted only once in the highest category for a given parameter based on the largest postbaseline value in the respective safety period. The percentages will be calculated relative to the number of subjects with non-PCS baseline values and at least one postbaseline assessment in the relevant safety population. A supportive listing will present all values for a parameter for subjects with at least one PCS value for that parameter.

Table 5: Criteria for Potentially Clinically Significant Abnormal ECG Values

Parameter	PCS Criteria
PR Interval	High: ≥220 msec
QRS Interval	High: ≥120 msec
QTcF	Low: <330 msec
	High: >450 msec; >480 msec; >500 msec
	Only cumulative incidence above the indicated limits
QTcF	Change from baseline increase: >30 msec; >60 msec
	Change from baseline decrease: >30 msec; >60 msec
Heart Rate	Low: ≤50 bpm and decrease ≥15 bpm
	High: ≥100 bpm and increase ≥15 bpm

3.6.7. Clinical Opiate Withdrawal Scale (COWS) Scores

Clinical Opiate Withdrawal Scale (COWS) scores will be analyzed for the Stage 2 Post-discontinuation Safety population. Baseline COWS score is defined as the Visit 13 COWS score. Adequate COWS baseline is defined as COWS baseline assessment performed within (≤) 2 days of the last dose of study drug. Subjects with inadequate baseline (ie, baseline COWS assessment performed more than (>) 2 days of the last dose) will be included in a supportive listing.

Subjects will be included in the COWS analysis if they have an adequate EOT COWS assessment and at least 1 post-EOT COWS assessment in the Post-discontinuation Safety period. COWS scores will be summarized by:

- Analysis of all post-EOT COWS assessments
- Analysis of post-EOT COWS assessments that occurred from >2 to 16 days post last dose of study drug

Subjects with inadequate EOT COWS (ie, EOT COWS assessment was performed more than (>) 2 days of the last dose) will be included in a supportive listing.

Although opioid withdrawal might not be expected in individuals with less than 4 weeks of drug exposure, COWS scores will be presented in all subjects with adequate baselines, and then COWS scores will be presented by subgroup of duration of study drug exposure. Three COWS analyses will be presented for the subjects with adequate baseline by the three exposure subgroups (any exposure, ≥4 week exposure, <4 week exposure):

- Total COWS scores (baseline and change from baseline, and days between last dose and assessment date) will be summarized by visit (baseline, post-discontinuation visit)
- Subject count and percentage will be provided by visit for each of the COWS total score categories indicated below:
  - No withdrawal: total score 0-4

  - Mild withdrawal: total score 5-12
  - Moderate withdrawal: total score 13-24
  - Moderately severe withdrawal: total score 25–36
  - Severe withdrawal: total score >36
- COWS category shift summary from baseline to postbaseline: the numerator is the number of subjects in each post-discontinuation COWS category with nonmissing baseline COWS scores. If there are more than one post-discontinuation COWS score (ie, a subject with an unscheduled visit), the highest value will be used. The denominator is the number of subjects in each baseline COWS category

Narratives will be provided for any clinically meaningful COWS score shifts.

3.6.8. Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire used to measure the presence and intensity of suicidal ideation and behavior.

Suicidal behavior and suicidal ideation will be summarized at baseline and postbaseline by treatment group for the Stage 1 Safety population over the Stage 1 treatment period and Post-discontinuation Safety period combined; the Stage 2 Safety Population 1 over the Stage 2 treatment period and Post-discontinuation Safety period combined; and the Stage 1 and Stage 2 treatment sequence for the Stage 2 Entire Safety population over the entire study. The proportion of subjects who met the criterion for each of these categories at any postbaseline visit will be summarized as described in Table 6.

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

Table 6: Columbia-Suicide Severity Rating Scale 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

Summary of treatment-emergent suicide-related events based on the C-SSRS during the treatment period will be presented by treatment group for the Stage 1 Safety population over the Stage 1 treatment period; the Stage 2 Safety population 1 over the Stage 2 treatment period; and the Stage 1 and Stage 2 treatment sequence for the Stage 2 Entire Safety population over the entire study. The degree and type of treatment-emergent suicide-related events will be summarized in a table as defined in Table 7. Post-discontinuation assessments will not be included in this analysis.

This analysis population consists of the safety population with nonmissing baseline and at least one postbaseline assessment during the treatment period. The percentage will be calculated for the treatment-emergent suicide-related event summary. The numerator is defined as the number of subjects with a nonmissing baseline and a post-baseline C-SSRS assessment that meets the treatment-emergent suicide-related numerator criteria defined in Table 7, and the denominator is defined as the number of subjects with a nonmissing baseline and at least one postbaseline C-SSRS assessment that meets the treatment-emergent suicide-related denominator criteria defined in Table 7 during the treatment period.

Table 7: Treatment-Emergent Suicide-Related Events for Analysis

Treatment Emergent Suicide-related Events	**Denominator Criteria**	**Numerator Criteria**
Increase in Suicidal Ideation from Baseline	Baseline suicidal ideation (“No” to all ideation items 1-5, or “Yes” to any ideation item ≤4 and “No” to item 5)	Baseline suicidal ideation (“No” to all ideation items 1-5, or “Yes” to any ideation item ≤4 and “No” to item 5) Post-baseline (increase in suicidal ideation severity from baseline at any post-baseline visit)
Emergence of Serious Suicidal Ideation	Baseline suicidal ideation (“No” to all ideation items 1-5, or “Yes” to any ideation item ≤3 and “No” to items 4 and 5)	Baseline suicidal ideation (“No” to all ideation items 1-5, or “Yes” to any ideation item ≤3 and “No” to items 4 and 5) Post-baseline (“Yes” to ideation item 4 or 5 at any post-baseline visit)
Emergence of Serious Suicidal Ideation in Subjects with no Suicidal Ideation at Baseline	Baseline ideation (“No” to all ideation items 1-5)	Baseline ideation (“No” to all ideation items 1-5) Post-baseline (“Yes” to ideation item 4 or 5 at any post-baseline visit)
Decrease in Suicidal Ideation from Baseline	Baseline ideation (“Yes” to any ideation items 1-5)	Baseline ideation (“Yes” to any ideation items 1-5) Post-baseline (decrease in suicidal ideation severity at any post-baseline visit compared to severity at baseline)
Emergence of Suicidal Behavior in Subjects with no Suicidal Behavior at Baseline	Baseline behavior (“No” to all behavior items 6-10)	Baseline behavior (“No” to all behavior items 6-10) Post-baseline behavior (“Yes” to any behavior items 6-10 at any post-baseline visit)

3.7. Pharmacokinetic/ Pharmacodynamic Data Analysis

For all subjects, plasma samples will be collected according to the schedule of events in order to quantify concentrations of SAM and its metabolites (RDC-9986 and RDC-1066), BUP and its metabolite (norbuprenorphine [nBUP]), and reported background ADTs.

Descriptive statistics of concentration data for SAM, RDC-9986, BUP, and nBUP will be calculated based on nominal sample collection time. Please refer to Section 6.5 for the handling of concentration data that are below the lower limit of quantification (BLOQ).

By-subject listings of plasma concentrations, including SAM, BUP, and their metabolites, and analytes from background ADTs will be provided.

Pharmacokinetic data may be used in a subsequent population pharmacokinetic evaluation conducted outside of this study.

4. INTERIM ANALYSES AND DATA MONITORING COMMITTEE

No interim analysis is planned for this study.

5. CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

The analyses specified here are consistent with those specified in the Study Protocol Amendment 3.0 (dated 02 Oct 2019) and the associated Unmasked Addendum Amendment 2.0 (dated 25 Jan 2018).

6. DEFINITIONS AND CONVENTIONS FOR HANDLING OF THE DATA

Dataset specifications will be provided in a separate document.

6.1. Analysis Visit Windows

Every attempt must be made to collect complete data for every subject. In cases where complete data cannot be collected, the principles to assign the analysis visits for inclusion in summary tables described in this section will be followed for data handling and analyses.

Early termination visits for efficacy measurements will be mapped to the next scheduled visit. For example, a subject who terminates shortly after Day 43 (eg, has assessments at baseline through Day 43, and Day 78 or early termination) would have assessments at early termination mapped to the next scheduled visit for each assessment. In this example, the MADRS scores from the early termination visit would be mapped to Day 50. For visits other than early termination/ Day 78, the visit number indicated on the case report form will be used as the analysis visit. Results from this mapping will be considered observed data and the mapping will be performed prior to any imputation.

Early termination visits for safety measurements will not be mapped to any scheduled postbaseline visit, but will be used as the last assessment during the treatment period.

Measurements collected from unscheduled visits will not be included in the by-visit summary tables or mean change analyses, but will be included in the analysis of PCS values and in the subject listings.

6.2. Efficacy Data Handling

The MADRS-10 is the sum of the 10 items from the MADRS. If only one of the items of the MADRS for a given visit is missing, then the MADRS-10 score will be calculated as follows: (sum of nonmissing items) × (total number of items) / (number of nonmissing items). If more than one of the items is missing, the MADRS-10 score will be set to missing.

For the LOCF on the total score, if a subject misses a postbaseline visit for a given stage, a record for the scheduled visit will be imputed using the value from the most recent postbaseline visit from the same stage. Individual items will not be carried forward.

6.3. Safety Data Handling

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

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

6.5. Pharmacokinetic Data Handling

Pharmacokinetic concentration values BLOQ will be treated as zero for the determination of summary and order statistics. Individual values that are BLOQ will be presented as “BLOQ” in the concentration data listing. For the presentation of summary and order statistics, if at least 1 subject has a concentration value BLOQ for the time point, then the minimum value will be displayed as “BLOQ”. If more than 50% of the subjects have a concentration data value BLOQ for the time point, then the minimum and median values will be displayed as “BLOQ”. If all subjects have concentration data values BLOQ for the time point, then all order statistics (minimum, first quartile [Q1], median, third quartile [Q3], and maximum) will be displayed as “BLOQ”. If the mean is less than the lower limit of quantification, the mean values will be displayed as “BLOQ”.

7. GENERAL STATISTICAL METHODOLOGY

7.1. Statistical Conventions

In general, summary statistics (n, mean, SD, median, minimum, and maximum for continuous variables, and number and percentage of subjects in each category for categorical variables) will be provided by treatment group. 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 derivation of the last postbaseline value during treatment, the analyses for the PCS postbaseline values, and subject listings. 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 Table 8, unless otherwise specified.

Table 8: Degree of Precision

Statistics	Degree of Precision
Mean, Geometric Mean, Median, Quartiles, Confidence limit boundaries	One more than the raw data, up to three decimal places
Standard deviation, Standard error	One more than the mean, up to three decimal places
Minimum, Maximum	The same as the raw data, up to two decimal places
P-value	Rounded to three 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 100.0%. Percentages of zero will be reported as 0.

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

For weight, height, and BMI, one decimal place will be used for summary statistics.

8. PROGRAMMING SPECIFICATIONS

Programming specifications will be provided in a separate document.

9. MOCK TABLES, LISTINGS AND FIGURES

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

10. REFERENCES

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Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics.* 1997;53(3):983-997.

Little RJ, Rubin DB. *Statistical Analysis with Missing Data.* 2nd ed. New York. John Wiley & Sons; 2002.

APPENDIX 1. INDEPENDENCE OF ESTIMATED TREATMENT EFFECTS IN 2 STAGES FOR SPCD WITH BINARY ENDPOINTS

Table 9 displays subject accounting by response status in the two stages according to the SPCD with rerandomization of placebo nonresponders at the start of Stage 2. The construction of the table is similar to Table I in (Ivanova et al, 2011). In Table 9, s is the probability of placebo nonresponders in Stage 1 being rerandomized into Stage 2, and the rerandomization ratio is 1:1. Rerandomization occurs only for placebo nonresponders in Stage 1 who complete Stage 1 and meet additional criteria for rerandomization into Stage 2.

Table 9: Subject Accounting by Response Status in 2 Stages of SPCD

Treatment in Stage 1	Response in Stage 1	Treatment in Stage 2	Response in Stage 2	Count	Probability
ALKS 5461 2/2	Yes	NA	NA	z_1	p_1
	No	NA	NA	$l_1 - z_1$	$1 - p_1$
Placebo	Yes	NA	NA	y_1	q_1
	No	ALKS 5461 2/2	Yes	z_2	$\frac{1}{2}(1-q_1)sp_2$
			No	$l_2 - z_2$	$\frac{1}{2}(1-q_1)s(1-p_2)$
		Placebo	Yes	y_2	$\frac{1}{2}(1-q_1)sq_2$
			No	$m_2 - y_2$	$\frac{1}{2}(1-q_1)s(1-q_2)$
		Not Re-randomized	NA	k_1	$(1-q_1)(1-s)$

Abbreviation: NA= not applicable for inference.

The notation is as follows:

p_1: response probability in Stage 1 for subjects randomized to ALKS 5461 2/2in Stage 1

q_1: response probability in Stage 1 for subjects randomized to placebo in Stage 1

s: probability of re-randomization for placebo nonresponders in Stage 1

p_2: response probability in Stage 2 for subjects rerandomized to ALKS 5461 2/2 in Stage 2

q_2: response probability in Stage 2 for subjects rerandomized to placebo in Stage 2

Let $m_1 = y_1 + l_2 + m_2 + k_1$ denote the total number of placebo subjects on Stage 1. The joint likelihood for (p_1, q_1, s, p_2, q_2) is:

$$L(p_1, q_1, s, p_2, q_2) \propto p_1^{z_1}(1-p_1)^{l_1-z_1}q_1^{y_1} \times ((1-q_1)sp_2)^{z_2}((1-q_1)s(1-p_2))^{l_2-z_2}$$

$$\times ((1-q_1)sq_2)^{y_2}((1-q_1)s(1-q_2))^{m_2-y_2}$$

$$\times (1-q_1\,)(1-s)^{m_1-y_1-\,l_2-m_2}$$

$$= {p_1}^{z_1}(1-p_1)^{l_1-z_1}{q_1}^{y_1}(1-q_1)^{m_1-y_1}$$

$$\times s^{l_2+m_2}(1-s)^{m_1-y_1-l_2-m_2}$$

$$\times {p_2}^{z_2}(1-p_2)^{\,l_2-z_2}{q_2}^{\,y_2}(1-q_2)^{m_2-y_2}$$

Since the joint loglikelihood decomposes into the sum of the loglikelihoods of the component parameters, the maximum likelihood estimates of the component parameters are mutually independent (Little and Rubin 2002). In particular, $(\hat{p}_1, \hat{q}_1)$ is independent of $(\hat{p}_2, \hat{q}_2)$. For the comparison of ALKS 5461 2/2 versus placebo, the treatment effect estimate for Stage 1 $\hat{\Delta}_1$ is a function of $(\hat{p}_1, \hat{q}_1)$ and for Stage 2 $\hat{\Delta}_2$ is a function of $(\hat{p}_2, \hat{q}_2)$. $\hat{\Delta}_1$ is independent of $\hat{\Delta}_2$. This establishes the validity of the linear combination test statistic for the SPCD design with binary endpoints.

APPENDIX 2. AESI – ABUSE POTENTIAL

Preferred Term	***Ad hoc* SOC**
Accidental overdose	AP_abuse behavior
Drug abuser	AP_abuse behavior
Drug diversion	AP_abuse behavior
Drug level above therapeutic	AP_abuse behavior
Drug level increased	AP_abuse behavior
Drug screen	AP_abuse behavior
Drug screen positive	AP_abuse behavior
Intentional overdose	AP_abuse behavior
Intentional product misuse	AP_abuse behavior
Intentional product use issue	AP_abuse behavior
Maternal use of illicit drugs	AP_abuse behavior
Needle track marks	AP_abuse behavior
Neonatal complications of substance abuse	AP_abuse behavior
Overdose	AP_abuse behavior
Prescription drug used without a prescription	AP_abuse behavior
Prescription form tampering	AP_abuse behavior
Product tampering	AP_abuse behavior
Substance abuse	AP_abuse behavior
Substance abuser	AP_abuse behavior
Substance use	AP_abuse behavior
Substance-induced mood disorder	AP_abuse behavior
Substance-induced psychotic disorder	AP_abuse behavior
Toxicity to various agents	AP_abuse behavior
Acute psychosis	AP_non-specific
Aggression	AP_non-specific
Cognitive disorder	AP_non-specific
Confusional state	AP_non-specific
Delirium	AP_non-specific
Delusional disorder, unspecified type	AP_non-specific
Depersonalisation/derealisation disorder	AP_non-specific
Disorientation	AP_non-specific

Preferred Term	***Ad hoc* SOC**
Dissociation	AP_non-specific
Disturbance in attention	AP_non-specific
Disturbance in social behaviour	AP_non-specific
Dizziness	AP_non-specific
Dopamine dysregulation syndrome	AP_non-specific
Emotional disorder	AP_non-specific
Flight of ideas	AP_non-specific
Medication overuse headache	AP_non-specific
Mental impairment	AP_non-specific
Mood altered	AP_non-specific
Mood swings	AP_non-specific
Narcotic bowel syndrome	AP_non-specific
Paranoia	AP_non-specific
Psychotic behaviour	AP_non-specific
Psychotic disorder	AP_non-specific
Sedation	AP_non-specific
Somnolence	AP_non-specific
Stupor	AP_non-specific
Euphoric mood	AP-euphoria related
Feeling abnormal	AP-euphoria related
Feeling drunk	AP-euphoria related
Feeling of relaxation	AP-euphoria related
Hallucination	AP-euphoria related
Hallucination, auditory	AP-euphoria related
Hallucination, gustatory	AP-euphoria related
Hallucination, mixed	AP-euphoria related
Hallucination, olfactory	AP-euphoria related
Hallucination, synaesthetic	AP-euphoria related
Hallucination, tactile	AP-euphoria related
Hallucination, visual	AP-euphoria related
Inappropriate affect	AP-euphoria related
Thinking abnormal	AP-euphoria related

APPENDIX 3. AESI – DEPENDENCE

Preferred Term
Dependence
Drug dependence
Drug dependence, antepartum
Drug dependence, postpartum
Drug tolerance
Drug tolerance decreased
Drug tolerance increased
Substance dependence

APPENDIX 4. AESI – WITHDRAWAL

Preferred Term
Drug detoxification
Reversal of opiate activity
Drug rehabilitation
Drug withdrawal convulsions
Drug withdrawal headache
Drug withdrawal maintenance therapy
Drug withdrawal syndrome
Drug withdrawal syndrome neonatal
Rebound effect
Steroid withdrawal syndrome
Withdrawal arrhythmia
Withdrawal syndrome
Anhedonia
Depressed mood
Depression
Dysphoria
Feeling of despair
Morose
Negative thoughts
Persistent depressive disorder
Dyssomnia
Headache
Insomnia
Obsessive thoughts
Poor quality sleep
Syncope
Terminal insomnia
Agitation
Irritability
Anxiety
Chills

Preferred Term
Hyperhidrosis
Nausea
Nervousness
Pain
Tremor
Vomiting
Abdominal pain
Arthralgia
Diarrhoea
Mydriasis
Piloerection
Restlessness
Rhinorrhoea
Tachycardia
Yawning

APPENDIX 5. AESI – SUICIDAL IDEATION AND BEHAVIOR

Preferred Term
Depression suicidal
Suicidal ideation
Suicide threat
Suicidal behavior
Suicide attempt
Intentional overdose
Multiple drug overdose
Multiple drug overdose intentional
Overdose
Poisoning deliberate
Completed suicide
Intentional self-injury
Self injurious behavior
Self mutilation
Self-injurious ideation
Columbia suicide severity rating scale abnormal

APPENDIX 6. AESI – HYPOMANIA/ MANIA

Preferred Term
Affective ambivalence
Affect lability
Agitation
Aggression
Anger
Bipolar disorder
Bipolar I disorder
Bipolar II disorder
Cyclothymic disorder
Delusion
Energy increased
Euphoric mood
Flight of ideas
Frustration tolerance decreased
Grandiosity
Hallucination
Hostility
Hypomania
Inappropriate affect
Irritability
Mania
Mood swings
Sexually inappropriate behavior

APPENDIX 7. AESI – CNS DEPRESSION AND SEDATION

Preferred Term
Apathy
Asthenia
Bradyphrenia
Decreased activity
Decreased interest
Depressed level of consciousness
Fatigue
Hypersomnia
Hypersomnia related to another mental condition
Hypokinesia neonatal
Hyporesponsive to stimuli
Hypotonic-hyporesponsive episode
Lethargy
Listless
Loss of consciousness
Neonatal oversedation
Prostration
Psychomotor retardation
Sedation
Sense of oppression
Sleep disorder due to general medical condition, hypersomnia type
Sluggishness
Somnolence
Somnolence neonatal
Sopor
Unresponsive to stimuli

APPENDIX 8. AESI – RESPIRATORY DEPRESSION

Preferred Term
Acute respiratory failure
Apnoea
Apnoeic attack
Bradypnoea
Breath holding
Breath sounds abnormal
Breath sounds absent
Central-alveolar hypoventilation
Hypopnoea
Hypoventilation
Hypoventilation neonatal
Infantile apnoea
Lung hypoinflation
Neonatal respiratory arrest
Neonatal respiratory depression
Neonatal respiratory failure
Postoperative respiratory failure
Respiratory arrest
Respiratory depression
Respiratory depth decreased
Respiratory failure
Respiratory paralysis
Respiratory rate decreased

APPENDIX 9. AESI – ORTHOSTATIC HYPOTENSION

Preferred Term
Autonomic nervous system imbalance
Blood pressure abnormal
Blood pressure ambulatory abnormal
Blood pressure ambulatory decreased
Blood pressure decreased
Blood pressure diastolic abnormal
Blood pressure diastolic decreased
Blood pressure fluctuation
Blood pressure immeasurable
Blood pressure orthostatic
Blood pressure orthostatic decreased
Blood pressure systolic abnormal
Blood pressure systolic decreased
Circulatory collapse
Circulatory failure neonatal
Diastolic hypotension
Dizziness exertional
Dizziness
Dizziness postural
Hypoperfusion
Hypotension
Labile blood pressure
Mean arterial pressure decreased
Neonatal hypotension
Neurogenic shock
Orthostatic heart rate response increased
Orthostatic hypotension
Orthostatic intolerance
Peripheral circulatory failure
Postural orthostatic tachycardia syndrome
Presyncope

Preferred Term
Procedural hypotension
Shock
Shock symptom
Syncope

APPENDIX 10. AESI – HYPERSENSITIVITY

Preferred Term
Acute generalised exanthematous pustulosis
Acute haemorrhagic oedema of infancy
Administration site dermatitis
Administration site eczema
Administration site hypersensitivity
Administration site rash
Administration site recall reaction
Administration site urticaria
Administration site vasculitis
Allergic bronchitis
Allergic colitis
Allergic cough
Allergic cystitis
Allergic eosinophilia
Allergic gastroenteritis
Allergic granulomatous angiitis
Allergic hepatitis
Allergic keratitis
Allergic myocarditis
Allergic oedema
Allergic otitis externa
Allergic otitis media
Allergic pharyngitis
Allergic respiratory disease
Allergic respiratory symptom
Allergic sinusitis
Allergic transfusion reaction
Allergy alert test positive
Allergy test positive
Allergy to immunoglobulin therapy
Allergy to surgical sutures

Preferred Term
Allergy to vaccine
Alveolitis allergic
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Anaphylaxis treatment
Angioedema
Antiallergic therapy
Antiendomysial antibody positive
Anti-neutrophil cytoplasmic antibody positive vasculitis
Aortitis
Application site dermatitis
Application site eczema
Application site hypersensitivity
Application site rash
Application site recall reaction
Application site urticaria
Application site vasculitis
Arteritis
Arteritis coronary
Arthritis allergic
Aspirin-exacerbated respiratory disease
Atopy
Behcet's syndrome
Blepharitis allergic
Blood immunoglobulin E abnormal
Blood immunoglobulin E increased
Bromoderma
Bronchospasm
Capillaritis

Preferred Term
Catheter site dermatitis
Catheter site eczema
Catheter site hypersensitivity
Catheter site rash
Catheter site urticaria
Catheter site vasculitis
Cerebral arteritis
Chronic eosinophilic rhinosinusitis
Chronic hyperplastic eosinophilic sinusitis
Chronic pigmented purpura
Circulatory collapse
Circumoral oedema
Cogan's syndrome
Conjunctival oedema
Conjunctivitis allergic
Contact stomatitis
Contrast media allergy
Contrast media reaction
Corneal oedema
Cutaneous vasculitis
Dennie-Morgan fold
Dermatitis
Dermatitis acneiform
Dermatitis allergic
Dermatitis atopic
Dermatitis bullous
Dermatitis contact
Dermatitis exfoliative
Dermatitis exfoliative generalised
Dermatitis herpetiformis
Dermatitis infected
Dermatitis psoriasiform

Preferred Term
Device allergy
Diabetic arteritis
Dialysis membrane reaction
Diffuse vasculitis
Distributive shock
Documented hypersensitivity to administered product
Drug cross-reactivity
Drug eruption
Drug hypersensitivity
Drug provocation test
Drug reaction with eosinophilia and systemic symptoms
Eczema
Eczema infantile
Eczema nummular
Eczema vaccinatum
Eczema vesicular
Eczema weeping
Encephalitis allergic
Encephalopathy allergic
Epidermal necrosis
Epidermolysis
Epidermolysis bullosa
Epiglottic oedema
Erythema induratum
Erythema multiforme
Erythema nodosum
Exfoliative rash
Eye allergy
Eye oedema
Eye swelling
Eyelid oedema
Face oedema

Preferred Term
Fixed drug eruption
Giant papillary conjunctivitis
Gingival oedema
Gingival swelling
Gleich's syndrome
Granulomatosis with polyangiitis
Haemorrhagic urticaria
Haemorrhagic vasculitis
Hand dermatitis
Henoch-Schonlein purpura
Henoch-Schonlein purpura nephritis
Heparin-induced thrombocytopenia
Hereditary angioedema
Hypersensitivity
Hypersensitivity vasculitis
Idiopathic angioedema
Idiopathic urticaria
Immediate post-injection reaction
Immune thrombocytopenic purpura
Immune tolerance induction
Immune-mediated adverse reaction
Implant site dermatitis
Implant site hypersensitivity
Implant site rash
Implant site urticaria
Incision site dermatitis
Incision site rash
Infusion site dermatitis
Infusion site eczema
Infusion site hypersensitivity
Infusion site rash
Infusion site recall reaction

Preferred Term
Infusion site urticaria
Infusion site vasculitis
Injection site dermatitis
Injection site eczema
Injection site hypersensitivity
Injection site rash
Injection site recall reaction
Injection site urticaria
Injection site vasculitis
Instillation site hypersensitivity
Instillation site rash
Instillation site urticaria
Interstitial granulomatous dermatitis
Intestinal angioedema
Iodine allergy
Kaposi's varicelliform eruption
Kawasaki's disease
Kounis syndrome
Langerhans' cell histiocytosis
Laryngeal oedema
Laryngitis allergic
Laryngospasm
Laryngotracheal oedema
Limbal swelling
Lip oedema
Lip swelling
Lupus vasculitis
Mast cell degranulation present
Medical device site dermatitis
Medical device site eczema
Medical device site hypersensitivity
Medical device site rash

Preferred Term
Medical device site recall reaction
Medical device site urticaria
Medical device site vasculitis
Microscopic polyangiitis
Mouth swelling
Mucocutaneous rash
Multiple allergies
Nephritis allergic
Nikolsky's sign
Nodular rash
Nodular vasculitis
Ocular vasculitis
Oculomucocutaneous syndrome
Oculorespiratory syndrome
Oedema mouth
Oral allergy syndrome
Oropharyngeal blistering
Oropharyngeal spasm
Oropharyngeal swelling
Palatal oedema
Palatal swelling
Palisaded neutrophilic granulomatous dermatitis
Palpable purpura
Pathergy reaction
Periorbital oedema
Pharyngeal oedema
Polyarteritis nodosa
Polymyalgia rheumatica
Pruritus allergic
Pseudovasculitis
Pulmonary vasculitis
Radiation vasculitis

Preferred Term
Radioallergosorbent test positive
Rash
Rash erythematous
Rash follicular
Rash generalised
Rash macular
Rash maculo-papular
Rash maculovesicular
Rash morbilliform
Rash neonatal
Rash papulosquamous
Rash pruritic
Rash pustular
Rash rubelliform
Rash scarlatiniform
Rash vesicular
Reaction to azo-dyes
Reaction to colouring
Reaction to drug excipients
Reaction to preservatives
Red man syndrome
Renal arteritis
Renal vasculitis
Retinal vasculitis
Rheumatoid vasculitis
Rhinitis allergic
Scleral oedema
Scleritis allergic
Scrotal oedema
Segmented hyalinising vasculitis
Serum sickness
Serum sickness-like reaction

Preferred Term
Shock
Shock symptom
Skin necrosis
Skin reaction
Skin test positive
Solar urticarial
Solvent sensitivity
Stevens-Johnson syndrome
Stoma site hypersensitivity
Stoma site rash
Swelling face
Swollen tongue
Takayasu's arteritis
Temporal arteritis
Thromboangiitis obliterans
Tongue oedema
Toxic epidermal necrolysis
Toxic skin eruption
Tracheal oedema
Type 2 lepra reaction
Type I hypersensitivity
Type II hypersensitivity
Type III immune complex mediated reaction
Type IV hypersensitivity reaction
Urticaria
Urticaria cholinergic
Urticaria chronic
Urticaria contact
Urticaria papular
Urticaria physical
Urticaria pigmentosa
Urticaria vesiculosa

Preferred Term
Urticarial vasculitis
Vaccination site dermatitis
Vaccination site eczema
Vaccination site exfoliation
Vaccination site hypersensitivity
Vaccination site rash
Vaccination site recall reaction
Vaccination site urticaria
Vaccination site vasculitis
Vaccination site vesicles
Vaginal exfoliation
Vaginal ulceration
Vascular purpura
Vasculitic rash
Vasculitis
Vessel puncture site rash
Vessel puncture site vesicles
Vulval ulceration
Vulvovaginal rash
Vulvovaginal ulceration

APPENDIX 11. AESI – HEPATIC EFFECTS

Preferred Term
Acute hepatic failure
Acute on chronic liver failure
Acute yellow liver atrophy
Ascites
Asterixis
Bacterascites
Biliary cirrhosis
Biliary cirrhosis primary
Biliary fibrosis
Cholestatic liver injury
Chronic hepatic failure
Coma hepatic
Cryptogenic cirrhosis
Diabetic hepatopathy
Drug-induced liver injury
Duodenal varices
Gallbladder varices
Gastric variceal injection
Gastric variceal ligation
Gastric varices
Gastric varices haemorrhage
Hepatectomy
Hepatic atrophy
Hepatic calcification
Hepatic cirrhosis
Hepatic encephalopathy
Hepatic encephalopathy prophylaxis
Hepatic failure
Hepatic fibrosis
Hepatic hydrothorax
Hepatic infiltration eosinophilic

Preferred Term
Hepatic lesion
Hepatic necrosis
Hepatic steato-fibrosis
Hepatic steatosis
Hepatitis fulminant
Hepatobiliary disease
Hepatocellular foamy cell syndrome
Hepatocellular injury
Hepatopulmonary syndrome
Hepatorenal failure
Hepatorenal syndrome
Hepatotoxicity
Intestinal varices
Intestinal varices haemorrhage
Liver and small intestine transplant
Liver dialysis
Liver disorder
Liver injury
Liver operation
Liver transplant
Lupoid hepatic cirrhosis
Minimal hepatic encephalopathy
Mixed liver injury
Nodular regenerative hyperplasia
Non-alcoholic fatty liver
Non-alcoholic steatohepatitis
Non-cirrhotic portal hypertension
Oedema due to hepatic disease
Oesophageal varices haemorrhage
Peripancreatic varices
Portal fibrosis
Portal hypertension

Preferred Term
Portal hypertensive enteropathy
Portal hypertensive gastropathy
Portal vein cavernous transformation
Portal vein dilatation
Portopulmonary hypertension
Renal and liver transplant
Retrograde portal vein flow
Reye's syndrome
Reynold's syndrome
Splenic varices
Splenic varices haemorrhage
Steatohepatitis
Subacute hepatic failure
Varices oesophageal
Varicose veins of abdominal wall
Anorectal varices
Anorectal varices haemorrhage
Intrahepatic portal hepatic venous fistula
Peritoneovenous shunt
Portal shunt
Portal shunt procedure
Small-for-size liver syndrome
Spider naevus
Splenorenal shunt
Splenorenal shunt procedure
Spontaneous intrahepatic portosystemic venous shunt
Stomal varices