A Phase 3 Multicenter Study of the Long-term Safety and Tolerability of ALKS 5461 for the Adjunctive Treatment of Major Depressive Disorder in Adults who Have an Inadequate Response to Antidepressant Therapy (the FORWARD-2 Study)

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STATISTICAL ANALYSIS PLAN

PHASE III

ALK5461-208

Study Title:	A Phase 3 Multicenter Study of the Long-term Safety and Tolerability of ALKS 5461 for the Adjunctive Treatment of Major Depressive Disorder in Adults who Have an Inadequate Response to Antidepressant Therapy (the FORWARD-2 Study)
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LIST OF ABBREVIATIONS

The following abbreviations are used in the statistical analysis plan.

Abbreviation	Definition
ADT	Antidepressant Therapy
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BDZ	Benzodiazapine
BMI	Body Mass Index
BUP	Buprenorphine
CGI-S	Clinical Global Impression - Severity
CI	Confidence Interval
CNS	Central Nervous System
COWS	Clinical Opiate Withdrawal Scale
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
eDISH	Evaluation of Drug-induced Serious Hepatotoxicity
EOT	End of Treatment
ET	Early Termination
FAS	Full Analysis Set
HAM-A	Hamilton Rating Scale for Anxiety
LLRR	Lower Limit of Reference Range
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	Moclobemide
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
PCS	Potentially Clinically Significant

Abbreviation	Definition
PDEAE	Post-discontinuation Emergent Adverse Event
PLI	Prospective Lead-in
PT	Preferred Term
QTcF	QTcF – Fridericia's Correction Formula
SAE	Serious Adverse Event
SAM	Samidorphan
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SNRI	Serotonin-norepinephrine Reuptake Inhibitor
SOC	System Organ Class
SSRI	Selective Serotonin Reuptake Inhibitor
TBILI	Total Bilirubin
TCA	Tricyclic Antidepressant
TEAE	Treatment Emergent Adverse Events
ULRR	Upper Limit of Reference Range
VS	Vital Sign
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 ALK5461-208 for the adjunctive treatment of Major Depressive Disorder (MDD) at study completion. This document has been prepared based on Alkermes ALK5461-208 study protocol amendment 3 (dated 03 March 2016) [1].

1.1. Study Objectives

The objective of this study is to assess the long-term safety and tolerability of ALKS 5461 for use as an adjunctive therapy to antidepressants for the treatment of MDD.

1.2. Summary of the Study Design and Schedule of Assessments

This is a Phase 3, multicenter, multinational, study to evaluate the long-term safety and tolerability, and to explore treatment effect of 52 weeks of ALKS 5461 administration for use as an adjunctive therapy to antidepressants (ADT) for the treatment of MDD in subjects who have had 1 or 2 inadequate response to an approved ADT in the current MDE.

ALKS 5461 was studied at a dose of 2 mg buprenorphine (BUP):2 mg samidorphan (SAM). Note that ALKS 5461 dose levels are referred to as doses of BUP/SAM expressed as weight in mg (eg, a 2 mg BUP:2 mg SAM dose is expressed as ALKS 5461 2/2).

All subjects in the study had been treated with an adequate dose of an approved ADT for at least 8 weeks, at a stable dose over the last 4 weeks prior to study entry.

Subjects will enter into the study in one of three ways, based on their prior experience with an ALKS 5461 study:

1. New Subjects: those who have not participated in a prior study of ALKS 5461 within 2 years.
2. Continuing Subjects: those who have completed the treatment period of study ALK5461-205, ALK5461-206, ALK5461-207, or ALK5461-210 within the past 10 days. Since some of these antecedent studies were randomized placebo-controlled studies, these subjects may or may not have received ALKS 5461 in the prior study.
3. Lead-in Subjects: those who participated in study ALK5461-205, ALK5461-206, or ALK5461-207 within the past 10 days, and met the criteria for response to ADT during the prospective lead-in (PLI) period of that antecedent study, but did not meet the criteria for remission. These subjects were not eligible for entry into the double-blind treatment period in the antecendent and received neither placebo nor ALKS 5461 in the antecedent study.

All New Subjects will be initially evaluated for eligibility at screening (Visit 1), to occur up to 28 days prior to Visit 2.

For Continuing Subjects and Lead-in Subjects, Visit 2 will be the first visit of this study and there will not be a separate screening visit. Identical assessments taken at the subject's last visit

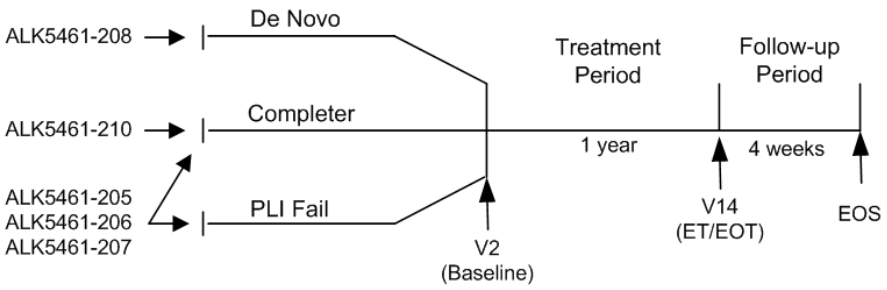
of the antecedent study do not need to be repeated at Visit 2 of this study unless more than 10 days elapses between these visits.

At Visit 2, all eligible, consenting subjects will begin the treatment period. Subjects entering the study already receiving ALKS 5461 will not require titration; all other subjects will require a 1-week ALKS 5461 titration period. Depending on the antecedent study, the titration may be blinded per blinding schemes as described in the protocol. From Week 2 to 52, all participating subjects will take ALKS 5461 2/2 and an approved ADT, with allowable ALKS 5461 dose adjustments for tolerability as described in the protocol.

During the 52-week treatment period, subjects will return to the clinic for periodic scheduled visits (Visits 2-14) at which safety, tolerability, and treatment effect over time will be assessed.

A 4-week safety follow-up period will occur following the ALKS 5461 treatment period. During the 4-week follow-up period, there are a total of 4 clinic visits (Visits 15-18), as well as 7 safety assessments by phone. Please refer to the protocol for a detailed schedule of assessments. A brief schematic of study design is provided in Figure 1. A summary of the schedule of safety assessments is presented in Table 1.

Figure 1: Study Design Schematic



Abbreviations: EOS=end of study; EOT=end of treatment; ET=early termination; PLI=prospective lead-in; V=visit

Table 1: Schedule of Safety Assessments

Study Number	Dosing Schedule (Days)	Vital Signs[a]	Clinical Laboratory Testing[b]	12-Lead ECG	C-SSRS[d]	COWS[e]	AEs
ALK5461-208	Treatment: 1-365 (1 year) Titration: 1-7 (1 week) Safety Follow Up: 366-393 (1 month)	Screening, Days 1[c], 8, 15, 29, 43, 57, 99, 141, 183, 225, 267, 309, 365, 366, 372, 379, 393	Screening, Days 1[c], 8, 99, 183, 267, 365, 393	Screening, Days 1[c], 8, 183, 365, 393	Screening, Days 1[c], 8, 15, 29, 43, 57, 99, 141, 183, 225, 267, 309, 365, 366, 372, 379, 393	Days 365, 366, 372, 379, 393[e]	Throughout

Abbreviations: ECG=electrocardiogram; C-SSRS=Columbia-Suicide Severity Rating Scale; COWS=Clinical Opiate Withdrawal Scale; AEs=Adverse Events

[a] Vital signs included weight, oral temperature, supine respiratory rate, blood pressure, and heart rate.

[b] Chemistry, hematology, and urinalysis.

[c] Conducted predose.

[d] At screening the "Baseline" version of the C-SSRS was administered and at all other visits the "Since Last Visit" version was administered.

[e] COWS was administered by a medical professional.

1.3. Criteria for Evaluation

Safety and Tolerability:

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

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

Efficacy:

The following assessments will be collected to measure treatment effect throughout the study:

- Montgomery-Asberg Depression Rating Scale (MADRS)
- Hamilton Rating Scale for Anxiety (HAM-A)
- Clinical Global Impression - Severity (CGI-S)

2. SAMPLE SIZE AND STATISTICAL POWER CONSIDERATION

Approximately 1,500 subjects will be enrolled in order to achieve at least 100 subjects with 12 months and 300 subjects with 6 months of exposure to ALKS 5461. Subjects will enter from four feeder studies or enter de novo. The antecedent studies included ALK5461-205, ALK5461-206, ALK5461-207, and ALK5461-210.

3. DATA ANALYSIS

3.1. General Statistical Methodology

The safety and efficacy endpoints will be summarized by prior ALKS 5461 exposure: no prior exposure to ALKS 5461 and prior exposure to ALKS 5461, as well as overall.

Subjects with no prior exposure to ALKS 5461 come from three sources: De Novo (i.e., New Subjects), PLI Failures (i.e., antecedent study Prospective Lead-in Subjects Failures) and Placebo (i.e., those who did not receive any active treatment in an antecedent study).

Prior exposure to ALKS 5461 subjects include Continuing Subjects who received active treatment (doses ALKS 5461 0.5/0.5, ALKS 5461 1/1, or ALKS 5461 2/2) in an antecedent study. Subjects with prior exposure are designated as such independent of the duration of exposure in the antecedent trial.

In general, summary statistics (n, mean, standard deviation [SD], median, minimum, and maximum for continuous variables, and number and percentage of subjects in each category for categorical variables) based on observed data will be provided by prior ALKS 5461 exposure and overall. 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 categorical outlier analyses of post-baseline values and subject listings.

In general, only data collected during the ALK5461-208 study will be summarized even though the baseline may come from an antecedent study.

Last assessment during treatment period, defined as the last non-missing value from scheduled post-baseline visit during the treatment period (i.e., from Visit 2 to Visit 14, inclusive), will be included in the by-visit summary tables for both efficacy and safety endpoints as appropriate.

Source data for the summary tables will be presented as subject data listings. Please refer to Section 6.1 on the handling of data collected at an early termination visit.

3.2. Study Population

3.2.1. Definitions of Analysis Populations (Analysis Sets)

Safety Population consists of all subjects who receive at least 1 dose of study drug in the ALK5461-208 study.

An AE will be considered as a treatment emergent adverse event (TEAE) if it starts or worsens (if present at baseline) on or after the baseline during treatment period. An AE will be

considered as a post-discontinuation emergent adverse events (PDEAE) if it starts or worsens after the last dose date plus 1 day.

Post-discontinuation Safety Population consists of subjects in the Safety Population who have at least 1 post-discontinuation measurement. There will be two Post-discontinuation Safety Populations, one is used to analyze PDEAE, and the other is to analyze COWS, grouped by whether having had exposure to study drug in a prior controlled trial or had no prior exposure.

Post-discontinuation Safety Population for PDEAE consists of subjects who received at least 1 dose of study drug, and met one of the following criteria:

- Subjects who entered the Post-discontinuation Period and had a Post-discontinuation Visit
- Subjects who did not enter the Post-discontinuation Period, but had at least 1 PDEAE reported
- Subjects who died after either completing the treatment or having an Early Termination (ET) Visit

Post-discontinuation Safety Population for COWS consists of subjects who received at least 1 dose of study drug, had an adequate COWS baseline (defined as end of treatment [EOT] COWS assessment) and had at least 1 post-EOT COWS assessment, where an adequate EOT COWS is defined as having been performed within (≤) 2 days of last dose of study drug.

Full Analysis Set (FAS) consists of subjects in the Safety Population who have at least 1 post-baseline complete MADRS assessment.

The baseline for efficacy endpoints is defined as the last non-missing observation on or before the date of baseline visit (Visit 2) of ALKS 5461-208 study for subjects who are new to ALKS 5461 (ie, De Novo, PLI Failures, and Continuing Subjects who received placebo in antecedent study); or the last non-missing observation on or before the first dose of ALKS 5461 in antecedent study for Continuing Subjects who received any dose of ALKS 5461 (i.e., ALKS 5461 0.5/0.5, ALKS 5461 1/1, or ALKS 5461 2/2) in antecedent study.

The baseline and study period are defined in Table 2 for each safety endpoint. Visit 2 is the first scheduled visit during treatment period and Visit 14 is the last scheduled visit including ET visit during treatment. Please refer to Protocol for detailed schedule of assessments.

Table 2: Baseline and Study Period for Safety Endpoints

Safety Endpoint	Population	Study Period and Baseline
AE	Safety Population	For AEs, treatment period will include the interval between the date of Visit 2 and the last dose date plus 1 day, inclusive. For new subjects, the baseline for TEAEs is defined as all AE data collected prior to Visit 2 in Study ALK5461-208. For all other subjects, Visit 2 will be their first visit of this study, so all the AEs occurred or worsened after Visit 2 during treatment period are considered as TEAE.
Lab, VS , ECG and C-SSRS	Safety Population	For safety endpoints lab, VS, ECG and C-SSRS, the treatment period will include assessments collected at the Visit 2 baseline visit and all post-baseline visits throughout the entire treatment period starting from Visit 2 to the last assessment visit date. The baseline for these safety endpoints is defined as the last non-missing value on or before the date of Visit 2.
PDEAE	Post-discontinuation Safety Population for PDEAE	For PDEAEs, the Post-discontinuation Safety Period will be defined as the interval starting from the last dose date plus 2 days to the end of study date. The baseline for PDEAEs is defined as all data collected prior to last dose date plus 2 days.
COWS	Post-discontinuation Safety Population for COWS	For COWS, Post-discontinuation Safety Period covers the values collected from the EOT visit (Visit 14) through the post-discontinuation visits. The post-discontinuation baseline for COWS is defined as EOT COWS assessment (Visit 14), and an adequate post-discontinuation baseline is defined as EOT COWS having been performed within (≤) 2 days of last dose of study drug.

3.2.2. Disposition

Subject disposition will be summarized for all subjects and for subjects categorized as having prior ALKS 5461 exposure and no prior ALKS 5461 exposure. Subjects with no prior ALKS 5461 exposure will be further summarized by the following sub-categories: De Novo (i.e., New Subjects), PLI Failures (i.e., Lead-in Subjects), and Placebo (i.e., Continuing subjects who received only placebo in the antecendent study). The number and percentage of subjects will be summarized for the following:

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

For subjects who prematurely discontinue from the study, the reasons for discontinuation as recorded on the disposition CRF will be presented. Percentage will be calculated based on Safety Population. Disposition for those subjects who had a down-titratration from the ALKS 5461 2/2 mg dose will be summarized similarly.

A listing of disposition will be provided for all subjects.

Additional analysis will include analysis of time to treatment discontinuation for subjects who discontinue from the study. Time to treatment discontinuation will be summarized for those with study discontinuation due to any cause and due to AE as indicated on the disposition CRF. For those subjects who discontinued due to AE or due to any other reason, time to discontinuation will be calculated from the date of the first dose of ALKS 5461 in the ALK5461-208 study (Visit 2), to the EOT visit date. In analysis of time to treatment discontinuation due to AE, subjects who discontinue for other reasons will be censored by day of EOT. The distribution of time to treatment discontinuation will be estimated and graphically displayed by prior ALKS 5461 experience and overall using Kaplan-Meier methods. Time to treatment discontinuation will also be summarized by descriptive statistics.

3.2.3. Protocol Deviations

Subjects with major protocol deviations will be summarized by prior ALKS 5461 exposure and overall along with supportive listings for each of the following categories:

- Did not meet the inclusion / exclusion criteria
- Received prohibited medications
- Lack of adherence with study medication, as defined by subjects taking less than 70% of the protocol specified amount of study medication
- Dosing error
- Other major protocol deviation

3.3. Demographics and Baseline Characteristics

For New Subjects only, demographic and baseline characteristics data (including MDD history) will be collected at screening visit. For Continuing Subjects and Lead-in Subjects, these data will be carried over from information recorded in the antecedent ALKS 5461 study in which they participated.

Demographics and baseline characteristics (age, gender, primary race, ethnicity, region (United States [US], non-US), duration of current MDE, ADT Class for current MDE, number of inadequate responses to ADT in the current MDE, lifetime number of MDEs, lifetime number of antidepressants, benzodiazepines (BDZ) use, opioid use, H1 antagonist use, height, weight, body mass index [BMI]) will be summarized by prior exposure to ALKS 5461, no prior exposure to ALKS 5461, and overall for the Safety Population. For no prior exposure to ALKS 5461, the group is divided further into 3 subgroups of De Novo, PLI Failures, and Placebo, as well as overall. Categories for missing data will be provided as necessary.

Baseline characteristics for efficacy measurments (MADRS-10 score, MADRS-6 score, HAM-A total score, CGI-S score and HAM-D total score) will be summarized by prior exposure to ALKS 5461, no prior exposure to ALKS 5461, and overall for the FAS Population. For no prior exposure to ALKS 5461, the group is divided further into three subgroups of De Novo, PLI Failures, and Placebo, as well as overall. The baseline for efficacy measurements is defined as the last non-missing value on or before the date of initiation of ALKS 5461 at any dose.

Medical and psychiatric history will be summarized using the number of observations and percentage of subjects reporting each category by prior ALKS 5461 exposure and overall for the Safety Population.

Demographic and baseline listings will be provided for all subjects.

3.4. Prior and Concomitant Medications

Prior medications are defined as medications started prior to the first dose of study drug. Concomitant medications are defined as medications taken during the period between the first dose date and 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 June 2016.

Prior medications and concomitant medications will be summarized by ATC code and Preferred Term, by Preferred Term, and by prior ALKS 5461 exposure and overall for the Safety Population. For the summary tables, if a subject has taken a prior or concomitant medication more than once, the subject will be counted only once for the medication.

In addition, the prior and concomitant ADTs by ADT class (selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI], Tricyclic Antidepressant [TCA], Moclobemide [MAOI] and other) and Preferred Term will be summarized similarly.

Summary tables for benzodiazepines use, opioid use, and sedating H1 antagonist use (prior medication / concomitant medication) by Preferred Term and by prior ALKS 5461 exposure and overall for the Safety Population will be produced, respectively.

A list of subjects taking ADTs, Benzodiazepines (BDZ) and BDZ-like drugs, Opioids, and sedating H1 antagonists will be provided.

3.5. Treatment Adherence Rate and Extent of Exposure

Treatment adherence to the daily dosing schedule of study drug is measured as the rate of actual compared to intended number of doses to be taken during the ALK5461-208 study. Percentage of treatment adherence will be calculated during 52-week treatment period for the Safety Population as follows:

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

Duration of exposure to study drug is defined as the number of days from the first dose date of study drug taken to the date of the last dose taken during the ALK5461-208 study, inclusive.

Treatment adherence and exposure of study drug will be summarized by prior ALKS 5461 exposure and overall for the Safety Population.

Treatment adherence will be summarized as a continuous measure using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) and as a categorical measure using the number and percentage of subjects in each adherence rate category (rounded to the whole number): <70%; ≥70% to 80%; >80% to 90%; >90% to 100%; >100% to 110%; >110% to 119%; and ≥120%.

The number of subjects exposed to study drug and the average days of treatment will be summarized as a continuous measure using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum).

The exposure to ADT will be summarized by ADT class (SSRI, SNRI, TCA, MAOI and other) and Preferred Term (ADT name) 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.

The descending cumulative exposure of study drug will be categorized as ≥1 day, ≥1 month, ≥3 months, ≥6 months, ≥9 months and ≥12 months, and will be summarized as a categorical measure using the number and percentage of subjects in each category.

The definitions in Table 3 will be used to define cumulative exposure.

Table 3: Definitions to Define Study Drug Cumulative Exposure

	Definition	**Programming Derivation**
≥ 1 day	≥ 1 day	
≥ 1 month	≥ 23 days (3 weeks)	≥ (365.25/12)-7 days
≥ 3 months	≥ 84 days (12 weeks)	≥ [(365.25/12)x3]-7 days
≥ 6 months	≥ 169 days (24 weeks)	≥ [(365.25/12)x6]-14 days
≥ 9 months	≥ 260 days (37 weeks)	≥ [(365.25/12)x9]-14 days
≥ 12 months	≥ 351 days (50 weeks)	≥ 365.25 -14 days

3.6. Efficacy Analysis

3.6.1. General Considerations

All efficacy analyses will be based on the FAS. Descriptive statistics will be summarized by prior ALKS 5461 exposure and overall based on observed data.

3.6.1.1. Pooling of Centers

No plan to pool study centers.

3.6.1.2. Multiple Comparisons/Multiplicity

Not applicable.

3.6.1.3. Examination of Subgroups

No subgroup analysis for efficacy is planned.

3.6.2. Efficacy Analysis

3.6.2.1. Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS measures the severity of depressive symptoms and consists of 10 items. The MADRS-10 is the sum of all 10 items and ranges from 0 to 60. The MADRS-6 is the sum of the following 6 items: item 1 reported sadness; item 2 apparent sadness; item 3 inner tension; item 7 lassitude; item 8 inability to feel; and item 9 pessimistic thoughts and ranges from 0 to 36. Section 6.2 describes the handling of MADRS-10 if any of the items of the MADRS is missing.

The following endpoints will be assessed:

- Change from baseline in MADRS-10 and MADRS-6 score
- Proportion of subjects demonstrating MADRS treatment response, defined as a ≥50% reduction in MADRS-10 from baseline
- Proportion of subjects achieving remission, defined as a MADRS-10 of ≤10

Descriptive summary statistics of baseline MADRS-10 and MADRS-6 score and change from baseline at each visit including the last assessment during treatment period will be provided by prior ALKS 5461 exposure and overall based on observed data. In addition, the figures of MADRS-10 and MADRS-6 score (including standard error), mean change from baseline (including standard error) over time including the last assessment during treatment period will be provided by prior ALKS 5461 exposure and overall based on observed data.

The responder and remission endpoints are derived based on the observed MADRS-10. The number and percentage of subjects demonstrating MADRS-10 treatment response and remission by visit including the last assessment during treatment period will be provided based on FAS. The figures of MADRS-10 responder rate and MADRS-10 remission rate over time including the last assessment during treatment period will be provided by prior ALKS 5461 exposure and overall.

The individual MADRS item scores will not be summarized but will be included in the subject listing.

3.6.2.2. Hamilton Rating Scale for Anxiety (HAM-A)

The HAM-A is a clinician-administered 14-item scale developed to measure the severity of anxiety symptoms. The HAM-A total score is the sum of all 14 items and ranges from 0 to 56. Section 6.2 describes the handling of total score if any of the items of the HAM-A is missing.

The following endpoints will be assessed

- Change from baseline in HAM-A total score
- Change from baseline in HAM-A psychic subscale, where the psychic subscale is the sum of HAM-A items 1 to 6, and item 14
- Change from baseline in HAM-A somatic subscale, where the somatic subscale is the sum of HAM-A items 7 to 13

Descriptive summary statistics of baseline, HAM-A total score and change from baseline at each visit including the last assessment during treatment period will be provided by prior ALKS 5461 exposure and overall based on observed data. The HAM-A psychic subscale and somatic subscale will be summarized in a similar way. In addition, a figure of HAM-A total score (including standard error), mean change from baseline (including standard error) over time including the last assessment during treatment period will be provided by prior ALKS 5461 exposure and overall.

The individual HAM-A item score will not be summarized but will be included in the subject listing.

3.6.2.3. Clinical Global Impression – Severity (CGI-S)

The CGI-S is a 7-point scale that requires the clinician to rate the severity of the subject's illness at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis. Considering total clinical experience, a subject is assessed on severity of mental illness at the time of rating 0=not assessed; 1=normal, not at all ill; 2=borderline mentally ill; 3= mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; or 7=extremely ill. The rating of 0 (not assessed) will be considered as missing.

Descriptive summary statistics of baseline, CGI-S score and change from baseline at each visit including the last assessment during treatment period and follow up period will be provided by prior ALKS 5461 exposure and overall based on observed data. The number and percentage of subjects for each CGI-S category at each visit including the last assessment during treatment period and follow up period will also be summarized. In addition, figures of CGI-S score (including standard error) and mean change from baseline (including standard error)over time including the last assessment during treatment period and follow up period will be provided by prior ALKS 5461 exposure and overall based on observed data.

3.7. Safety Analysis

3.7.1. General Considerations

All safety endpoints will be summarized by prior ALKS 5461 exposure and overall based on observed data for the Safety Population.

3.7.2. Adverse Events

Adverse events will be coded by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities MedDRA version 19.0. The verbatim term will be included in the AE listings. An AE will be considered as a treatment emergent adverse event (TEAE) if it starts or worsens (if present at baseline) on or after the baseline during treatment period. An AE will be considered as a PDEAE if it starts or worsens during the Post-discontinuation Safety Period which is after the last dose date plus 1 day. For the determination of TEAEs during the treatment period, AEs with the greatest severity before the baseline will be used as the benchmark for the comparison of the AEs occurring during the treatment period. For PDEAEs, 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. TEAEs / PDEAEs, deaths, serious adverse events (SAEs), AEs leading to study discontinuation will be included in the summary tables. Summary tables will be provided by prior ALKS 5461 exposure and overall for the Safety Population. For AEs leading to study discontinuation or deaths, the AEs will be summarized in the period in which the discontinuation or death occurred. Drug related TEAEs include those scored as definitely related, probably related, and possibly related by the investigator.

The following summary tables will be produced for the treatment period / Post-discontinuation Safety Period by prior ALKS 5461 exposure and overall for the Safety Population:

- Overview AE summary tables (TEAEs / PDEAEs)
- TEAEs / PDEAEs by System Organ Class and Preferred Term
- TEAEs / PDEAEs by Preferred Term in decreasing frequency
- TEAEs / PDEAEs experienced by ≥5% of subjects (in any group) by Preferred Term
- TEAEs / PDEAEs by System Organ Class, Preferred Term, and Severity
- Drug-related TEAEs by System Organ Class and Preferred Term
- SAEs (fatal and non-fatal) by System Organ Class and Preferred Term
- SAEs (fatal and non-fatal) by Preferred Term in decreasing frequency
- AEs leading to study discontinuation by System Organ Class and Preferred Term
- AEs leading to study discontinuation by Preferred Term in decreasing frequency
- TEAEs by System Organ Class, Preferred Term, and Duration of Exposure
- TEAEs by Preferred Term in decreasing frequency and Duration of Exposure
- Duration of TEAEs experienced by ≥5% of All Subjects by Preferred Term

- Incidence of TEAEs experienced by ≥5% of All Subjects by Preferred Term and Exposure Interval

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

The number and percentage of subjects with TEAE during the ALK5461-208 study will be summarized by System Organ Class, Preferred Term, and duration of exposure since the first dose of the study drug in the ALK5461-208 study (1 day to <1 month, ≥1 to <3 months, ≥3 to <6 months, ≥6 to <9 months, ≥9 to <12 months, and ≥12 months). For each exposure interval, the percentage will be calculated as the number of subjects with a new TEAE that started during the exposure interval, relative to the number of subjects exposed during the interval. Separate tables for prior ALKS 5461 exposure and overall will be provided.

Descriptive statistics (number of subjects, mean, SD, median, 10th percentile, 90th percentile, minimum, and maximum) of duration (days) of TEAEs experienced by ≥5% of All Subjects will be provided by Preferred Term during treatment period for the Safety Population. The duration is defined as number of days from the TEAE start date to the TEAE stop date during the ALK5461-208 study, inclusive. If a TEAE is ongoing at the end of the treatment period, the TEAE stop date is imputed by last dose date plus 1 day. For those subjects who have the same event (same PT term) that is treatment emergent on multiple occasions, we will choose the longest duration as stated above. For partial TEAE start or stop date:

- If only day is missing but month available, TEAE start date will be imputed as the first day of the month and TEAE stop date will be imputed as the last day of the month.
- If both month and day are missing, TEAE start date will be imputed as the Visit 2 date or January 1st whenever applicable, and TEAE stop date will be imputed as the last dose date or December 31st whenever applicable.

The Incidence (%) of TEAEs experienced by ≥5% of All Subjects by Preferred Term and Exposure Interval (1 day to <1 month, ≥1 to <3 months, ≥3 to <6 months, ≥6 to <9 months, ≥9 to <12 months, and ≥12 months) will be presented by prior ALKS 5461 exposure and overall during treatment period for the Safety Population. For those subjects who have the same event (same PT term) that is treatment emergent on multiple occasions, the first instance where that event was treatment emergent will be used, as stated above. The incidence (%) is calculated by n/m x 100%, where n is defined as the number of subjects with newly emergent or worsened adverse events during the exposure interval; m is defined as the number of subjects who had

treatment exposure during the exposure interval. The incidence (%) of TEAE over time will also be presented graphically. For each preferred term, a bar graph will be presented by prior ALKS 5461 exposure and overall. The number of n/m of three groups will be listed below the figure.

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

- Demographics (age [<55 years, ≥55 years], race [white, all other races], gender [female, male])
- Region (US, non-US)
- ADT class (SSRI, SNRI, and other)
- Benzodiazepines use (yes, no)
- Opioid use (yes, no)

A subject is considered as having used a Benzodiazepine (BDZ) or BDZ-like drug ("yes" subgroup) if the subject was taking any concomitant medication in the Benzodiazepine group for any duration in the treatment period of interest. A subject is considered as not having used a Benzodiazepine (BDZ) or BDZ-like drug ("no" subgroup) if the subject was not taking any concomitant medication in the Benzodiazepine group and sedating H1 antagonist group.

Similarly, a subject is considered as having used an opioid drug ("yes" subgroup) if the subject was treated with any concomitant medication in the opioid classification for any duration in the treatment period of interest. A subject is considered as not having used an opioid drug ("no" subgroup) if the subject was not treated with any concomitant medication in the opioid classification. A table of SAE by System Organ Class and Preferred Term for opioid use will be presented.

Subject listings for AEs will be included.

3.7.3. Adverse Events of Special Interest

Adverse events of special interest (AESIs) will be summarized by Preferred Term and by prior ALKS 5461 exposure and overall during treatment period for the Safety Population / Post-discontinuation Safety Population for any TEAEs or PDEAEs of special interest. The following summaries will be created for AESI:

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

- TEAEs associated with slowing of ventricular repolarization
- TEAEs associated with hepatic effects
- TEAEs associated with sexual dysfunction

TEAEs associated with abuse potential will be presented by Adhoc System Organ Class and Preferred Term, where Adhoc System Organ Class is manually classified by Alkermes medical director as 3 categories: abuse behavior, euphoria related, and non-specific.

TEAEs associated with dependence will be presented for subjects with any exposure, ≥4 weeks exposure, and <4 weeks exposure, respectively.

PDEAEs associated with withdrawal will be preseneted for subjects with any exposure, ≥4 weeks exposure, and <4 weeks exposure, respectively. AESIs 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 presents by considering half-lives of both BUP and SAM.

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

3.7.4. Clinical Laboratory Parameters

Laboratory parameters will be presented in conventional units. Only scheduled laboratory assessments will be included in the summaries of mean and change from baseline descriptive analyses. Laboratory assessments from both scheduled and unscheduled visits will be included in outlier analyses. Outlier analyses will not include post-discontinuation assessments. All laboratory data will be included in the listings. Parameter order for summary tables and listings will be by system (renal, hepatic, etc.).

3.7.4.1. Descriptive Analysis of Laboratory Parameters

Numerical laboratory results (baseline and change from baseline) for chemistry and hematology parameters and urinalysis (pH and Specific Gravity) for each visit during the entire study (including last assessment during treatment period and visits in Post-discontinuation Safety Period) will be summarized (number of subjects, mean, SD, median, minimum, and maximum) by prior ALKS 5461 exposure and overall for the Safety Population.

In addition, baseline and post-baseline observed values (lowest, highest, last assessment during treatment period), and change from baseline to lowest, highest and last assessment values during the treatment period for chemistry and hematology parameters, urinalysis (pH and Specific Gravity), will be summarized by prior ALKS 5461 exposure and overall for the Safety Population.

The following graphical displays for laboratory parameters (chemistry, hematology, and urinalysis) will be presented during the entire study (including last assessment during treatment period and Post-discontinuation Safety Period) by prior ALKS 5461 exposure and overall for the Safety Population:

- Line graphs for mean change from baseline along with the corresponding standard error (SE; including Post-discontinuation Safety Period)
- Box-and-Whisker figures for baseline and post-baseline observed values (lowest, highest, last assessment during treatment period)
- Box-and-Whisker figures for change from baseline to the lowest post-baseline value, the highest post-baseline value, and the last scheduled post-baseline value during treatment period
- Scatter plots for baseline and post-baseline observed values (lowest, highest, last assessment during treatment period)

3.7.4.2. Outlier Analyses of Laboratory Parameters

The number and percentage of subjects with values considered potentially clinically significant (PCS) occurring at any post-baseline visit during treatment period for selected parameters will be summarized. For PCS, the summary will be provided by prior ALKS 5461 exposure and overall for the Safety Population. These analyses do not include Post-discontinuation Safety Period.

Clinical laboratory test values, scheduled or unscheduled, will be considered PCS if they meet the PCS criteria listed in Table 4. The percentage will be calculated relative to the number of subjects with available non-PCS baseline values with respect to the specific criterion and at least 1 post-baseline assessment. The numerator is the total number of subjects with a non-PCS baseline value with respect to the specific criterion and at least 1 post-baseline PCS value. A supportive listing will present all values for a parameter for subjects with at least 1 PCS value for that parameter.

Shift tables for shift from within normal reference limits / high to low and shift from within normal reference limits / low to high during treatment period will be provided for chemistry, hematology, and urinalysis parameters with conventional reference limits (limits provided by the performing laboratories) by prior ALKS 5461 exposure and overall for the Safety Population. For parameters which have gender and / or age specific limits, the categories will be based on the specific limits. High is defined as values greater than the upper limit of the reference range (ULRR). Low is defined as values less than the lower limit of the reference range (LLRR). Normal reference limits is defined as values within normal range. The analysis population consists of subjects in the Safety Population with a baseline value outside the specific shift direction. All laboratory values collected during the treatment period will be considered in this analysis.

The percentages will be calculated for the shift summary as follows:

- For the shifts from within normal reference limits / high to low: the numerator is defined as the number of subjects with a post-baseline result below the LLRR, and the denominator is defined as the number of subjects with a baseline value within the limits or above the ULRR.
- For the shifts from within normal reference limits / low to high: the numerator is defined as the number of subjects with a post-baseline results above the ULRR, and the denominator is defined as the number of subjects with a baseline value within the limits or below the LLRR.

Pregnancy and drug screening data will be listed. For urinalysis, rate of abnormalities at any post-baseline visit during treatment period will be summarized.

Table 4: Potentially Clinically Significant Abnormal Laboratory Values

Category	Parameter	Criteria
Hematology	Eosinophils	>1.0x10^3/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	≤2.8x10^3/µL ≥16x10^3/µL
	Neutrophils, Absolute	<1.5x10^3/µL
	Platelets	<75.1x10^3/µL ≥700x10^3/µL
Chemistry	Alanine Aminotransferase	≥3xULRR
	Albumin	<2.5 g/dL
	Alkaline Phosphatase	≥3xULRR
	Aspartate Aminotransferase	≥3xULRR
	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	>3xULRR
	Creatinine	≥2 mg/dL

Table 4: Potentially Clinically Significant Abnormal Laboratory Values (Continued)

Category	Parameter	Criteria
	Gamma Glutamyltransferase	≥3xULRR
	Glucose	<50 mg/dL >200 mg/dL
	HDL Cholesterol	≤30 mg/dL
	Lactate Dehydrogenase	>3xULRR
	LDL Cholesterol	≥160 mg/dL
	Phosphate	<2 mg/dL >5 mg/dL
	Potassium	<3 mmol/L >5.5 mmol/L
	Prolactin	>1xULRR
	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 Protein	at least 2+

Abbreviations: BUN=blood urea nitrogen; HDL=high density lipoproteins; LDL=low density lipoprotein; ULRR=upper limit of referene range

3.7.4.3. Hepatic Effects

Analyses on hepatic analytes will be performed on some laboratory measures to assess potential hepatic effects and will include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TBILI). Hepatic effects will be explored using drug induced liver injury (DILI) criteria from the FDA guidance as well as Hy's Law criteria and through individual frequencies of abnormalities compared to reference limits. Summaries will be presented by prior ALKS 5461 exposure and overall for the Safety Population. DILI and Hy's Law criteria are defined relative to the ULRR as follows:

- ((ALT or AST) ≥3xULRR) & (TBILI≥1.5xULRR)
- ((ALT or AST) ≥3xULRR) & (TBILI≥1.5xULRR) & (ALP<2xULRR)
- ((ALT or AST) ≥3xULRR) & (TBILI≥2xULRR)
- ((ALT or AST) ≥3xULRR) & (TBILI≥2xULRR) & (ALP<2xULRR)

To complement the DILI and Hy's Law analyses described above, an "evaluation of drug-induced serious hepatotoxicity" (eDISH) plot will present maximum TBILI versus maximum ALT / AST by study group during treatment period for the Safety Population. Individual subject values for the maximum ALT / AST value expressed as the multiple of the ULRR versus the maximum TBILI value also expressed as the multiple of the ULRR will be presented. Reference lines will indicate values that fall within the range of DILI or Hy's Law criteria.

The listing of subjects meeting the DILI or Hy's Law citeria with all values of relevant laboratory parameters will be provided.

The number and percentage of subjects with certain baseline values for ALT, AST, TBILI and who have any post-baseline values meeting the shift criteria specified in Table 5, Table 6 and Table 7 during treatment period will be summarized, respectively. The numerator is the number of subjects with baseline meeting the specific baseline criterion and at least 1 post-baseline assessment. The denominator is the number of subjects with baseline meeting the specific baseline criterion and at least 1 post-baseline ALT / AST / TBILI elevation value.

Table 5: Shift Criteria and Denominator for Alanine Aminotransferase (ALT)

ALT Elevations During Treatment Period	Denominator		
	All Subjects	Subjects with Baseline Values ≤1xULRR	Subjects with Baseline Values >1xULRR
≥3xULRR	Baseline <3xULRR	Baseline ≤1xULRR	Baseline >1xULRR
≥5xULRR	Baseline <5xULRR		
≥10xULRR	Baseline <10xULRR		
≥20xULRR	Baseline <20xULRR		

Abbreviations: ULRR=upper limit of reference range

Table 6: Shift Criteria and Denominator for Aspartate Aminotransferase (AST)

AST Elevations During Treatment Period	Denominator		
	All Subjects	Subjects with Baseline Values ≤1xULRR	Subjects with Baseline Values >1xULRR
≥3xULRR	Baseline <3xULRR	Baseline ≤1xULRR	Baseline >1xULRR
≥5xULRR	Baseline <5xULRR		
≥10xULRR	Baseline <10xULRR		
≥20xULRR	Baseline <20xULRR		

Abbreviations: ULRR=upper limit of reference range

Table 7: Shift Criteria and Denominator for Total Bilirubin (TBILI)

Total Bilirubin Elevations During Treatment Period	Denominator
≥2xULRR	All Subjects with Baseline <2xULRR
≥2xULRR	Baseline ≤1xULRR
≥2xBaseline	Baseline >1xULRR

Abbreviations: ULRR=upper limit of reference range

3.7.5. Vital Signs

Vital signs (supine systolic and supine diastolic blood pressure, heart rate, respiratory rate, temperature, weight, and BMI) will be summarized for baseline and change from baseline (BMI baseline only) by prior ALKS 5461 exposure and overall for the Safety Population, and will include post-discontinuation assessments.

In addition, baseline and post-baseline observed values (lowest, highest, last assessment during treatment period), and change from baseline to lowest, highest and last assessment values during treatment period for vital sign parameters will be summarized by prior ALKS 5461 exposure and overall for the Safety Population, and will not include post-discontinuation assessments.

The following graphical displays for vital sign parameters will be presented by prior ALKS 5461 exposure and overall for the Safety Population:

- Line graphs for mean change from baseline along with the corresponding SE (including Post-discontinuation Safety Period)
- Box-and-Whisker figures for baseline and post-baseline observed values (lowest, highest, and last assessment during treatment period)
- Box-and-Whisker figures for change from baseline to the lowest post-baseline value, the highest post-baseline value, and the last scheduled post-baseline value during treatment period
- Scatter plots for baseline and post-baseline observed values (lowest, highest, and last assessment during treatment period)

Vital signs will also be evaluated using PCS criteria as indicated in Table 8 and summarized by prior ALKS 5461 exposure and overall for the Safety Population. Post-discontinuation assessments will not be included in this analysis.

Table 8: 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%

A supportive listing will present for subjects and parameter for cases where at least 1 value was potentially significant.

3.7.6. Electrocardiograms

Electrocardiogram (ECG) parameters (heart rate, RR interval, PR interval, QRS interval, QT interval, and QTcF [QT interval corrected using Fridericia's method]) will be summarized (baseline and change from baseline) for each visit during the entire study, including last assessment during treatment period and post-discontinuation assessments.

In addition, baseline and post-baseline observed values (lowest, highest, last assessment during treatment period), and change from baseline to lowest, highest and last assessment values during treatment period for ECG parameters will be summarized by prior ALKS 5461 exposure and overall for the Safety Population. These analyses will not include post-discontinuation values.

The following graphical displays for ECG will be presented by prior ALKS 5461 exposure and overall for the Safety Population:

- Line graphs for mean change from baseline along with the corresponding SE (including Post-discontinuation Safety Period)
- Box-and-Whisker figures for baseline and post-baseline observed values (lowest, highest, last assessment during treatment period)
- Box-and-Whisker figures for change from baseline to the lowest post-baseline value, the highest post-baseline value, and the last scheduled post-baseline value during treatment period
- Scatter plots for baseline and post-baseline observed values (lowest, highest, last assessment during treatment period)

ECG will be evaluated using PCS criteria as indicated in Table 9 by prior ALKS 5461 exposure and overall for the Safety Population. These analyses will not include post-discontinuation assessments.

Table 9: Potentially Clinically Significant Abnormal ECG Values

ECG 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/decrease >30 msec
	Change from baseline increase/decrease >60 msec
Heart Rate	Low: ≤50 bpm and decrease ≥15 bpm
	High: ≥100 bpm and increase ≥15 bpm

A supportive listing will present all values for a parameter for subjects with at least 1 PCS value for that parameter.

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

Columbia Suicide Severity Rating Scale items of suicidal behavior and suicidal ideation will be summarized at baseline and post-baseline by prior ALKS 5461 exposure and overall for the Safety Population. The proportion of subjects who meet the criterion for each of these categories will be summarized as described in Table 10. Each item will be presented separately within each category (suicidal behavior, suicidal ideation, self-injurious behavior without suicidal intent). Any suicide attempt (aborted, interrupted, and actual) will also be summarized as a category. Data will be presented for baseline, any post-baseline (i.e. on treatment), and any post-discontinuation values.

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

Table 10: C-SSRS Summary Categories for Analysis

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

Summary of treatment emergent suicide-related events based on the C-SSRS during treatment period will be presented by prior ALKS 5461 exposure and overall for the Safety Population. The degree and type of treatment emergent suicide-related events will be summarized in a table as defined in Table 11. Post-discontinuation assessments will not be included in this analysis.

This analysis population consists of safety population with non-missing baseline and at least 1 post-baseline assessment during 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 non-missing baseline and a post-baseline C-SSRS assessment meeting the treatment emergent suicide-related numerator criteria defined in Table 11, and the denominator is defined as the number of subjects with a non-missing baseline and at least 1 post-baseline C-SSRS assessment meeting the treatment emergent suicide-related denominator criteria defined in Table 11 during treatment period.

Table 11: 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)

3.7.8. Clinical Opiate Withdrawal Scale (COWS) Scores

COWS will be administered only at EOT and post-discontinuation visits, so COWS will be analyzed for Post-discontinuation Safety Population. For Post-discontinuation Safety Population, baseline COWS is defined as EOT COWS assessment. Adequate COWS baseline is defined as EOT COWS assessment being performed within (≤) 2 days of last dose of study drug.

Subjects will be included in the COWS analysis if they have an adequate EOT COWS and at least 1 post-EOT COWS in the post-discontinuation safety period. COWS 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, i.e. EOT COWS assessment was performed more than (>) 2 days of 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 will be presented in all subjects with adequate EOT COWS, and then COWS will be subset by duration of study drug exposure. Three COWS analyses will be presented for the subjects with adequate EOT COWS by the 3 exposure subgroups (any exposure, ≥4 weeks exposure, <4 weeks 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 visits)
- Subject count and incidence 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 post-baseline: the numerator is the number of subjects in each post-discontinuation COWS category with non-missing baseline COWS. If there are more than one post-discontinuation COWS, i.e. a subject with an unscheduled visit, the highest value will be used. The denominator is the number of subjects in each baseline COWS category.

Data listing of COWS scores at each visit will be provided. Narratives will be provided for any clinically meaningful COWS shifts.

4. INTERIM ANALYSES

No interim analysis is planned.

5. CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

N/A.

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 provide complete data. 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 29 (e.g., has assessments at baseline through Day 29, and Day 365 or early termination) would have assessments at early termination mapped to the next scheduled visit for each assessment. In this example, the MADRS and CGI-S from the early termination visit would be mapped to Day 43; and the HAM-A results would be mapped to Day 57. For other visits other than early termination / Day 365, the visit number indicated on the CRF (i.e., CRF visit) will be used as the analysis visit.

Early termination visits for safety measurements will not be mapped to any scheduled post-baseline visit, but will be used as the last assessment during 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 outlier and PCS values and in the subject listings.

6.2. Efficacy Data Handling

MADRS-10 is the sum of the 10 items from the MADRS. HAM-A total score is the sum of 14 items from the HAM-A. If only one of the items of the MADRS, or HAM-A for a given visit is missing, then the total score will be calculated using (sum of non-missing items) × (total number of items) / (number of non-missing items). If more than one of the items are missing, the total score will be set to missing. The MADRS-6 and HAM-A subscale scores will be set to missing if any item is missing.

6.3. Handling of Partial Dates of Prior and Concomitant Medications

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

7. GENERAL STATISTICAL METHODOLOGY

7.1. Statistical Conventions

In general, summary statistics (n, mean, standard deviation [SD], median, minimum and maximum for continuous variables, and number and percentage of subjects in each category for categorical variables) will be provided by study 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 or mean change tables or figures, but will be included in the analyses for the outlier / PCS post-baseline 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 12, unless otherwise specified.

Table 12: Degree of Precision

Statistics	Degree of Precision
Mean, Median, Quartiles, Confidence limit boundaries	One more than the raw data, up to 3 decimal places.
Standard deviation, Standard error	One more than the mean, up to 3 decimal places.
Minimum, Maximum	The same as the raw data.
p-value	Rounded to 3 decimal places and therefore presented as 0.xxx; p-values smaller than 0.001 as '<0.001'; p-values greater than 0.999 as '>0.999'.
Percentage	One decimal place. A percentage of 100% will be reported as 100%. Percentages of zero will be reported as 0.

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

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

8. PROGRAMMING SPECIFICATIONS

Programming specifications will be provided in a separate document.

9. MOCK TABLES, LISTINGS AND FIGURES (TLFS)

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

10. REFERENCES

1. Alkermes ALK5461-208 Study Protocol Amendment 3 (dated 03 March 2016).

APPENDIX 1. AESI – ABUSE POTENTIAL

Preferred Term	Adhoc 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
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

Preferred Term	Adhoc SOC
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 2. AESI – DEPENDENCE

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

APPENDIX 3. 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
Hyperhidrosis
Nausea
Nervousness
Pain
Tremor
Vomiting
Abdominal pain
Arthralgia

Preferred Term
Diarrhoea
Mydriasis
Piloerection
Restlessness
Rhinorrhoea
Tachycardia
Yawning

APPENDIX 4. 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 5. 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 6. 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 7. 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 8. AESI – ORTHOSTASIS 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
Procedural hypotension
Shock
Shock symptom
Syncope

APPENDIX 9. 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
Allergy to vaccine
Alveolitis allergic
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Anaphylaxis treatment

Preferred Term
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
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

Preferred Term
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
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

Preferred Term
Eye oedema
Eye swelling
Eyelid oedema
Face oedema
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
Infusion site urticaria
Infusion site vasculitis
Injection site dermatitis
Injection site eczema
Injection site hypersensitivity
Injection site rash

Preferred Term
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
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

Preferred Term
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
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

Preferred Term
Scleral oedema
Scleritis allergic
Scrotal oedema
Segmented hyalinising vasculitis
Serum sickness
Serum sickness-like reaction
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
Urticarial vasculitis
Vaccination site dermatitis
Vaccination site eczema
Vaccination site exfoliation

Preferred Term
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 10. AESI – SLOWING OF VENTRICULAR REPOLARIZATION

Preferred Term
Electrocardiogram QT interval abnormal
Electrocardiogram QT prolonged
Long QT syndrome
Long QT syndrome congenital
Torsade de pointes
Ventricular tachycardia

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
Hepatic lesion
Hepatic necrosis
Hepatic steato-fibrosis
Hepatic steatosis
Hepatitis fulminant
Hepatobiliary disease
Hepatocellular foamy cell syndrome
Hepatocellular injury

Preferred Term
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
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

Preferred Term
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

APPENDIX 12. AESI – SEXUAL DYSFUNCTION

Preferred Term
Anorgasmia
Disturbance in sexual arousal
Dyspareunia
Ejaculation delayed
Ejaculation disorder
Ejaculation dysfunction
Ejaculation failure
Erectile dysfunction
Female orgasmic disorder
Female sexual arousal disorder
Female sexual dysfunction
Inadequate lubrication
Libido decreased
Libido disorder
Loss of libido
Male orgasmic disorder
Male sexual arousal disorder
Male sexual dysfunction
Orgasm abnormal
Orgasmic sensation decreased
Sexual dysfunction
Vulvovaginal dryness