STATISTICAL ANALYSIS PLAN

Study Title:	A Randomized, Double-Blind, Parallel-Group, Placebo Controlled Study to Evaluate the Efficacy and Safety of 2 Fixed Doses (5.0 mg or 2.5 mg) of MIN-117 in Adult Patients with Major Depressive Disorder
Phase:	2b
Protocol No.:	MIN-117C03
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Prepared By:	[redacted]
Prepared For:	Minerva Neurosciences, Inc. 1601 Trapelo Road, Suite 286 Waltham, MA 02451

CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared, reviewed, and approved by the following:

Prepared by:

[redacted]

Review & Approval:

[redacted]

[redacted]

[redacted]

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1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of data from Protocol MIN-117C03. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and case report forms (CRFs) for details of study conduct and data collection.

1.1. STUDY OVERVIEW

Protocol MIN-117C03 is a 6-week, 3-arm, randomized, double-blind, placebo- controlled study to investigate the safety and efficacy of MIN-117 in male and female patients with Major Depressive Disorder (MDD), aged 18 to 65. Approximately 324 patients will be randomly assigned to 1 of 3 treatment arms, including placebo, 5.0 mg MIN-117, or 2.5 mg MIN-117, in a 2:1:1 ratio.

The study design has 3 phases: a screening phase of up to 3 weeks (including washout), a 6-week double-blind treatment phase, and a post-study follow-up visit, occurring approximately 2 weeks after completing the double-blind treatment phase.

Screening Phase: Patients with an acute exacerbation of a major depressive episode will be screened for this study. Screening will include informed consent (for the overall study as well as for optional pharmacogenomic research), evaluation for eligibility in the study, and assessment of medical history. Patients must meet Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) diagnostic criteria for moderate to severe MDD, with anxious distress and without psychotic features. The diagnosis should be confirmed by the Structured clinical interview for DSM-5 (SCID-5). Patients will undergo additional physical and psychiatric evaluations, as well as safety evaluations. If patients give informed consent to participate and meet all study entry criteria at Screening, they will be tapered off their current psychotropic medications. Patients will be free of any psychotropic medications for a period of 1 week [or 2 weeks for a monoamine oxidase (MAO) inhibitor, 4 weeks for fluoxetine] prior to randomization.

Double-blind Treatment Phase: After at least 1-week of psychotropic drug-free period, patients will undergo evaluation for eligibility, and if they still meet the study entry criteria, they will be randomly assigned in a 2:1:1 ratio to receive placebo, 5.0 mg MIN-117, or 2.5 mg MIN-117, respectively, once daily for 6 weeks. Clinic visits will occur at Visits 2, 3, 4, and 5/Early Withdrawal (Weeks 1, 2, 4, and 6, respectively).

Post-Study Visit: At the end of the study, patients will be evaluated for safety/tolerability at the Post-Study Visit, approximately 2 weeks after completing the Double-blind Treatment Phase. Any patient who terminates from the study early will undergo the Early Withdrawal visit procedures and will have a Post-Study Visit within approximately 2 weeks.

1.2. TIME AND EVENTS SCHEDULE

Procedures and Evaluations	Screening	Baseline	Double-Blind Phase			Post Study Follow-Up
Visit#[a]	**1**	**2**	**3**	**4**	**5 / EW[b]**	**6**
Week	**-3**	**1**	**2**	**4**	**6**	**8**
Day	**-21 to -1**	**1**	**15**	**29**	**43**	**57**
Screening/Administrative						
Informed consent	X					
Pharmacogenomic informed consent[c]	X					
Inclusion/exclusion criteria	X	X				
Medical history, SCID-5, MGH-SAFER	X					
Prior medications	X	X				
Preplanned surgery/procedures	X					
Height	X					
Pregnancy test[d]	X	X		X	X	X
Alcohol and Drug Screen	X	X				
TSH, serology	X					
Taper of psychotropic drugs	X[e]	X[e]				
Randomization		X[f]				
Study Drug						
Administer/Dispense study drug		X	X	X	X[g]	
Study drug accountability			X	X	X	
Pharmacokinetics						
Blood sample collection[h]		X	X	X	X	X
Pharmacodynamics						
Blood sample collection		X			X	
Pharmacogenomics						
Blood sample collection		X[i]				
Efficacy						
Investigator-Rated: MADRS, HAM-A, CGI-S	X	X	X	X	X	
Investigator-Rated: CGI-I			X	X	X	
Investigator-Rated: DSST		X	X	X	X	
Subject-Rated: SHAPS, A-SEX	X	X	X	X	X	
Subject-Rated: IDS-SR_{30}	X	X			X	
Subject-Rated: PSS		X			X	
Sleep recording (Somno-Art)[j]	X	X			X	
Safety						
Physical examination	X	X			X	X
12-Lead ECG (triplicate)[k]	X	X		X	X	X
Vital signs, temperature, weight[l]	X	X	X	X	X	X
Clinical laboratory tests[m]	X	X			X	X
C-SSRS	X	X	X	X	X	X
Adverse Events	Continuous					
Concomitant therapy	Continuous					

Abbreviations: A-SEX = Arizona Sexual Experiences Scale; CGI-I = Clinical Global Impression of Improvement Scale; CGI-S = Clinical Global Impression of Severity Scale; C-SSRS = Columbia Suicide Severity Rating Scale; DSST = digit symbol substitution test; HAM-A = Hamilton anxiety scale; IDS-SR_{30} = Inventory of Depressive Symptoms – Subject-Related; MADRS = Montgomery-Asberg Depression Rating Scale; PSS = Perceived Stress Scale; SCID-5 = Structured clinical interview for DSM-5; SHAPS = Snaith-Hamilton Pleasure Scale.
[a]Visits 3 to 6 may occur within a ±3-day window relative to Baseline (Visit 2). Visit 2 may occur within a +7 day window relative to Visit 1 (i.e., the screening period may be extended to 28 days) upon Sponsor's decision.
[b]Visit 5 represents the end-of-treatment or early withdrawal (EW) visit, and patients who discontinue the study prematurely should undergo all assessments indicated for this visit.
[c]To participate in the optional pharmacogenomic component of this study, patients must sign the pharmacogenomic informed consent form, indicating their willingness to participate.
[d]For all women of childbearing potential, serum pregnancy testing will be performed at Screening (Visit 1), Baseline (Visit 2), and post study visit. Urine pregnancy testing will be performed at Baseline (Visit 2), and Visits 4, 5, and 6.
[e]After meeting eligibility criteria during their Screening visit, patients will taper off their current psychotropic medications. Patients will be free of any psychotropic medications for a period of 1 week (or 2 weeks for MAO inhibitor, 4 weeks for fluoxetine) prior to randomization.
[f]All procedures (except dispensing of study medication) should be completed on Day 1 before randomization.
[g] Only drug administration at Visit 5.
[h] Samples will be obtained within 1 hour prior to dosing and approximately 2 to 4 hours after dosing (the approximate time of maximum plasma concentration for MIN-117) on Visits 2, 3, 4, and 5. Additionally, 1 sample will be taken on Visit 6.
[i] A 10-mL blood sample will be collected only from patients who give informed consent for the pharmacogenomic component of this study. A sample collected at a later time point does not constitute a protocol violation and would not require protocol amendment.
[j] Sleep recording by using Somno-Art for 1 night after Screening, 1 night before dosing, and 1 night after dosing on Visit 2 and Visit 5.
[k] Triplicate ECGs to be performed at least 1 minute apart within 5 minutes, while the patient is supine for ≥ 10 minutes.
[l] Patients will be weighed clothed (lightly) and without shoes.
[m] Clinical laboratory tests will include hematology, serum chemistry (including serum lipid profile, and fasting blood glucose), and urinalysis. Patients must fast for 8 hours before the blood sample is taken.

1.3. GLOSSARY OF ABBREVIATION

AE	Adverse event
ANCOVA	Analysis of covariance
A-SEX	Arizona Sexual Experiences Scale
BMI	Body mass index
C-SSRS	Columbia-Suicide Severity Rating Scale
CGI-I	Clinical Global Impression – Improvement Rating
CGI-S	Clinical Global Impression – Severity Rating
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition
DSST	Digital Symbol Substitution Test
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
HAM-A	Hamilton Anxiety Scale
IDS-SR_{30}	Inventory of Depressive Symptoms – Subject Rated
IWRS	Interactive Web Response System
ITT	Intent to Treat
KR	Kenward-Roger
LOCF	Last Observation Carried Forward
MADRS	Montgomery-Asberg Depression Rating Scale
MAO	Monoamine oxidase
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects Model Repeated Measurement
PCS	Potentially Clinically Significant
PD	Pharmacodynamic

PK	Pharmacokinetic
PSS	Perceived Stress Scale
QTc	QT interval value corrected for heart rate
QTcF	QT interval value corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAF	Safety set
SCID-5	Structured clinical interview for DSM-5
SD	Standard Deviation
SHAPS	Snaith-Hamilton Pleasure Scale
TE	Treatment-emergent
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

2. OBJECTIVES

Primary Objective:

- To evaluate the efficacy of 2 fixed doses (5.0 mg or 2.5 mg) of MIN-117 compared with placebo in reducing the symptoms of major depression measured by the change in Montgomery-Asberg Depression Rating Scale (MADRS) total score over 6 weeks of treatment in adult patients with MDD.

Secondary Objectives:

1. To assess the change from Baseline of 2 fixed doses (5.0 mg or 2.5 mg) of MIN-117 compared with placebo over 6 weeks of treatment on:
   - The symptoms of anxiety using the HAM-A (key secondary).
   - The severity of illness and improvement using the Clinical Global Impression – Severity Rating (CGI-S) and Clinical Global Impression – Improvement Rating (CGI-I).
2. To evaluate the safety of 2 fixed doses (5.0 mg or 2.5 mg) of MIN-117 compared with placebo over 6 weeks of treatment in adult patients with MDD.

Exploratory Objectives:

1. To assess the change from Baseline of 2 fixed doses (5.0 mg or 2.5 mg) of MIN-117 compared with placebo over 6 weeks of treatment on:
   - Commonly associated symptoms of MDD by using the Inventory of Depressive Symptoms – Subject Rated ($IDS\text{-}SR_{30}$).
   - The ability to experience hedonic capacity by using the Snaith-Hamilton Pleasure Scale (SHAPS).
   - Cognitive function as measured by Digital Symbol Substitution Test (DSST).
   - Perception of stress using the Perceived Stress Scale (PSS).
   - Sexual functioning by using the Arizona Sexual Experiences Scale (A-SEX).
   - Sleep parameters as assessed by Somno-Art methodology (at select sites).
   - Neurotrophic/inflammatory factors.

2. To explore the pharmacokinetics (PK) of MIN-117 [redacted] and assess the PK/pharmacodynamics (PD) relationship.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. SAMPLE SIZE AND POWER

The sample size for this study is based on the assumption of a treatment difference of at least 4 points in the mean change from Baseline to to endpoint in MADRS total score between

any MIN-117 dose group and placebo. A standard deviation of 9 in the change in MADRS total score from Baseline is used. Using the Bonferroni multiplicity adjustment for multiple comparisons of 2 MIN-117 dose groups with placebo and assuming an allocation of 2:1:1 for placebo and the 2 MIN-117 doses, 146 patients in the placebo group and 73 patients in each MIN-117 dose group are required to detect the treatment difference of 4 points with a power of 80% at an overall 2-sided significance level of 0.05. When adjusted for a rate of 10% of patients who will not have either Baseline or post-Baseline efficacy assessments, the required number of patients becomes 162 for the placebo group and 81 for each of the 2 MIN-117 dose groups. Therefore, the total number of patients across the 3 treatment groups will be 324.

3.2. RANDOMIZATION AND BLINDING

Central randomization will be implemented in this study. Patients will be randomized to 1 of 3 treatment arms, based on a computer-generated randomization schedule prepared by or under the supervision of Minerva before the study. The randomization will be balanced by using permuted blocks. The Interactive Web Response System (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the patient.

Approximately 324 eligible patients will be randomized in a 2:1:1 ratio to the following groups:

- Placebo
- 5.0 mg MIN-117
- 2.5 mg MIN-117

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual patient, if needed.

Under normal circumstances, the blind should not be broken until all patients have completed the study and the database is locked. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment the patient is receiving. In such cases, the investigator may in an emergency determine the identity of the treatment by IWRS.

In the event the blind is broken, then sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the investigator in the appropriate section of the electronic case report form (eCRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the patient's source documents in a secure manner (e.g., sealed envelope) so as not to unblind the treatment assignment to the study site, sponsor/contract research organization (CRO)

personnel. The investigator is also advised not to reveal the study treatment assignment to the study site or sponsor personnel.

3.3. HANDLING OF DATA

3.3.1. Strata and Covariates

The primary efficacy analysis and corresponding sensitivity analyses will have Baseline MADRS as a covariate. Similarly, secondary endpoints and select additional efficacy analyses will contain covariates of their respective Baseline values.

3.3.2. Examination of Patient Subsets

Select efficacy analyses will be presented by region, which will consist of the following grouping:

- US and Finland combined
- All other countries

3.3.3. Multiple Testing and Comparisons

The adjustment for multiplicity within the family of primary hypotheses will utilize the Hochberg procedure for the purpose of reporting of results. The procedure will allow the null hypothesis of no treatment difference for both the 5.0 mg and 2.5 mg doses versus placebo to be rejected if the largest p-value of comparing either of these 2 doses versus placebo is at or below 0.05. Otherwise, the lowest of these 2 p-values must be at or below 0.025 to allow for rejecting the null hypothesis for the representative dose.

The overall type I error rate for testing the 2 MIN-117 doses versus placebo for the primary and the key secondary endpoints will be controlled at the 2-sided 0.05 level. The primary family of hypotheses (corresponding to the primary endpoint) and the secondary family hypotheses (corresponding to the key secondary endpoint, the change from Baseline in HAM-A total score) will be tested in a sequential manner with suitable adjustment for multiplicity within the family of primary hypotheses and within the family of the secondary hypotheses such that a MIN-117 dose versus placebo null hypothesis contrast testing within the secondary family can be evaluated only when the same null hypothesis contrast in the primary family was rejected (the truncated Hochberg procedure).

3.3.4. Missing Data and Outliers

Every effort will be made to obtain required data at each scheduled evaluation from all patients who have been treated. Imputation of incomplete dates is detailed in Section 3.3.5.

As part of sensitivity analyses on the primary and key secondary endpoint, patients who are missing MADRS and HAM-A scores, respectively, will have this value imputed using the

last-observation-carried-forward (LOCF) method and multiple imputation. An additional sensitivity analysis will impute scores missing due to early study discontinuation using the mean score of the placebo group. Additionally, the LOCF method may be used to impute missing MADRS and CGI-I values for the analyses of secondary and exploratory endpoints. Only post-Baseline scores will be eligible to be carried forward for this imputation. The primary analysis will use observed data without imputation.

3.3.5. Imputation of Incomplete Dates

An incomplete date is any date for which either the day, month, or year is unknown, but all three fields are not unknown. An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a patient. For many of the analyses, a complete date is necessary in order to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed.

In an effort to minimize bias, the project statistician will impute dates in a systematic but reasonable manner. If the month/year is the same as the Day 1 month/year then the date will be set to the date of Day 1. In other cases, missing days will be imputed as the day component of Day 1; missing months/years will be imputed as the month/year of Day 1. If this method of imputation produces and invalid date, the last date of the month will be used.

3.3.6. Imputation of Alphanumeric Data

Should there be instances where laboratory data are recorded as for example, "<0.1" or ">10", the data will be imputed for the purpose of quantitative summaries. The data will appear in data listings unchanged.

For incorporation in quantitative summaries, the following imputation rules will be employed:

The limit of quantitation will be increased by one level of precision in the direction of the symbol that precedes the value. For example, "< 0.1" will be imputed to "0.09", while ">0.1" will be imputed to "0.11", and ">10" will be imputed to "10.1". Value reported as "≤" or "≥" will be imputed similarly. For example, "≤ 0.1" will be imputed to "0.09".

3.3.7. Presentations by Time Point

Nominal Time Points as obtained from the CRF or laboratory will be utilized for summary displays. If assessments are collected multiple times within a given nominal time point, the result closest to the scheduled time will be used for summary presentations. If two measurements have the same distance to the expected time, the earlier value will be used. If a scheduled assessment and an Unscheduled or Early Termination assessment are collected on the same day, the scheduled assessment will be used for summary presentations, unless

otherwise indicated by the sponsor. Unscheduled and Early Termination assessments will be windowed to a study visit using the analysis window described below in case the scheduled visit was not performed. All assessments will be presented in the listings.

Visit	Target Day	Window Days
3: Week 2	15	9 - 22
4: Week 4	29	23 - 36
5: Week 6	43	37 - 50
6: Follow-Up	57	51 - 64

3.3.8. Definitions and Terminology

Baseline Value

Baseline will be defined as the last valid evaluation done before the study drug administration on Day 1.

Day 1

Day 1 is the earliest day that study drug is first initiated.

Study Day

Study Day is defined relative to Baseline (Day 1). Thus, the study day of an event is calculated as:

For events occurring on or after Day 1, Study Day = event date – date of Day 1+ 1.

For events occurring prior to Day 1, Study Day = event date – dated of Day 1

Study Visit

Study Visit is the nominal visit as recorded on the CRF.

Last Dose of Study Drug

Last Dose of Study Drug is defined as the last date that the patient received study drug as determined by last date of dosing as recorded on the Study Drug Administration and Accountability CRF for Visit 5/Early Termination.

Days on Treatment

Days on treatment will be calculated as the number of days from the date of first dose to the date of last dose, inclusive.

Treatment Compliance

Treatment compliance during a specified period of time is defined as the total number of tablets taken by a patient during that time divided by the number of tablets prescribed during that time, multiplied by 100. The number of tablets prescribed during a specified period of time will be calculated as the number of days in that timeframe multiplied by the number of tablets prescribed per day.

Change from Baseline

Change from baseline for a given endpoint is defined as the Study Visit X value minus the Baseline Value.

MADRS Response

MADRS response is defined as a decrease from Baseline in MADRS total score of ≥ 50%.

Time to ≥ 50% MADRS Improvement (Days)

Time to ≥ 50% MADRS improvement is defined as the time, in days, from initiation of study treatment to the first observed ≥ 50% decrease from Baseline in MADRS total score. Any patient who does not experience a ≥ 50% decrease from Baseline in MADRS total score during the study will have their time to ≥ 50% MADRS improvement censored at the time of his or her last non-missing MADRS assessment.

Time to ≥ 30% MADRS Improvement (Days)

Time to ≥ 30% MADRS improvement is defined as the time, in days, from initiation of study treatment to the first observed ≥ 30% decrease from Baseline in MADRS total score. Any patient who does not experience a ≥ 30% decrease from Baseline in MADRS total score during the study will have their time to ≥ 30% MADRS improvement censored at the time of his or her last non-missing MADRS assessment.

Early Response

Early response is defined as experiencing a ≥ 50% decrease from Baseline in MADRS total score along with a CGI-I score ≤ 2 at any post-Baseline visit.

Additionally, the same analysis will be repeated using ≥ 30% decrease from Baseline in MADRS total score along with a CGI-I score ≤ 2 at any post-Baseline visit.

Sustained Response

Sustained response is defined as experiencing a ≥ 50% decrease from Baseline in MADRS total score along with a CGI-I score ≤ 2 at Week 2 or Week 4 that continues to Week 6.

Additionally, the same analysis will be repeated using ≥ 30% decrease from Baseline in MADRS total score along with a CGI-I score ≤ 2 at Week 2 or Week 4 that continues to Week 6.

Remission in MADRS (sustained or occasional)

Remission in MADRS is defined as a MADRS total score < 12.

MADRS Core Mood Items

MADRS core mood items are defined as a combination of the first two items on the MADRS questionnaire, Apparent Sadness and Reported Sadness.

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study patient administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the Baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

All adverse events will be recorded on the Adverse Event CRF.

Treatment-emergent Adverse Event

Any recorded Adverse Event that occurs on or after the initiation of study treatment is considered treatment-emergent (TE). Additionally, it is assumed that an Adverse Event which was reported to have started on Day 1 without an associated onset time may have occurred after the initiation study treatment. Hence, Adverse Events occurring on Day 1 without an onset time are assumed to be TE.

Concomitant Medications

Concomitant medications are those medications taken on or after the initiation of study treatment. This definition includes medications started prior to the initiation of study treatment, but continuing concomitantly with study treatment.

Prior Medications

Prior medications are those medications taken and completed prior to the initiation of study treatment.

3.4. TIMING OF ANALYSIS

A final analysis will be conducted once the last patient completes or discontinues the study, and the resulting clinical database has been cleaned, quality checked, the final database lock has occurred, and the treatments are unblinded.

4. ANALYSIS POPULATIONS

The populations for analysis will include the intent to treat population (ITT), and the safety population (SAF).

4.1. INTENT TO TREAT POPULATION

The ITT population is defined as all randomized patients who receive at least 1 dose of study drug. Patients in this population will be analyzed according to the treatment to which they were randomized, regardless of what treatment they received. All efficacy analyses will be based on this population and treatment assignment.

4.2. SAFETY POPULATION

The SAF is the population of all patients who receive at least 1 dose of study treatment. Patients in this population will be analyzed according to the treatment they received, regardless of which treatment they were randomly assigned. All safety and tolerability analyses will be based on this population and treatment assignment.

5. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study, with hypothesis testing performed for selected endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of patients (n), mean, median, standard deviation (SD), minimum, and maximum for continuous data and frequencies and percentages for categorical data. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted by treatment group, patient number, and by date within each patient number.

The term 'treatment group' refers to the three treatment arms of this study: Placebo, 2.5 mg MIN-117, and 5.0 mg MIN-117.

All statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.050 unless stated otherwise, as described in section 3.3.3.

The statistical analyses will be conducted with the SAS® System version 9.4 or higher. All analyses will be patient to formal verification procedures. Specifically, results will be verified utilizing independent programming prior to issuance of the draft statistical report. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

5.1. PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patient disposition will be presented for all patients. The number of patients who meet all eligibility criteria will be presented, as well as the number of patients included in the ITT,

and safety populations. The number of patients who completed all study treatment and discontinued from the study will be provided. The reasons for early discontinuation at any point also will be presented by treatment group. The proportion of premature discontinuations will be compared between treatment groups using the Fisher exact test. Similarly, the percentages for each discontinuation reason will be compared between treatment groups using the Fisher exact test. Additionally, the number of days on study will be summarized for all treated patients.

Demographic data and baseline characteristics including age, weight, height, body mass index (BMI), gender, and race will be summarized using descriptive statistics for the safety population, and will be presented by treatment group, combined MIN-117 doses, and overall. The number and percent of patients with a current or historical presence of abnormal finding in medical history will be summarized by treatment group and overall. This information will be reviewed for baseline differences, but no statistical testing will be performed.

Baseline disease characteristics, including MADRS, HAM-A, IDS-SR30, CGI-S, SHAPS, DSST, PSS, and A-SEX scores at Baseline will be summarized using descriptive statistics for the safety population, and will be presented by treatment group, combined MIN-117 doses, and overall.

Additionally, study treatment exposure and treatment compliance will be summarized by treatment group. The number of days on study treatment will be summarized for all treated patients. Treatment compliance over the treatment period will be similarly summarized by treatment group. Additionally, treatment compliance between consecutive visits will be summarized by visit and treatment group.

5.2. EFFICACY ANALYSIS

5.2.1. Primary Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following components:

Population: patients with a pre-defined minimum threshold and fluctuation of depressive symptoms as captured by IDS-SR_{30} score before randomization.

Endpoint: change in MADRS total score from Baseline to the end of Week 6.

Measure of Intervention: the effect of the initially randomized treatment that would have been observed had all patients remained on their treatment throughout the double-blind phase.

Intercurrent events: early study discontinuation for any reason.

Summary measure: difference in treatment means.

5.2.2. Primary Efficacy Analysis

MADRS total score values and change from Baseline will be summarized by treatment group and study visit. Change from Baseline in MADRS total score will be analyzed using a mixed-effect model repeated measurement (MMRM) with fixed effects for treatment group (placebo, 2.5 mg MIN-117, and 5.0 mg MIN-117), region, visit, and treatment group-by-visit interaction, a random effect for patient within treatment group, and Baseline MADRS total score as a covariate. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The Kenward-Roger (KR) approximation will be used to estimate denominator degrees of freedom. Comparisons against placebo will be performed using the appropriate contrasts from this model at Week 6.

As a sensitivity analysis of the primary endpoint, change from Baseline to Week 6 in MADRS total score will additionally be analyzed using an analysis of covariance (ANCOVA) model with factors for treatment and region and Baseline MADRS score as a covariate. This analysis will be repeated for change from Baseline to Week 2 and 4 as well. For this analysis, patients missing MADRS total score at any visit will have this value imputed using the LOCF method.

An additional sensitivity analysis of the primary endpoint will be performed to determine the impact of how data missing due to early discontinuation for any reason is handled. This analysis will use the same ANCOVA model described above. This analysis will be repeated for change from Baseline to Week 2 and 4 as well. For this analysis, any MADRS total scores that are missing due to early discontinuation of a subject will be imputed using the value of the mean MADRS total score in the placebo group at that timepoint. All missing MADRS total scores that are not due to early discontinuation will be imputed using the LOCF method.

A final sensitivity analysis of the primary endpoint will be performed using the same ANCOVA model described above, wherein all missing MADRS total scores will be imputed using multiple imputation. Missing values will be imputed using the following auxiliary information: treatment, Baseline MADRS total score, region, sex, Baseline age, and visit. Treatment, Baseline MADRS total score, region, sex, Baseline age, and visit are included as auxiliary information because it is believed that subjects with similar values for each of these parameters would respond similarly. A total of 10 imputations will be performed. The least square (LS) Mean, standard error (SE), LS Mean difference and p-value from the PROC MIANALYZE will be presented. Additionally, the range of p-values from all 10 imputations will be presented.

5.2.3. Key Secondary Estimand

The key secondary estimand is defined by the following components:

Population: patients with a pre-defined minimum threshold and fluctuation of depressive symptoms as captured by IDS-SR_{30} score before randomization.

Endpoint: change in HAM-A total score from Baseline to the end of Week 6.

Measure of Intervention: the effect of the initially randomized treatment that would have been observed had all patients remained on their treatment throughout the double-blind phase.

Intercurrent events: early study discontinuation for any reason.

Summary measure: difference in treatment means.

5.2.4. Key Secondary Efficacy Analysis

HAM-A total score and change from Baseline will be summarized by treatment group and study visit. Change from Baseline in HAM-A total score will be analyzed using an MMRM model with fixed effects for treatment group, region, visit, and treatment group-by-visit interaction, a random effect for patient within treatment group, and Baseline HAM-A total score as a covariate. Comparisons against placebo will be performed using the appropriate contrasts from this model at Week 6.

As a sensitivity analysis of the primary endpoint, change from Baseline to Week 6 in HAM-A total score will additionally be analyzed using an ANCOVA model with factors for treatment and region and Baseline HAM-A score as a covariate. This analysis will be repeated for change from Baseline to Week 2 and 4 as well. For this analysis, patients missing HAM-A total score at any visit will have this value imputed using the LOCF method.

An additional sensitivity analysis of the primary endpoint will be performed to determine the impact of how data missing due to early discontinuation for any reason is handled. This analysis will use the same ANCOVA model described above. This analysis will be repeated for change from Baseline to Week 2 and 4 as well For this analysis, any HAM-A total scores that are missing due to early discontinuation of a subject will be imputed using the value of the mean HAM-A total score in the placebo group at that timepoint. All missing HAM-A total scores that are not due to early discontinuation will be imputed using the LOCF method.

A final sensitivity analysis of the key secondary endpoint will be performed using the same ANCOVA model described above, wherein all missing HAM-A total scores will be imputed using multiple imputation. Missing values will be imputed using the following auxiliary information: treatment, Baseline HAM-A total score, region, sex, Baseline age, and visit. Treatment, Baseline HAM-A total score, region, sex, Baseline age, and visit are included as auxiliary information because it is believed that subjects with similar values for each of these parameters would respond similarly. A total of 10 imputations will be performed. The least square (LS) Mean, standard error (SE), LS Mean difference and p-value from the PROC MIANALYZE will be presented. Additionally, the range of p-values from all 10 imputations will be presented.

5.2.5. Additional Secondary and Exploratory Endpoints

Other secondary and exploratory endpoints include

- Change from Baseline in CGI-S score
- Observed CGI-I score
- Change from Baseline in IDS-SR_{30}
- Change from Baseline in SHAPS
- Change from Baseline in DSST
- Change from Baseline in PSS
- Change from Baseline in A-SEX
- Rate of MADRS responders
- Time to ≥ 50% MADRS improvement
- Time to ≥ 30% MADRS improvement
- Rate of early responders
- Rate of sustained responders
- Rate of remission in MADRS
- Changes from Baseline in single MADRS rating scale items
- Changes from Baseline in MADRS core mood items
- Change from Baseline in sleep onset latency
- Change from Baseline in REM sleep latency
- Change from Baseline in wake after sleep onset
- Change from Baseline in time spent in each sleep stage
- Change from Baseline in total sleep time
- Change from Baseline in sleep efficiency index
- Change from Baseline in number of awakenings
- Change from Baseline in number of sleep cycles

5.2.6. Secondary and Exploratory Analyses

CGI-S scores and change from Baseline will be summarized by treatment group and study visit. Differences between treatment groups in change from Baseline at Week 6 will be analyzed by means of an ANCOVA model run on ranked change, with treatment group as a factor and Baseline CGI-S value as a covariate.

CGI-I scores will be summarized by treatment group and study visit. Differences between treatment groups in CGI-I score at Week 6 will be analyzed by means of an ANCOVA model run on ranked score, with treatment group as a factor and Baseline CGI-S value as a covariate.

IDS-SR_{30} total score and change from Baseline will be summarized by treatment group and study visit. Change from Baseline in IDS-SR_{30} total score will be analyzed using an MMRM model with fixed effects for treatment group, region, visit, and treatment group-by-visit interaction, a random effect for patient within treatment group, and Baseline IDS-SR_{30} total score as a covariate. Comparisons against placebo will be performed using the appropriate contrasts from this model at Week 6.

SHAPS total score and change from Baseline will be summarized by treatment group and study visit. Change from Baseline in SHAPS total score will be analyzed using an MMRM model with fixed effects for treatment group, region, visit, and treatment group-by-visit interaction, a random effect for patient within treatment group, and Baseline SHAPS total score as a covariate. Comparisons against placebo will be performed using the appropriate contrasts from this model at Week 6.

DSST score and change from Baseline will be summarized by treatment group and study visit. Change from Baseline in DSST score will be analyzed using an MMRM model with fixed effects for treatment group, region, visit, and treatment group-by-visit interaction, a random effect for patient within treatment group, and Baseline DSST score as a covariate. Comparisons against placebo will be performed using the appropriate contrasts from this model at Week 6.

PSS total score and change from Baseline will be summarized by treatment group and study visit. Change from Baseline in PSS total score will be analyzed using an MMRM model with fixed effects for treatment group, region, visit, and treatment group-by-visit interaction, a random effect for patient within treatment group, and Baseline PSS total score as a covariate. Comparisons against placebo will be performed using the appropriate contrasts from this model at Week 6.

A-SEX total score and change from Baseline will be summarized by treatment group and study visit. Change from Baseline in A-SEX total score will be analyzed using an MMRM

model with fixed effects for treatment group, region, visit, and treatment group-by-visit interaction, a random effect for patient within treatment group, and Baseline A-SEX total score as a covariate. Comparisons against placebo will be performed using the appropriate contrasts from this model at Week 6.

The rate of responders will be presented by treatment group and study visit. Treatment differences in responder rate at Week 6 will be analyzed using a logistic regression model with factors for treatment group and Baseline MADRS total score. Any patients who are missing Week 6 MADRS total score will have this value imputed using LOCF for this analysis.

Time to ≥ 50% MADRS improvement will be summarized by treatment group using the Kaplan-Meier method. Treatment differences in time to ≥ 50% MADRS improvement will be analyzed using a Cox-regression model with treatment group and Baseline MADRS total score as a covariate. If a patient does not experience ≥ 50% improvement during the duration of the study, his or her time to ≥ 50% MADRS improvement will be censored at the time of their last non-missing MADRS assessment.

Time to ≥ 30% MADRS improvement will be summarized by treatment group using the Kaplan-Meier method. Treatment differences in time to ≥ 30% MADRS improvement will be analyzed using a Cox-regression model with treatment group and Baseline MADRS total score as a covariate. If a patient does not experience ≥ 30% improvement during the duration of the study, his or her time to ≥ 30% MADRS improvement will be censored at the time of their last non-missing MADRS assessment.

The rate of early responders (≥ 50% and ≥ 30% MADRS) will be presented by treatment group and study visit. Treatment differences in responder rate will be analyzed using a logistic regression model with factors for treatment group and Baseline MADRS total score. Any missing MADRS and CGI-I scores will be imputed using LOCF for this analysis.

The rate of sustained responders (≥ 50% and ≥ 30% MADRS) will be presented by treatment group. Treatment differences in responder rate will be analyzed using a logistic regression model with factors for treatment group and Baseline MADRS total score Any missing MADRS and CGI-I scores will be imputed using LOCF for this analysis.

The rate of remission in MADRS will be presented by treatment group. Treatment differences in remission rate will be analyzed using a logistic regression model with factors for treatment group and Baseline MADRS total score.

Single MADRS rating scale items and their change from Baseline will be summarized by treatment group and study visit. Differences between treatment groups in change from

Baseline to Week 6 will be analyzed using an ANCOVA of ranked data, with treatment group as a factor and Baseline rating value as a covariate.

MADRS core mood items and their change from Baseline will be summarized by treatment group and study visit. Differences between treatment groups in change from Baseline to Week 6 will be analyzed using an ANCOVA of ranked data, with treatment group as a factor and Baseline rating value as a covariate.

All changes in sleep parameters will be analyzed using an MMRM model with fixed effects for treatment group, region, visit, and treatment group-by-visit interaction, a random effect for patient within treatment group, and Baseline sleep parameter as covariate. Comparisons against placebo will be performed using the appropriate contrasts from this model at Week 6.

If the data is not amenable to analysis by logistic regression for any of the responder endpoints included in this section, then comparisons between treatment groups may be performed using Cochran-Mantel-Haenszel (CMH) testing instead.

5.3. PHARMACOKINETIC ANALYSES

The primary objective of the PK statistical analysis will be to estimate the relative bioavailability of MIN-117 and the effect of MIN-117 dose. Details of this analysis can be found in the PK Analysis Plan.

5.4. SAFETY ANALYSES

5.4.1. Adverse Events

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 preferred term and system organ classification. If a patient experiences multiple events that map to a single preferred term, the greatest severity grade and strongest investigator assessment of relation to study medication will be assigned to the preferred term for the appropriate summaries. Should an event have a missing severity or relationship, it will be classified as having the highest severity and/or strongest relationship to study medication.

The occurrence of TE adverse events (TEAEs) will be summarized by treatment group using preferred terms, system organ classifications, and severity. Separate summaries of TE serious adverse events (SAE), TEAE related to study treatment, TEAE leading to discontinuation of study treatment, and TE fatal adverse events will be generated. All adverse events reported will be listed for individual patients showing both verbatim and preferred terms, as well as system organ class. All adverse events that occurred prior to the

initiation of study treatment will be excluded from the tables but will be included in the listings. Any TEAE occurring after the End of Study visit will not be summarized.

Missing onset dates will be imputed as previously outlined in Section 3.3.5 as required to determine TE events. Adverse events occurring on Day 1 with missing onset times will be assumed to be TE.

5.4.2. Clinical Laboratory Assessments

Descriptive summaries of selected (quantitative) clinical laboratory results and change from baseline will be presented by treatment group and visit. Laboratory abnormalities will be determined using pre-defined normal ranges. The number and percentage of patients experiencing TE clinically significant (CS) laboratory abnormalities as reported by the central laboratory, and potentially clinically significant (PCS) abnormalities for select parameters per the table below will be summarized by treatment group. Additionally, shifts in Laboratory values with reference to the normal range from Study Baseline to Week 6 will be summarized by treatment group.

Listings will be provided for patients with any laboratory results outside the reference ranges, as well as for patients with any CS and PCS (select parameters) laboratory results.

Criteria for Potentially Clinically Significant Laboratory Tests

Laboratory Parameter		*SI Units*	*Conversion Factor*[a]	*Traditional Units*	*PCS Criteria*[b] *Low Values*	*PCS Criteria*[b] *High Values*
Hematology						
Hemoglobin	F	g/L	0.1	g/dL	< 100	—
	Male				< 120	
Hematocrit	F	ratio	100	%	≤ 32% and ≥3% decrease from baseline	—
	Male				≤ 37% and ≥3% decrease from baseline	
White cell count		10^9/L	1	10^3/µL	≤ 2.5	≥ 15
Eosinophils absolute cell count		10^9/L	1	10^3/µL	—	≥ 1.50
Neutrophils absolute cell count		10^9/L	1	10^3/µL	≤ 1.50	≥ 12.0

Lymphocyte absolute cell count	10^9/L	1	10^3/µL	≤ 0.8	≥ 4.0
Platelet count	10^9/L	1	10^3/µL	≤ 75	≥ 700
Chemistry					
Albumin	g/L	0.1	g/dL	< 28	—
Alkaline phosphatase	U/L	1	U/L	—	≥ 2 × UNL
ALT	U/L	1	U/L	—	≥ 3 × UNL
AST	U/L	1	U/L	—	≥ 3 × UNL
Blood urea nitrogen	mmol/L	2.8011	mg/dL	—	> 1.4 × UNL
Calcium	mmol/L	4.008	mg/dL	< 1.97	> 2.77
Cholesterol	mmol/L	38.6698	mg/dL	—	> 7.75
Creatinine	µmol/L	0.0113	mg/dL	—	> 1.4 × UNL
Glucose, fasting	mmol/L	18.015	mg/dL	< 3.0	> 7.6 × UNL
Potassium	mmol/L	1	mEq/L	< 3.3	> 5.5
Sodium	mmol/L	1	mEq/L	< 130	> 150
Total bilirubin	µmol/L	0.0585	mg/dL	—	> 1.5 × UNL
Urinalysis					
Protein	—	—	—	—	≥ 2 +
Glucose	—	—	—	—	≥ 1 +

[a] **Conversion factor is the multiplication factor to convert from SI units to traditional units.**

[b] **Criteria refer to SI units.**

LNL = lower normal limit of laboratory reference range; PCS = potentially clinically significant; SI = *Le Système International d'Unités* (International System of Units); UNL = upper normal limit of laboratory reference range.

5.4.3. Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) dictionary version March 2018. Prior and concomitant medications will be presented in a data listing. Concomitant medications will additionally be summarized by treatment group.

5.4.4. Other Safety Analyses

Descriptive summaries of vital signs data including body temperature, pulse, respiratory rate, and blood pressure (systolic and diastolic) and respective changes from Baseline, will be presented by time point and treatment group. The number and percentage of patients with PCS vital signs per the table below, as determined in the eCRF, occurring post-baseline will

also be summarized by time point and treatment group. All vital signs will be listed with clinically significant values flagged, as well as for patients with any PCS results.

CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT VITAL SIGNS

Parameter	***Flag***	***Criteria***
		Observed Value
Systolic blood pressure (mm Hg)	High	≥ 150
	Low	≤ 90
Diastolic blood pressure (mm Hg)	High	≥ 100
	Low	≤ 50
Pulse rate (bpm)	High	≥ 110
	Low	≤ 50
Temperature (°C)	High	≥ 38
	Low	< 35

Electrocardiogram (ECG) variables and their change from baseline will be summarized with descriptive statistics by time point and treatment group. ECG variables will include heart rate, PR interval, QRS interval, QT interval, and QTc interval corrected for heart rate using QTcF. QTcF values will also be tabulated for their absolute values and tabulated relative to baseline measurements in order to detect individual QTcF changes. Additionally, the number and percentage of patients with PCS values defined in the table below

Use header of the convention table for all relevant safety parameters.

Criteria for Potentially Clinically Significant ECG Parameters

Parameter	***Flag***	***Criteria***	
		Observed Value	*Change from Baseline or Observed Value*
Heart Rate (bpm)	High	> 110	
	Low	≤ 50	

QTcF[a] Interval (msec)	High Male	> 450	30-60, > 60, > 500
	High Female	> 470	
QRS Interval (msec)	High	> 120	
PR Interval (msec)	High	> 220	

[a] QTc interval (Fridericia's) is derived as: QTcF=QT Interval (msec) / (RR (msec)/1000)$^{(1/3)}$

For these summaries, worst-case assignments will be made to ensure patients with such values are not counted more than once. For example, a patient with QTcF interval > 500 msec will count once in the > 500 msec category and will not appear in the > 450 or > 480 msec categories. Similar conventions will be used for the 30 to 60 and > 60 msec categories. All ECG analyses will be based on the average of triplicate measurements.

Important abnormalities in ECG waveform that are changes from Baseline readings will also be reported in a listing. All ECG will be listed with clinically significant values flagged, as well as for patients with any PCS results.

All physical examination results will be listed.

Results from the Columbia-Suicide Severity Rating Scale (C-SSRS) will be summarized by visit and treatment group. All C-SSRS results will also be reported in a listing.

6. PROTOCOL VIOLATIONS

Possible protocol deviations will be identified and displayed in a data listing and sorted by patient and study day (where applicable). The following deviations may be identified as protocol deviations from the database:

- Violations of inclusion/exclusion criteria
- Non-compliance with MIN-117

7. CHANGES IN THE PLANNED ANALYSES

No deviations in the conduct of the study or the planned analysis are anticipated. Should any deviations from the analyses specified in the authorized statistical analysis plan arise, such deviations will be documented in the final clinical study report.

8. PROGRAMMING CONVENTIONS

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1.25" boundary on the upper (bound) edge, and a minimum of a 1.0" boundary on the remaining three edges. Output should be printed in Courier New with a point size of 8. Titles may be printed using a larger font (e.g., Arial point size 10).
- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all patients.
- Group headers: In the summary tables, the group headers will identify the summary group and the sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of patients actually summarized within any given summary module; some patients in the analysis population may have missing values and thus may not be summarized.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of patients actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of patients in the analysis population due to missing data.
    - ♦ In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations. The number of missing observations, if any, will be noted.
    - ♦ For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented so as to indicate clearly to a reviewer the method of calculation. The number of missing observations, if any, will be noted.
- Sorting: Listings will be sorted by treatment group, patient number and date, if applicable. If a listing is sorted in a different manner, a footnote will indicate as such.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate

rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.

- The presentation of numerical values will adhere to the following guidelines:
  - Raw measurements will be reported to the number of significant digits as captured electronically or on the CRFs.
  - Standard deviations will be reported to one decimal place beyond the number of decimal places the original parameter is presented.
  - Means will be reported to the same number of significant digits as the parameter.
- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on CRFs.
  - Time will be presented according to the 24-hour clock (HH:MM).

9. PROPOSED TABLES, LISTINGS, AND FIGURES

Summary Tables

Accountability and Baseline Characteristics

14.1.1	Final Patient Disposition, All Enrolled Patients
14.1.2.1	Demographics, Safety Population
14.1.2.2	Baseline Disease Characteristics, Safety Population
14.1.3	Drug Exposure and Compliance, Safety Population
14.1.4	Concomitant Medications by ATC Classification and Preferred Term, Safety Population

Efficacy

14.2.1.1.1	Summary of MADRS Total Score by Visit, ITT Population
14.2.1.1.2	Summary of MADRS Total Score by Visit – Sensitivity with LOCF, ITT Population
14.2.1.1.3	Summary of MADRS Total Score by Visit – Sensitivity with LOCF and Placebo Average, ITT Population
14.2.1.1.4	Summary of MADRS Total Score – Sensitivity with Multiple Imputation, ITT Population
14.2.2.1.1	Summary of HAM-A Score by Visit, ITT Population
14.2.2.1.2	Summary of HAM-A Score by Visit – Sensitivity with LOCF, ITT Population
14.2.2.1.3	Summary of HAM-A Score by Visit – Sensitivity with LOCF and Placebo Average, ITT Population
14.2.2.1.4	Summary of HAM-A Score– Sensitivity with Multiple Imputation, ITT Population
14.2.2.2	Summary of CGI-S and CGI-I Score by Visit, ITT Population
14.2.2.3	Summary of IDS-SR_{30} Score by Visit, ITT Population
14.2.2.4	Summary of SHAPS Score by Visit, ITT Population
14.2.2.5	Summary of DSST Score by Visit, ITT Population
14.2.2.6	Summary of PSS Score by Visit, ITT Population
14.2.2.7	Summary of A-SEX Score by Visit, ITT Population
14.2.3.1	MADRS Response by Visit, ITT Population
14.2.3.2	Remission and Sustained Response in MADRS, ITT Population
14.2.3.3	Time to MADRS Improvement, ITT Population
14.2.3.4	Summary of Single MADRS Rating Scale Items by Visit, ITT Population
14.2.3.5	Summary of MADRS Core Mood Items by Visit, ITT Population
14.2.4.1	Summary of Sleep Parameters by Visit, ITT Population

Safety

14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events, Safety Population
14.3.1.2	Treatment-Emergent Adverse Events by System Organ Classification, Preferred Term and Maximum Severity, Safety Population
14.3.1.3	Treatment-Emergent Adverse Events Related to Study Treatment by System Organ Classification, Preferred Term and Maximum Severity, Safety Population

14.3.1.4	Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment by System Organ Classification, Preferred Term and Maximum Severity, Safety Population
14.3.1.5	Treatment-Emergent Fatal Adverse Events by System Organ Classification and Preferred Term, Safety Population
14.3.2.1	Treatment-Emergent Serious Adverse Events by System Organ Classification and Preferred Term, Safety Population
14.3.4.1	Clinical Laboratory Hematology Parameters by Time Point, Safety Population
14.3.4.2	Clinical Laboratory Chemistry Parameters by Time Point, Safety Population
14.3.4.3.1	Clinically Significant Laboratory Values, Safety Population
14.3.4.3.2	Clinically Significant and Potentially Clinically Significant Laboratory Values, Safety Population
14.3.4.4	Clinical Laboratory Parameter Shifts from Study Baseline to Week 6, Safety Population
14.3.5.1	Vital Signs by Time Point, Safety Population
14.3.5.2.1	Patients with Clinically Significant Vital Signs Occurring Post-Baseline, Safety Population
14.3.5.2.2	Patients with Clinically Significant or Potentially Clinically Significant Vital Signs Occurring Post-Baseline, Safety Population
14.3.5.3.1	12-Lead ECG Assessments by Time Point, Safety Population
14.3.5.3.2	Summary of QTcF (msec) Categories, Safety Population
14.3.5.4	Patients with Significant ECG Abnormalities Occurring Post-Baseline, Safety Population
14.3.6.1	Summary of C-SSRS by Visit, Safety Population

Data Listings

16.2.1	Patient Disposition
16.2.2.1	Protocol Deviations
16.2.2.2	Inclusion/Exclusion Criteria
16.2.4.1	Demographics
16.2.4.2	Medical and Surgical History
16.2.5.1	Study Drug Administration
16.2.5.2	Prior and Concomitant Medications
16.2.5.3.1	Pharmacokinetic Plasma Concentrations
16.2.6.1	MADRS Rating Scale
16.2.6.2	CGI-S and CGI-I Questionnaires
16.2.6.3	HAM-A Questionnaires
16.2.6.4	IDS-SR_{30} Questionnaires
16.2.6.5	SHAPS Questionnaires
16.2.6.6	DSST Questionnaires
16.2.6.7	PSS Questionnaires
16.2.6.8	A-SEX Questionnaires
16.2.6.9	C-SSRS Questionnaires

Figures