Official Title: **A Randomized, Double-blind, Placebo-controlled Study of the Safety, Tolerability, and Efficacy of SAGE-217 Compared to Placebo in Adult Subjects With Comorbid Major Depressive Disorder and Insomnia**

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SAGE THERAPEUTICS INCORPORATED

Statistical Analysis Plan

Methods

Protocol Number SAGE-217-MDD-304

A Randomized, Double-blind, Placebo-controlled Study of the Safety, Tolerability, and Efficacy of SAGE-217 Compared to Placebo in Adult Subjects with Comorbid Major Depressive Disorder and Insomnia

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2. LIST OF ABBREVIATIONS

Abbreviation or specialist term	Explanation
AE	adverse event
AHI	Apnea-Hypopnea Index
ANCOVA	Analysis of Covariance
ATC	anatomical therapeutic chemical
BLQ	below the limit of quantitation
BMI	body mass index
CGI-I	Clinical Global Impression scale for improvement
CGI-S	Clinical Global Impression scale for severity
[redacted]	
CS	Clinical significance
CSD-C	Consensus Sleep Diary – Core
C-SSRS	Columbia Suicide Severity Rating Scale
[redacted]	
ECG	Electrocardiogram
eCRF	electronic case report form
EEG	Electroencephalogram
EODBT	End of double-blind treatment
EOT	end of treatment
ET	early termination
FSH	follicle stimulating hormone
HAM-D	Hamilton Depression Rating Scale
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
[redacted]	
IRT	interactive response technology
ISI	Insomnia Severity Index
[redacted]	
LLOQ	lower limit of quantification
LPD	latency to persistent sleep
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
mDURAW	mean duration of awakenings
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effects model for repeated measures
NAW	number of awakenings
PCS	potentially clinically significant
PCSC	potentially clinically significant change
PHQ-9	Patient health Questionnaire
[redacted]	
PSG	Polysomnography
QTcF	QT corrected according to Fridericia's formula

Abbreviation or specialist term	Explanation
REM	Rapid Eye Movement
REMA	REM Activity
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEFF	sleep efficiency
SI	International System of Units
sNAW	subjective number of awakenings
SOC	system organ class
[redacted]	
SS	Safety Set
sSL	subjective sleep latency
sSQ	subjective sleep quality
sTST	subjective total sleep time
sWASO	subjective wake after sleep onset
TEAE	treatment-emergent adverse event
TIB	time in bed
TST	total sleep time
[redacted]	
WASO	wake after sleep onset
WHO-DDE	World Health Organization-Drug Dictionary Enhanced

3. INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis of 217-MDD-304 study, and is based on the approved clinical study protocol, dated 17 JULY 2019, version 4.0.

The purpose of the SAP is to describe in detail the statistical methodology and the statistical analyses to be conducted for the above-mentioned protocol. The SAP will be approved and finalized before database lock.

4. STUDY OBJECTIVES

4.1. Primary Objective

The primary objective of this study is to determine the effect of SAGE-217 on overall insomnia symptoms in subjects with comorbid major depressive disorder (MDD) and insomnia.

4.2. Secondary Objectives

Secondary objectives of this study are:

- To measure the effects of SAGE-217 on individual objective and subjective symptoms of insomnia including difficulties with sleep maintenance and sleep onset.
- To measure the effects of SAGE-217 on sleep architecture.
- To evaluate the effect of SAGE-217 on depressive symptoms.
- To assess patient-reported outcome (PRO) measures as they relate to depressive symptoms.
- To evaluate the safety and tolerability of SAGE-217.

5. STUDY ENDPOINTS

5.1. Primary Endpoint

The primary endpoint of this study is change from baseline in sleep efficiency (SEFF), defined as the percentage of time in bed spent asleep, at end of double-blind treatment (EODBT) as assessed by Polysomnography (PSG).

5.2. Secondary Endpoints

Secondary endpoints of this study are:

- Change from baseline of the following PSG-derived endpoints at EODBT:
  - Wake after sleep onset (WASO, defined as the total wake time in minutes) from persistent sleep onset to lights-on (final wake time)
  - WASO by quarter (2-hour period) of the PSG recording (8-hour period)
  - Total sleep time (TST) and TST by quarter of the PSG recording
  - Latency to persistent sleep (LPS)
  - Number of awakenings (NAW) and mean duration of awakenings (mDURAW), in total and by quarter of the PSG recording
  - Minutes and percent of stage N1, N2, N3, and rapid eye movement (REM) sleep
  - Latency to the first period of REM Sleep and latency to each subsequent period of REM Sleep
  - REM Density
  - REM Activity
- Change from baseline in subjective sleep endpoints to EODBT:
  - Insomnia Severity Index (ISI)
  - Consensus Sleep Diary – Core (CSD-C) endpoints
    - Subjective total sleep time (sTST)
    - Subjective wake after sleep onset (sWASO)
    - Subjective sleep latency (sSL)
    - Subjective sleep quality (sSQ)
- Change from baseline in Clinical Global Impression - Severity (CGI-S) at EODBT and all other timepoints (based on the insomnia disorder).
- Clinical Global Impression - Improvement (CGI-I) at EODBT (based on the insomnia disorder).
- Change from baseline in the 17-item Hamilton Depression Rating Scale (HAM-D) total score at EODBT.Change from baseline Patient-reported outcome measures of depressive symptoms, as assessed by the 9-item Patient Health Questionnaire (PHQ-9) at the EODBT.

- Safety: Incidence and severity of adverse events (AEs)/serious adverse events (SAEs); changes from baseline in vital sign assessments, clinical laboratory data, electrocardiogram (ECG) parameters, and suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS). Evaluation of withdrawal symptoms as measured by the Physician Withdrawal Checklist (PWC-20).

[redacted]

6. STUDY DESIGN

6.1. Overall Design

This is a randomized, double-blind, parallel group, placebo-controlled study of the safety, tolerability, efficacy, [redacted] of SAGE-217 compared to placebo in adult subjects with insomnia (ISI ≥15) and comorbid MDD (MADRS total score ≥28, HAM-D score ≥20). The study schematic is shown in Figure 1.

The Screening Period begins with the signing of the informed consent form (ICF) at the Screening Visit; the ICF must be signed prior to beginning any screening activities. At the time of providing informed consent for the study, subjects will also be required to authorize that their unique subject identifiers be entered into a registry (www.subjectregistry.com) with the intent of identifying subjects who may meet exclusion criteria due to participation in another clinical study.

After the subject has provided written informed consent, eligibility will be determined by applying the inclusion/exclusion criteria. The diagnosis of insomnia and MDD must be confirmed according to Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (SCID-5-CT) performed by a qualified healthcare professional.

Subjects will complete an electronic sleep diary during the screening period. Between Day -9 and awakening on Day -2, subjects are required to complete the sleep diary for a minimum of 5 of the 7 nights. Eligibility for the study will be based on subjects having a sleep diary with the following: a minimum of 5 nights completed and a TST of <390 minutes (<6.5 hours) on at least 3 nights between Day -9 and Day-2.

The PSG qualification visit (Visit 2) will begin on Day -2 and will continue to Day 1. The clinical research coordinator (CRC) will determine each subject's habitual bedtime from their sleep diary. Subjects should arrive at the clinic approximately 2 hours prior to their habitual bedtime for the 2-night PSG qualification visit. For each night, subjects will receive a standard meal and be prepared for overnight PSG recording. Lights out and PSG recording will begin within approximately 1 hour of their habitual bedtime. Subjects will receive a single-blind placebo, with food, 30 (±15) minutes prior to PSG lights out. Subjects will be required to remain in bed for 8 hours, after which time the PSG recording will end, lights will turn on, and subjects will be awakened if asleep. [redacted] The electronic CSD-C will be completed at the clinic on all days following the PSG recordings.

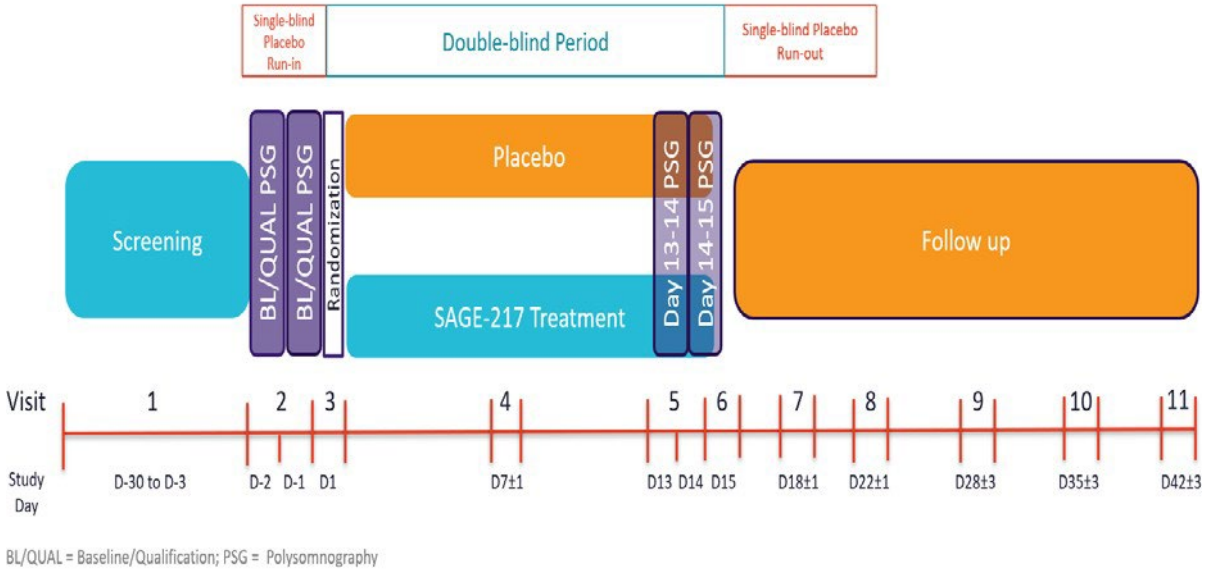
Eligible subjects who meet the PSG qualification criteria will be randomized to 1 of 2 treatment groups (SAGE-217 30-mg or placebo) on a 1:1 basis. Starting on Day 1, subjects will self-administer a single dose of study drug once daily in the evening with food, on an outpatient basis, for 12 days.

Subjects will return to the clinic for Visit 5 (Day 13) for a 2-night overnight stay; subjects will be administered study drug on Days 13 and 14 in the clinic. Subjects will have 2 consecutive PSGs as described above which will begin on Study Day 13 and will continue to Study Day 15. On Days 13 and 14, subjects will be administered study drug in clinic, 30 minutes (±15 minutes) prior to lights out (PSG).

On Days 15 through 21, inclusive, all subjects will self-administer a single dose of single-blind study drug (placebo) daily in the evening with food, on an outpatient basis. Follow-up visits include Visits 8 -11.

Subjects will return to the study center during the treatment and follow-up periods as outlined in Appendix A.

Figure 1: Study Design (217-MDD-304)



BL/QUAL = Baseline/Qualification; PSG = Polysomnography

6.2. Sample Size and Power

Assuming a 2-sided test at an alpha level of 0.05, a sample size of 41 subjects per group would provide 90% power to a treatment difference of 11 points between the SAGE-217 and matching placebo groups with regard to the primary outcome variable of change from baseline in SE score, assuming a standard deviation of 15 points.

By including 2 treatment groups and using a 1:1 randomization, a total of 82 evaluable subjects are required. Evaluable subjects are defined as those randomized subjects who received double-blinded study drug and have a valid baseline and at least 1 post-baseline SEFF assessment. Assuming a non-evaluability rate of 20%, up to 102 subjects will be randomized.

Additional subjects may be enrolled if the drop-out rate is higher than 20%.

6.3. Randomization

This is a randomized double-blind, placebo-controlled study. Subjects who meet the entrance criteria will be randomized in a stratified manner based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥60 days) at baseline; randomization will be done within each stratum in a 1:1 ratio to receive SAGE-217 30 mg or matched placebo. Subjects, clinicians, and the study team will be blinded to treatment allocation. Randomization will be performed centrally via an interactive response technology (IRT) system.

6.4. Blinding and Unblinding

Subjects in run-in period and run-out placebo period are single-blinded.

Subjects, clinicians, and the study team will be blinded to treatment allocation.

Randomization schedules will be generated by an independent statistician. The allocation to treatment group (SAGE-217 30 mg or placebo) will be based on the randomization schedule. The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding.

In case of medical emergency, the Investigator may request unblinding of an individual subject's treatment in the study via the IRT.

7. MODIFICATIONS

7.1. Modifications to the Approved Clinical Study Protocol

[redacted]

Key changes to protocol amendment 2 Version 2.0, 25April 2019:
Criterion of HAM-D total score of ≥20 at Visit 1 and Visit 3 (prior to dosing) was added
Visits 10 and 11 (Days 35 and 42) was added

Key changes to protocol amendment 3.0, Version 4.0, 17July2019:

The apnea-hypopnea index (AHI) exclusion has been modified such that individuals with mild obstructive sleep apnea (OSA) (ie, AHI<15) may be eligible to participate; individuals with moderate and severe OSA (AHI ≥15) are excluded.

Mean wakefulness after persistent sleep onset (WASO) entry criteria were modified to be less restrictive and to be consistent with criteria defined in similar studies: Subject has a mean wakefulness after persistent sleep onset (WASO) ≥30 minutes on combined baseline PSG nights (Days -2 and -1), with neither night ≤20 minutes.

7.2. Modifications to the Approved Statistical Analysis Plan

This is the first version of the SAP for the final analysis.

7.3. Modifications to the Approved DMC Charter

Not applicable.

8. ANALYSIS SETS

8.1. All Randomized Set

The All Randomized Set is defined as all subjects who have been randomized.

8.2. Run-in Safety Set

The Run-in Safety Set is defined as all subjects who took at least 1 dose of run-in placebo but did not receive any double-blind study drug.

8.3. Safety Set

The Safety Set (SS) is defined as all subjects receiving at least 1 dose of double-blind study drug.

8.4. Full Analysis Set

The Full Analysis Set (FAS) is defined as all randomized subjects in the SS with valid baseline and at least 1 post-baseline efficacy evaluation.

8.5. Per Protocol Set

The Per Protocol Set is defined as all subjects in the Full Analysis Set and without major protocol deviations, which could potentially affect efficacy. The review of major protocol deviations will be completed, and the decision on whether the deviation affects efficacy will be documented before database unblinding.

9. STATISTICAL ANALYSIS

9.1. General Considerations

Since insomnia is known to be intermittent in nature and prone to adaption effects, to reduce variability and to reduce selection bias, PSG will be performed with single-blind placebo administration for 2 consecutive nights before randomization. Following the double-blind treatment period, possible rebound insomnia and withdrawal effects will be evaluated during a 1-week single-blind placebo run-out period.

For the purpose of all safety, efficacy, and other analyses, where applicable, baseline is defined as the last non-missing measurement prior to the start of double-blind study drug administration. For sleep parameters from PSG and subjective sleep measures, this is the average of 2 nights values from Day -1 and Day -2 when both values are available; otherwise, the single available assessment at either Day -2 or Day -1 will be used as the baseline. For PWC-20, the baseline is defined as the measurement on Day 15 for subjects who complete double-blind treatment or the last measurement on double-blind treatment for subjects who discontinue early from double-blind treatment.

Unless otherwise specified, continuous endpoints will be summarized with n, mean standard deviation (SD), median, minimum (min) and maximum (max). The minimum and maximum will be reported with the same degree of precision (ie, the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (standard deviation) will be reported to 2 degrees of precision more than the observed data. In addition, change from baseline values (visit value – baseline value) will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages. Percentages will be presented to 1 decimal place unless otherwise specified; the denominator of percentages will be the number of subjects in the analysis set used unless specified otherwise.

All analyses and summary outputs will be generated using SAS® 9.4 or higher.

All summaries and figures will be provided by treatment group. Efficacy data are analyzed using the Full Analysis Set by the randomized treatment. Safety data are analyzed using the Safety Set by the actual treatment received. If the subject takes any dose of SAGE-217 during the study, the subject will be considered under SAGE-217 for treatment received.

All subject data, including those derived, to support tables and figures will be presented in the subject data listings. In general, the subject data listings will be sorted by treatment group, subject number and assessment visit and date (and time, if applicable).

9.1.1. Study Day Definition

Study day is defined as number of days since the first dose of double-blind study drug:

- The day of subject receiving the first dose of double-blind study drug is designated as Day 1.
- For visit days after Day 1, study day = visit date – Day 1 date + 1.
- For visit days prior to Day 1, study day = visit date – Day 1 date. Thus, study days for screening visit and run-in period are negative numbers. There is no “Day 0”.

9.1.2. Missing Data

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis populations, using all non-missing data available. Imputation of missing data in scoring of questionnaires is discussed in respective sections below. Handling of missing or incomplete dates has been discussed in Appendix C.

9.2. Background Characteristics

9.2.1. Subject Disposition

The analyses of subject disposition will use all subjects who provided written informed consent to the study.

These data will be presented by single-blind run-in, double-blind, single-blind run-out periods of the study; and by treatment the subject is randomized to within double-blind period. The summaries of subject disposition will include the number of subjects who screened, screened failed, received any study drug (placebo or SAGE-217), the number of subjects randomized, number of subjects who completed each period, who prematurely discontinued from each period, and primary reasons for discontinuation of the study, and/or treatment. If a subject has been rescreened because the subject had been a screen failure the first time, the status of the subject will be determined from the second screening. In the count of screened subjects, this subject will be counted only once. A completer for the study is defined as one who completed the final follow up visit (Day 42), and is derived from the study conclusion CRF page with completion question answered Yes. A subject who is marked as discontinuing treatment prematurely in the treatment discontinuation CRF page is considered prematurely discontinuing treatment; the main reason is provided in the same CRF page.

Separate data listings will be provided for subject randomization and screen failures/run-in failures.

The number and percentage of subjects in each analysis set will be provided.

A separate data listing will be provided for all subjects who prematurely withdrew from the study or prematurely discontinued study drug with reasons.

9.2.2. Protocol Deviations

Protocol deviations identified during site monitoring will be captured on an electronic case report form (eCRF) and categorized by the study team as major and minor deviations, without any unblinding information. These deviations will be summarized by type and by randomized treatment group using the All Randomized Set. The subjects who were not randomized, but who had protocol deviations identified will be presented in a data listing.

Major protocol deviations are identified as affecting efficacy analysis. This list will be finalized before database lock by a study team review in a blinded review of data and will be documented as such. Subjects with any of these deviations will be excluded from the FAS to define the Per Protocol Set. The major protocol deviations that are potentially affecting efficacy analysis include, but are not limited to:

- Did not meet key inclusion/meet key exclusion criteria
- Received any disallowed concomitant medication during the treatment period
- Had overall treatment compliance rate < 75% Other

A summary of the reasons for exclusion from analysis sets will be presented by treatment group.

9.2.3. Demographics and Baseline Characteristics

The following analyses will use the Safety Set (using actual treatment received) and the FAS (using randomized treatment).

Demographic data (age, race, gender, ethnicity, employment status, highest education level category, marital/civil status) and baseline characteristics, such as height, weight, body mass index (BMI), baseline Montgomery-Asberg Depression Rating Scale (MADRS) score, HAM-D total score, ISI total score, Apnea-Hypopnea Index (AHI) score, Periodic Limb Movement Arousal Index (PLMAI) scores and WASO score, will be summarized by treatment groups, where AHI score, PLMAI score, and WASO score were from central lab read . Highest education level will be categorized in the summary tables as follows:

Less than or equal to 12th grade, no diploma
12th grade diploma or GED
Some college but no degree
Associate degree
Bachelor's degree
Master's degree
Professional degree
Doctoral degree

Baseline subgroups will also be summarized for the following categories:

- Race (Black or African American, White, Other)
- Gender (Male, Female)
- Age (18-24, 25-50, 51-64 years)
- Baseline antidepressant use (Yes, No)
- BMI ($\leq$18.4, 18.5-24.9, 25-29.9, $\geq$30 kg/m^2)
- ISI score (15-21 moderate, 22-28 severe)

Diagnostic labs are part of screening; a data listing using Safety Set will be provided. The following diagnostic screening test results will be included in this listing.

Table 1: Diagnostic Screening Test Results

Diagnostic Screening		
Serum	**Urine**	**Breathalyzer**
Hepatitis B Hepatitis C Reflex HCV RNA HIV-1 and -2 Female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal: serum hCG Female subjects, if menopause is suspected and not surgically sterile: FSH	Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and phencyclidine Female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal: urine hCG	Alcohol

9.2.4. Medical/Surgical History

The following analyses will use the FAS (using randomized treatment).

Medical/surgical history collected at screening will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 21.0 or higher.

Medical/surgical history data will be summarized by system organ class (SOC) and preferred term (PT). A summary of medical/surgical history that is ongoing at the time of screening will be provided separately. Subject history of psychiatric disorders, family psychiatric history, and sleep history will be summarized. These data will be provided by treatment groups.

The history related to MDD (date of initial diagnosis of MDD, lifetime antidepressant medication usage, information of depressive episodes, etc.) will be collected. Years since initial diagnosis of MDD, lifetime anti-depressant medication usage, and information of depressive episodes will be summarized. Years since initial diagnosis of MDD, days since start of current episode and days since first episode will be calculated using: first dose date of double-blind study drug – date of interest). For imputation of incomplete dates in disease history, please see Section 12.3.3.

The medical history related to sleep disorders will be collected and summarized. In addition, Days since start of current episode of insomnia, history of recurrent insomnia will be summarized by treatment.

9.2.5. Prior and Concomitant Medications

The following analyses will use the FAS (using randomized treatment).

Medications will be recorded at each study visit during the study and will be coded using World Health Organization-Drug Dictionary Enhanced (WHO-DDE) March 2018, or later.

All medications taken within 30 days prior to informed consent through the duration of the study will be recorded. In addition, all psychotropic medications taken in the previous 6 months prior to

Screening and GABAergic medications taken 12 months prior to Screening will be recorded on the eCRF.

Medications will be presented according to whether they are being taken prior to and/or after first administration of double-blind study drug. Prior medications are defined as those taken prior to the initiation of the start of double-blind study drug. Concomitant medications are defined as those taken prior to the initiation of the double-blind study drug and continuing beyond the initiation of the double-blind study drug or those medications started at the same time or after the initiation of the double-blind study drug (i.e., those with a start date on or after the first dose of double-blind study drug, or those with a start date before the first dose of double-blind study drug that are ongoing or with a stop date on or after the first dose of study drug). If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant. For imputation of missing concomitant medication dates, please refer to Appendix C, Section 12.3.

Concomitant medications will be further divided by period (double-blind, run-out, or post-treatment) as follows (if time is missing, the date will be used for this algorithm):

- Double-blind period concomitant medications are those that have been used any time from start of first double-blind dose to the last dose of double-blind study drug + 1 Day.
- Run-out period concomitant medications are those that have been started after 1 day from the end of double-blind study drug, but on or before the last dose of run-out treatment period
- Post-treatment period concomitant medications are those that have been started after the end of run-out treatment period.

Prior and concomitant non-psychotropic medication use will be summarized by anatomical therapeutic chemical (ATC) level 2 and Standard Medication Name. Similar summary tables will be provided for psychotropic medications. Separate but similar summaries will be provided for concomitant medication use for on-treatment and post-treatment periods as defined above.

Antidepressants that have been taken at the same dose for at least 60 days prior to Day 1 are permitted if the subject intends to continue the stable dose through the follow-up period (Day 42). Anti-depressant medications are identified by (ATC3 code of N06A. A summary of anti-depressant use at first dose of double-blind treatment and any change in these medications post-baseline (including the follow up period) will be summarized.

Anti-insomnia treatments are identified by ATC3 code N05C and will be summarized and listed separately.

Details of prior and concomitant medications will be listed by subject, start date, and verbatim term.

Concomitant procedures will be presented in a listing by subject and will not be summarized.

9.2.6. Study Drug Exposure

The following analyses will use the Safety Set (using actual treatment) and will only be performed for the double-blind period.

Total drug exposure (in mg) is defined as the total study drug in mg for SAGE-217 that was taken during the double-blind period of the study. Total drug exposure for subjects randomized to placebo is zero unless the subject has taken SAGE-217 by mistake, in which case the total exposure comes from SAGE-217 exposure. If the patient skips the dose on any of the days, the dose taken is 0 mg.

Total exposure duration to study drug (in days) is defined as total number of days treated with study drug during the double-blind period of the study: date of last dose – date of first dose + 1. Note that this includes days when the dose has been missed.

Percent of planned exposure received is defined as the total drug exposure (in mg) divided by total amount of planned doses exposure (in mg), times 100, which mathematically is equivalent to [the total drug exposure (in mg) / (30*14], times 100 for subjects who complete the treatment. For subjects who discontinued the treatment early, the planned exposure is (Last dose date – First dose date + 1), times 30 mg for subjects randomized to SAGE-217. For subjects randomized to placebo, this measure is not applicable.

Total drug exposure, total exposure duration and percent of the planned exposure received will be summarized descriptively.

9.2.7. Study Drug Adherence

The following analyses will use the Full Analysis Set (using randomized treatment). Study drug adherence (%) is defined as the total number of capsules taken divided by total number of planned capsules, times 100.

The schedule of study drug is one capsule per day, so the number of days planned for study drug intake is same as the number of capsules planned to be taken. Number of planned days for study drug intake is defined as follows:

1. If the subject discontinues treatment within Day 2 and Day 14 (both inclusive), the planned number of days is the last dose day of study drug.
2. If the subject does not discontinue treatment, the planned number of days is 14.

Study drug adherence will be summarized descriptively.

9.3. Efficacy Analysis

All efficacy analyses will be performed for the FAS unless otherwise specified.

9.3.1. Visit Windows for Efficacy Analysis

The scheduled visits will not be windowed and will be used at nominal visit value for analysis purposes. The unscheduled, end-of-treatment (EOT) and early termination (ET) visit will be mapped to a scheduled visit for analysis. Unscheduled visits that happens on or before EOT visit (date (including EOT visit) will be mapped using the date of collection/assessment and Day 1 date of first double-blind dose) will be used as a basis to determine study day, which will be mapped to the intended visit according to the visit windows specified in the table below. Unscheduled visits after EOT visit date, including ET visit, will be windowed using relative days since last dose date; the mapping will follow the table below. In order to accommodate as much data as possible into analysis, these windows have been widened compared to protocol-specified operational window, to have no gap between them; these windows are used for analysis purposes only. Note that Day 18 data will not be windowed; it will be presented in summaries as nominal visit values, and will not be included in the modeling or in figures.

Once analysis visit windows are assigned, all visits, including scheduled visits, unscheduled visits, and EOT/ET visits will be eligible for being flagged as the “analyzed record” within the analysis window; a subject’s individual analysis visit window could potentially contain more than 1 visit. In

the event of multiple visits falling within an analysis window or in case of a tie, the following rules will be used in sequence to determine the "analyzed record" for the analysis visit window:

- If the data from the scheduled visit is available, then the scheduled visit data will be used.
- If there is no data from the scheduled visit available, the data closest to the scheduled study day for that window will be used
- If there is a tie between the data in the number of days before and after the scheduled day, the later data will be used.

The summary by visit will use the "analyzed records" only – at most one per subject. The data not flagged as the "analyzed record" will be included in listings. An unscheduled visit that does not fall under any analysis window will remain in the database, and will be included in the listings.

Table 2 and Table 3 display windows for efficacy analysis.

Table 2: Visit Windows for Analysis of Efficacy Endpoint Assess by Unscheduled PSG

Scheduled Day (Visit)	Target Study Day	Study Day Window for Visit
Day (-2) (Visit 2)	Day -2	Two consecutive Days between Day -3 to Day -1. Map the first measurement to Day -2 and the last one to Day -1, if only one measurement, Day -3 or Day -2, it will be mapped to Day -2.
Day (-1) (Visit 2)	Day -1	Two consecutive Days between Day -3 to Day -1. Map the first measurement to Day -2 and the last one to Day -1, if only one measurement, Day -1 will be mapped to Day -1.
Day 13 (Visit 5)	Day 13	Two consecutive Days between Day 12 to 15. Map the first measurement to Day 13 and the last one to Day 14. If only one measurement, Day 12 or Day 13 will be mapped to Day 13
Day 14 (Visit 5)	Day 14	Two consecutive Days between Day 12 to 15. Map the first measurement to Day 13 and the last one to Day 14. If only one measurement, Day 14 or Day 15, it will be mapped to Day 14.

Table 3: Visit Windows for Efficacy Analysis Other than Endpoints Assessed by PSG at Unscheduled Visit

Scheduled Day (Visit)	Target Study	Study Day Window for Visit
Day 1 (Visit 3)	Day 1 Pre-dose	Day 1 Pre-dose
Day 7 (Visit 4)	Day 7	Day 1 Post-dose -Day 11
Day 15(Visit 6)	Day 15	Day 12 - Day 17
Day 18 (±1 day) (Visit 7)	Day 18	NA
Day 22 (±1 day) (Visit 8)	Day 22 (last dose date +8 Days)	Day 18 - Day 24 (last dose date +4 days, +10 days)
Day 28 (±3 day) (Visit 9)	Day 28 (last dose date +14 Days)	Day 25 - Day 31 (last dose date +11 days, +17 days)
Day 35 (±3 day) (Visit 10)	Day 35 (last dose date +21 Days)	Day 32 - Day 38 (last dose date +18 days, +24 days
Day 42 (±3 day) (Visit 11)	Day 42 (last dose date +28 Days)	Day 39- Day 45 (last dose date +25 days, +31 Days)

Note: Parenthesized study day and study day window are for unscheduled visits, EOT and ET for subjects who have discontinued treatment prematurely and such visit date is >=4 days from the last dose of study drug intake (i.e. visit date – last dose date + 1 >=4).

9.3.2. Analysis of Primary Efficacy Endpoint

9.3.2.1. Definition of Primary Efficacy Variable

The primary endpoint, change from baseline in sleep efficiency (SEFF), is defined as the percentage of time in bed spent asleep) at end of double-blind treatment (EODBT) as assessed by 8-hour overnight PSG recordings. The PSG recordings used to derive the primary endpoint are performed over 2 nights at visit 2 (Day -2 and Day -1) prior to randomization (baseline) and Visit 5 (Day 13 and Day 14) (EODBT).

9.3.2.2. Visit Windows

For efficacy analyses, visit windows do not apply for scheduled PSGs. Unscheduled/EOT/ET PSG measurements will only be included if a scheduled measurement is not available and the unscheduled/EOT/ET measurement falls in the window of the same Visit, as defined in Section 9.3.1.

9.3.2.3. Analysis of Primary Endpoint

The FAS will be used for all efficacy summary tables. Subjects will be analyzed according to the randomized treatment.

Observed values and change/percent change from baseline to EODBT in SEFF total score will be summarized descriptively by scheduled visit and treatment.

The estimand for the primary efficacy analysis is the difference between SAGE-217 and placebo treatments in mean change from baseline in sleep efficiency at EODBT.

The primary efficacy endpoint, the change from baseline in SEFF at EODBT, will be analyzed using ANCOVA. The model will include treatment, antidepressant treatment use (current/stable or not treated/withdrawn ≥ 60 days), baseline SEFF score, as exploratory variables, change from baseline in SEFF at end of double-blind treatment as the response variable. The main comparison will be between SAGE-217 and placebo at EODBT. Model based point estimates (i.e., least square [LS] means, 95% confidence intervals, and p-values) will be reported, where applicable. The baseline value of SEFF is defined as the average of over 2 nights PSG measurements at Day -2 and Day -1 or the PSG measurement at Day -2 or Day -1 if only one night measurement is available. The post-baseline PSG SEFF value at EODBT is defined as the average of over 2 nights PSG measurements at Day 13 and 14 or the PSG measurement at Day 13 or Day 14 if only one night measurement is available.

Line plot of model-based LS Mean (± standard error) will be prepared for change from baseline in SEFF at end of double-blinded period.

A sensitivity analysis will be performed to account for the possible scenario that the data is not normally distributed. Stratified Wilcoxon rank-sum test on change from baseline in SEFF at Day 15, stratified by antidepressant use. If necessary (e.g., serious violation of the primary analysis model assumptions on normality, as assessed by quantile-quantile plot of the residual values from the primary analysis for SEFF), this will be considered the primary analysis.

9.3.2.4. Subgroup Analyses for Primary Endpoint

Subgroups defined in Section 9.2.3 will be used for subgroup analyses of the primary efficacy endpoint of change from baseline in SEFF.

An ANCOVA model for subgroup analysis will be used. Antidepressant use may be excluded from the model due to the potential small number of subjects in antidepressant use group in each subgroup. Observed values and change/percent change from baseline to the EODBT (Day 15 – Baseline) in SEFF total score will be summarized by treatment group and subgroup.

A forest plot will be generated to show the model-based estimates of LS mean difference along with 95% CI and p-values within each subgroup.

9.3.2.5. Multiplicity Adjustment

No adjustments for multiplicity will be performed for this Phase 3 trial. Only the primary endpoint analysis will be treated as a formal hypothesis test, and the secondary endpoints will be considered as supportive of the primary endpoint.

9.3.3. Analysis of Secondary Efficacy Endpoints

All secondary analyses will be conducted using the FAS. Subjects will be analyzed according to the randomized treatment.

9.3.3.1. Definition of Secondary Efficacy Variables

9.3.3.1.1. PSG-derived Sleep Variables

The PSG measures the physiological process of sleep by monitoring body functions including brain waves via electroencephalogram (EEG), eye movements via electrooculography, muscle activity or skeletal muscle activation via electromyography, heart rhythm via ECG, blood oxygen saturation via pulse oximetry, and breathing functions. Stages of sleep are scored through evaluation of the EEG signal. Sleep stage scoring includes REM, non-rapid eye movement (NREM), NREM stage 1 (N1),

NREM stage 2 (N2), and NREM stage 3 (N3) sleep. Other sleep efficacy variables listed as secondary endpoints to be quantified and/or examined, include:

- LPS: Duration in minutes from lights off to the first epoch of 20 consecutive non-wake epochs
- WASO: Total wake time in minutes from persistent sleep onset to lights on
- TST: Duration of total sleep time (NREM + REM) from lights off to lights on during recording
- NAW and mDURAW: Number of awakenings from the onset of persistent sleep until lights on. An awakening is defined as at least 2 consecutive epochs of wake. Individual awakenings must be separated by at least 1 epoch of stage N2, N3, or REM. mDURAW is an arithmetic mean calculated as the sum of awakenings in minutes divided by the number of awakenings
- Minutes and percent of stage N1, N2, N3, and REM sleep (from lights off to lights on)
- Latency to REM sleep (REML): The number of non-REM epochs (stages N1, N2, N3) from LPS to the first epoch of REM sleep.
  - –REML for second and subsequent REM periods: The number of non-REM and REM epochs (stages N1, N2, N3, and REM) from LPS to the first epoch of the 2nd REM period, or subsequent REM period.
- REM density: Total number of rapid eye movements divided by the total duration of REM sleep in minutes during time in bed (TIB).
- REM Activity (REMA): Total number of rapid eye movements during REM sleep, observed on the ECG channels of the PSG. The rapid eye movements must be at least 25 uV in amplitude.

9.3.3.1.2. Hamilton Rating Scale for Depression (HAM-D)

The 17-item HAM-D will be used to rate the severity of depression in subjects who are already diagnosed as depressed. HAM-D is collected during the clinic visit on Days 1, 7, 15, 18, 22, 28, 35, and 42. The 17-item HAM-D comprises individual ratings related to the following symptoms: depressed mood (sadness, hopeless, helpless, worthless), feelings of guilt, suicide, insomnia (early, middle, late), work and activities, retardation (slowness of thought and speech; impaired ability to concentrate; decreased motor activity), agitation, anxiety (psychic and somatic), somatic symptoms (gastrointestinal and general), genital symptoms, hypochondriasis, loss of weight, and insight. Each item is scored in a range of 0 to 2 or 0 to 4, with higher scores indicating a greater degree of depression. The score for each item will be summed to compute a total score, which ranges from 0 to 52. If more than 3 individual items are missing, the HAM-D total score will not be calculated and will be left as missing. If less than or equal to 3 individual item scores are missing, the missing item scores will be imputed by the mean of all other available item scores, or the maximum possible values for the missing responses, whichever is smaller, to calculate the HAM-D total score.

Four HAM-D subscale scores will be calculated will be calculated as the sum of the individual rating scores related to each subscale, divided by the total possible score within the subscale, multiplied by 100, and rounded to a whole number. If more than one item is missing or HAM-D total score is missing, the subscale score is left as missing; if one item on a particular subscale is missing, but has been imputed for the calculation of total score, the imputed value from total score calculation will be

used in subscale score calculation for that item. Following table describes the subscale score calculation:

Table 4: HAM-D Subscale Score Calculations

HAM-D Subscales	Items	Calculation
Core	Depressed mood Feeling of guilt Suicide Work and activities Retardation	Sum of the 5-item responses/20 x 100. If more than one item responses are missing or HAM-D total score is missing, leave as missing; otherwise, use the imputed item score used to calculate HAM-D total score to calculate the subscale.
Anxiety	Anxiety psychic Anxiety somatic Somatic symptoms gastrointestinal Somatic symptoms general Hypochondriasis Loss weight	Sum of the 6-item responses/18 x 100. If more than one item responses are missing or HAM-D total score is missing, leave as missing; otherwise, use the imputed item score used to calculate HAM-D total score to calculate the subscale.
Bech-6	Depressed mood Feeling of guilt Work and activities Retardation Anxiety psychic Somatic symptoms general	Sum of the 6-item responses/22 x 100. If more than one item responses are missing or HAM-D total score is missing, leave as missing; otherwise, use the imputed item score used to calculate HAM-D total score to calculate the subscale.
Maier	Depressed mood Feeling of guilt Work and activities Retardation Agitation Anxiety psychic	Sum of the 6-item responses/24 x 100. If more than one item responses are missing or HAM-D total score is missing, leave as missing; otherwise, use the imputed item score used to calculate HAM-D total score to calculate the subscale.

HAM-D Response will be defined as having a 50% or greater reduction from baseline in HAM-D total score; only subjects who have non-missing total score of HAM-D at baseline as well as the visit will be considered in HAM-D response evaluation. HAM-D Remission will be defined as having a HAM-D total score of ≤7; if HAM-D total score is missing, remission will not be defined. For a sensitivity analysis, missing response and remission will be considered as No response/remission. Subjects with missing values, even after treatment discontinuation, will be considered as a Non-responder/non-remitter.

9.3.3.1.3. Clinical Global Impression – Improvement (CGI-I)

The CGI-I employs a 7-point Likert scale to measure the overall improvement in the subject's condition post-treatment. The Investigator will rate the subject's total improvement whether or not it is due entirely to drug treatment. Response choices include: 0=not assessed, 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and

7=very much worse. The CGI-I is only rated at post-treatment assessments on Days 7, 15, 18, 22, 28, 35, 42. By definition, all CGI-I assessments are evaluated against baseline conditions. CGI-I response will be defined as having a CGI-I score of "very much improved" or "much improved." In this study the CGI-I will be assessed based on the improvement of their insomnia disorder. Missing CGI-I at the visit will not be evaluated for response.

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

The CGI-S uses a 7-point Likert scale 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 as 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; and 7=extremely ill. The CGI-S is rated on Days 1, 7, 15, 18, 22, 28, 35, and 42. In this study the CGI-S will be assessed based on the severity of their insomnia disorder.

9.3.3.1.5. Insomnia Severity Index (ISI)

The ISI is a validated, 7-item questionnaire designed to assess the nature, severity, and impact of insomnia. It is collected at Screening, and during the clinic visit on Days 1, 7, 15, 18, 22, 28, 35, and 42. The ISI uses a 5-point Likert Scale to measure various aspects of insomnia severity (0 = none, 1 = mild, 2 = moderate; 3 = severe; 4 = very severe), satisfaction with current sleep pattern (ranging from 0 = very satisfied, 1 = satisfied, 2 = neutral, 3 = dissatisfied, 4 = very dissatisfied), and various aspects of the impact of insomnia on daily functioning (0 = not at all, 1 = a little, 2 = somewhat, 3 = much, 4 = very much). The total score is derived as the sum of item scores. If more than 1 individual item is missing, the ISI total score will not be calculated and will be left as missing. If 1 individual item score is missing, the missing item score will be imputed by the mean of all other available item scores to calculate the ISI total score. A total score of 0 to 7 = "no clinically significant insomnia," 8 to 14 = "subthreshold insomnia," 15 to 21 = "clinical insomnia (moderate severity)," and 22 to 28 = "clinical insomnia (severe)." Missing ISI total score will not be categorized.

9.3.3.1.6. Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a subject-rated depressive symptom severity scale. It is collected during the clinic visit on Days 1, 13, 15, 18, 22, 28, 35, and 42. To monitor severity over time for newly diagnosed subjects or subjects in current treatment for depression, subjects may complete questionnaires at baseline and at regular intervals thereafter. Scoring is based on responses to specific questions, as follows: 0=not at all; 1=several days; 2=more than half the days; and 3=nearly every day.

The PHQ-9 total score will be calculated as the sum of the 9 individual item scores. If more than 1 individual item is missing, the PHQ-9 total score will not be calculated and will be left as missing. If 1 individual item score is missing, the missing item score will be imputed by the mean of all other available item scores to calculate the PHQ-9 total score. The PHQ-9 total score will be categorized as follows: 0 to 4=minimal depression, 5 to 9=mild depression, 10 to 14=moderate depression, 15 to 19=moderately severe depression; and 20 to 27=severe depression. Missing PHQ-9 total score will not be categorized.

9.3.3.1.7. Consensus Sleep Diary-Core (CSD-C)

The Consensus Sleep Diary-Core collects subjective responses to a series of questions related to their daily sleep pattern (ie, time to bed, time to fall asleep, time to final awakening and a question related to quality of sleep). From the CSD-C responses sleep parameters including sleep latency, TST, WASO, and sleep quality will be derived. The take-home subject sleep diary assessment will be administered using an eDiary solution. The eDiary will be captured using either a provisioned smartphone device or bring-your-own-device solution, depending on the subject's preference.

Subjects will complete an electronic sleep diary during the screening period. Between Day -9 and awakening on Day -2, subjects are required to complete the sleep diary for a minimum of 5 of the 7 nights. Eligibility for the study will be based on subjects having a sleep diary with the following: a minimum of 5 nights completed and a TST of <390 minutes (<6.5 hours) on at least 3 nights between Day -9 and Day-2.

Eligible subjects will complete the sleep diary each day through Day 42, preferably in the morning after awakening from sleep, regarding the last night's sleep. Subjective sleep parameters will be derived for clinic visit Days 1, 7, 15, 18, 22, 28, 35 and 42 using the mean of non-missing assessments between the previous visit day (exclusive) and the current visit day (inclusive):

Scheduled Visit	**No. of Days b/w Visits**	**Date stamp from the sleep diary used for averaging**
Day 1(Baseline)	7d	Day 1 date -7 days, and <= Day 1 VS date
Day 7	6d/number of days b/w V4 and V3	>Day 1 VS date, and <= Day 7 VS date
Day 15	8d/ number of days b/w V6 and V5	>Day 7 VS date, and <= Day 15 VS date
Day 18*	3d/ number of days b/w V7 and V6	> Day 15 VS date, and <= Day 18 VS date
Day 22	7d/ number of days b/w V8 and V7	> Day 18 VS date, and <= Day 22 VS date
Day 28	6d/ number of days b/w V9 and V8	> Day 22 VS date, and <= Day 28 VS date
Day 35	7d/ number of days b/w V10 and V9	> Day 28 VS date, and <= Day 35 VS date
Day 42	7d/ number of days b/w V11 and V10	> Day 35 VS date, and <= Day 42 VS date

*only for descriptive summary, not in the MMRM model.

The baseline subjective sleep parameters will be calculated as the mean of 7 days immediately preceding Day 1.

Parameters to be analyzed are as follows:

- sTST (in minutes) (Total sleep time) = (Time of final awakening - Time when tried to sleep) - time taken to fall asleep-sWASO
- sSL (in minutes) (Sleep Latency)
- sWASO (in minutes) (Wake after Sleep Onset)
- sNAW (Number of awakenings)
- sSQ (Sleep Quality)

The date/time stamp on the day's entry is compared to clinic visit date to identify records that go into the calculation of a visit assessment. In case of duplicate assessment on the same day, the first assessment will be counted toward the mean, but all assessments will be listed. The times entered in the diary by the subject, e.g. time when went to bed, time when tried to fall asleep, etc. need to be associated with a date in order to make meaningful comparisons or to be used in calculations. The following algorithm will be followed for this purpose: If Time to Bed is AM, then all time questions are associated with stamped date. If Time to Bed is PM or Time out of Bed is PM, then all time questions are associated with date one day before the stamped date. Otherwise, when Time to Bed is PM, all times in diary marked as PM are associated with day before the stamped date, and all times in diary marked as AM are associated with stamped date.

Since the data is subject-entered and not monitored, a record may be invalid when it fails to make logical sense. A record is considered invalid if any of the following holds true (use date/time combination to do these comparisons):

1. Any of the eight response or date stamp is missing.
2. sTST > sTTB (Total time in bed, in minutes, calculated as Time out of bed – Time to bed)
3. sTST < 0
4. sTTB <= 0
5. Time to bed > Time when tried to sleep
6. Time to bed > Time of final awakening
7. Time when tried to sleep > Time of final awakening
8. Time tried to sleep > Time out of bed
9. Time of final awakening > Time out of bed

An invalid record will be dropped from analysis of sTST, but not from the analysis of other sleep diary endpoints. The sleep diary data will not be windowed.

Sleep quality (sSQ) response will be defined as having a sSQ score of “very good” or “good.” Missing sSQ at the visit will not be evaluated for response.

9.3.4. Analysis of Secondary Efficacy Endpoints

The FAS will be used for all secondary efficacy summary tables. Subjects will be analyzed according to the randomized treatment.

9.3.4.1. Descriptive Summary of Secondary Efficacy Endpoints

The following continuous efficacy endpoints will be summarized descriptively by scheduled assessment time point using observed values, change from baseline (for post-baseline visits only) and percentage change from baseline (for post-baseline visits only):

- WASO (in minutes) in total and by quarter
- TST (in minutes) in total and by quarter
- LPS (in minutes)
- NAW in total and by quarter
- mDURAW in total and by quarter
- Minutes and percent of stage N1, N2, N3
- Minutes and percent of REM
- Latency to REM sleep (REML): The number of non-REM epochs (stages N1, N2, N3) from LPS to the first epoch of REM sleep
- REML for second and subsequent REM periods: The number of non-REM and REM epochs (stages N1, N2, N3, and REM) from LPS to the first epoch of the 2nd REM period, or subsequent REM period
- REM density: Total number of rapid eye movements divided by the total duration of REM sleep in minutes during TIB.
- REM activity: Total number of rapid eye movements during REM sleep.
- HAM-D total score
- HAM-D subscale
- HAM-D individual item score
- CGI-I score (observed value only)
- CGI-S score
- ISI total score
- PHQ-9 total scoreCSD-C derived endpoints including sTST (in minutes), sWASO (in minutes), sSL (in minutes), and sNAW

The following categorical efficacy endpoints will be summarized descriptively by scheduled assessment time point using counts and percentages:

- HAM-D response – missing response not accounted
- HAM-D response – missing response counted as No response
- HAM-D remission – missing remission not accounted

- HAM-D remission – missing remission counted as No remission
- CGI-I response
- Sleep Quality response
- ISI total score categories (0 to 7 = "no clinically significant insomnia," 8 to 14 = "subthreshold insomnia," 15 to 21 = "clinical insomnia (moderate severity)," and 22 to 28 = "clinical insomnia (severe))

Bar chart will be prepared for HAM-D response, HAM-D remission, ISI total score categories and CGI-I response by treatment group.

9.3.4.2. ANCOVA - PSG-derived Sleep Secondary Endpoints

Similar to those methods described above for the primary endpoint, an ANCOVA model will be used for the analysis of the change from baseline in other PSG-derived sleep variables (WASO, TST and TST by quarter of the PSG recording,LPS, NAW and mDURAW, in total and by quarter of the PSG recording,minutes and percent of stage N1, N2, N3, and REM sleep, latency to the first period of REM Sleep and latency to each subsequent period of REM Sleep, REM density) at EODBT, which are described in Section 9.3.3.1.1.

For each model, the comparison of interest will be between SAGE-217 and matching placebo at the end of double-blind treatment. Model based point estimates (i.e., least square [LS] means, 95% confidence intervals, and p-values) will be reported where applicable.

Line plot of model-based LS Mean (± standard error) over time will be prepared for HAM-D score, %SEFF, WASO, TST, LPS and ISI total score by treatment group.

9.3.4.3. Mixed effects model for repeated measures (MMRM) – Non PSG-derived Sleep Secondary Endpoints

The secondary efficacy endpoint, the change from baseline in ISI total score at end of double-blind treatment, will be analyzed using a MMRM. The model will include treatment, antidepressant treatment use (current/stable or not treated/withdrawn ≥60 days), baseline ISI total score, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All post-baseline time points will be included in the model. The main comparison will be between SAGE-217 and placebo at end of double-blind treatment. Model based point estimates (i.e., LS means, 95% confidence intervals, and p-values) will be reported for all time points. An unstructured (UN) covariance structure will be used to model the within-subject errors. If there is a convergence issue with the unstructured covariance model, Toeplitz or Autoregressive (1) [AR (1)] covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with AR (1) structure, no results will be reported. The p-value will be interpreted at 5% level of significance.

Similar to those methods described above for ISI total score, a MMRM will be used for the analysis of the change from baseline in CSD-C derived variables (sTST (in minutes), sWASO (in minutes), sSL (in minutes) and sNAW, HAM-D total score, HAM-D subscales and individual item scores, and PHQ-9 total score.

For each model, the comparison of interest will be between SAGE-217 and matching placebo at end of double-blind period. Model-based point estimates (i.e., LS means), 95% confidence intervals, and p-values will be reported for all time points.

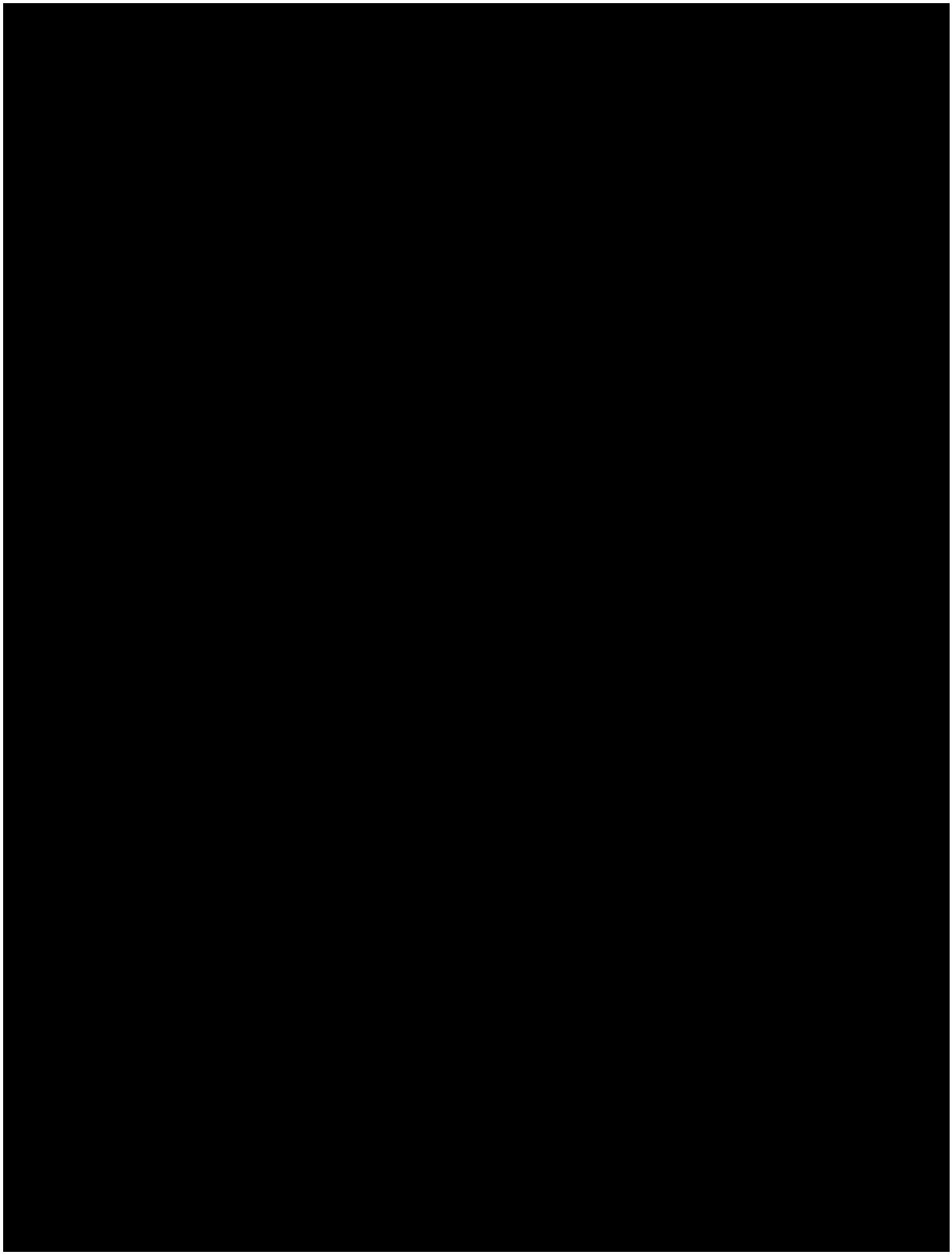
Line plot of model-based LS Mean (± standard error) will be prepared for change from baseline in ISI total score and HAM-D total score over time.

9.3.4.4. Generalized Estimating Equations (GEE)

The GEE method will be used for the analysis of HAM-D response and HAM-D remission. GEE models will include treatment, baseline HAM-D total score, antidepressant treatment use (current/stable or not treated/withdrawn ≥60 days), assessment time point, and time point-by-treatment interaction as explanatory variables. The comparison of interest will be the difference between SAGE-217 and matching placebo at end of double-blind period. Model-based point estimates (i.e., odds ratios), 95% confidence intervals, and p-values will be reported for all time points.

A GEE method will also be used for the analysis of CGI-I response including terms of treatment, baseline CGI-S score, antidepressant treatment use (current/stable or not treated/withdrawn ≥60 days), assessment time point, and time point-by-treatment as explanatory variables.

A GEE method will also be used for the analysis of sleep quality (sSQ) response including terms of treatment, baseline sSQ, antidepressant treatment use (current/stable or not treated/withdrawn ≥60 days), assessment time point, and time point-by-treatment as explanatory variables.



9.4. Safety Analysis

Safety and tolerability of SAGE-217 will be evaluated by AEs/SAEs, changes from baseline in vital signs, clinical laboratory evaluations, and 12-lead ECG. Suicidality will be monitored by the C-SSRS. Withdrawal symptoms will be measured by PWC-20. Safety data will be listed by subject and summarized by treatment group. All safety summaries will be performed on the Safety Set. The data will be presented by the treatment received rather than the treatment to which the subject has been randomized; for definition of actual treatment assignment, please see Section 9.1.

The safety endpoints evaluated at scheduled visits are taken as done in nominal visit, without any windowing. If a value is available for a nominal scheduled visit, that value will be used in summary by visit. The summary will also include "Last Value on Treatment (counts the last available measurement that is after baseline and on or before Day 15, this will include EODBT visit values) and Last Value on Study (count the last available measurement after baseline, this will include ET visit and Day 42). The safety endpoints and variables considered in the summary tables for this study are summarized in Table 5.

Table 5: Safety endpoints and variables in the summary tables

Safety Evaluation	Incidence	Observed Value	Change from Baseline	Shift from Baseline	Abnormality/ Clinical Significance (CS)	Potentially Clinical Significance (PCS)
AEs	X					
Labs		X	X	X	X	X
ECG		X	X	X	X	X
Vital Signs		X	X			X
C-SSRS	X	X	X			

Note: PCS criteria are outlined in sections 9.4.2-9.4.4.

X = to be summarized in tables

9.4.1. Adverse Events

AEs are collected starting at the time of informed consent and throughout the duration of the subject's participation in the study.

A treatment-emergent adverse event (TEAE) is defined as an AE with onset on or after the start of double-blind study drug. The term study drug includes any Sage investigational product, a comparator, or a placebo administered in a clinical trial. The TEAEs will be further categorized by the phase of occurrence as follows:

A double-blind treatment period TEAE is defined as an adverse event with onset on or after the start of double-blind study drug, but on or before the last dose of double-blind study drug + 1 Day.

A run-out treatment period TEAE is defined as an adverse event with onset after 1 day from the end of double-blind study drug, but on or before the last dose of run-out treatment period.

A follow-up TEAE is defined as an adverse event with onset after the end of run-out treatment period to the end of the study. If the date of an adverse event is incomplete and an unambiguous determination could not be made with respect to its onset time versus the first dose of double-blind study drug and/or last dose of double-blind study drug, the adverse event will be assumed to be a TEAE. For imputation of missing AE dates, please refer to Appendix C, Section 12.3.1. All adverse events will be coded using MedDRA version 21.0 or higher. An overview summary table of AEs will present the number and percentage of subjects as well as the number of events for the following:

- TEAE
  - Double-Blind Treatment Period TEAEs
  - Run-out Treatment Period TEAEs
  - Follow-up Period TEAEs
- TEAEs by maximum severity (severe>moderate>mild)
  - Double-Blind Treatment Period TEAEs
  - Run-out Treatment Period TEAEs

    - Follow-up Period TEAEs
- Double-Blind Treatment Period TEAE leading to discontinuation of study drug
- TEAE leading to withdrawal from the study
    - Double-Blind Treatment Period TEAEs
    - Run-out Treatment Period TEAEs
    - Follow-up Treatment Period TEAEs
- Death
    - Double-Blind Treatment Period TEAEs
    - Run-out Treatment Period TEAEs
    - Follow-up Period TEAEs
- SAE
    - Double-Blind Treatment Period TEAEs
    - Run-out Treatment Period TEAEs
    - Follow-up Period TEAEs

Incidence of TEAEs in following categories will be provided by SOC and PT. A subject is counted only once under each SOC and PT in case of multiple occurrences of the same AE.

- TEAE
- Double-Blind Treatment Period TEAE
- Run-out Treatment Period TEAE
- Follow-up Period TEAE
- TEAEs by maximum severity
- TEAEs by relationship to study drug
- TEAEs leading to discontinuation of study drug
- TEAEs leading to withdrawal from the study
- Serious TEAEs
- Run-out Treatment Period Serious TEAEs
- Follow-up Period Serious TEAEs
- Double-Blind Treatment Period TEAEs leading to dose interruption of study drug

Most common TEAEs are defined as those, which occurred in more than 5% of subjects in either treatment group. A summary of most common TEAE just by preferred term where the incidence is more than 5% will be provided, sorted by decreasing frequency by SAGE-217.

For maximum severity, subjects will be counted only once within each SOC and PT at the maximum severity in the following order: severe> moderate> mild; an AE with missing severity will be omitted from severity presentation. For relationship to study drug, subjects will be counted only once within each SOC and PT at the strongest relationship to study drug in the following order: probably related >

possibly related > not related. 'Related' is defined as relationship being "possible" or "probable" or missing., The incidences will be presented by descending frequency of SOC in SAGE-217 group and then, within a SOC, by descending frequency of PT based on the subject count, and in alphabetical order of PT if the incidence within a PT is a tie.

Adverse events with onset before the first dose of double-blind study drug will be provided in a separate listing. Separate data listings for deaths and non-fatal SAEs will be provided.

In addition, TEAE summary by SOC/PT will also be presented by the following subgroups:

1. Anti-depressant use at baseline
2. Age group: 18-24, 25-50, 51-65 years
3. Gender: Male, Female
4. Race: White, Black or African American, Other

In addition, AEs that occurred during placebo run-in period will be summarized for Safety Set separately according to treated received during double-blind treatment period. AEs that occurred for run-in failure subjects will be summarized and listed.

9.4.2. Clinical Laboratory

The clinical laboratory tests to be performed for monitoring of safety are listed in Table 6. They are collected at Screening and during clinic visits on Days 1, 7, 15, 22, 28, 42.

Table 6: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Coagulation
Red blood cell count Hemoglobin Hematocrit White blood cell count with differential Platelet count Red blood cell indices (MCV, MCH, MCHC) Reflex to red blood cell morphology if indices are abnormal	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Total bilirubin Direct bilirubin Indirect bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase Gamma-glutamyl transferase Potassium Sodium Lactate dehydrogenase Glucose Chloride Bicarbonate Calcium Phosphorus Triglycerides Thyroid stimulating hormone (TSH) Reflex to free T3/T4 if TSH is abnormal	pH Specific gravity Protein Glucose Red blood cell Nitrite Leukocyte esterase Ketones Bilirubin Urobilinogen	Activated partial thromboplastin time Prothrombin time International normalized ratio

All parameters will be converted to consistent units according to the International System of Units (SI) before presentation.

For the laboratory results that are "< or = x", where x is a number as collected in the data, the numeric part of the result will be used in calculation in the summary tables. Same is true if the result is presented as below the limit of quantitation (BLQ) and a lower limit of quantification (LLOQ) value is provided – LLOQ value will be used for calculation in the summary tables. The actual results as collected will be displayed in the listings.

Summary tables on lab parameters will include descriptive statistics for the observed values and changes from baseline by scheduled assessment timepoint in hematology, serum chemistry, coagulation and quantitative urinalysis test results. It will also include the summary of last values on treatment and on study. If a normal range is provided for the parameter, out-of-range values will be flagged as low or high, where applicable, in the subject data listings. A shift table for these parameters from baseline to each scheduled assessment time point will be provided. This table will also include the shift from normal at baseline to high or low at any time during treatment on or after first dose, on or before last dose + 7 days), any time post-baseline during the study (on or after first dose) and at the end of study (i.e. the last available value in the database). Qualitative urinalysis parameters will be summarized descriptively.

The number and percentage of subjects with PCS values will be provided in separate displays in hematology, serum chemistry and liver function tests provided for such occurrence any time post-baseline (irrespective of whether it happens in scheduled or unscheduled assessments). Potentially clinically significant values will be identified for specific laboratory parameters as outlined in the following table.

Table 7: Laboratory Parameters - Criteria for PCS Values

Laboratory Parameter	**Gender**	**Units**	**Criteria for PCS Values (Observed values)**	
			High	Low
Hematology				
Hemoglobin	Male	g/L	>185	<115
	Female	g/L	>170	<100
Hematocrit	Male	Fraction of 1	>0.55	<0.385
	Female	Fraction of 1	>0.49	<0.345
Platelet count		10^9/L	>600	<125
White blood cell		10^9/L	>15	<2.5
Basophils		10^9/L	>0.5	NA
Eosinophils		10^9/L	>1.5	NA
Neutrophils		10^9/L	NA	<1.5
Lymphocytes		10^9/L	>6.0	<0.5
Monocytes		10^9/L	>1.4	NA
Serum Chemistry				
Albumin		g/L	>70	<28
Blood urea nitrogen		mmol/L	>10.71	NA
Calcium		mmol/L	>2.75	<2.0
Chloride		mmol/L	>120	<90
Creatinine		mmol/L	>3xULN or >3x Baseline	
Gamma Glutamyl Transferase			>3xULN	
Glucose		mmol/L	>13.9	<2.8
Sodium		mmol/L	>150	<132

Potassium		mmol/L	>5.4	<3.3
Protein		g/L		<45
Bicarbonate		mmol/L	>34	<18
Phosphorus		mmol/L	>1.94	<0.61
Liver Function Tests (LFT)				
Bilirubin		µmol/L	>2xULN	NA
Aspartate Aminotransferase		U/L	>3xULN	NA
Alanine Aminotransferase		U/L	>3xULN	NA
Alkaline Phosphatase		U/L	>1.5xULN	NA

Liver function tests will be monitored closely for potentially clinically significant values, and will be summarized for occurrence any time post-baseline for the following parameters for these PCS threshold (for condition involving more than one parameters, the results need to be from the same timepoint):

Alanine Aminotransferase: >3xULN, >5xULN, >10xULN
Aspartate Aminotransferase: >3xULN, >5xULN, >10xULN
Alanine Aminotransferase or Aspartate Aminotransferase: >3xULN, >5xULN, >10xULN
Alkaline Phosphatase: >1.5xULN, >2xULN
Total Bilirubin: >1.5xULN, >2xULN
Total Bilirubin > 2xULN **AND** (Alanine Aminotransferase or Aspartate Aminotransferase >3xULN)
Total Bilirubin >2xULN **AND** Alkaline Phosphatase >2xULN **AND** (Alanine Aminotransferase or Aspartate Aminotransferase >3xULN)

Any lab results considered clinically significant by the investigator will be captured as adverse events, hence will show up in AE displays.

Pregnancy test results will be listed but not summarized.

9.4.3. Vital Signs

Vitals for the following parameters - Supine Systolic Blood Pressure (mmHg), Standing Systolic Blood Pressure (mmHg), Supine Diastolic Blood Pressure (mmHg), Standing Diastolic Blood Pressure (mmHg), Supine Heart Rate (beats/minute), Standing Heart Rate (beats/minute), Respiratory Rate (breaths/minute), Pulse Oximetry (SpO2, %), Temperature (degrees C) – are collected at Screening, and during clinic visits on Days -2, 1, 7, 13, 14, 15, 18, 22, 28, 35, 42. Descriptive summaries of observed values and changes from baseline will be provided for vital sign parameters - by scheduled assessment time point. It will also include the summary of last values on treatment and on study.

Additionally, the number and percentage of subjects with PCS and potentially clinically significant change (PCSC) values will be summarized for such occurrence any time post-baseline. PCS and PCSC values will be identified for vital sign parameters as outlined in the following table.

Table 8: Vital Signs - Criteria for PCS and PCSC Values

Vital Sign	Units	Criteria for PCS Values (Observed values)		Criteria for PCSC values (Change from Baseline values)	
		High	Low	Increase	Decrease
Heart rate (supine and standing)	Beats/min	>120	<40	NA	NA
Systolic Blood Pressure (supine and standing)	mmHg	>180	<90	≥30	≥30
Diastolic Blood pressure (supine and standing)	mmHg	>110	<50	≥20	≥20
Supine - Standing Systolic Blood Pressure*	mmHg	≥20			
Supine - Standing Diastolic Blood Pressure*	mmHg	≥10			
Orthostatic hypotension: supine – standing SBP and DBP	mmHg	SBP >= 20 and DBP >= 10			
	mmHg	SBP >= 20 or DBP >= 10			

*Orthostatic systolic/diastolic blood pressure is defined as supine -standing systolic/diastolic blood pressure.

The change from supine to standing (Supine – Standing) vital signs – heart rate, systolic and diastolic blood pressure – will be summarized by scheduled assessment timepoint.

Any vital signs results considered clinically significant by the investigator will be captured as adverse events, hence will show up in AE displays.

9.4.4. Electrocardiogram

Supine 12-lead ECGs will be performed in triplicate, and are collected during the clinic visits at Screening, Days 1, 15, 28. The following ECG parameters will be listed for each subject: heart rate (beats per minute), PR (msec), QRS (msec), QT (msec), QTc (msec) and QTcF (msec).

The average of the triplicate values will be used in the summary, including baseline ECG values. The observed value at each time point and change from baseline at each post-baseline scheduled time point will be summarized. This summary will also include the last values on treatment and on study. Each ECG is evaluated as 'normal', 'abnormal, not clinically significant' and 'abnormal, clinically significant'; the number and percentage of subjects with at least one of the triplicate values in the categories of 'abnormal, clinically significant' and 'abnormal, not clinically significant' will be provided at baseline and each post-baseline scheduled assessment time point.

Additionally, the number and percentage of subjects with PCS and PCSC values will be summarized for such occurrence any time post-baseline. PCS and PCSC values will be identified for ECG parameters as outlined in the following table. This analysis includes triplicate values individually and is not based on average value. In addition, any PCS value at any time post-baseline will be summarized.

Table 9: ECG Parameters - Criteria for PCS and PCSC Values

ECG	Units	Criteria for PCS Values (Observed values)		Criteria for PCSC values (Change from Baseline)	
		High	Low	Increase	Decrease
QTcF Interval	msec	females: >450 to 480, male: >450 to 470 females: >480 to 500, male: >470 to 500 >500	NA	>=30 to 60 >60	NA

9.4.5. Physical Examination

Physical examination is scheduled at Screening, Days 1, 22, 28, and 42. Only clinically significant abnormalities are captured in the database – for post-baseline observations, these will be reported as adverse events, hence these will be included in AE displays; for pre-baseline observations, these will be reported as medical history, hence these will be included in Medical History displays. The dates of physical examination will be listed to confirm that the examination was done.

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

C-SSRS scale consists of a screening evaluation that assesses the lifetime experience as well as past 24 months experience of the subject for suicidal ideation and behavior, and baseline and post-baseline evaluations that focuses on suicidality since the last study visit. The C-SSRS includes ‘yes’ or ‘no’ responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe). The score on suicidal ideation is derived as the highest question number (out of five questions) that is answered ‘yes’; if all five responses are ‘no’, the score is 0.

The “Baseline/Screening” C-SSRS form will be completed at Screening (lifetime history and past 24 months). The “Since Last Visit” C-SSRS form will be completed on Days -2, 1, 7, 13, 14, 15, 18, 22, 28, 35, 42. Baseline suicidal ideation/behavior is defined as the worst of suicidal ideation/behavior before the first dose of double-blind study drug, excluding the lifetime experience assessment.

Summary of shift from baseline in C-SSRS suicidal ideation and suicidal behavior will be presented for the following categories - no suicidal ideation/behavior, suicidal ideation, suicidal behavior - by scheduled assessment time point. The number and percentage of subjects with at least one response of ‘Yes’ to any C-SSRS suicidal ideation or suicidal behavior item will be summarized for baseline, any time post-baseline, and by each scheduled assessment time point separately. In addition, summary of shift from baseline in C-SSRS maximum severity score in suicidal ideation for any time post-baseline will be presented. The distribution of subjects with suicide-related events will be plotted.

9.4.7. Physician Withdrawal Checklist (PWC-20)

The PWC is based on the 35-item Penn Physician Withdrawal Checklist that was developed in the 1960s to measure benzodiazepine and benzodiazepine-like discontinuation symptoms. The PWC-20 is a shorter version of the Penn Physician Withdrawal Checklist based on the 20 items that provided the best differentiation from placebo in previous trials. It is collected during the clinic visit on Days 1, 15, 18, 22, 28, 35, 42. The PWC-20 is made up of a list of 20 symptoms (eg, loss of appetite, nausea-vomiting, diarrhea, anxiety-nervousness, irritability, etc) that are rated on a scale of 0 (not present) to 3 (severe). The total score is derived as the sum of individual item scores, which ranges from 0 to 60. Missing item score will not be imputed to calculate the total score. The PWC-20 will be used to monitor for the presence of potential withdrawal symptoms following discontinuation of SAGE-217.

Potential withdrawal symptoms collected on the PWC-20 will be summarized by visit and treatment group.

[redacted]

10. SUMMARY OF INTERIM AND DMC ANALYSES

Not applicable.

11. REFERENCES

Clinical Study Protocol: Version 4.0 (17 July 2019), Company: Sage Therapeutics Inc

12. LIST OF APPENDICES

12.1. Appendix A: Schedule of Assessments

	Screening	Single-blind Placebo Run-in		Double-blind Period				Follow-up Visits					
Visit	**1**	**2**		**3**	**4**	**5**		**6**	**7**	**8**	**9**	**10**	**11**
Day	**-30 to -3**	**-2**	**-1**	**1**	**7 (±1 d)**	**13**	**14**	**15/EODBT[a]**	**18 (±1 d)**	**22 (±1 d)**	**28 (±3 d)**	**35 (±3 d)**	**42/ET[a] (±3 d)**
Study Procedure													
Informed consent	X												
Duplicate subject check[b]	X												
Inclusion/ exclusion criteria	X	X[c]		X[c]									
Demographics	X												
Medical/family history	X												
Serum FSH test[d]	X												
Pregnancy test[g]	X	X[c]		X[c]				X					X
MGH ATRQ	X												
SCID-CT	X												
Physical examination[e]	X			X				X		X	X		X
RLS-DI	X												
Body weight	X							X					X
Height	X												
Clinical laboratory assessments[f]	X			X[c]	X[c]			X		X	X		X
Drug and alcohol test[h]	X	X[c]	X[c]		X[c]	X[c]	X[c]		X	X	X	X	X
Hepatitis and HIV Screen	X												

	Screening	Single-blind Placebo Run-in		Double-blind Period				Follow-up Visits					
Visit	**1**	**2**		**3**	**4**	**5**		**6**	**7**	**8**	**9**	**10**	**11**
Day	**-30 to -3**	**-2**	**-1**	**1**	**7 (±1 d)**	**13**	**14**	**15/EODBT[a]**	**18 (±1 d)**	**22 (±1 d)**	**28 (±3 d)**	**35 (±3 d)**	**42/ET[a] (±3 d)**
[redacted]													
Vital signs[j]	X	X[c]		X[c]	X[c]	X[c]	X[c]	X[c]	X	X	X	X	X
12-lead ECG[k]	X			X[c]				X[c]					X
C-SSRS[l]	X	X[c]		X[c]	X[c]	X[c]	X[c]	X[c]	X	X	X	X	X
MADRS	X			X[c]									
CGI-I					X[c]			X[c]	X	X	X	X	X
CGI-S				X[c]	X[c]			X[c]	X	X	X	X	X
HAM-D[m]	X			X[c]	X[c]			X[c]	X	X	X	X	X
PWC-20				X[c]				X[c]	X	X	X	X	X
ISI	X			X[c]	X[c]			X[c]	X	X	X	X	X
PHQ-9				X		X		X	X	X	X	X	X
[redacted]													
PSG		X	X			X	X						
Sleep Diary[t]	X	X											
[redacted]													
Subject training	X[r]	X[r]											
Study Drug Dispensation		X	X	X	X	X	X	X					

	Screening	Single-blind Placebo Run-in		Double-blind Period				Follow-up Visits					
Visit	**1**	**2**		**3**	**4**	**5**		**6**	**7**	**8**	**9**	**10**	**11**
Day	**-30 to -3**	**-2**	**-1**	**1**	**7 (±1 d)**	**13**	**14**	**15/EODBT[a]**	**18 (±1 d)**	**22 (±1 d)**	**28 (±3 d)**	**35 (±3 d)**	**42/ET[a] (±3 d)**
Study Drug Administration		Single-blind Placebo		Double-blind (SAGE-217 or placebo)				Single-blind Placebo (Day 15 to Day 21)[u]					
Study Drug Adherence Review					X	X				X			X (ET only)
AEs /SAEs	X												
Prior/ concomitant medications[s]	X												

AE = adverse event; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression Severity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EODBT = End of double-blind treatment; ET = early termination; FSH = follicle stimulating hormone; HAM-D = Hamilton Rating Scale for Depression, 17 item; ISI = Insomnia Severity Index; [redacted]; MADRS=Montgomery-Åsberg Depression Rating Scale; MGHATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; O = optional; PHQ-9 = 9-item Patient Health Questionnaire; [redacted] PSG = Polysomnography; PWC = Physician Withdrawal Checklist; RLS-DI = The Restless Legs Syndrome-Diagnostic Index; SAE = serious adverse event; SCID-CT = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Clinical Trials version.

[a] Subjects who discontinue study drug early during the double-blind treatment period should return to the site for the end of double-blind treatment (EODBT) visit as soon as possible, preferably the day after treatment is discontinued. [redacted] Follow-up visits should take place as scheduled. If at any time after the EODBT visit, a subject decides to terminate the study, the subject should return for an early termination (ET) visit. The EODBT and ET visits can be on the same day if a subject discontinues study drug and terminates the study on the same day during a clinic visit; in this case, all events scheduled for the ET visit will be conducted.

[b] Subjects will be required to authorize that their unique subject identifiers be entered into a registry (www.subjectregistry.com) with the intent of identifying subjects who may meet exclusion criteria for participation in another clinical study.

[c] To be completed predose

[d] A serum FSH test will be conducted for female subjects who are not surgically sterile to confirm whether a female subject with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being post-menopausal.

[e] A full physical examination will be conducted at Screening and abbreviated physical examinations will be conducted thereafter. A full physical examination includes assessment of body systems (eg, head, eye, ear, nose, and throat; heart; lungs; abdomen; and extremities). An abbreviated physical exam includes a brief medical history followed by targeted physical exam.

[f] Clinical laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis.

[g] Serum pregnancy test at screening and urine pregnancy test thereafter for female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal.

[h] Urine toxicology for selected drugs of abuse and breath test for alcohol.

[i] Optional blood sample, where consent is given.

[j] Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). Heart rate and blood pressure to be collected in supine position at all scheduled time points after the subject has been resting for 5 minutes and then after approximately 3 minutes in the standing position. Vital signs may be repeated at the discretion of the Investigator as clinically indicated. When vital signs are scheduled at the same time as blood draws, vital signs will be obtained first.
[k] Triplicate ECGs will be collected. When ECGs and [redacted] collection occur on the same day, the 12-lead ECGs will be performed before [redacted] collection.
[l] "Baseline/Screening" C-SSRS form will be completed at Visit 1. The "Since Last Visit" C-SSRS form will be completed at all subsequent time points.
[m] HAM-D is to be completed as early during the visit as possible. The assessment timeframe for HAM-D will refer to the past 7 days (1 week) at the first HAM-D administration and "Since Last Visit" for all other visits.

[redacted]

[r] Subjects will be trained on use of software applications and devices necessary for the conduct of the study by site personnel
[s] Prior medications and cognitive behavioral therapy will be collected at Visit 1 and concomitant medications and/or procedures will be collected at each subsequent visit.
[t] Sleep diary (eDiary) will be distributed during the Screening visit (Visit 1). Subjects who pass initial screening will be asked to complete an electronic sleep diary during the screening period and for a minimum of 4 of 7 nights from evening of Day -9 to the morning of Day -2 (inclusive.)
[u] Following the double-blind treatment period, subjects will take single-blind placebo treatment once daily until Visit 8.

12.2. Appendix B: Details of Statistical Methodology

Sample SAS code for Analysis of Covariance (ANCOVA):

```
proc mixed data=&data;
class trtan antidep;
model chg=base trtan antidep;
lsmeans trtan /diff cl;
run;
```

Sample SAS code for Mixed Effects Model for Repeated Measures (MMRM):

```
proc mixed data=&data;
by param;
class trtan antidep  avisitn usubjid;
model chg=base trtan antidep avisitn trtan*avisitn / ddfm=kr;
repeated avisitn / subject=usubjid type=un;
* if type= un does not converge, use type= toep;
* if type= toep still not converge, use type=ar(1);
lsmeans trtan*avisitn /cl diff adjdfe=row;
ods output ConvergenceStatus=conv LSMeans=lsmean Diffs=diff;
run;
```

Sample SAS code for Generalized Estimating Equation (GEE):

```
proc genmod data=&data;
by param;
class usubjid trtan antidep avisitn;
```

```
model resp=base trtan antidep avisitn trtan*avisitn/dist=bin link=logit;
repeated subject=usubjid / type=un;
* if convergence not met, use type=exch;
* if type= exch still not converge or has error, use type=ind;
* if type= ind still not converge or has error, use type=cs;
lsmeans trtan*avisitn / diff exp cl adjdfe=row;
ods output ConvergenceStatus=conv LSMeans=lsmean Diffs=diff;
run;
```

Sample SAS code for Stratified Wilcoxon Rank Sum Test:

```
PROC FREQ DATA = xxx;
WHERE trtan in (1, 2);
TABLES strata*trtan*chg/cmh2 scores=modridit noprint;
RUN;
```

12.3. Appendix C: Handling of Missing Dates

Dates missing the day or both the day and month of the year will adhere to the following conventions in order to classify TEAEs and to classify prior and concomitant medications.

In general, listings will present the actual partial or missing values rather than the imputed values that may be used in derivation. In instances where imputed values will be presented, imputed values will be flagged.

12.3.1. Adverse Events

If the AE start date is completely missing, do not impute a date but consider it as TEAE, unless the AE end date is before the first dose of treatment, in which case the AE will be considered prior.

For partial AE start dates:

- When the year is known, but the month and day is unknown, then:
  - If the year matches the year of first dose date and the end date (if present) is after first dose date, or AE is ongoing, then impute the month as the month of the first dose date, and day as the day of the first dose date + 1 day.
  - If the year of AE onset < year of initiation of the treatment, then the month and day will be set to December 31st .
  - If the year of AE onset > the year of initiation of treatment, then the month and day will be set to January 1st.

- If the year and month are known, but the day is unknown, then:
  - If the year of AE onset = the year of initiation of the treatment and:
    - the month of AE onset = the month of initiation of the treatment, then the day will be set to the day of first dose day + 1 day.
    - the month of AE onset < the month of initiation of the treatment, then the day will be set to the last day of month.
    - if the month of AE onset > the month of initiation of the treatment, then the day will be set to the 1st day of month.
  - If the year of AE onset < the year of initiation of the treatment, then the day will be set to the last day of month.
  - If the year of AE onset > the year of initiation of the treatment, then the day will be set to the 1st day of month.
    - If the imputed AE onset date is after the AE stop date, then the onset date will be set to the stop date.

- When the year and day are present and the month is missing, treat it as if the day is missing, and only year is present. Follow the imputation rules for “year is known, but the month and day is unknown”.

- When the year is missing, but the month and/or day is known, treat this date as missing; do not impute.

12.3.2. Prior and Concomitant Medications

If the conmed start date is completely missing, do not impute a date but consider it as a concomitant medication, unless the conmed end date is before the initiation of treatment, in which case the conmed will be considered prior.

For the partial start date of medication:

- If the year is present and the month and day are missing, then the month and day will be set to January 1.
- If the year and day are present and the month is missing, then treat it as if the day is also missing. Set the month and day to be January 1.
- If the year and month are present and the day is missing, then the day will be set to the 1st day of month.
- If the imputed start date of medication is after the non-imputed end date of medication, then the start date will be set to the end date of medication.

For the partial end date of medication:

- If the year is present and the month and day are missing, then the month and day will be set to December 31.
- If the year and month are present and the day is missing, then the day will be set to the last day of the month.
- If the year and day are present and the month is missing, then treat it as if the day is also missing. Set the month and day to be December 31.

12.3.3. Dates in Disease History (Dates of diagnosis, current episode, first episode)

- If the year is present and the month and day are missing, then the month and day will be set to January 1.
- If the year and day are present and the month is missing, then the month will be set to January.
- If the year and month are present and the day is missing, then the day will be set to the 1st day of month

12.4. Appendix D: List of Displays

12.4.1. Index of Tables

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Table 14.1.1.3	Reasons for Exclusion from Analysis Sets	All Randomized Set
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Table 14.1.3.1.3	Summary of Medical and Surgical History Which are Ongoing at the Time of Screening	Full Analysis Set
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Table 14.1.3.2.2	Summary of Concomitant Non-Psychotropic Medications	Full Analysis Set
Table 14.1.3.2.3	Summary of Double-blind Period Concomitant Non-Psychotropic Medications	Full Analysis Set
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