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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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

PROTOCOL NUMBER: 217-MDD-304

Study Drug	SAGE-217
Clinical Phase	Phase 3
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted] Tel: [redacted] email: [redacted]
Sponsor Medical Monitor	[redacted] MD, PhD Tel: [redacted] E-mail: [redacted]
Date of Original Protocol	Version 1.0, 11 October 2018
Date of Amendment 1	Version 2.0, 22 February 2019
Date of Amendment 2	Version 3.0, 25 April 2019
Date of Amendment 3	Version 4.0, 17 July 2019

Protocol Number:	217-MDD-304
Study Drug:	SAGE-217
IND No.:	132131
Study Phase:	Phase 3
Sponsor:	Sage Therapeutics, Inc.
Protocol Date:	Version 4.0, 17 July 2019

Sponsor Approval

[redacted]
MD, PhD Date (DD MMM YYYY)

[redacted]
RAC Date (DD MMM YYYY)

[redacted]
Date (DD MMM YYYY)

[redacted]
MS Date (DD MMM YYYY)

[redacted]
DVM, MS, MPH Date (DD MMM YYYY)

[redacted]
PhD Date (DD MMM YYYY)

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the 217-MDD-304 clinical protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed name of Investigator

_____

Signature of Investigator

_____

Date (DD MMM YYYY)

PROCEDURES IN CASE OF EMERGENCY

Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Sage Study Physician	[redacted] MD, PhD	Email [redacted] Tel: [redacted]
Syneos Health Medical Monitor	[redacted] MD	Email: [redacted] Office: [redacted] Mobile [redacted]
24-Hour Serious Adverse Event reporting	IQVIA Lifecycle Safety	Email: [redacted] SAE Hotline Tel: [redacted] Fax: [redacted]
Product Complaints	Sage Therapeutics, Inc.	Email: productcomplaints@sagerx.com Tel: [redacted]

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics, Inc. (hereafter referred to as Sage Therapeutics, or Sage)

Name of Study Drug:
SAGE-217 Capsules

Name of Active Ingredient:
SAGE-217

Title of Study:
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

Number of Sites and Study Location: This study will take place at approximately 25 sites in the United States.

Phase of Development: 3

Planned Duration of Subject Participation:
The planned duration of subject participation is approximately 72 days. During this time, there will be 11 study visits, which will include 4 overnight stays.

Objectives:

Primary:

- To determine the effect of SAGE-217 on overall insomnia symptoms in subjects with comorbid Major Depressive Disorder (MDD) and insomnia.

Secondary:

- 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.

[redacted]

Endpoints:

Primary:

- Change from baseline in sleep efficiency (SE), defined as the percentage of time in bed spent asleep, at end of double-blind treatment (EODBT) as assessed by polysomnography (PSG)

Secondary:

- 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, 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 at 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 (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 Rating Scale for Depression (HAM-D) total score at EODBT
- Change from baseline in the 9-item subject-rated Patient Health Questionnaire (PHQ) at the EODBT
- Safety: Incidence and severity of adverse events/serious adverse events; 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]

[redacted]

Study Description:

Insomnia symptoms have been reported in a majority of people with MDD. The relationship between MDD and insomnia disorder is bidirectional where the presence of one increases the risk of developing the other and people with severe depression are likely to also have severe insomnia. In previous studies, SAGE-217 significantly improved depression in subjects with MDD and improved sleep in a phase-advance model of transient insomnia in healthy adults. The purpose of this study is to examine the effects of SAGE-217 on symptoms of sleep disruption in subjects with comorbid insomnia and MDD.

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.

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 who pass initial screening will be asked to complete an electronic sleep diary for a minimum of 4 of 7 nights from evening of Day -9 to the morning of Day -2. Continued eligibility for the study will be based on subjects having a sleep diary with the following: a minimum of 4 nights completed and a TST of <390 minutes (<6.5 hours) on at least 3 nights between Day -9 and Day -2. Subjects who do not meet the sleep diary eligibility criteria will not qualify for continued participation in the study.

Subjects who meet the sleep diary continuation criteria will return for a PSG qualification visit. The PSG qualification visit (Visit 2) will begin on Day -2 and will continue to Day 1. The clinical research coordinator (CRC) will determine the 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 lights out prior to the PSG qualification (Visit 2). 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. Practically, subjects may consider taking the study medication within 1 hour following a dinner including solid food, or taking study medication later in the evening with solid food. Given the substantially improved absorption of SAGE-217 with food, administering the study medication in the presence of food is important. Subjects will return to the study center during the treatment and follow-up periods as outlined in Table 1. Efficacy and safety assessments will be performed at pre-specified times during the study, and blood samples will be collected for analysis of SAGE-217, as outlined in the Schedule of Assessments (Table 1). 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 Day 13 and will continue to Day 15. Subjects will be allowed to remain in the clinic between the consecutive PSG visits. At the discretion of the Investigator, subjects may be allowed to leave the clinic between consecutive PSG visits following all post-treatment evaluations and return to the clinic 2 hours prior to their habitual bedtime as determined by the CRC.

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 will be conducted on Days 18, 22, 28, 35, and 42. The blind will be maintained through the Follow-up period. Subjects who cannot tolerate study drug will be discontinued from study drug and will receive treatment as clinically indicated. Subjects who discontinue treatment during the double-blind treatment period should return to the site for an end of double-blind treatment visit (Visit 6) as soon as possible, preferably the day after treatment is discontinued. If at any time after Visit 6, a subject decides to terminate the study (ie, not be available for the last follow-up visit 4 weeks after the last double-blind study treatment), the subject should return for an early termination (ET) visit. The end of double-blind treatment 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, events scheduled for these visits will be conducted.

Number of Subjects (Planned): Approximately 102 subjects will be randomized and dosed to obtain 82 evaluable subjects, with a total of 41 subjects per treatment arm.

Eligibility Criteria:

Inclusion Criteria:

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject agrees to adhere to the study requirements.
3. Subject is a male or female between 18 and 64 years of age, inclusive, at the time of consent.
4. Subject has a diagnosis of MDD as diagnosed by SCID-5-CT, with symptoms that have been present for at least a 4-week period.
5. Subject has insomnia that has been present for ≥4 weeks and is confirmed at Screening based on the DSM-5 diagnostic criteria (using the SCID-5-CT) for insomnia disorder, excluding DSM-5 criterion D (requiring 3 months duration) and allowing the presence of coexistent MDD as it applies to DSM-5 criterion H.
6. Subject has an Insomnia Severity Index (ISI) score ≥15 (moderate to severe insomnia) at Visits 1 and 3.
7. Subject has completed the Consensus Sleep Diary-Core (CSD-C) for a minimum of 4 days between the evening of Day -9 and after awakening on the morning of Day -2, inclusive.
8. Subject reports a total sleep time (TST) of <390 minutes (<6.5 hours) based on CSD-C Questions #2 through 6, on at least 3 nights between the evening of Day -9 and after awakening on the morning of Day -2, inclusive.
9. Subject has a habitual bedtime between 9:00 PM and 12:00 AM (midnight).
10. 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.

11. Subject has a MADRS score of ≥28 and a HAM-D total score ≥20 at Visit 1 and Visit 3 (prior to dosing).
12. Subject taking antidepressants must have been taking these medications at the same dose for at least 60 days prior to Day 1.
13. Subject is willing to delay start of other antidepressant or antianxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics and sleep aids, and Cognitive Behavioral Therapy for Insomnia (CBTI) until after study completion.
14. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests. Subject has a body mass index (BMI) within the range of 18.0 to 40.0 kg/m^2, inclusive.
15. Female subject agrees to use one of the following methods of highly effective contraception during participation in the study and for 30 days following the last dose of study drug, unless she is postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle stimulating hormone [FSH] level >40 mIU/mL) and/or surgically sterile (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence):
    - Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation.
    - Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
    - Intrauterine device.
    - Intrauterine hormone-releasing system.
    - Bilateral tubal occlusion/ligation.
    - Vasectomized partner.
16. Male subject agrees to use an acceptable method of effective contraception for the duration of study and for 5 days after receiving the last dose of the study drug, unless the subject does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence). Acceptable methods of effective contraception for males includes vasectomy, or a condom with spermicide used together with highly effective female contraception methods if the female partner(s) is of child-bearing potential (see Inclusion Criteria #15 for acceptable contraception methods).
17. Male subject is willing to abstain from sperm donation for the duration of the study and for 5 days after receiving the last dose of the study drug.
18. Subject agrees to refrain from drugs of abuse and alcohol for the duration of the study.

Exclusion Criteria:

1. Subject has attempted suicide associated within the current episode of MDD.
2. Subject had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the subject has presented for screening during the 6-month postpartum period.

3. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study.
4. Subject has treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants within the current major depressive episode (excluding antipsychotics) from 2 different classes for at least 4 weeks of treatment. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire will be used for this purpose.
5. Subject has undergone vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine (including esketamine) within the current major depressive episode.
6. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
7. Subject has a positive pregnancy test at Visit 1, 2, or 3 prior to the start of study drug administration or is breastfeeding at Visit 1, 2, or 3 prior to the start of study drug administration and plans to continue to breastfeed through the treatment period or within 7 days from the last dose of study drug.
8. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at Visit 1.
9. Subject has a clinically significant abnormal 12-lead ECG at Visit 1 or 3 prior to study drug administration. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study.
10. Subject has active psychosis per Investigator assessment.
11. Subject has a medical history of seizures.
12. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
13. Subject has a history of mild, moderate, or severe substance use disorder (including benzodiazepines) diagnosed using DSM-5 criteria in the 12 months prior to Visit 1.
14. Subject has a PSG-confirmed or clinically suspected diagnosis of obstructive sleep apnea (OSA, AHI ≥15), or a reported history of moderate to severe sleep apnea, or a clinically suspected or PSG-confirmed diagnosis of restless leg syndrome (RLS), periodic limb movements in sleep (PLMS or PLMD), or narcolepsy.
15. Subject has a Restless Leg Syndrome – Diagnostic Index (RLS-DI) score of ≥11 at Visit 1.
16. Subject has an Apnea-Hypopnea Index (AHI) ≥15 and/or a Periodic Limb Movement Arousal Index (PLMAI) ≥10 as determined at the Day -2 PSG.
17. Subject has a recent history of circadian rhythm disorder or has done shift work or rotating shifts within 30 days prior to Visit 1.
18. Subject is taking or participating in any of the following:
    a. benzodiazepines, barbiturates, or $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, zolpidem, brexanolone) within 28 days prior to Visit 2,
    b. benzodiazepines, barbiturates, or $GABA_A$ modulators daily or near-daily (≥4 days per week) for 1 year in the last year prior to Visit 2,
    c. CBTI and/or psychotherapy for insomnia within 28 days prior to Visit 2,

d. benzodiazepine or GABA modulator with a half-life of ≥48 hours (eg, diazepam) from 60 days prior to Day 1.

19. Subject is taking non-GABA anti-insomnia medications (eg, prescribed therapeutics specifically for insomnia and/or over the counter sleep aids), or first generation or second generation (typical/atypical) antipsychotics at Day -14. Note that non-sedating anti-histamines are permitted.
20. Subject has had exposure to another investigational medication or device within 30 days prior to Visit 1.
21. Subject has previously participated in a SAGE-217 or a SAGE-547 (brexanolone) clinical trial.
22. Subject has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to Visit 2.
23. Subject has used any of the following strong CYP3A inducers within 28 days prior to Visit 2: rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort.
24. Subject has a positive drug and/or alcohol screen at Visit 1 or Visit 2 prior to dosing.
25. Subject plans to undergo elective surgery during participation in the study.
26. Subject has traveled >1 time zone within 7 days prior to Visit 1 or is planning to travel >1 time zone through study completion.
27. Subject has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and melanoma in situ) within the past year prior to Screening.
28. Subject has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
29. Subject has been taking psychostimulants (eg, methylphenidate, amphetamine) or opioids regularly or as needed within 28 days prior to Visit 2.
30. Subject uses a continuous positive airway pressure (CPAP) machine.

Study Drug, Dosage, and Mode of administration:

SAGE-217 capsules (30 mg) for oral administration.

Reference Therapy, Dosage and Mode of Administration:

Matched placebo capsules for oral administration.

Duration of Treatment:

On Days -2 and -1, subjects will be given a single-blind placebo dose orally, once daily with food, 30 minutes (±15 minutes) prior to lights out (PSG). Starting on Day 1, Subjects will self-administer SAGE-217 (30 mg) or matching placebo orally once daily in the evening with food for 12 days. On Days 13 and 14, subjects will be given a double-blind dose of SAGE-217 or matching placebo orally, once daily with food, 30 minutes (±15 minutes) prior to lights out (PSG). On Days 15 through 21, subjects will self-administer a single-blind placebo dose, orally, once daily with food, in the evening.

Statistical Methods:

A separate statistical analysis plan (SAP) will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the clinical study report.

Randomization:

On Day 1, eligible subjects will be randomized to receive SAGE-217 Capsules or matching placebo capsules in a 1:1 ratio. Randomization will be stratified by based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥60 days). Subjects, clinicians, and the study team will be blinded to treatment assignment. Randomization will be performed centrally via an interactive response technology (IRT) system.

General Considerations

Since insomnia is known to be intermittent in nature and prone to adaptation effects, to reduce variability and to reduce selection bias, PSG is performed for 2 consecutive nights before randomization as well as at end of double-blind treatment. In analysis, the average of values over 2 nights measurement will be used as the parameter value. Subjective measures of sleep will also be similarly analyzed. Following the double-blind treatment period, possible rebound insomnia and withdrawal effects will be evaluated during a single-blind placebo run-out period.

For the purpose of all safety, efficacy, and other analyses where applicable, baseline is defined as the last measurement prior to the start of double-blinded 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.

Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

Analysis Sets

The All Randomized Set, defined as all subjects who have been randomized, will be used for subject disposition. Subjects will be classified according to randomized treatment.

The Safety Set is defined as all subjects receiving at least 1 dose of study drug and will be used to provide descriptive summaries of safety data, demographics, and baseline characteristics. Data will be summarized according to treatment received.

The Full Analysis Set, defined as all randomized subjects in the Safety Set who have at least one post-baseline efficacy evaluation, will be used for analysis of efficacy data. Data will be summarized according to randomized treatment.

[redacted]

Determination of Sample Size

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 detect 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. 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%. Randomization will be performed centrally via an IRT system.

Analysis of Primary Endpoint

The change from baseline to post-baseline SE at end of double-blind treatment will be analyzed using Analysis of Covariance (ANCOVA); the model will include treatment, antidepressant treatment use (current/stable or not treated/withdrawn ≥60 days), baseline SE score, as explanatory variables, change from baseline in SE at end of double-blind treatment as the response variable. The Kenward and Roger correction to the degrees of freedom will be used. The main comparison will be between SAGE-217 and placebo at end of double-blind treatment. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported where applicable. The baseline value

of SE was defined as the average of over 2 nights PSG measurements at Day -2 and Day -1. The post-baseline PSG SE value at end of double-blind treatment was defined as the average of over 2 nights PSG measurements at Day 13 and 14.

Analysis of Secondary Endpoints

The secondary endpoints of the change from baseline to post-baseline will be analyzed using a mixed effects model for repeated measures; the model will include treatment, baseline score, antidepressant treatment use (current/stable or not treated/withdrawn ≥60 days), 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.

[redacted]

Safety Analysis

Safety and tolerability of study drug will be evaluated by adverse events/serious adverse events, vital signs, clinical laboratory evaluations, and 12-lead ECGs. Suicidal ideation and behavior will be monitored by the C-SSRS. Safety data will be listed by subject and summarized by treatment group. All safety summaries will be performed on the Safety Set.

[redacted]

Table 1: 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					
Study Drug Administration		Single-blind Placebo		Double-blind (SAGE-217 or placebo)				Single-blind Placebo (Day 15 to Day 21)[u]					

	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 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]

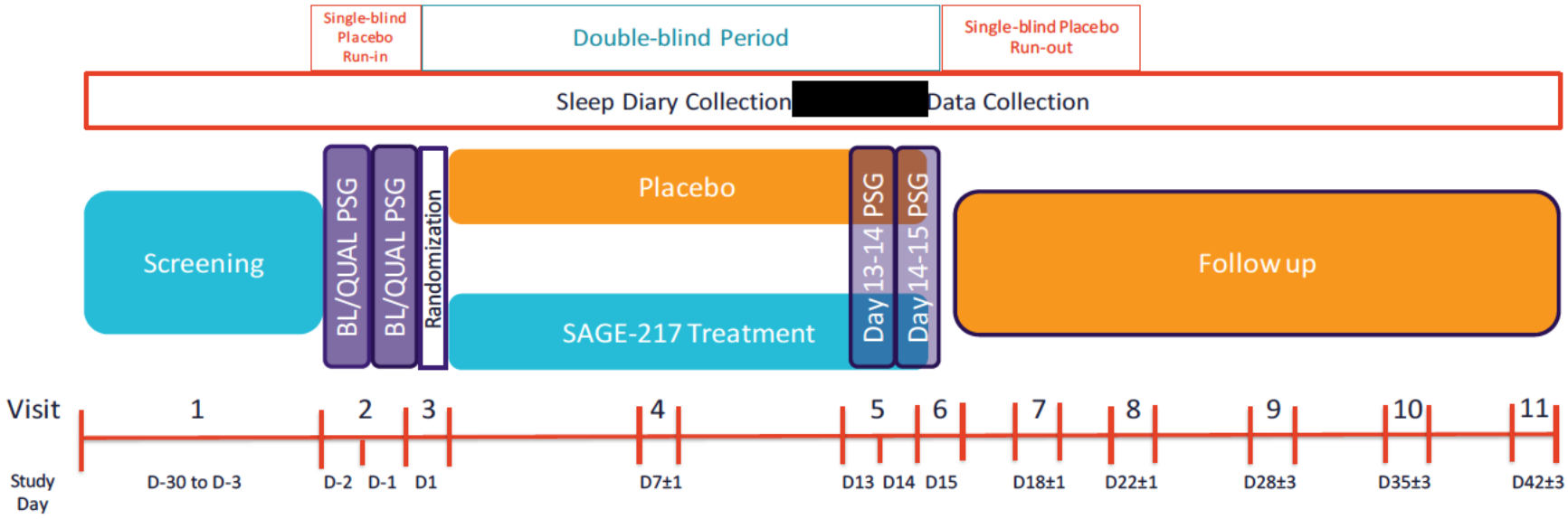
[r] Subjects will be trained on use of software applications and devices necessary for the conduct of the study by site personnel

[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.

Figure 1: Study Schematic



BL/QUAL = Baseline/Qualification; PSG = Polysomnography

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and specialist terms

Abbreviation or specialist term	Explanation
AE	adverse event
AHI	Apnea-Hypopnea Index
ANCOVA	Analysis of Covariance
BMI	body mass index
CBTI	Cognitive Behavioral Therapy for Insomnia
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression - Severity
CL/F	apparent total body clearance following extravascular administration
CPAP	continuous positive airway pressure
CRC	clinical research coordinator
[redacted]	[redacted]
CS	clinically significant
CSD-C	Consensus Sleep Diary – Core
CSSR-S	Columbia Suicide Severity Rating Scale
CYP	cytochrome
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
[redacted]	[redacted]
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EODBT	End-of-Double-blind-Treatment
EOG	electrooculographic
ET	early termination
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GABA	γ-aminobutyric acid
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Rating Scale for Depression

Abbreviation or specialist term	Explanation
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
ICF	informed consent form
ICD-10	International Statistical Classification of Diseases and Related Health Problems
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSD-3	International Classification of Sleep Disorders Third Edition
IMP	investigational medicinal product
IND	investigational new drug
IRT	interactive response technology
ISI	Insomnia Severity Index
[redacted]	[redacted]
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
NCS	not clinically significant
OSA	obstructive sleep apnea
PHQ-9	9-item Patient Health Questionnaire
PI	Principal Investigator; the investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
PK	pharmacokinetic
PLMS	periodic limb movements in sleep
PLMAI	Periodic Limb Movement Arousal Index
PWC-20	Physician Withdrawal Checklist
QTcF	QT corrected according to Fridericia's formula
REM	Rapid Eye Movement
REMA	REM Activity

Abbreviation or specialist term	Explanation
RLS	restless leg syndrome
RLS-DI	Restless Leg Syndrome – Diagnostic Index
SAE	serious adverse event
SAP	statistical analysis plan
SE	sleep efficiency
SMCC	silicified microcrystalline cellulose
SOC	system organ class
[redacted]	[redacted]
SS	Safety Set
sSL	subjective sleep latency
sSQ	subjective sleep quality
SSRIs	selective serotonin reuptake inhibitors
SUSARs	serious, adverse reactions
sTST	subjective total sleep time
sWASO	subjective wake after sleep onset
TEAE	treatment-emergent adverse event
TIB	time in bed
TST	total sleep time
WASO	wakefulness after sleep onset
WHO	World Health Organization

5. INTRODUCTION

The World Health Organization (WHO) has identified depression as the leading cause of disability worldwide, and as a major contributor to the overall global burden of disease (http://www.who.int/mediacentre/factsheets/fs369/en/). Globally, depression has been estimated to affect over 300 million people.

In the United States, the economic burden of depression, including workplace costs, direct costs and suicide-related costs, was estimated to be $210.5 billion in 2010 (Greenberg 2015). As per WHO statistics, over 800,000 people die due to suicide every year, and suicide is the second leading cause of death in 15- to 29-year-olds. The rate of US adults making a suicide attempt has increased (0.62% from 2004 to 2005 to 0.79% from 2012 to 2013), with a shift to more attempts among younger adults (42% to 50%, respectively) and among those with a depressive disorder (26% to 54%, respectively; Olfson 2017).

In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association 2013), depression refers to an overarching set of diagnoses, including major depressive disorder (MDD). Diagnostic criteria for MDD includes a set of at least 5 depressive symptoms out of 9, including depressed mood and/or loss of interest or pleasure, and other changes affecting appetite or weight, sleep, psychomotor activity, energy level, feelings of guilt, concentration ability and suicidality during the same 2-week period, that represents a change from previous functioning.

Antidepressants are a mainstay of pharmacological treatment for depressive disorders. Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and other compounds that affect monoaminergic neurotransmission, such as mirtrazapine and bupropion, represent the major classes of antidepressants. While antidepressants are widely used, large scale studies have demonstrated their limited efficacy, including low remission rates and untreated symptoms (Trivedi 2006; Conradi 2011; Romera 2013).

Converging preclinical and clinical evidence (Gerner 1981; Honig 1988; Drugan 1989; Luscher 2011; Mann 2014) implicates deficits in γ-aminobutyric acid (GABA)-ergic neurotransmission in the pathophysiology of depressive disorders including MDD. Furthermore, experimental data implicate deficiencies in the normal regulation of endogenous neuroactive steroids in depressive disorders (Maguire 2008; Maguire 2009). Depressed patients show low levels of GABA in the brain and of neurosteroids in the cerebrospinal fluid and plasma, and antidepressant therapy restores GABA levels in relevant animal models and neurosteroid concentrations in depressed patients (Luscher 2011; Schüle 2014).

With the publication of the DSM-5 in 2013, a single, overarching diagnosis of insomnia disorder replaced the previous diagnoses of primary and secondary insomnia defined in the DSM-IV and is closely aligned with the International Classification of Sleep Disorders Third Edition (ICSD-3) (Sateia 2014). Key DSM-5 diagnostic criteria for insomnia disorder include a predominant complaint of poor sleep quality or quantity and can include one or more of the following: difficulty falling asleep, difficulty staying asleep and/or early morning awakening. For an insomnia diagnosis, the sleep difficulty occurs at least 3 nights per week, is present for at least 3 months, and occurs despite adequate opportunity for sleep (DSM-5).

Cognitive behavioral therapy and other psychological therapies are recommended as first-line for the treatment of insomnia by both the American Academy of Sleep Medicine and the European Sleep Research Society (Schutte-Rodin 2008; Riemann 2017). Benzodiazepines and benzodiazepine receptor agonists, which enhance GABAergic function, are the predominant pharmacologic options available for the treatment of insomnia. Additionally, H1 histamine, melatonin, and orexin receptor antagonists have been approved for the treatment of insomnia.

Insomnia disorder commonly occurs with comorbid medical and mental health disorders. Insomnia symptoms have been reported in up to 80% of subjects in a major depressive episode and up to 90% of subjects with concomitant anxiety and MDD (Ohayon 2002). The relationship between MDD and insomnia disorder is bidirectional where the presence of one increases the risk of developing the other and people with severe depression are likely to also have severe insomnia. In addition, symptoms of insomnia and changes in sleep architecture, observed in patients with MDD, may worsen following treatment with antidepressants (eg, SSRIs and TCAs) that are commonly prescribed for MDD (Lam 2006). Residual insomnia symptoms are common and have been reported to occur in up to 60% of patients who are in remission following treatment for MDD (Carney 2007, Iovieno 2011).

Development of a pharmacotherapy that effectively treats both symptoms of comorbid major depressive and insomnia disorders remains an unmet medical need.

5.1. SAGE-217

SAGE-217 is a synthetic positive allosteric modulator of $GABA_A$ receptors, the major class of inhibitory neurotransmitter receptors in the brain. In pharmacokinetic (PK) studies in mice and rats, SAGE-217 demonstrated rapid penetration and equilibrium across the blood brain barrier and is generally expected to have good extravascular exposure. In exploratory in vitro receptor and ion channel assays and in vivo safety pharmacology studies, SAGE-217 was highly selective for $GABA_A$ receptors, and, consistent with the actions of other $GABA_A$ receptor potentiators (Rudolph 2011), exhibits potent anticonvulsant, anxiolytic, and sedative activity when administered in vivo.

Data from an open-label Phase 2a study of SAGE-217 administered to subjects with moderate to severe MDD showed clinically significant improvements from baseline in depression and anxiety scale scores (Hamilton Rating Scale for Depression [HAM-D], Montgomery-Åsberg Depression Rating Scale [MADRS], Hamilton Anxiety Rating Scale [HAM-A], and Clinical Global Impression – Improvement [CGI-I]) as early as Day 2 of the 14-day treatment period, with durable responses following the end of treatment. This result was further supported by the randomized, double-blind portion of this study including 89 subjects, in which a rapid and substantial decrease in HAM-D scores was observed at Day 15 (primary endpoint, following 14 days of double-blind treatment), starting at Day 2. This response pattern was also observed with other efficacy scales, including MADRS, CGI-I, and HAM-A.

The effect of SAGE-217, at 30 and 45 mg doses, on sleep was studied in a double-blind, placebo-controlled, 3-way crossover study in healthy adults using a 5-hour phase advance model of transient insomnia. The 5-hour phase-advance model of (transient) insomnia, has been shown to be most sensitive and appropriate for measuring changes in sleep maintenance and less sensitive to changes in sleep onset and REM minutes and latency to REM sleep (Horoszok, 2014). SAGE-217 at both doses (30 and 45 mg) resulted in significant improvements in sleep

efficiency (SE), decreased wakefulness after sleep onset (WASO), increased total sleep time (TST), and decreased mean duration of awakenings (mDURAW) compared with placebo. There were no differences in the median number of awakenings (NAW) or latency to persistent sleep (LPS) following administration of SAGE-217 (at either dose level) compared with placebo.

In addition, analysis of sleep architecture changes following treatment with SAGE-217 compared with placebo showed an increase in time spent in NREM Stages N2 and N3 sleep without a significant decrease in total time spent in N1 or rapid-eye movement (REM) sleep. The greatest numerical increases were observed for time spent in N2 sleep (approximately 60 to 70 minutes) followed by N3 sleep (approximately 10 to 20 minutes). Therefore, when measured as a percent of time spent asleep, the percent of time spent in N2 sleep was increased following SAGE-217 treatment compared to placebo with decreases observed in overall percent of N1 and REM sleep and no significant effect on percent of N3 sleep.

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

SAGE-217 has been generally well tolerated in clinical studies to date. The most common treatment-emergent adverse events (TEAEs) were sedation, somnolence, and dizziness. Most adverse events (AEs) were reported as mild or moderate in intensity. Among the over 260 subjects exposed to SAGE-217 in clinical trials, there have been no deaths and only one subject with essential tremor experienced a serious adverse event (SAE) of transient confusion leading to discontinuation of study drug. No other SAEs have been reported in any study of SAGE-217.

Additional information on nonclinical and clinical data is provided in the Investigator's Brochure.

5.2. Potential Risks and Benefits

Non-serious events of sedation, somnolence, and dizziness were the most commonly reported AEs with SAGE-217. Given the outcome of the Phase 2a study of SAGE-217 in subjects with MDD, improvement in sleep outcomes following treatment with SAGE-217 in a model of transient insomnia in healthy adults, the current significant unmet need in the treatment of comorbid insomnia disorder and MDD, and a favorable benefit-risk profile, further investigation of SAGE 217 in patients with comorbid insomnia and MDD is justified.

5.3. Dose Justification

The dose level of 30 mg per day was considered effective and generally well tolerated in a Phase 2 study in subjects with MDD (217-MDD-201). In the Phase 1 study of SAGE-217 in a model of transient insomnia, single doses of 30 mg and 45 mg SAGE-217, compared to placebo, showed similar benefits on measures of sleep maintenance (SE) and duration of sleep (SE and TST) and was generally well tolerated. Phase advance models in healthy adults show disruption in sleep parameters that are very similar to that observed in insomnia disorder and improvement in sleep parameters with pharmacotherapy in this model may predict treatment responses in chronic insomnia (Bonnet and Arand 2003). Therefore, 2-week nightly treatment with SAGE-217 (30 mg) will be used to test for the durability of the improved sleep response in subjects who have comorbid insomnia and MDD disorders. Due to sedation/somnolence observed in previous

clinical trials when administered in the morning, and improved tolerability when given in the evening, SAGE-217 will be administered as a 30 mg single dose in the evening with food, in this study. There is no dose reduction allowed during the treatment period.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Study Objective

6.1.1. Primary Objective

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

6.1.2. Secondary Objective(s)

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.

[redacted]

6.2. Endpoints

6.2.1. Primary Endpoint

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

6.2.2. 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 and TST by quarter of the PSG recording
  - Latency to persistent sleep
  - Number of awakenings and mean duration of awakenings, 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
  - REM activity
- Change from baseline in subjective sleep endpoints at 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 (based on the insomnia disorder)
- Clinical Global Impression - Improvement at EODBT (based on the insomnia disorder)
- Change from baseline in the 17-item HAM-D total score at EODBT
- Change from baseline in the 9-item Patient Health Questionnaire (PHQ-9) at the EODBT
- Safety: Incidence and severity of adverse events/serious adverse events; 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]

7. INVESTIGATIONAL PLAN

7.1. Overall Study 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 total 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 (Section 8.2).

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 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 4 of the 7 nights. Continued eligibility for the study will be based on subjects having a sleep diary with the following: a minimum of 4 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 study center during the treatment and follow-up periods as outlined in Table 1.

Subjects will be allowed to remain in the clinic between the consecutive PSG visits. At the discretion of the Investigator, subjects may be allowed to leave the clinic between consecutive

PSG visits following all post-treatment evaluations and return to the clinic approximately 2 hours prior to their habitual bedtime, as determined by the CRC, for the subsequent PSG visit.

7.2. Number of Subjects

Approximately 102 subjects will be randomized and dosed to obtain 82 evaluable subjects, with a total of 41 subjects per treatment arm.

7.3. Treatment Assignment

Subjects will be randomly assigned to a treatment group on Day 1. Randomization will be performed in a 1:1 ratio to receive SAGE-217 30 mg or matching placebo. Randomization will be stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥60 days) at baseline.

7.4. Dose Adjustment Criteria

Dose adjustments are not permitted in this study. Subjects who cannot tolerate study drug will be discontinued from study drug and will receive treatment as clinically indicated (Section 8.3).

7.5. Criteria for Study Termination

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of adverse events (AEs) or other findings suggesting unacceptable risk to subjects, or for administrative reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their ethics committee and initiate withdrawal procedures for participating subjects.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

Qualified subjects will meet all of the following criteria:

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject agrees to adhere to the study requirements.
3. Subject is a male or female between 18 and 64 years of age, inclusive, at the time of consent.
4. Subject has a diagnosis of MDD as diagnosed by SCID-5-CT, with symptoms that have been present for at least a 4-week period.
5. Subject has insomnia that has been present for ≥4 weeks and is confirmed at Screening based on the DSM-5 diagnostic criteria (using the SCID-5-CT) for insomnia disorder, excluding DSM-5 criterion D (requiring 3 months duration) and allowing the presence of coexistent MDD as it applies to DSM-5 criterion H.
6. Subject has an ISI score ≥15 (moderate to severe insomnia) at Visits 1 and 3.
7. Subject has completed the CSD-C for a minimum of 4 days between the evening of Day -9 and after awakening on the morning of Day -2, inclusive.
8. Subject reports a TST of <390 minutes (<6.5 hours) based on CSD-C Questions #2 through 6, on at least 3 nights between the evening of Day -9 and after awakening on the morning of Day -2, inclusive.
9. Subject has a habitual bedtime between 9:00 PM and 12:00 AM (midnight).
10. 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.
11. Subject has a MADRS score of ≥ 28 and a HAM-D total score of ≥20 at Visit 1 and Visit 3 (prior to dosing).
12. Subject taking antidepressants must have been taking these medications at the same dose for at least 60 days prior to Day 1.
13. Subject is willing to delay start of other antidepressant or antianxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics and sleep aids, and Cognitive Behavioral Therapy for Insomnia (CBTI) until after study completion.
14. Subject is in good physical health and has no clinically significant findings, as determined by the Investigator, on physical examination, 12-lead ECG, or clinical laboratory tests. Subject has a body mass index (BMI) within the range of 18.0 to 40.0 kg/m^2, inclusive.
15. Female subject agrees to use one of the following methods of highly effective contraception during participation in the study and for 30 days following the last dose of study drug, unless she is postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle stimulating hormone [FSH] level >40 mIU/mL) and/or surgically sterile (hysterectomy, bilateral oophorectomy, or bilateral

salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence):

- Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation.
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion/ligation.
- Vasectomized partner.

16. Male subject agrees to use an acceptable method of effective contraception for the duration of study and for 5 days after receiving the last dose of the study drug, unless the subject does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence). Acceptable methods of effective contraception for males includes vasectomy, or a condom with spermicide used together with highly effective female contraception methods if the female partner is of child-bearing potential (see Inclusion Criteria #15 for acceptable contraception methods).
17. Male subject is willing to abstain from sperm donation for the duration of the study and for 5 days after receiving the last dose of the study drug.
18. Subject agrees to refrain from drugs of abuse and alcohol for the duration of the study.

8.2. Subject Exclusion Criteria

Subjects who meet any of the following criteria are disqualified from participation in this study:

1. Subject has attempted suicide associated within the current episode of MDD.
2. Subject had onset of the current depressive episode during pregnancy or 4 weeks postpartum, or the subject has presented for screening during the 6-month postpartum period.
3. Subject has a recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, nose, and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study.
4. Subject has treatment-resistant depression, defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants within the current major depressive episode (excluding antipsychotics) from 2 different classes for at least 4 weeks of treatment. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire will be used for this purpose.
5. Subject has undergone vagus nerve stimulation, electroconvulsive therapy, or has taken ketamine (including esketamine) within the current major depressive episode.

6. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
7. Subject has a positive pregnancy test at Visit 1, 2, or 3 prior to the start of study drug administration or is breastfeeding at Visit 1, 2, or 3 prior to the start of study drug administration and plans to continue to breastfeed through the treatment period or within 7 days from the last dose of study drug.
8. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and positive HCV viral load, or human immunodeficiency virus (HIV) antibody at Visit 1.
9. Subject has a clinically significant abnormal 12-lead ECG at Visit 1 or 3 prior to study drug administration. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study.
10. Subject has active psychosis per Investigator assessment.
11. Subject has a medical history of seizures.
12. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
13. Subject has a history of mild, moderate, or severe substance use disorder (including benzodiazepines) diagnosed using DSM-5 criteria in the 12 months prior to Visit 1.
14. Subject has a PSG-confirmed or clinically suspected diagnosis of obstructive sleep apnea (OSA, AHI ≥15), or a reported history of moderate to severe sleep apnea, or a clinically suspected or PSG-confirmed diagnosis of restless leg syndrome (RLS), periodic limb movements in sleep (PLMS or PLMD), or narcolepsy.
15. Subject has a Restless Leg Syndrome – Diagnostic Index (RLS-DI) score of ≥11 at Visit 1.
16. Subject has an Apnea-Hypopnea Index (AHI) ≥15 and/or a Periodic Limb Movement Arousal Index (PLMAI) ≥10 as determined at the Day -2 PSG.
17. Subject has a recent history of circadian rhythm disorder or has done shift work or rotating shifts within 30 days prior to Visit 1.
18. Subject is taking or participating in any of the following:
    a. benzodiazepines, barbiturates, or $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, zolpidem, brexanolone) within 28 days prior to Visit 2,
    b. benzodiazepines, barbiturates, or $GABA_A$ modulators daily or near-daily (≥4 days per week) for 1 year in the last year prior to Visit 2,
    c. CBTI and/or psychotherapy for insomnia within 28 days prior to Visit 2,
    d. benzodiazepine or GABA modulator with a half-life of ≥48 hours (eg, diazepam) from 60 days prior to Day 1.
19. Subject is taking non-GABA anti-insomnia medications (eg, prescribed therapeutics specifically for insomnia and/or over-the-counter sleep aids) or first or second generation (typical/atypical) antipsychotics at Day -14. Note that non-sedating antihistamines are permitted.

20. Subject has had exposure to another investigational medication or device within 30 days prior to Visit 1.
21. Subject has previously participated in a SAGE-217 or a SAGE-547 (brexanolone) clinical trial.
22. Subject has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to Visit 2.
23. Subject has used any of the following strong CYP3A inducers within 28 days prior to Visit 2: rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, or St John's Wort.
24. Subject has a positive drug and/or alcohol screen at Visit 1 or Visit 2 prior to dosing.
25. Subject plans to undergo elective surgery during participation in the study.
26. Subject has traveled >1 time zone within 7 days prior to Visit 1 or is planning to travel >1 time zone through study completion.
27. Subject has been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and melanoma in situ) within the past year prior to Screening.
28. Subject has had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
29. Subject has been taking psychostimulants (eg, methylphenidate, amphetamine) or opioids regularly or as needed within 28 days prior to Visit 2.
30. Subjects uses a continuous positive airway pressure (CPAP) machine.

8.3. Subject Withdrawal Criteria

Subjects may withdraw from the study drug or terminate from the study at any time for any reason. The Investigator may withdraw the subject from the study drug or terminate the subject from the study for any of the following reasons:

- The subject is unwilling or unable to adhere to the protocol
- The subject experiences an intolerable AE
- Other medical or safety reason, at the discretion of the Investigator and/or the Medical Monitor

The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject withdraws from study drug or terminates the study for any reason. The reason must be recorded in the subject's electronic case report form (eCRF).

If a subject is persistently noncompliant, the Investigator should discuss with the Sponsor the potential discontinuation of the subject. Any reasons for unwillingness or inability to adhere to the protocol must be recorded in the subject's eCRF, including:

- missed visits
- interruptions in the schedule of study drug administration

- non-permitted medications (Section 9.2.2).

Subjects who discontinue the study drug due to an AE, regardless of Investigator-determined causality, should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant.

Subjects who discontinue study drug early during the double-blind treatment period should return to the site for the end of double-blind treatment visit as soon as possible, preferably the day after treatment is discontinued. Follow-up visits should take place according to the Schedule of Assessments. If at any time after the end of double-blind treatment visit, a subject decides to terminate the study, the subject should return for an early termination (ET) visit. The end of double-blind treatment 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.

A subject will be deemed lost to follow-up after attempts at contacting the subject have been unsuccessful.

If a subject failed to attend scheduled assessments during the course of the study, the Investigators must determine the reasons and the circumstances as completely and accurately as possible, and document this in the subject's source documents.

If it is necessary for the Investigator to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

8.3.1. Replacement of Subjects

Subjects will not be replaced. Additional subjects may be randomized if the drop-out rate is higher than anticipated (Section 13.8).

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

Subjects will be treated with SAGE-217 or matching placebo capsules according to the study and randomization schedules.

9.2. Prior Medications, Concomitant Medications, and Restrictions

9.2.1. Prior and Concomitant Medications and/or Supplements

The start and end dates, route, dose/units, frequency, and indication for all medications and/or supplements taken within 30 days prior to Screening and throughout the duration of the study will be recorded. In addition, psychotropic medications taken 6 months prior to Screening and GABAergic medications taken 12 months prior to Screening will be recorded.

Any medication and/or supplement determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study.

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).

9.2.2. Prohibited Medications

The following specific classes of medications are prohibited:

- Initiation of new psychotropic medications at any time during the study
- Initiation of new antidepressant therapy from 60 days prior to Visit 2 through the duration of the study
- Use of any benzodiazepines, barbiturates, $GABA_A$ modulators/GABA-containing agents from 28 days prior to Visit 2 through the duration of the study
- Use of any non-GABA anti-insomnia medications (eg, prescribed therapeutics specifically for insomnia and/or over-the-counter sleep aids) from 14 days prior to Visit 2 through the duration of the study. Note that non-sedating anti-histamines are permitted.
- First or second generation (typical/atypical) antipsychotics from 14 days prior to Visit 2 through the duration of the study
- Use of psychostimulants (eg, methylphenidate, amphetamine) or opioids regularly or as needed from 28 days prior to Visit 2 through the duration of the study.
- Exposure to another investigational medication or device from 30 days prior to Screening through the duration of the study
- Use of any known strong CYP3A4 inhibitors from 28 days prior to Visit 2 or 5 half-lives prior to Visit 2 (whichever is longer) through the duration of the study

- Use of strong CYP inducers, such as rifampin, carbamazepine, enzalutamide, mitotane, phenytoin, and St John's Wort from 28 days prior to Visit 2 through the duration of the study

9.2.3. Other Restrictions

The consumption of grapefruit juice, grapefruit, or Seville oranges, or products containing these is prohibited throughout the treatment period.

Consumption of alcohol or use of drugs of abuse is discouraged throughout the duration of the study.

Female subjects who are lactating or actively breastfeeding must stop giving breast milk to the baby(ies) starting on Day -2 until 7 days after the last dose of study drug following the treatment period.

Elective surgeries or procedures are prohibited during participation in the study.

Subjects are prohibited from participating in CBTI and/or psychotherapy for insomnia within 28 days prior to Visit 2 and through the duration of the study.

Use of CPAP machines is prohibited.

Subjects are restricted from traveling >1 time zone within 7 days prior to Visit 1 and any time through study completion.

9.3. Treatment Adherence

SAGE-217 or placebo will be self-administered by subjects once daily in the evening with food. Practically, subjects may consider taking the study medication within 1 hour following a dinner including solid food or taking study medication later in the evening with solid food. Given the substantially improved absorption of SAGE-217 with food, administering the study medication in the presence of food is important.

Sites will dispense study drug to the subjects with instructions for use (see Section 10.3 and Table 1).

In addition, the subject will be instructed to bring their dosing kit to the site as outlined in Table 1, at which time the Investigator or designee will be responsible for ensuring the kit contains sufficient doses for the duration of the treatment period.

All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

The Investigator(s) will record any reasons for non-compliance in the source documents.

9.4. Randomization and Blinding

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.

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 exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment in the study via the IRT (see Section 12.6 for more details related to unblinding).

9.4.1. Single-blind Placebo Treatment

Before a subject is randomized, there is a 2-day single-blind placebo treatment. In addition, following the double-blind treatment period subjects will take single-blind placebo treatment once daily until Visit 8.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

SAGE-217 and matched placebo are to be stored at room temperature (59 to 86°F; 15 to 30°C), safely and separately from other drugs.

10.2. Study Drug Packaging and Labeling

Not applicable.

10.3. Study Drug Storage

SAGE-217 capsules and matched placebo capsules will be provided to the clinic pharmacist and/or designated site staff responsible for dispensing the study drug in appropriately labeled, subject-specific kits containing sealed unit doses. Additional information regarding the packaging and labeling is provided in the Pharmacy Manual.

Study drug labels with all required information and conforming to all applicable FDA Code of Federal Regulations and Good Manufacturing Practices/Good Clinical Practices guidelines will be prepared by the Sponsor.

10.4. Study Drug Administration

On Days -2 and -1, subjects will be given a single-blind placebo dose orally, once daily with food, 30 minutes (±15 minutes) prior to lights out (PSG).

Starting on Day 1, Subjects will self-administer SAGE-217 (30 mg) or matching placebo orally once daily in the evening with food for 12 days. Practically, subjects may consider taking the study medication within 1 hour following a dinner including solid food or taking study medication later in the evening with solid food. Given the substantially improved absorption of SAGE-217 with food, administering the study medication in the presence of food is important.

On Days 13 and 14, subjects will be given a double-blind dose of SAGE-217 or matching placebo orally, once daily with food, 30 minutes (±15 minutes) prior to lights out (PSG).

On Days 15 through 21, subjects will self-administer a single-blind placebo dose, orally, once daily with food, in the evening.

10.5. Study Drug Accountability

Upon receipt of study drug, the Investigator(s), or the responsible pharmacist or designee, will inspect the study drug and follow the instructions regarding receipt in the Pharmacy Manual. A copy of the shipping documentation will be kept in the study files.

The designated site staff will dispense the supplied subject-specific kits to subjects at the planned dispensation visit intervals outlined in Table 1.

Site staff will access the IRT at the Screening Visit to obtain a subject identification (ID) number for each subject. On Day 1, site staff will access the IRT and provide the necessary subject-identifying information, including the subject ID number assigned at Screening, to randomize the eligible subject into the study and obtain the medication ID number for the study drug to be

dispensed to that subject. The medication ID number and the number of capsules dispensed must be recorded.

At the subsequent study drug-dispensing visit, the investigator or designee will access the IRT, providing the same subject ID number assigned at Screening, to obtain the medication ID number for the study drug to be dispensed at that visit. The medication ID number, the number of capsules dispensed, and the number of capsules returned by the subject at this visit must be recorded.

If dispensing errors or discrepancies are discovered by site staff or sponsor's designee, the Sponsor must be notified immediately.

The study drug provided is for use only as directed in this protocol. After the study is completed, all unused study drug must be returned as directed or destroyed on site per the Sponsor's instructions. The Investigator or designee must keep a record of all study drug received, dispensed and discarded.

Sage Therapeutics will be permitted access to the study supplies at any time and with appropriate notice during or after completion of the study to perform drug accountability and reconciliation.

10.6. Study Drug Handling and Disposal

At the end of the study, all used and unused study drug will be reconciled and returned to Sage for destruction or destroyed locally; disposition of study drug will be documented.

A copy of the inventory record and a record of any clinical supplies that have been received, dispensed or destroyed must be documented by the site as directed. This documentation must include at least the information below:

- the number of dispensed units
- the number of unused units
- the number of units destroyed at the end of the study
- the date, method and location of destruction.

10.7. Study Drug

SAGE-217 is available as hard gelatin capsules containing a white to off-white powder. In addition to the specified amount of SAGE-217 Drug Substance, active SAGE-217 Capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose (SMCC), colloidal silicon dioxide, and sodium stearyl fumarate as excipients. Colloidal silicon dioxide may be either a component of the SMCC or a standalone excipient in the formulation. Capsules will be available in 30-mg dose strengths.

Matching placebo capsules are hard gelatin capsules containing only the excipients listed for the active capsule.

10.8. Product Complaints

A product complaint is any written, electronic, or verbal expression of dissatisfaction regarding the identity, quality, reliability, safety, purity, potency, effectiveness or performance (applicable for approved marketed products) of a drug product after it is released for distribution.

In the course of conduct of the study, study personnel may become aware of a product complaint associated with the use of a Sage product. Personnel shall notify Sage within 24 hours by forwarding the product complaint information via the contact information listed in the Emergency Contact Information table . Where possible, personnel should segregate any product, materials, or packaging associated with the product complaint.

11. ASSESSMENT OF EFFICACY [redacted]

All assessments will be conducted according to the schedule of assessments (Table 1). Study assessments that involve subject interviews, including the HAM-D, may be audiotaped for independent quality control purposes. All assessments must be conducted by raters that have been trained and certified to conduct assessments in this study.

11.1. Screening Assessments

11.1.1. Montgomery-Åsberg Depression Rating Scale

The MADRS is a 10-item questionnaire that psychiatrists use to measure the severity of depressive episodes in patients with mood disorders. It was designed as an adjunct to the HAM-D, which would be more sensitive than the Hamilton Scale to the changes brought on by antidepressants and other forms of treatment.

Higher MADRS scores indicate more severe depression, and each item yields a score of 0 to 6. The overall score ranges from 0 to 60 (Williams 2008). The MADRS total score was calculated as the sum of the individual item scores.

11.2. Efficacy assessments

11.2.1. Polysomnogram (PSG)

The primary endpoint, SE, defined as the percentage of time in bed spent asleep, will be determined during an 8-hour overnight PSG recording. Subjects will be allowed to remain in the clinic between the consecutive PSG visits. At the discretion of the Investigator, subjects may be allowed to leave the clinic between consecutive PSG visits following all post-treatment evaluations and return to the clinic approximately 2 hours prior to their habitual bedtime, as determined by the CRC, for the subsequent PSG visit.

The PSG measures the physiological process of sleep by monitoring body functions including brain waves via 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 will be 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:

- Latency to persistent sleep: Duration in minutes from lights off to the first epoch of 20 consecutive non-wake epochs
- Wakefulness after sleep onset: Total wake time in minutes from persistent sleep onset to lights on and by quarter (2-hour periods) of the 8-hour PSG recording
- Total sleep time: Duration of total sleep time (NREM + REM) from lights off to lights on during recording
- Number of awakenings and mean duration of awakenings: 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. Mean duration of awakenings 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 electrooculographic (EOG) channels of the PSG. The rapid eye movements must be at least 25 uV in amplitude.

11.2.2. Hamilton Rating Scale for Depression

The 17-item HAM-D will be used to rate the severity of depression in subjects who are already diagnosed as depressed (Williams 2013a; Williams 2013b). 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.

Every effort should be made for the same rater to perform all HAM-D assessments for an individual subject. An assessment timeframe of 7 days will be used at first HAM-D administration and "Since Last Visit" will be used for all other visits.

The HAM-D total score will be calculated as the sum of the 17 individual item scores.

11.2.3. Clinical Global Impression

The CGI is a validated measure often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. The CGI scale consists of 3 items. Only the first 2 items are being used in this study.

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 (Busner 2007a). In this study the CGI-S will be assessed based on the severity of their insomnia disorder.

The CGI-I employs a 7-point Likert scale to measure the overall improvement in the subject's condition posttreatment. 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 (Busner 2007b). The CGI-I is only rated at posttreatment assessments. 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.

11.2.4. Insomnia Severity Index

The ISI is a validated questionnaire designed to assess the nature, severity, and impact of insomnia (Morin 2011). 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). 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)."

11.2.5. Consensus Sleep Diary-Core

The Consensus Sleep Diary-Core (Carney 2012) 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.

[redacted]

11.2.9. Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a subject-rated depressive symptom severity scale. 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. The PHQ-9 total score will be categorized as follows: 1 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.

[redacted]

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

All assessments will be conducted according to the schedule of assessments (Table 1).

12.1.1. Demographic/Medical History

Demographic characteristics (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and a full medical history, including psychotherapeutic treatment for insomnia, and family psychiatric and sleep disorder history, will be documented. The diagnoses of MDD and insomnia will be determined using the SCID-5-CT. If available, the disease code associated with the diagnoses of MDD and insomnia based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) should be recorded.

The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire will be used to determine whether the subject has treatment-resistant depression, defined as persistent depressive symptoms despite treatment during the current major depressive episode with adequate doses of antidepressants from 2 different classes for at least 4 weeks of treatment.

The RLS-DI will be used as a tool to screen for subjects with RLS. The RLS-DI is made up of 10 items that are based on the essential International RLS Study Group diagnostic criteria for RLS (5 items) combined with supportive criteria and additional features of RLS (5 items). The RLS-DI is administered as a structured diagnostic interview. Total possible RLS-DI scores range from -14 to 14, with a score of ≥11 considered diagnostic for RLS (Benes, 2009; Walters, 2014).

12.1.2. Weight and Height

Height (Screening only) and weight will be measured and documented.

12.1.3. Physical Examination

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. Whenever possible, the same individual is to perform all physical examinations for a given subject. Unscheduled brief, symptom-driven physical examinations may also be conducted per the Investigator's discretion.

Any abnormality in physical examinations will be interpreted by the Investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section 12.2.

12.1.4. Vital Signs

Vital signs comprise both supine and standing for systolic and diastolic blood pressure and heart rate measurements. Heart rate and blood pressure are to be collected in supine position after the subject has been resting for 5 minutes and then after approximately 3 minutes in the standing

position. Respiratory rate and temperature are collected once, in either position. Vital signs will be documented. When vital signs are scheduled at the same time as blood draws, vital signs will be obtained first.

Any abnormality in vital signs will be interpreted by the Investigator as abnormal, NCS or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section 12.2.

12.1.5. Electrocardiogram

Supine 12-lead ECGs will be performed in triplicate at all scheduled time points. The standard intervals (heart rate, PR, QRS, QT, and QTcF) as well as any rhythm abnormalities will be recorded. When ECG and [redacted] collection occur during the same visit, the ECGs will be conducted first.

Any abnormality in ECGs will be interpreted by the Investigator as abnormal, NCS or abnormal, CS in source documents. New or worsening abnormalities that are judged to be clinically significant will be recorded as AEs, assessed according to Section 12.2.

12.1.6. Laboratory Assessments

Samples will be collected in accordance with acceptable laboratory procedures detailed in the laboratory manual.

The clinical laboratory tests to be performed are listed in Table 3.

Table 3: 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 Color Protein Glucose Red blood cell Nitrite Leukocyte esterase Ketones Bilirubin Urobilinogen	Activated partial thromboplastin time Prothrombin time International normalized ratio

Table 3: Clinical Laboratory Tests (Continued)

Diagnostic			
Serum	**Urine**	**Breathalyzer**	
Hepatitis B surface antigen Hepatitis C antibody Reflex HCV RNA if Hepatitis C antibodies are detected HIV-1 and -2 serology 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	

Abbreviations: FSH = follicle stimulating hormone; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus

The central laboratory will perform laboratory tests for hematology, serum chemistry, urinalysis, and coagulation. The results of laboratory tests will be returned to the Investigator, who is responsible for reviewing and filing these results. All laboratory safety data will be transferred electronically to Sage Therapeutics or designee in the format requested by Sage Therapeutics.

Laboratory reports must be signed and dated by the Investigator or subinvestigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Any abnormalities identified prior to first dose will require clear and complete documentation in the source documents as to the Investigator's assessment of not clinically significant before proceeding with randomization.

All clinical laboratory test results outside the central laboratory's reference range will be interpreted by the Investigator as abnormal, NCS; or abnormal, CS in source documents. New or worsening abnormalities that are judged to be CS will be recorded as AEs, assessed according to Section 12.2. A clinically significant laboratory abnormality following subject randomization will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

A serum follicle stimulating hormone test will be conducted at Screening to confirm whether a female subject with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being post-menopausal (Section 8.1).

[redacted]

[redacted]

12.1.6.1. Drugs of Abuse and Alcohol

Urine toxicology tests will be performed for selected drugs of abuse (Table 3). A breath test for alcohol will be performed.

12.1.6.2. Pregnancy Screen

For female subjects that are not surgically sterile and do not meet the protocol-defined criteria for being post-menopausal, a serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at all other scheduled timepoints thereafter, including the ET visit for subjects who prematurely discontinue treatment.

12.1.7. Columbia-Suicide Severity Rating Scale

Suicidality will be monitored during the study using the C-SSRS (Posner, 2011). This scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicidal ideation and behavior, and a post-baseline evaluation 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 "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 at all subsequent time points, as outlined in Table 1.

12.1.8. Physician Withdrawal Checklist

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. 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) (Rickels, 2008). The PWC-20 will be used to monitor for the presence of potential withdrawal symptoms following discontinuation of SAGE-217.

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

A treatment-emergent adverse event is an AE that occurs after the first administration of double-blind study drug. The term study drug includes any Sage investigational product, a comparator, or a placebo administered in a clinical trial.

Laboratory abnormalities and changes from baseline in vital signs, ECGs, and physical examinations are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) and/or if the Investigator considers them to be clinically significant. Laboratory values and vital signs that meet the criteria for an SAE should be reported in an expedited manner. Laboratory abnormalities and changes from baseline in vital signs, ECGs, and physical examinations that are clearly attributable to another AE do not require discrete reporting (eg, electrolyte disturbances in the context of dehydration, chemistry and hematologic disturbances in the context of sepsis).

All AEs that occur after any subject has signed the informed consent and throughout the duration of the study, whether or not they are related to the study, must be reported to Sage Therapeutics.

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. The Sponsor or its representative retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.1.2. Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect

An SAE may also be any other medically important event that, in the opinion of the Investigator may jeopardize the subject or may require medical intervention to prevent 1 of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive

treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

All SAEs that occur after any subject has signed the ICF and throughout the duration of the study, whether or not they are related to the study, must be recorded on the SAE report form provided by Sage Therapeutics within 24 hours of first awareness (Section 12.5). Serious adverse events occurring after a subject's final visit (including the last follow-up visit) should be reported to Sage, or designee, only if the Investigator considers the SAE to be related to study treatment.

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject is hospitalized. The site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress, in the opinion of the Investigator, between the subject's consent to participate in the study and at the time of the procedure or treatment.

12.3. Relationship to Study Drug

The Investigator must make the determination of relationship to the study drug for each adverse event (not related, possibly related or probably related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the adverse event should be classified as "not related." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the adverse event, then the adverse event should be considered at least "possibly related."

Table 4: Relationship to Study Drug

Relationship	Definition
Not Related:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possibly Related:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probably Related:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

If the relationship between the adverse event/serious adverse event and the investigational product is determined to be "possible" or "probable", the event will be considered related to the investigational product for the purposes of expedited regulatory reporting.

12.4. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study drug or withdraw early from the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.2.1.2 . An AE of severe intensity may not be considered serious.

If a female subject becomes pregnant during this study, pregnancy information must be collected and recorded on the Sage Therapeutics pregnancy form and submitted to the sponsor within 24 hours of learning of the pregnancy. The investigator will also attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is participating in study. After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will follow the same pregnancy reporting procedures specified for pregnant female subjects.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. If the pregnancy ends for any reason before the anticipated date, the investigator should notify Sage.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly/birth defects), the investigator should follow the procedures for reporting an SAE.

12.5. Reporting Adverse Events

All SAEs must be reported to Sage Therapeutics, or designee, immediately. A written account of the SAE must be sent to Sage, or designee, within 24 hours of the first awareness of the event by the investigator and/or his or her staff. The Investigator must complete, sign, and date the SAE report form, verify the accuracy of the information recorded on the SAE report form with the corresponding source documents, and send a copy to Sage, or designee.

Additional follow-up information, if required or available, should all be sent to Sage Therapeutics, or designee, within 24 hours of receipt on a follow-up SAE report form and placed

with the original SAE information and kept with the appropriate section of the CRF and/or study file.

Any SAEs discovered by the Investigator after the designated follow up time for the study, should be promptly reported to Sage, or designee, according to the timelines noted above.

The contact information for reporting SAEs and/or pregnancies is located in the study reference manual.

Sage, or designee, is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the ethics committee of all SAEs that occur at his or her site. Investigators will also be notified of all suspected, unexpected, serious, adverse reactions (SUSARs) that occur during the clinical study. Ethics Committee (EC)/Institutional Review Boards (IRBs) will be notified of SAEs and/or SUSARs as required by local law. In addition, appropriate Sage Drug Safety and Pharmacovigilance personnel, or designee, will unblind SUSARs for the purpose of regulatory reporting. Sage, or designee, will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Sage, or designee, will submit SUSARs to investigators in a blinded fashion.

12.6. Emergency Identification of Study Drug

During the study, the blind is to be broken by the Investigator only when the safety of a subject is at risk and the treatment plan is dependent on the study treatment received. Unless a subject is at immediate risk, the Investigator must make diligent attempts to contact Sage prior to unblinding the study treatment administered to a subject. Any request from the Investigator about the treatment administered to study subjects must be discussed with Sage. If the unblinding occurs without Sage's knowledge, the Investigator must notify Sage as soon as possible and no later than the next business morning. All circumstances surrounding a premature unblinding must be clearly documented in the source records. Unless a subject is at immediate risk, any request for the unblinding of individual subjects must be made in writing to Sage and approved by the appropriate Sage personnel, according to standard operating procedures.

In all cases where the study drug allocation for a subject is unblinded, pertinent information (including the reason for unblinding) must be documented in the subject's records and on the eCRF. If the subject or study center personnel have been unblinded, the subject will be permanently discontinued from the study.

13. STATISTICS

A separate statistical analysis plan (SAP) will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the clinical study report.

13.1. Data Analysis Sets

The All Randomized Set, defined as all subjects who have been randomized, will be used for subject disposition. Subjects will be classified according to randomized treatment.

The Safety Set (SS) is defined as all subjects receiving at least 1 dose of study drug and will be used to provide descriptive summaries of safety data, demographics, and baseline characteristics. Data will be summarized according to treatment received.

The Full Analysis Set, defined as all randomized subjects in the SS who have at least 1 post-baseline efficacy evaluation, will be used for analysis of efficacy data. Data will be summarized according to randomized treatment.

[redacted]

13.2. Handling of 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. No imputation process will be used to estimate missing data.

13.3. General Considerations

Since insomnia is known to be intermittent in nature and prone to adaptation effects, to reduce variability and to reduce selection bias, PSG will be performed for 2 consecutive nights before randomization as well as at end of double-blind treatment. In the primary endpoint analysis, the average of values over 2 nights measurement will be used as the parameter value. Subjective measures of sleep will also be similarly analyzed. Following the double-blind treatment period, possible rebound insomnia and withdrawal effects will be evaluated during a single-blind placebo run-out period.

For the purpose of all safety, efficacy, and other analyses, where applicable, baseline is defined as the last measurement prior to the start of double-blinded 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.

Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

13.4. Demographics and Baseline Characteristics

Demographic data, such as age, race, and ethnicity, and baseline characteristics, such as height, weight, and BMI, will be summarized using the SS.

Pregnancy results will be listed but not summarized.

Medical history will be listed by subject.

13.5. Efficacy Analyses

The primary efficacy endpoint, the change from baseline in SE at end of double-blind treatment, will be analyzed using Analysis of Covariance (ANCOVA); the model will include treatment, antidepressant treatment use (current/stable or not treated/withdrawn ≥60 days), baseline SE score, as explanatory variables, change from baseline in SE at end of double-blind treatment as the response variable. The Kenward and Roger correction to the degrees of freedom will be used. The main comparison will be between SAGE-217 and placebo at end of double-blind treatment. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported where applicable. The baseline value of SE was defined as the average of over 2 nights PSG measurements at Day -2 and Day -1. The post-baseline PSG SE value at end of double-blind treatment is defined as the average of over 2 nights PSG measurements at Day 13 and 14.

The secondary endpoints of the change from baseline to post-baseline will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include treatment, antidepressant treatment use (current/stable or not treated/withdrawn ≥60 days), baseline 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.

[redacted]

13.6. Safety Analyses

Safety and tolerability of SAGE-217 will be evaluated by AEs/SAEs, concomitant medication usage, changes from baseline in vital signs, clinical laboratory evaluations, and 12-lead ECG. Suicidality will be monitored by the C-SSRS. Safety data will be listed by subject and summarized by treatment group. All safety summaries will be performed on the SS.

13.6.1. Adverse Events

The analysis of adverse events will be based on the concept of TEAEs. The incidence of TEAEs will be summarized overall and by Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 or higher, system organ class (SOC), and preferred term. Incidences will be presented in order of decreasing frequency. In addition, summaries will be provided by intensity (mild, moderate, severe) and by causality (related, not related) to study drug.

Any TEAEs leading to discontinuation and SAEs with onset after the start of study drug will also be summarized.

All AEs and SAEs (including those with onset or worsening before the start of study drug) through the end of the study will be listed.

13.6.2. Clinical Laboratory Evaluations

Results of clinical laboratory parameters in each scheduled visit and mean changes from baseline will be summarized.in standard units. Normal range of each parameter is provided by the laboratory; shift from baseline to post-baseline values in abnormality of results will be provided. Potentially clinically significant values will be summarized by treatment. Any abnormal values deemed clinically significant by the investigator will be reported as an AE (see Section 12.2). Clinical laboratory results will be listed by subject and timing of collection.

13.6.3. Physical Examinations

The occurrence of a physical examination (Y/N) and the date performed will be listed by subject. Any clinically significant observation in physical examination will be reported as an AE (see Section 12.2).

13.6.4. Vital Signs

Results from each visit and mean changes from baseline in vital signs will be summarized by scheduled visit. Any abnormality deemed clinically significant by the investigator will be reported as an AE (see Section 12.2). Potentially clinically significant values will be summarized by treatment. Vital sign results will be listed by subject and timing of collection.

13.6.5. 12-Lead Electrocardiogram

The following ECG parameters will be listed for each of the triplicate ECGs for each subject: heart rate, PR, QRS, QT, and QTcF; the derived mean of each parameter will also be listed. Any clinically significant abnormalities or changes in mean ECGs should be reported as an AE (see Section 12.2). Mean ECG data will be summarized by visit. Potentially clinically significant values of QTcF will be summarized by treatment. Electrocardiogram findings will be listed by subject and visit.

13.6.6. Prior and Concomitant Medications

Medications will be recorded at each study visit during the study and will be coded using World Health Organization-Drug dictionary (WHO-DD) September 2015, 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. Those medications taken prior to the initiation of the start of study drug will be denoted “Prior”. Those medications taken prior to the initiation of the study drug and continuing beyond the initiation of the study drug or those medications started at the same time or after the initiation of the study drug will be denoted “Concomitant” (ie, those with a start date on or after the first dose of study drug, or those with a start date before the first dose of study drug that are ongoing or with a stop date on or after the first dose of study drug).

Medications will be presented according to whether they are "Prior" or "Concomitant" as defined above. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

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

13.6.7. Columbia Suicide Severity Rating Scale

Suicidality data collected on the C-SSRS at baseline and by visit during the Treatment Period will be listed for all subjects. Listings will include behavior type and/or category for Suicidal Ideation and Suicidal Behavior of the C-SSRS.

13.6.8. Physician Withdrawal Checklist

Potential withdrawal symptoms collected on the PWC-20 will be summarized by visit and treatment. Listings will include all data by subject.

13.8. Determination of Sample Size

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 detect 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. 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%.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Sage Therapeutics will visit the investigational study site per Sage SOPs to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Sage Therapeutics or its representatives. This will be documented in a Clinical Trial Agreement between Sage Therapeutics and the investigator.

During the study, a monitor from Sage Therapeutics or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Sage Therapeutics.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Sage Therapeutics and those SAEs that met criteria for reporting have been forwarded to the IRB or EC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

14.2. Audits and Inspections

Authorized representatives of Sage Therapeutics, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Sage Therapeutics audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Board (IRB) or Ethics Committee (EC)

The Principal Investigator must obtain IRB (or EC) approval for the investigation. Initial IRB (or EC) approval, and all materials approved by the IRB (or EC) for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Sage Therapeutics may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or EC as appropriate. The investigator must submit written approval to Sage Therapeutics before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB or EC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or EC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or EC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB or EC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Sage Therapeutics will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or EC according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)/Good Clinical Practice, applicable regulatory requirements.

16.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject’s signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

Sage Therapeutics will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

17.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for the period outlined in the site contract, or for a period of 2 years after the last marketing application approval, whichever is longer. If not approved, documentation must be maintained for 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Sage Therapeutics or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18. PUBLICATION POLICY

All information concerning SAGE-217 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

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