Official Title:	**A 2-Part Study (Open-label Followed by Double-blind, Randomized, Placebo - Controlled, Parallel Group) of the Safety, Tolerability, Pharmacokinetics, and Efficacy of SAGE-217 in the Treatment of Subjects With Bipolar I/II Disorder With a Current Major Depressive Episode**
NCT Number:	NCT03692910
Document Dates:	Protocol Version 4.0: 16 January 2019 Protocol Version 3.0: 18 October 2018 Protocol Version 2.0: 13 September 2018 Protocol Version 1.0: 03 July 2018

1. PROTOCOL AND AMENDMENTS

Protocol Version 1.0, 03 July 2018

Protocol Amendment 1, Version 2.0, 13 September 2018

- Amendment 1 Summary of Changes

Protocol Amendment 2, Version 3.0, 18 October 2018

- Amendment 2 Summary of Changes

Protocol Memo to Sites, 18 November 2018

Protocol Amendment 3, Version 4.0, 16 January 2019

- Amendment 3 Summary of Changes

STUDY TITLE: A 2-PART STUDY (OPEN-LABEL FOLLOWED BY DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUP) OF THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF SAGE-217 IN THE TREATMENT OF SUBJECTS WITH BIPOLAR I/II DISORDER WITH A CURRENT MAJOR DEPRESSIVE EPISODE

PROTOCOL NUMBER: 217-BPD-201

Study Drug	SAGE-217
Clinical Phase	Phase 2
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted] Tel: [redacted] email: [redacted]
Sponsor Medical Monitor	[redacted], MD, MBA Tel: [redacted] email: [redacted]
Date of Original Protocol	Version 1.0, 03 JUL 2018

Protocol Number:	217-BPD-201
Study Drug:	SAGE-217
Study Phase:	Phase 2
Sponsor:	Sage Therapeutics, Inc.
Protocol Date:	Version 1.0, 03 July 2018

Sponsor Approval

[redacted] MD, MBA — 03 Jul 2018 — Date (DD/MMM/YYYY)

[redacted] RAC — 03JUL2018 — Date (DD/MMM/YYYY)

[redacted] — 03 JUL 2018 — Date (DD/MMM/YYYY)

[redacted] PhD — 09 Jul 2018 — Date (DD/MMM/YYYY)

[redacted] DVM, MS, MPH — 03-JUL-2018 — Date (DD/MMM/YYYY)

[redacted] — 03 JUL 2018 — Date (DD/MMM/YYYY)

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the 217-BPD-201 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 Month YYYY)

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics

Name of Investigational Product:
SAGE-217 Capsule

Name of Active Ingredient:
SAGE-217

Title of Study:
A 2-Part Study (Open-label followed by Double-blind, Randomized, Placebo-controlled, Parallel Group) of the Safety, Tolerability, Pharmacokinetics, and Efficacy of SAGE-217 in the Treatment of Subjects with Bipolar I/II Disorder with a Current Major Depressive Episode

Number of Sites and Study Location:
Part A: Approximately 10 sites in the United States
Part B: Approximately 40 sites in the United States

Phase of Development: 2

Planned Duration of participation: Up to 87 days (28-day Screening Period; 28-day Treatment Period, and 28-day [±3 days] Follow-up Period)

Objectives:

Part A Primary:

- To evaluate the safety and tolerability of SAGE-217 in subjects with bipolar I or II disorder with a current major depressive episode (MDE).

Part A Secondary:

- To assess the efficacy of SAGE-217 in reducing depressive symptoms in subjects with bipolar I/II disorder with a current MDE.
- To assess the effect of SAGE-217 on sleep.

Part B Primary:

- To assess the efficacy of SAGE-217 in reducing depressive symptoms in subjects with bipolar I/II disorder with a current MDE.

Part B Secondary:

- To evaluate the safety and tolerability of SAGE-217 in subjects with bipolar I/II disorder with a current MDE.
- To assess the effect of SAGE-217 on sleep.

[redacted]

Endpoints:

Part A Primary:

- The safety and tolerability of SAGE-217 as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and electrocardiogram (ECGs); and suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS); and mania using the Young Mania Rating Scale (YMRS).

Part A Secondary:

- The reduction in depressive symptoms, as assessed by:
  - Change from baseline in the 17-item Hamilton Depression Rating Scale (HAM-D) total score at Day 25 and all other time points as outlined in Table 1;
  - HAM-D response at Day 25 and all other time points as outlined in Table 1;
  - HAM-D remission at Day 25 and all other time points as outlined in Table 1;
  - Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Day 25 and all other time points as outlined in Table 1;
  - Change from baseline in MADRS individual item scores at Day 25 and all other time points as outlined in Table 1;
  - The response to the Clinical Global Impression scale for severity and improvement (CGI-S and CGI-I, respectively) at Day 25 and all other time points as outlined in Table 1.
- The reduction in insomnia severity, as assessed by Insomnia Severity Index (ISI).

Part B Primary:

- The primary endpoint in Part B is the reduction in depressive symptoms with SAGE-217 treatment, as assessed by the change from baseline in the HAM-D total score at Day 25.

Part B Secondary:

- The reduction in depressive symptoms, as assessed by:
  - Change from baseline in HAM-D total score at all other time points as outlined in Table 1;
  - HAM-D response at Day 25 and all other time points as outlined in Table 1;
  - HAM-D remission at Day 25 and all other time points as outlined in Table 1;
  - Change from baseline in the MADRS total score at Day 25 and all other time points as outlined in Table 1;
  - Change from baseline in MADRS individual item scores at Day 25 and all other time points as outlined in Table 1;
  - CGI-S and CGI-I response at Day 25 and all other time points as outlined in Table 1.
- The safety and tolerability of SAGE-217 as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and ECGs; and suicidal ideation and behavior using the C-SSRS; and mania using the YMRS.
- The reduction in insomnia severity, as assessed by ISI.

[redacted]

[redacted]

Study Description:

This study will be conducted in 2 sequential parts: Part A (open-label) and Part B (randomized, double-blind, placebo-controlled, parallel group). Part B will be initiated pending the review of Part A data. The methods of the 2 parts will be identical unless otherwise noted. Subjects who participate in Part A will not be allowed to participate in Part B. The study is designed to assess the safety, tolerability, [redacted] and efficacy of SAGE-217 in adult subjects with bipolar I/II disorder, who are currently experiencing an MDE.

The assessments are summarized in the Schedule of Events (Table 1).

Screening begins with the signing of the informed consent form at the Screening Visit The diagnosis of bipolar I or II disorder will be made using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) for clinical trials (SCID-5-CT) performed by a qualified healthcare professional.

Beginning on Day 1, qualified subjects will self-administer the study drug once daily in the evening with food for 28 days. In Part A, all subjects will receive SAGE-217. For Part B, subjects will be randomized in a 1:1 ratio to receive SAGE-217 or placebo; randomization will be stratified based on use of mood stabilizers (Y/N). Subjects on antidepressants or mood stabilizers (lamotrigine, lithium, and valproic acid only) that have been taken at the same dose for at least 60 days prior to Day 1 are to continue the stable dose throughout the treatment period. The planned dosing regimen is as follows:

Treatment	Days 1-3	Days 4-24	Days 25-28
SAGE-217	SAGE-217, 20 mg	SAGE-217, 30 mg	SAGE-217, 20 mg
Placebo (Part B only)	Placebo	Placebo	Placebo

If at any time, 30 mg is not tolerated, as assessed by the occurrence of a severe AE judged by the investigator to be related to study drug, the dose on the next day will be reduced to 20 mg and continued for the remainder of the treatment period. Dose adjustments related to moderate AEs will be judged by the Investigator. If a dose adjustment from 30 mg to 20 mg is deemed necessary by the Investigator, the subject will return to the site for the adjusted dose to be dispensed. Subjects who cannot tolerate the 20-mg dose at any time will be discontinued from study drug.

If at any time during the study, a subject has a YMRS score of ≥13, the Investigator will clinically assess the subject for a manic or hypomanic switch. If the clinical assessment is consistent with hypomania or mania, the subject will be discontinued from study drug and treated as clinically appropriate. These incidents will be documented as AEs.

Subjects will return to the study center during the treatment and follow-up periods as outlined in Table 1.

Number of Subjects (planned):

Part A: Approximately 30 subjects will be dosed.

Part B: Approximately 132 subjects will be randomized and dosed to obtain a total of 112 evaluable subjects.

Eligibility criteria:

Inclusion Criteria:

1. Subject has signed an informed consent form (ICF) prior to the conduct of any study-specific procedures.
2. Subject agrees to adhere to the study requirements, including use of prior, concomitant, and prohibited medications.
3. Subject is an ambulatory man or woman, aged 18 to 65 years, inclusive, at Screening.
4. 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.
5. Subject has a documented history of hypomanic or manic episode (verified by medical records and/or treating healthcare professional) and a diagnosis of bipolar I or bipolar II disorder with a current MDE as per DSM-5 SCID-5-CT.
6. Subject has a HAM-D score of ≥22 at Screening.
7. Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are 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 or bilateral oophorectomy):
   - 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 ligation/occlusion.
   - Vasectomized partner.
   - Sexual abstinence (no sexual intercourse).
8. 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. Acceptable methods of effective contraception for males includes sexual abstinence, 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 #7 for acceptable method of contraception for females).
9. 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.

Exclusion Criteria:

1. Subject has a history of suicide attempt within the last 2 years.
2. Subject has current suicidal ideation with plans based on Investigator clinical assessment and/or the C-SSRS response at Screening or Day 1.
3. Subject has a history of rapid cycling bipolar disorder as per DSM-5 SCID-5-CT.

4. Subject's current depressive episode meets the DSM-5 specifier criteria for mixed features.
5. Subject has ≥25% reduction in HAM-D score from Screening to Day 1.
6. 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.
7. Subject has abnormal liver function as shown by an abnormal liver function profile at screening (eg, repeated values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥2x the upper limit of normal).
8. Subject has a clinically significant abnormal 12-lead ECG at the Screening or Day 1 visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in male or >470 msec in female subjects will be the basis for exclusion from the study.
9. Subject has a YMRS score ≥13 at Screening or Day 1.
10. Subject presents for the study receiving a mood stabilizer other than lamotrigine, lithium, or valproic acid.
11. Subject presents for the study receiving psychotropic medications, which have not been taken at the same dose for at least 60 days prior to Day 1.
12. Subject that presents for the study receiving psychotropic medications and does not intend to continue the current treatment regimen during the treatment period.
13. Subject is taking typical or atypical antipsychotics, monoamine oxidase inhibitors (MAOIs), and/or benzodiazepines at the Screening Visit.
14. Subject has a history of severe rashes or Stevens-Johnson Syndrome associated with lamotrigine and is currently taking lamotrigine.
15. Subject's current depressive episode is treatment resistant; defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants from two different classes for an adequate amount of time (ie, at least 4 weeks of treatment). This will be assessed using the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.
16. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
17. Subject has a positive pregnancy test at the Screening Visit or on Day 1 (prior to administration of study drug).
18. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and HCV viral load, or human immunodeficiency virus (HIV) antibody at screening.
19. Subject has active psychosis per Investigator assessment.
20. Subject has a medical history of seizures.
21. Subject has a medical history schizophrenia, and/or schizoaffective disorder.
22. Subject has a history of mild, moderate, or severe substance use disorder diagnosed using DSM-5 criteria in the 12 months prior to screening.

23. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
24. Subject has had exposure to another investigational medication or device within 30 days prior to the Screening visit.
25. Subject has been previously treated or randomized in any study using SAGE-217. Subjects who participate in Part A are not eligible to participate in Part B.
26. Subject has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to receiving the first dose of study drug.
27. Subject has used any CYP inducer, such as such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort, within 28 days prior to the first dose of study drug.
28. Subject plans to undergo elective surgery during participation in the study.

SAGE-217 dosage and mode of administration:

SAGE-217 Capsules are available as hard gelatin capsules containing a white to off-white powder. In addition to SAGE-217 Drug Substance, the SAGE-217 Capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose, and sodium stearyl fumarate as excipients. Subjects will take the assigned dose orally once daily in the evening with food.

Reference therapy, dosage and mode of administration (Part B only):

In Part B, placebo capsules are visually matched to the active capsules and are available as hard gelatin capsules containing only the excipients listed above for the active capsule treatment. Study drug will be administered orally once daily in the evening, with food.

Duration of Treatment: 28 days

Statistical methods:

A separate statistical analysis plan (SAP) for each part (Part A and Part B) will provide a detailed description of the analyses to be performed in the respective part of the study. The SAPs 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.

General:

The data from Part A and Part B will be analyzed separately. For the purpose of all safety and efficacy analyses where applicable, baseline is defined as the last available measurement prior to the start of study drug administration.

Continuous endpoints will be summarized with 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:

Randomized set (Part B only) will be defined as all subjects who are randomized. This analysis set will be used of all data listings in Part B. Data listings for Part A will be based on Safety or Efficacy Set, as appropriate.

The Safety Set, defined as all subjects received at least 1 dose of study drug, will be used to provide descriptive summaries of safety data.

The Efficacy Set, defined as all subjects who are in Safety Set and have at least one post-baseline HAM-D evaluation, will be used to analyze efficacy data unless otherwise specified.

[redacted]

Safety Analysis:

The overall incidence of adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Data for vital signs, clinical laboratory measurements, ECG, and concomitant medication usage will also be summarized.

Safety data will be summarized and examined for possible relationships between subject characteristics and plasma SAGE-217 concentrations, as appropriate. Suicidality data collected using the C-SSRS and evaluation of mania collected using the YMRS at baseline and at each visit during the active Treatment Period will be listed for all subjects. Out-of-range safety endpoints may be categorized as low or high, where applicable. Subjects will be summarized according to treatment received for the purpose of safety.

Efficacy Analysis:

The primary endpoint in Part B, the change from baseline in HAM-D total score, will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include treatment, baseline HAM-D total score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be considered as fixed effects and the subject effect will be considered random in the model. All post-baseline time points will be included in the model. The primary comparison will be between SAGE-217 and matching placebo at Day 25. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported. An unstructured covariance structure will be used to model the within-subject errors. Other continuous endpoints will be analyzed using similar methods.

Other efficacy analyses, including those in Part A, will be specified in the SAP. In general, data will be analyzed using appropriate descriptive statistics or pre-specified statistical methods as applicable; subject listings will be provided for all efficacy data. Subjects will be analyzed according to randomized treatment for the purpose of efficacy unless otherwise specified.

[redacted]

Sample Size Calculation

Part A: The sample size of approximately 30 subjects was selected based on clinical and not statistical considerations.

Part B: Assuming a two-sided alpha level of 0.05, a sample size of 112 total evaluable subjects (56 per treatment group) would provide 80% power to detect a placebo-adjusted treatment difference of approximately 4 points in the primary endpoint, change from baseline in HAM-D total score at Day 25, assuming standard deviation (SD) of 7.5 points.

Assuming a 15% dropout rate, approximately 132 total randomized subjects will be required to obtain a total of 112 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have a valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the drop-out rate is higher than 15%.

Table 1: Schedule of Events

Study Period	**Screening Period**	**Treatment Period**							**Follow-up Period[a]**			
Visit Day	**D-28 to D-1**	**D1**	**D4 (+1d)**	**D8 (±1d)**	**D11 (±1d)**	**D18 (±1d)**	**D25 (±1d)**	**D29 (±1d)/ EOT[a]**	**D35 (±3d)**	**D42 (±3d)**	**D49 (±3d)**	**D56 (±3d)/ ET**
Study Procedure												
Informed Consent	X											
Inclusion/Exclusion	X	X										
Demographics	X											
Medical/Family History	X											
SCID-5-CT	X											
MGH-ATRQ	X											
Serum FSH test	X											
Randomization (Part B only)		X										
Physical Examination	X	X						X				X
Body Weight/Height[c]	X							X				X
Clinical Laboratory Assessments[d]	X	X		X		X	X	X	X	X		X
Drug & Alcohol Screen[e]	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[f]	X	X						X				X
Hepatitis & HIV Screen	X											
[redacted]												
Vital Signs[i]	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[j]	X	X	X			X		X				X
C-SSRS[k]	X	X	X	X	X	X	X	X	X	X	X	X
HAM-D[l]	X	X	X	X	X	X	X	X	X	X	X	X
MADRS[l]		X	X	X	X	X	X	X	X	X	X	X
CGI-S		X	X	X	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X	X	X	X	X
YMRS[l]	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]												
ISI		X					X					X
[redacted]												

Study Period	**Screening Period**	**Treatment Period**							**Follow-up Period[a]**			
Visit Day	**D-28 to D-1**	**D1**	**D4 (+1d)**	**D8 (±1d)**	**D11 (±1d)**	**D18 (±1d)**	**D25 (±1d)**	**D29 (±1d)/ EOT[a]**	**D35 (±3d)**	**D42 (±3d)**	**D49 (±3d)**	**D56 (±3d)/ ET**
[redacted]												
Study Drug Dispensation[o]		X	X		X	X	X					
Study Drug Administration		X (Day 1 – Day 28)										
Study Drug Accountability/Return			X	X	X	X	X	X				
Adverse Events/Serious Adverse Events[p]	X											
Prior/Concomitant Medications/ Procedures[q]	X											

CGI-I = Clinical Global Impression - Improvement; CGI-S – Clinical Global Impression - Severity; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; EOT = end of treatment; ECG = electrocardiogram; ET = early termination; [redacted] FSH = follicle stimulating hormone; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; ISI = Insomnia Severity Index; MADRS = Montgomery-Åsberg Depression Rating Scale; MGH-ATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; O = optional; [redacted] SCID-5-CT = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition for clinical trials; [redacted] YMRS = Young Mania Rating Scale

[a] For subjects that discontinue study drug prior to Day 29, all efforts should be made for these subjects to complete the 28-day follow-up period starting 7 days after the last dose of study drug.

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

[c] Height measured at screening only

[d] Safety laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis. Laboratory assessments are to be completed in the morning.

[e] Urine toxicology for selected drugs of abuse, and breath test for alcohol (as per the standard procedures at each site).

[f] For women of child-bearing potential, serum pregnancy test at screening and urine pregnancy test at all other scheduled timepoints.

[redacted]

[i] Vital signs include oral temperature (°C), respiratory rate, heart rate, pulse oximetry 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 in the standing position. Vital signs may be repeated at the discretion of the Investigator as clinically indicated.

[j] Triplicate 12-lead ECGs will be performed with the subject in the supine position. When ECG [redacted] sample collection occur during the same visit, ECGs will be collected first.

[k] The "Baseline/Screening" C-SSRS form will be completed at screening. The "Since Last Visit" C-SSRS form will be completed at any time of day at all subsequent time points.

[l] For MADRS, HAM-D, and YMRS, the "Since Last Evaluation" forms will be completed at all subsequent time points following the initial assessment.

[redacted]

[o] Additional unscheduled dispensation visits may be needed for dose reductions or titration.

[p] AEs/SAEs will be collected starting at the time of informed consent and throughout the duration of the subject's participation in the study.

[q] Prior medications will be collected at Screening and concomitant medications will be collected at each subsequent visit. All medications taken within 30 days prior to Screening through the duration of the study will be recorded. In addition, all psychotropic medications taken within 6 months prior to Screening will be recorded.

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

LIST OF TABLES

LIST OF FIGURES

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
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CGI-I	Clinical Global Impression scale for improvement
CGI-S	Clinical Global Impression scale for severity
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
ET	early termination
[redacted]	[redacted]
FSH	follicle-stimulating hormone
GABA	γ-aminobutyric acid
HAM-D	Hamilton Depression Rating Scale
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ID	identification
IRT	interactive response technology
ISI	Insomnia Severity Index
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MDE	major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
MGH-ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire

Abbreviation or specialist term	Explanation
MMRM	mixed effects model for repeated measures
PI	Principal Investigator; the investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
[redacted]	[redacted]
QTcF	QT corrected according to Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SCID-5-CT	Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition for clinical trials
SD	standard deviation
[redacted]	[redacted]
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
YMRS	Young Mania Rating Scale

5. INTRODUCTION

5.1. Background of Bipolar Disorders and Unmet Medical Need

Bipolar disorder is a chronic and episodic illness that is associated with significant disability worldwide (Sachs 2007). The Global Burden of Disease Study revealed that in 2013, there were 48.8 million cases of bipolar disorder globally (Ferrari 2016). Bipolar disorder accounted for 9.9 million disability-adjusted life years (DALYs) globally, explaining 0.4% of total DALYs and 1.3% of total years lived with disability.

There are subtypes of bipolar disorder; this study includes the bipolar I and II subtypes. Bipolar I is characterized by a manic episode, whereas bipolar II is characterized by a hypomanic episode. The difference in the severity of the manic features relies on functional impairment that is caused by these episodes (DSM-5). The National Comorbidity Survey estimate of the lifetime prevalence of bipolar disorder is 2.1% in the US population when bipolar I disorder and bipolar II Disorder are combined (Merikangas 2007).

While the manic or hypomanic episodes represent distinct departure from the baseline mood state and easily attract attention, evidence suggests that depressive episodes of both bipolar I and II are associated with more disability than any other aspect of the illness. A seminal long-term study of patients with bipolar I disorder demonstrated that over the 13-year follow-up period, patients were symptomatic about 47% of the time, and depressive symptoms were present in 32% of the follow-up weeks vs manic features, which were present in 9% (Judd 2002). A similar analysis in patients with bipolar II disorder with a longer follow up of up to 20 years found that patients were symptomatic more than half of the time (54%) where depressive symptoms dominated the course at 50% of the follow-up weeks vs 1.3% for the hypomanic symptoms (Judd 2003). A study in patients with unipolar depression found a prevalence of depressive symptoms 47% of the time (Judd 1998), suggesting a comparable time spent with depressive symptoms in the bipolar spectrum. These naturalistic studies have also found that about half the time patients reported taking psychotropic medications. In another large-scale study with a follow-up period of up to 2 years, 58% of nearly 1500 patients with bipolar disorder who were symptomatic at study entry achieved recovery (Perlis 2006). Similarly, during the follow-up period, 49% of these individuals experienced recurrent episodes, where depressive episodes (38%) outweighed manic, hypomanic, or mixed episodes combined (13.8%). In the Stanley Foundation Bipolar Network Study, in which year-long, daily clinician ratings were included, despite treatment with an average of 4.1 psychotropic medications, patients with bipolar disorder spent 3 times as much time with depressive symptoms as manic symptoms (Post 2003).

There are only 3 medications approved in the US for the treatment of bipolar depression, (lurasidone, olanzapine-fluoxetine combination, and quetiapine), all of which include atypical antipsychotics that are associated with significant adverse metabolic effects. None of the currently available antidepressants are indicated for bipolar depression due to their limited efficacy, and the possibility that their use may be associated with a manic switch and rapid cycling. While some studies reported varying levels of efficacy with antidepressants (Gijsman 2004), a large-scale, double-blind, placebo-controlled clinical trial sponsored by the National Institutes of Mental Health, The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), found that only 23.5% of patients with bipolar depression receiving a mood stabilizer and adjunctive antidepressants vs 27.3% of those receiving a mood

stabilizer and placebo experienced a durable recovery, confirming the lack of effectiveness of antidepressants in bipolar depression (Sachs 2007). The tolerability profile of the approved atypical antipsychotics and limited efficacy of available antidepressants highlight the critical unmet need in the treatment of bipolar depression.

In 1998, the lifetime cost of bipolar disorder in the US was estimated at $24 billion. The cost of a single manic episode was estimated at $11,720 to $624,785 for persons with nonresponsive/chronic episodes (Begley 1998); the cost of bipolar depression specifically, is less well studied, however, available estimates indicate a higher cost associated with bipolar depression than for mania (Bowden 2004).

Kessler has studied the impact of mood disorders on work performance in a representative sample of over 3,000 US workers (Kessler 2006). Bipolar disorder and major depressive disorder were associated with 65.5 and 27.2 lost workdays per worker per year, respectively. Moreover, it was found that the increase in bipolar disorder was attributable to depressive symptoms rather than manic episodes in bipolar disorder.

Taken together, these findings point to substantial predominance of depressive symptoms across the spectrum of bipolar disorder. In particular, they also highlight the importance of successful depressive symptom control, and an unmet need in the treatment of depressive episodes for both bipolar I and bipolar II disorder.

5.2. SAGE-217

SAGE-217 is a positive allosteric modulator of γ-aminobutyric acid $(GABA)_A$ 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 portion of the Phase 2a study of SAGE-217 administered to subjects with moderate to severe major depressive disorder (MDD) showed clinically significant improvements from baseline in depression scale scores (HAM-D, Montgomery-Åsberg Depression Rating Scale [MADRS], 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 (N=89) in which a rapid and substantial decrease in HAM-D scores was observed at Day 15 (primary endpoint), starting at Day 2. This response pattern was also observed with other efficacy scales, including MADRS and CGI-I. Statistically significant differences from the placebo group favoring the SAGE-217 arm were observed for 2 weeks in the follow-up period.

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 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.

5.3. 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 2 study of SAGE-217 in subjects with MDD and the current significant unmet need in the treatment of depressive episodes associated with bipolar I/II disorders, a favorable risk-benefit balance and investigation of SAGE-217 in patients with bipolar I/II disorders are justified.

5.4. Dose Justification

The highest dose level of SAGE-217 to be administered in this study (30 mg) was determined based on the maximum tolerated dose in the multiple ascending dose study of SAGE-217 in healthy subjects and is the same dose level that has been used and generally well tolerated in clinical studies in various patient populations, including patients with MDD. Due to the observed improved tolerability of sedation/somnolence effects when taken in the evening in previous clinical studies, SAGE-217 will be administered in the evening in this study as well.

Further consideration was given to the duration of dosing in this trial. Bipolar depression is known to be more difficult to treat compared to unipolar depression. This is evident by the fact that none of the available 25 antidepressants have been approved for the treatment of bipolar depression (Sachs 2007). Given this foreseen challenge, the duration in this trial has been set at a total of 28 days, including a titration of 20 mg for 3 days, then a dose at 30 mg for 21 days, and a titration down to 20 mg for 4 days. The first 3 days at 20 mg of SAGE-217 are thought to provide immediate tolerability data at this relatively lower dose when combined with other concomitant medications including mood stabilizers and increase the probability of tolerance on the 30 mg dose level. The 30 mg dose level is based on previous clinical trial data with SAGE-217 demonstrating highly effective improvement in depressive symptoms in patients with MDD. Based on the absence of clinical data for a treatment duration longer than 2 weeks at this time, and the GABAergic mechanism of action of SAGE-217, a titration down to 20 mg is included in the study design.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Study Objective

6.1.1. Primary Objective

Part A

The primary objective of Part A of this study is to evaluate the safety and tolerability of SAGE-217 in subjects with bipolar I/II disorder with a current major depressive episode (MDE).

Part B

The primary objective of Part B of this study is to assess the efficacy of SAGE-217 in reducing depressive symptoms in subjects with bipolar I/II disorder with a current MDE.

6.1.2. Secondary Objectives

Part A

Secondary objectives of Part A of this study are:

- To assess the efficacy of SAGE-217 in reducing depressive symptoms in subjects with bipolar I/II disorder with a current MDE.
- To assess the effect of SAGE-217 on sleep.

Part B

Secondary objectives of Part B of this study are:

- To evaluate the safety and tolerability of SAGE-217 in subjects with bipolar I/II disorder with a current MDE.
- To assess the effect of SAGE-217 on sleep.

6.2. Endpoints

6.2.1. Primary Endpoint

Part A

The primary endpoint for Part A of this study is the safety and tolerability of SAGE-217, as assessed by the frequency and severity of adverse events (AEs); changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs); suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS); and mania using the Young Mania Rating Scale (YMRS).

Part B

The primary endpoint of Part B of this study is the reduction in depressive symptoms with SAGE-217 treatment, as assessed by the change from baseline in the 17-item HAM-D total score at Day 25.

6.2.2. Secondary Endpoints

Part A

Secondary endpoints of Part A of this study are:

- The reduction in depressive symptoms, as assessed by:
  - Change from baseline in the 17-item HAM-D total score at Day 25 and all other time points as outlined in Table 1;
  - HAM-D response at Day 25 and all other time points as outlined in Table 1;
  - HAM-D remission at Day 25 and all other time points as outlined in Table 1;
  - Change from baseline in the MADRS total score at Day 25 and all other time points as outlined in Table 1;
  - Change from baseline in MADRS individual item scores at Day 25 and all other time points as outlined in Table 1;
  - The response to the CGI-S and CGI-I at Day 25 and all other time points as outlined in Table 1.
- The reduction in insomnia severity as assessed by the Insomnia Severity Index (ISI).

Part B

Secondary endpoints of Part B of this study are:

- The reduction in depressive symptoms, as assessed by:
  - Change from baseline in total HAM-D score at all other time points as outlined in Table 1;
  - HAM-D response at Day 25 and all other time points as outlined in Table 1;

  - HAM-D remission at Day 25 and all other time points as outlined in Table 1;
  - Change from baseline in the MADRS total score at Day 25 and all other time points as outlined in Table 1;
  - Change from baseline in MADRS individual item scores at Day 25 and all other time points as outlined in Table 1;
  - CGI-S and CGI-I response at Day 25 and all other time points as outlined in Table 1.

- The safety and tolerability of SAGE-217 as assessed by the frequency and severity of AEs; changes from baseline in clinical laboratory measures, vital signs, and ECGs; and suicidal ideation and behavior using the C-SSRS, and the YMRS.
- The reduction in insomnia severity, as assessed by the ISI.

[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This study will be conducted in 2 sequential parts: Part A (open-label) and Part B (randomized, double-blind, placebo-controlled, parallel group). Part B will be initiated pending the review of Part A data.The methods of the 2 parts will be identical unless otherwise noted. The study is designed to assess the safety, tolerability, [redacted] and efficacy of SAGE-217 in adult subjects with bipolar I/II disorder, who are currently experiencing an MDE.

Screening begins with the signing of the informed consent form (ICF) at the Screening Visit. The diagnosis of bipolar I or II disorder will be made using the Structured Clinical Interview for DSM-5 for clinical trials (SCID-5-CT) performed by a qualified healthcare professional. Subjects on antidepressants or mood stabilizers (lamotrigine, lithium, and valproic acid only) that have been taken at the same dose for at least 60 days prior to Day 1 are to continue the stable dose throughout the treatment period.

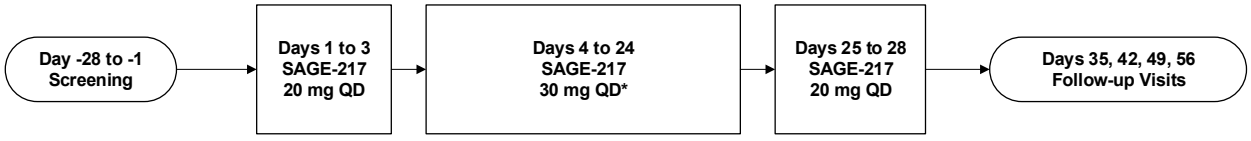
Subjects will return to the study center during the treatment and follow-up periods as outlined in the Schedule of Events (Table 1). All assessments to be performed are summarized in Table 1.

If at any time during the study, a subject has a YMRS score of ≥13, the Investigator will clinically assess the subject for a manic or hypomanic switch. If the clinical assessment is consistent with hypomania or mania, the subject will be discontinued from study drug and treated as clinically appropriate (see Section 8.3).

Part A

The study design for Part A is presented in Figure 1. In Part A, all subjects will receive SAGE-217. Beginning on Day 1, qualified subjects will self-administer the study drug once daily in the evening with food for 28 days: 20 mg SAGE-217 for 3 days, 30 mg SAGE-217 for 21 days, and then 20 mg-SAGE-217 for 4 days. Dose adjustments based on study drug tolerability are permitted following the guidelines outlined in Section 7.4.

Figure 1: Study Design (Part A)



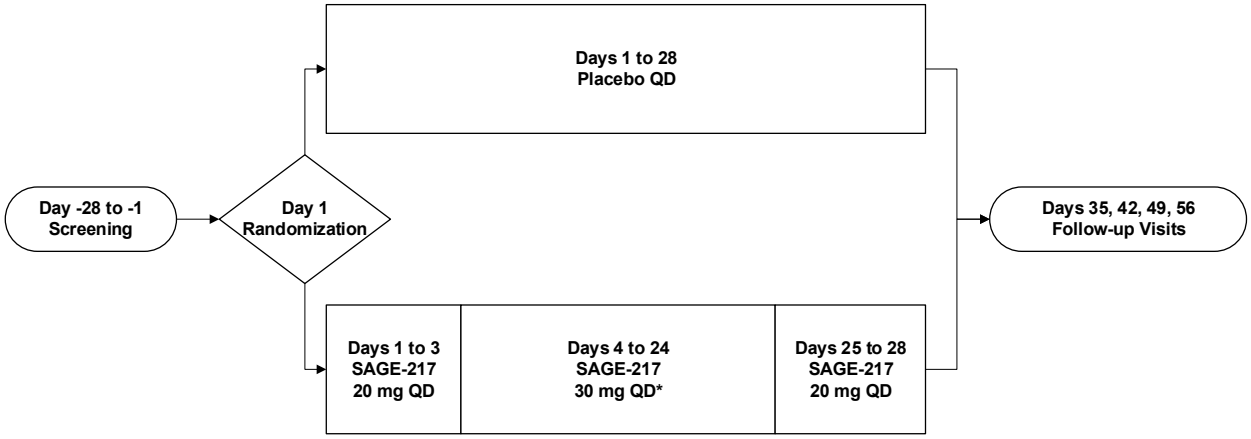
QD = once daily
*A dose adjustment to 20-mg SAGE-217 is permitted if the 30-mg dose is not tolerated at any time during Days 4 to 24.

Part B

The study design for Part B is presented in Figure 2. In Part B, subjects will be randomized in a 1:1 ratio to receive SAGE-217 or placebo; randomization will be stratified based on use of mood stabilizers (Y/N). Beginning on Day 1, qualified subjects will self-administer the study drug once daily in the evening with food for 28 days: 20 mg SAGE-217 for 3 days, 30 mg SAGE-217 for

21 days, and then 20 mg-SAGE-217 for 4 days. Dose adjustments based on study drug tolerability are permitted following the guidelines outlined in Section 7.4.

Figure 2: Study Design (Part B)



QD = once daily
*A dose adjustment to 20-mg SAGE-217 is permitted if the 30-mg dose is not tolerated at any time during Days 4 to 24.

7.2. Number of Subjects

Part A

Approximately 30 subjects will be dosed in Part A.

Part B

After review of Part A data, approximately 132 subjects will be randomized and dosed in Part B to obtain a total of 112 evaluable subjects (see Section 13.8).

7.3. Treatment Assignment

Part A

In Part A, all subjects will receive SAGE-217 in an open-label manner.

Part B

In Part B, subjects will be randomized to a treatment group (SAGE-217 or placebo) in a 1:1 ratio; randomization will be stratified based on use of mood stabilizers (Y/N).

7.4. Dose Adjustment Criteria

If at any time, 30 mg is not tolerated, as assessed by the occurrence of a severe AE judged by the investigator to be related to study drug, the dose on the next day will be reduced to 20 mg and continued for the remainder of the treatment period. Dose adjustments related to moderate AEs will be judged by the Investigator. If a dose adjustment from 30 mg to 20 mg is deemed necessary by the Investigator, the subject will return to the site for the adjusted dose to be

dispensed. Subjects who cannot tolerate the 20-mg dose at any time will be discontinued from study drug (see Section 8.3).

7.5. Study Termination

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of 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 the conduct of any study-specific procedures.
2. Subject agrees to adhere to the study requirements, including use of prior, concomitant, and prohibited medications.
3. Subject is an ambulatory man or woman, aged 18 to 65 years, inclusive, at Screening.
4. 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.
5. Subject has a documented history of hypomanic or manic episode (verified by medical records and/or treating healthcare professional) and a diagnosis of bipolar I or bipolar II disorder with a current MDE as per DSM-5 SCID-5-CT.
6. Subject has a HAM-D score of ≥22 at Screening.
7. Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are 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 or bilateral oophorectomy):
    - 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 ligation/occlusion.
    - Vasectomized partner.
    - Sexual abstinence (no sexual intercourse).
8. 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. Acceptable methods of effective contraception for males includes sexual abstinence, 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 #7 for acceptable method of contraception for females).
9. 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.

8.2. Subject Exclusion Criteria

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

1. Subject has a history of suicide attempt within the last 2 years.
2. Subject has current suicidal ideation with plans based on Investigator clinical assessment and/or the C-SSRS response at Screening or Day 1.
3. Subject has a history of rapid cycling bipolar disorder as per DSM-5 SCID-5-CT.
4. Subject's current depressive episode meets the DSM-5 specifier criteria for mixed features.
5. Subject has ≥25% reduction in HAM-D score from Screening to Day 1.
6. 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.
7. Subject has abnormal liver function as shown by an abnormal liver function profile at screening (eg, repeated values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥2x the upper limit of normal).
8. Subject has a clinically significant abnormal 12-lead ECG at the Screening or Day 1 visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in male or >470 msec in female subjects will be the basis for exclusion from the study.
9. Subject has a YMRS score ≥13 at Screening or Day 1.
10. Subject presents for the study receiving a mood stabilizer other than lamotrigine, lithium, or valproic acid.
11. Subject presents for the study receiving psychotropic medications, which have not been taken at the same dose for at least 60 days prior to Day 1.
12. Subject that presents for the study receiving psychotropic medications and does not intend to continue the current treatment regimen during the treatment period.
13. Subject is taking typical or atypical antipsychotics, MAOIs, and/or benzodiazepines at the Screening Visit.
14. Subject has a history of severe rashes or Stevens-Johnson Syndrome associated with lamotrigine and is currently taking lamotrigine.
15. Subject's current depressive episode is treatment resistant; defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants from two different classes for an adequate amount of time (ie, at least 4 weeks of treatment). This will be assessed using the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.
16. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.

17. Subject has a positive pregnancy test at the Screening Visit or on Day 1 (prior to administration of study drug).
18. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and HCV viral load, or human immunodeficiency virus (HIV) antibody at screening.
19. Subject has active psychosis per Investigator assessment.
20. Subject has a medical history of seizures.
21. Subject has a medical history schizophrenia, and/or schizoaffective disorder.
22. Subject has a history of mild, moderate, or severe substance use disorder diagnosed using DSM-5 criteria in the 12 months prior to screening.
23. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
24. Subject has had exposure to another investigational medication or device within 30 days prior to the Screening visit.
25. Subject has been previously treated or randomized in any study using SAGE-217. Subjects who participate in Part A are not eligible to participate in Part B.
26. Subject has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to receiving the first dose of study drug.
27. Subject has used any CYP inducer, such as such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort, within 28 days prior to the first dose of study drug.
28. Subject plans to undergo elective surgery during participation in the study.

8.3. Subject Withdrawal Criteria

8.3.1. Withdrawal from the Study or Discontinuation of Study Drug

Subjects may discontinue study drug or withdraw from the study at any time for any reason. The Investigator may discontinue the subject from the study drug 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

In addition, if at any time during the study, a subject has a YMRS score of ≥13, the Investigator will clinically assess the subject for a manic or hypomanic switch. If the clinical assessment is consistent with hypomania or mania, the subject will be discontinued from study drug and treated as clinically appropriate. These incidents will be documented as AEs.

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the

Sponsor and/or the Medical Monitor immediately when a subject has discontinued or been withdrawn for any reason.

Subjects who discontinue study drug early/withdraw during the treatment period should, if possible, have an end of treatment (EOT) visit, including the EOT assessments as summarized in the Schedule of Events (see Table 1). The EOT visit should be scheduled as soon as possible, preferably the day after the subject's last dose. All details of the EOT visit should be recorded in the subject's medical source documents. For subjects that discontinue study drug early, follow-up visits should take place every 7 days after the last dose of treatment for 28 days. If at any time after the EOT visit, a subject decides to terminate the study early, the subject should return for an early termination (ET) visit. The EOT 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 both visits will be conducted only once.

If the subject fails or refuses to return to the study center, an attempt must be made to contact the subject by telephone in order to assess as many safety and efficacy parameters as possible. All data collected over the telephone must be documented and kept in the subject's record. A subject will be deemed lost to follow-up after 3 attempts at contact have been made and it has been at least 1 month since the last subject contact. The third attempt at contact must be a certified letter accompanied by a survey inquiring the reason for study discontinuation. All attempts at contact will be documented.

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.

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.

8.3.2. Replacement of Subjects

Part A

In Part A, subjects will not be replaced.

Part B

In Part B, subjects will not be replaced. Additional subjects may be randomized if the drop-out rate is higher than anticipated (see Section 13.8).

9. TREATMENT OF SUBJECTS

9.1. Study Drug

Subjects will self-administer study drug orally once daily in the evening with food for 28 days as outlined in Section 7.1.

9.2. Prior Medications, Concomitant Medications, and Restrictions

9.2.1. Prior and Concomitant Medications and/or Supplements

The start and end dates, route of administration, dose/units, frequency, and indication for all medications and/or supplements taken within 60 days prior to Day 1 and throughout the duration of the study will be recorded. In addition, psychotropic drugs taken within 6 months prior to Screening will be recorded.

Any concomitant medication determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study under the guidance outlined in these sections.

Antidepressants and mood stabilizers (lamotrigine, lithium, and valproic acid only) 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 throughout the treatment period.

Medications intended for contraception are permitted for female subjects (see Section 8.1):

9.2.2. Prohibited Medications

The following medications are prohibited throughout the treatment period:

- Benzodiazepines
- Typical or atypical antipsychotics
- MAOIs
- Any known strong inhibitors of CYP3A4
- Use of any CYP inducer, such as such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort.

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 drugs of abuse and alcohol is discouraged throughout the duration of the study.

9.3. Treatment Adherence

SAGE-217 or placebo (Part B only) will be self-administered by subjects once every evening with food. Sites will dispense study drug to the subjects to take at home with instructions for use (see Section 10.4).

Administration of study drug will be monitored by a medication adherence monitoring platform used on smartphones to visually confirm medication ingestion. Subjects will receive a reminder within a predefined time window to take study drug while using the application. Subjects will follow a series of prescribed steps in front of the front-facing webcam to visually confirm their ingestion of the medication. The application will record the date and time of study drug administration by dose level, as well as missed doses.

In addition, the subject will be instructed to bring their dosing kit to each visit during the treatment period, at which time the Investigator or designee will be responsible for ensuring the kit contains sufficient doses until the next scheduled dispensation.

If the subject is persistently noncompliant with the study drug, the Investigator should discuss with Sage Therapeutics the potential discontinuation of the subject (see Section 8.3). Dosing requirements will be reviewed with each subject during all study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.4. Randomization and Blinding

Part A

Part A is an open-label design in which all subjects will receive SAGE-217.

Part B

Part B is a randomized, double-blind, placebo-controlled, parallel group design. Subjects who meet the entrance criteria will be stratified based on use of mood stabilizers (Y/N) and randomly assigned within each stratum in a 1:1 ratio to receive SAGE-217 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 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.

During the study, the blind is to be broken only if the safety of a subject is at risk and the treatment plan is dependent on the study treatment received. See Section 12.6 for details of unblinding in the event of a medical emergency or pregnancy.

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.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Description of 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, and sodium stearyl fumarate as excipients. Capsules will be available in 10-mg, 20-mg, and 30-mg strengths to achieve the target dose of 20 mg or 30 mg. Subjects will be administered 2 capsules per dose.

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

10.2. Study Drug Packaging and Labeling

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 each containing sealed unit doses. Each unit dose consists of 2 capsules. 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 Code of Federal Regulations and Good Manufacturing Practices/Good Clinical Practices guidelines will be prepared by the clinical research organization.**Study Drug Storage**

SAGE-217 and matched placebo are to be stored at room temperature, safely and separately from other drugs.

10.4. Study Drug Preparation

Not applicable.

10.5. Study Drug Administration

SAGE-217 is to be administered orally in the evening with food.

10.6. Study Drug Accountability

Upon receipt of study drug, the Investigator(s), or the responsible pharmacist or designee, will inspect the study drug and complete 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.

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. In the event of an unscheduled dose reduction (Section 7.4), a new subject-specific kit will be dispensed.

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 medication 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 within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

10.7. Study Drug Handling and Disposal

At the end of the study, all used and unused study drug will be reconciled and returned to Sage Therapeutics 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.

11. ASSESSMENT OF EFFICACY [redacted]

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

11.1. Efficacy Assessments

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

The primary outcome measure is the change from baseline in the 17-item HAM-D total score at Day 25.

The 17-item HAM-D will be used to rate the severity of depression in subjects who are identified as experiencing an MDE (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.

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

In addition to the primary efficacy endpoint of change from baseline in HAM-D total score, several secondary efficacy endpoints will be derived for the HAM-D. Hamilton Rating Scale for Depression subscale scores will be calculated as the sum of the items comprising each subscale. Hamilton Rating Scale for Depression response will be defined as having a 50% or greater reduction from baseline in HAM-D total score. Hamilton Rating Scale for Depression remission will be defined as having a HAM-D total score of ≤7.

The HAM-D subject interview may be audio-recorded for independent quality control purposes.

11.1.2. Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a 10-item diagnostic questionnaire used to measure the severity of depressive episodes in subjects with mood disorders. It was designed as an adjunct to the HAM-D that 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 will be calculated as the sum of the ten individual item scores.

The MADRS subject interview may be audio-recorded for independent quality control purposes.

11.1.3. Clinical Global Impression (CGI)

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.

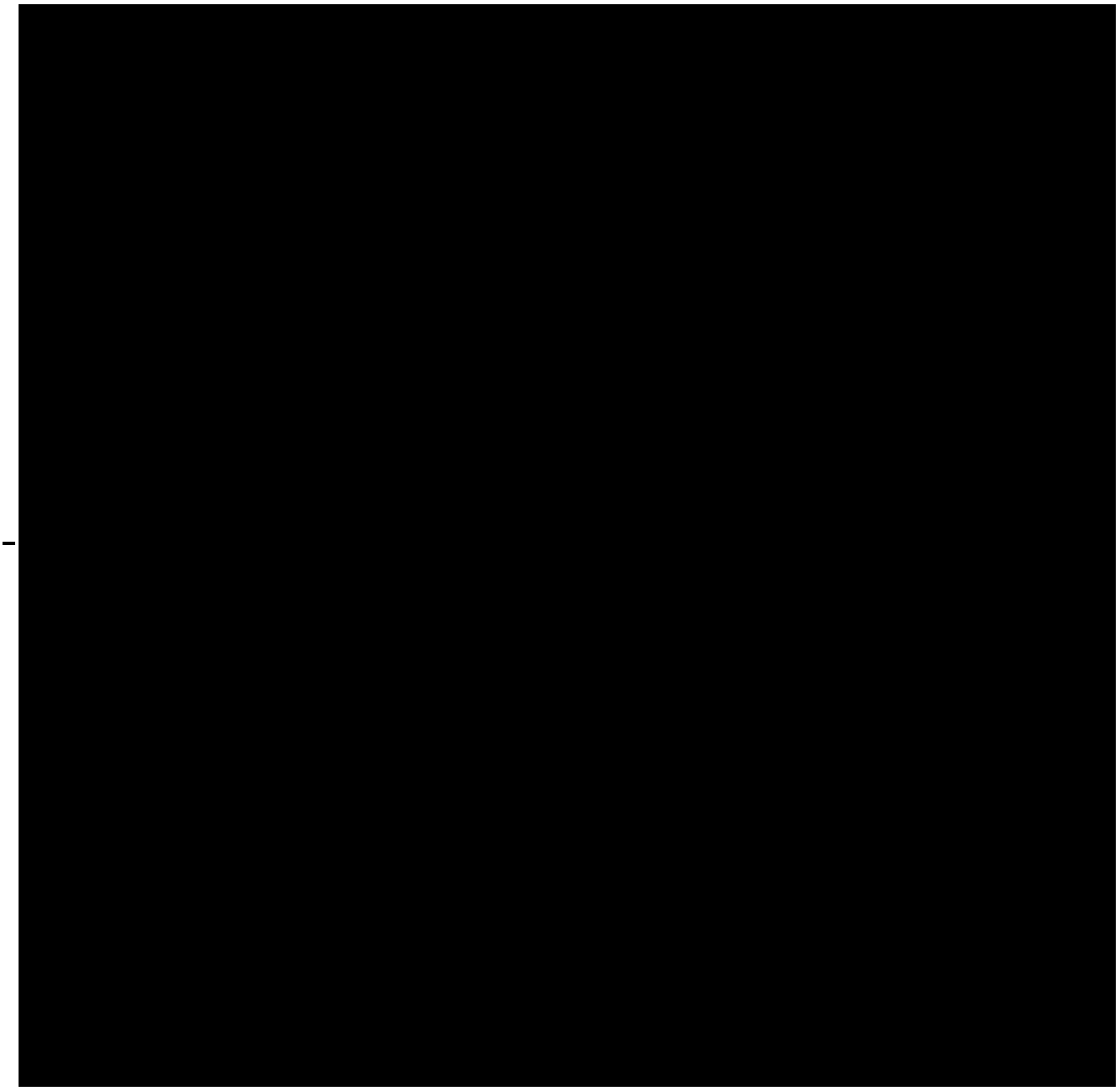
The Clinical Global Impression - Severity (CGI-S) uses a 7-point Likert scale to rate the severity of the subject's illness at the time of assessment, relative to the clinician's past experience with

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).

The Clinical Global Impression - Improvement (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."

11.1.4. Insomnia Severity Index (ISI)

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 (0 = very satisfied, 1 = satisfied, 2 = moderately satisfied, 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)."



12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

The safety and tolerability of SAGE-217 will be assessed by the frequency and severity of AEs; changes from baseline in clinical laboratory measures, vital signs, and ECGs; suicidal ideation and behavior using the C-SSRS; and the YMRS. All assessments will be conducted according to the schedule of assessments (Table 1).

12.1.1. Demographic/Medical History

Demographic and baseline characteristics (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and a full medical history, including family psychiatric history, will be documented. The diagnosis of bipolar I or II disorder will be determined using the SCID-5-CT.

12.1.2. Weight and Height

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

12.1.3. Physical Examination

Physical examinations assessing body systems (eg, head, eye, ear, nose, and throat; heart; lungs; abdomen; and extremities), as well as cognitive and neurological examinations and mental status examinations will be conducted and documented. Whenever possible, the same individual is to perform all physical examinations for a given subject. Unscheduled brief 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 12.2.1.1.

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 in the standing position. Respiratory rate, pulse oximetry 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, with the blood sample collected as close to the scheduled time as possible.

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 12.2.1.1.

12.1.5. Electrocardiogram (ECG)

Supine 12-lead ECGs will be performed in triplicate. The standard intervals (heart rate, PR, QRS, QT, and QTcF) as well as any rhythm abnormalities will be recorded. When ECG [redacted] sample 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 12.2.1.1.

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 Reticulocytes Platelet count Red blood cell morphology	ALT Albumin Alkaline phosphatase AST Total bilirubin Direct bilirubin Indirect bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase GGT Potassium Sodium Lactate dehydrogenase Glucose Chloride Bicarbonate Calcium Phosphorus Triglycerides	pH Specific gravity Protein Glucose Red blood cells Nitrite Leukocyte esterase Ketones Bilirubin Urobilinogen	Activated partial thromboplastin time Prothrombin time International normalized ratio

Table 3: Clinical Laboratory Tests (Continued)

Hematology	**Serum Chemistry**	**Urinalysis**	**Coagulation**
Diagnostic Screening			
Serum	**Urine**	**Breathalyzer**	
Hepatitis B Hepatitis C HIV-1 and -2 Female subjects of child bearing potential: serum human chorionic gonadotropin Female subjects, if menopause is suspected and not surgically sterile: FSH	Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, and propoxyphene Female subjects of child bearing potential: urine human chorionic gonadotropin	Alcohol	

The central laboratory will perform laboratory tests for hematology, serum chemistry, and urinalysis. 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, 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 12.2.1.1. 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.

Follicle stimulating hormone testing 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]

12.1.6.1. Drugs of Abuse and Alcohol

Urine toxicology will be performed for selected drugs of abuse (see Table 3). A breath test will be performed for alcohol at the Screening visit only.

12.1.6.2. Pregnancy Screen

A serum pregnancy test in women of child-bearing potential will be conducted at Screening and a urine pregnancy test will be conducted at all other scheduled timepoints (see Table 3).

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

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. Young Mania Rating Scale (YMRS)

Manic symptoms will be assessed during the study using the YMRS (Young 1978). The clinician-administered scale is based on 11 items of core symptoms of mania. Four of the items (irritability, speech, thought content, and disruptive/aggressive behavior) are graded on a scale of 0 to 8 (choices given as even numbers), with the remaining 7 items graded on a scale of 0 to 4. Scoring between the points given (whole or half points) is possible.

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 TEAE is an AE that occurs after the first administration of any study drug. The term study drug includes any Sage investigational product, a comparator, or a placebo administered in a clinical trial.

An abnormal laboratory value will be considered an AE if the value represents a clinically significant change from baseline as determined by the Investigator.

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

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 been enrolled and throughout the duration of the study, whether or not they are related to the study, must be recorded on the SAE form provided by Sage Therapeutics.

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.

Should a pregnancy occur, it must be reported and recorded on the Sage Therapeutics pregnancy notification form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented on the Sage Therapeutics pregnancy outcome form even if the subject was discontinued from the study. Reports of congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs.

12.5. Reporting Serious Adverse Events

All SAEs must be reported to Sage, 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 staff on the SAE report form. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE 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.

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. Each site is responsible

for notifying its ethics committee of these SUSARs. In addition, appropriate Sponsor Drug Safety and Pharmacovigilance personnel, or designee, will unblind SUSARs for the purpose of regulatory reporting. The Sponsor, or designee, will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. The Sponsor, 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 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. The blinding of the study will be broken after the database has been locked. Electronic copies of the randomization code will be made available to the laboratory performing the bioanalytical analyses in order to allow for limited analysis of samples from subjects receiving placebo.

In the event of a medical emergency or pregnancy, the Investigator will discuss with the Medical Monitor if unblinding is warranted for medical management of the subject. If there is agreement to unblind treatment assignment, the unblinding procedure described in the Safety Management Plan for the study will be followed. If the Investigator is unable to contact the Medical Monitor in a medical emergency, and it is deemed clinically necessary by the Investigator, the treatment group for that subject may be unblinded in the IRT system.

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) for each part (Part A and Part B) will provide a detailed description of the analyses to be performed in the respective part of the study. The SAPs will be finalized and approved prior to database lock. Any deviations from or changes to the respective SAP following database lock will be described in detail in the clinical study report.

13.1. Data Analysis Sets

The Safety Set, defined as all subjects that received at least 1 dose of study drug, will be used to provide descriptive summaries of safety data.

The Efficacy Set, defined as all subjects in the Safety Set that have at least 1 post-baseline HAM-D evaluation, will be used to analyze efficacy data, unless otherwise specified.

[redacted]

Part B will also include a Randomized Set, defined as all subjects who are randomized. This analysis set will be used for all data listings in Part B.

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 sets, using all non-missing data available. No imputation process will be used to estimate missing data.

13.3. General Considerations

For the purpose of all primary and secondary analyses where applicable, baseline is defined as the last measurement prior to receipt of study drug.

Continuous endpoints will be summarized with number (n), mean, standard deviation (SD), 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 (see Section 12.1.1) and baseline characteristics, such as height, weight, and body mass index, will be summarized using the Safety Set.

Pregnancy results will be listed but not summarized.

Medical history will be listed by subject.

13.5. Efficacy Analysis

The primary efficacy endpoint, the change from baseline in HAM-D total score, will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include center, treatment, baseline HAM-D total score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be considered as fixed

effects and the subject effect will be considered random in the model. All post-baseline time points will be included in the model. The primary comparison will be between SAGE-217 and matching placebo at Day 25. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported. An unstructured covariance structure will be used to model the within-subject errors. In case of convergence issues, other covariance structures will be considered; this will be detailed in the statistical analyses plan. Other continuous endpoints will be analyzed using similar methods.

Other efficacy analyses will be specified in the statistical analysis plan. In general, data will be analyzed using appropriate descriptive statistics or pre-specified statistical methods as applicable; subject listings will be provided for all efficacy data. Subjects will be analyzed according to randomized treatment for the purpose of efficacy unless otherwise specified.

13.6. Safety Analyses

Safety and tolerability of SAGE-217 will be assessed by the frequency and severity of AEs; changes from baseline in clinical laboratory measures, vital signs, and ECGs. Suicidal ideation and behavior will be evaluated using the C-SSRS. Mania will be evaluated using the YMRS. Safety data will be listed by subject and summarized by treatment group. All safety summaries will be performed on the Safety Set.

13.6.1. Adverse Events

The analysis of AEs 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 20.1 or higher, system organ class (SOC), and preferred term (PT). 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 (see Section 13.6.1).

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

Clinical laboratory results will be listed by subject and timing of collection. Mean changes from baseline in clinical laboratory measures will be evaluated.

13.6.3. Physical Examinations

Physical examination data will be listed by subject, but not summarized.

13.6.4. Vital Signs

Vital sign results will be listed by subject and timing of collection. Mean changes from baseline in vital signs will be evaluated by time point.

13.6.5. 12-Lead Electrocardiogram

The following ECG parameters will be listed for each subject: heart rate, PR, QRS, QT, and QTcF. Any clinically significant abnormalities or changes in ECGs should be listed as an AE. 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.

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 will be summarized and 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. Young Mania Rating Scale

Mania data collected on the YMRS at baseline and by visit will be summarized and listed for all subjects.

[redacted]

13.8. Determination of Sample Size

Part A

For Part A, the sample size of approximately 30 subjects was selected based on clinical and not statistical considerations.

Part B

For Part B, assuming a two-sided alpha level of 0.05, a sample size of 112 total evaluable subjects (56 per treatment group) would provide 80% power to detect a placebo-adjusted treatment difference of approximately 4 points in the primary endpoint, change from baseline in HAM-D total score at Day 25, assuming standard deviation (SD) of 7.5 points.

Assuming a 15% dropout rate, approximately 132 total randomized subjects will be required to obtain a total of 112 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have a valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the drop-out rate is higher than 15%.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the study site guarantee access to source documents by Sage Therapeutics or sponsor's designee and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by Sage Therapeutics or sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

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. Protocol Deviations

Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the Sage Therapeutics or sponsor's designee (and IRB, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

14.4. 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 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 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.

19. LIST OF REFERENCES

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STUDY TITLE: A 2-PART STUDY (OPEN-LABEL FOLLOWED BY DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUP) OF THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF SAGE-217 IN THE TREATMENT OF SUBJECTS WITH BIPOLAR I/II DISORDER WITH A CURRENT MAJOR DEPRESSIVE EPISODE

PROTOCOL NUMBER: 217-BPD-201

Study Drug	SAGE-217
Clinical Phase	Phase 2
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted] Tel: [redacted] email: [redacted]
Sponsor Medical Monitor	[redacted], MD, MBA Tel: [redacted] email: [redacted]
Date of Original Protocol	Version 1.0, 03 JUL 2018
Date of Amendment 1	Version 2.0, 13 SEP 2018

Protocol Number:	217-BPD-201
Study Drug:	SAGE-217
Study Phase:	Phase 2
Sponsor:	Sage Therapeutics, Inc.
Protocol Date:	Version 2.0, 13 Sept 2018

Sponsor Approval

[redacted] 18 SEP 2018
[redacted] MD — Date (DD/MMM/YYYY)

[redacted] 13 SEP 2018
[redacted] MD, MBA — Date (DD/MMM/YYYY)

[redacted] 13 Sep 2018
[redacted] AC — Date (DD/MMM/YYYY)

[redacted] 13 Sep 2018
[redacted] MSHS — Date (DD/MMM/YYYY)

[redacted] 13 SEP 2018
[redacted] PhD — Date (DD/MMM/YYYY)

[redacted] 13 SEP 2018
[redacted] DVM, MS, MPH — Date (DD/MMM/YYYY)

[redacted] 13 Sep 2018
[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-BPD-201 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 Month YYYY)

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics

Name of Investigational Product:
SAGE-217 Capsule

Name of Active Ingredient:
SAGE-217

Title of Study:
A 2-Part Study (Open-label followed by Double-blind, Randomized, Placebo-controlled, Parallel Group) of the Safety, Tolerability, Pharmacokinetics, and Efficacy of SAGE-217 in the Treatment of Subjects with Bipolar I/II Disorder with a Current Major Depressive Episode

Number of Sites and Study Location:
Part A: Approximately 10 sites in the United States
Part B: Approximately 40 sites in the United States

Phase of Development: 2

Planned Duration of participation: Up to 73 days (28-day Screening Period; 14-day Treatment Period, and 28-day [±3 days] Follow-up Period)

Objectives:
Part A Primary:

- To evaluate the safety and tolerability of SAGE-217 in subjects with bipolar I or II disorder with a current major depressive episode (MDE).

Part A Secondary:

- To assess the efficacy of SAGE-217 in reducing depressive symptoms in subjects with bipolar I/II disorder with a current MDE.
- To assess the effect of SAGE-217 on sleep.

Part B Primary:

- To assess the efficacy of SAGE-217 in reducing depressive symptoms in subjects with bipolar I/II disorder with a current MDE.

Part B Secondary:

- To evaluate the safety and tolerability of SAGE-217 in subjects with bipolar I/II disorder with a current MDE.
- To assess the effect of SAGE-217 on sleep.

[redacted]

Endpoints:

Part A Primary:

- The safety and tolerability of SAGE-217 as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and electrocardiogram (ECGs); and suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS); and mania using the Young Mania Rating Scale (YMRS).

Part A Secondary:

- The reduction in depressive symptoms, as assessed by:
  - Change from baseline in the 17-item Hamilton Depression Rating Scale (HAM-D) total score at Day 15 and all other time points
  - HAM-D response at Day 15 and all other time points
  - HAM-D remission at Day 15 and all other time points
  - Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Day 15 and all other time points
  - Change from baseline in HAM-D individual item scores at Day 15 and all other time points
  - The response to the Clinical Global Impression scale for severity and improvement (CGI-S and CGI-I, respectively) at Day 15 and all other time points.
- The reduction in insomnia severity, as assessed by Insomnia Severity Index (ISI).

Part B Primary:

- The primary endpoint in Part B is the reduction in depressive symptoms with SAGE-217 treatment, as assessed by the change from baseline in the HAM-D total score at Day 15.

Part B Secondary:

- The reduction in depressive symptoms, as assessed by:
  - Change from baseline in HAM-D total score at all other time points
  - HAM-D response at Day 15 and all other time points
  - HAM-D remission at Day 15 and all other time points
  - Change from baseline in the MADRS total score at Day 15 and all other time points
  - Change from baseline in HAM-D individual item scores at Day 15 and all other time points
  - CGI-S and CGI-I response at Day 15 and all other time points.
- The safety and tolerability of SAGE-217 as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and ECGs; and suicidal ideation and behavior using the C-SSRS; and mania using the YMRS.
- The reduction in insomnia severity, as assessed by ISI.
- [redacted]

Study Description:

This study will be conducted in 2 sequential parts: Part A (open-label) and Part B (randomized, double-blind, placebo-controlled, parallel group). Part B will be initiated pending the review of Part A data. The methods of the 2 parts will be identical unless otherwise noted. Subjects who participate in Part A will not be allowed to participate in Part B. The study is designed to assess the safety, tolerability, [redacted] and efficacy of SAGE-217 in adult subjects with bipolar I/II disorder, who are currently experiencing an MDE.

The assessments are summarized in the Schedule of Events (Table 1).

Screening begins with the signing of the informed consent form at the Screening Visit. The diagnosis of bipolar I or II disorder will be made using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) for clinical trials (SCID-5-CT) performed by a qualified healthcare professional.

Beginning on Day 1, qualified subjects will self-administer the study drug once daily in the evening with food for 14 days. In Part A, all subjects will receive SAGE-217. For Part B, subjects will be randomized in a 1:1 ratio to receive SAGE-217 or placebo; randomization will be stratified based on use of mood stabilizers (Y/N). Subjects on antidepressants or mood stabilizers (lamotrigine, lithium, and valproic acid only) that have been taken at the same dose for at least 60 days prior to Day 1 are to continue the stable dose throughout the treatment period.

If at any time, 30 mg is not tolerated, as assessed by the occurrence of a severe AE judged by the investigator to be related to study drug, the dose on the next day will be reduced to 20 mg and continued for the remainder of the treatment period. Dose adjustments related to moderate AEs will be judged by the Investigator. If a dose adjustment from 30 mg to 20 mg is deemed necessary by the Investigator, the subject will return to the site for the adjusted dose to be dispensed. Subjects who cannot tolerate the 20-mg dose at any time will be discontinued from study drug.

If at any time during the study, a subject has a YMRS score of ≥13, the Investigator will clinically assess the subject for a manic or hypomanic switch. If the clinical assessment is consistent with hypomania or mania, the subject will be discontinued from study drug and treated as clinically appropriate. These incidents will be documented as AEs.

Subjects will return to the study center during the treatment and follow-up periods as outlined in Table 1.

Number of Subjects (planned):

Part A: Approximately 30 subjects will be dosed.

Part B: Approximately 132 subjects will be randomized and dosed to obtain a total of 112 evaluable subjects.

Eligibility criteria:

Inclusion Criteria:

1. Subject has signed an informed consent form (ICF) prior to the conduct of any study-specific procedures.
2. Subject agrees to adhere to the study requirements, including use of prior, concomitant, and prohibited medications.
3. Subject is an ambulatory man or woman, aged 18 to 65 years, inclusive, at Screening.
4. 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.
5. Subject has a documented history of hypomanic or manic episode (verified by medical records and/or treating healthcare professional) and a diagnosis of bipolar I or bipolar II disorder with a current MDE as per DSM-5 SCID-5-CT.
6. Subject has a HAM-D score of ≥22 at Screening.
7. Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are 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 or bilateral oophorectomy):
   - 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 ligation/occlusion.
   - Vasectomized partner.
   - Sexual abstinence (no sexual intercourse).
8. 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. Acceptable methods of effective contraception for males includes sexual abstinence, 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 #7 for acceptable method of contraception for females).
9. 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.

Exclusion Criteria:

1. Subject has a history of suicide attempt within the last 2 years.
2. Subject has current suicidal ideation with plans based on Investigator clinical assessment and/or the C-SSRS response at Screening or Day 1.
3. Subject has a history of rapid cycling bipolar disorder as per DSM-5 SCID-5-CT.

4. Subject's current depressive episode meets the DSM-5 specifier criteria for mixed features.
5. Subject has ≥25% reduction in HAM-D score from Screening to Day 1.
6. 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.
7. Subject has abnormal liver function as shown by an abnormal liver function profile at screening (eg, repeated values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥2x the upper limit of normal).
8. Subject has a clinically significant abnormal 12-lead ECG at the Screening or Day 1 visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in male or >470 msec in female subjects will be the basis for exclusion from the study.
9. Subject has a YMRS score ≥13 at Screening or Day 1.
10. Subject presents for the study receiving a mood stabilizer other than lamotrigine, lithium, or valproic acid.
11. Subject presents for the study receiving psychotropic medications, which have not been taken at the same dose for at least 60 days prior to Day 1.
12. Subject that presents for the study receiving psychotropic medications and does not intend to continue the current treatment regimen during the treatment period.
13. Subject is taking typical or atypical antipsychotics, monoamine oxidase inhibitors (MAOIs), benzodiazepines or $GABA_A$ modulators other than the allowed mood stabilizers at the Screening Visit.
14. Subject has a history of severe rashes or Stevens-Johnson Syndrome associated with lamotrigine and is currently taking lamotrigine.
15. Subject's current depressive episode is treatment resistant; defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants from two different classes for an adequate amount of time (ie, at least 4 weeks of treatment). This will be assessed using the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.
16. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
17. Subject has a positive pregnancy test at the Screening Visit or on Day 1 (prior to administration of study drug) or, if she is breastfeeding at Screening or on Day 1 (prior to administration of study drug), she does not agree to temporarily cease giving breast milk to her child(ren) from just prior to receiving study drug on Day 1 until 7 days after the last dose of study drug.
18. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and HCV viral load, or human immunodeficiency virus (HIV) antibody at screening.
19. Subject has active psychosis per Investigator assessment.

20. Subject has a medical history of seizures.
21. Subject has a medical history schizophrenia, and/or schizoaffective disorder.
22. Subject has a history of mild, moderate, or severe substance use disorder diagnosed using DSM-5 criteria in the 12 months prior to screening.
23. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
24. Subject has had exposure to another investigational medication or device within 30 days prior to the Screening visit.
25. Subject has been previously treated or randomized in any study using SAGE-217. Subjects who participate in Part A are not eligible to participate in Part B.
26. Subject has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to receiving the first dose of study drug.
27. Subject has used CYP inducers, such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort, within 28 days prior to the first dose of study drug.
28. Subject plans to undergo elective surgery during participation in the study.

SAGE-217 dosage and mode of administration:

SAGE-217 is available as hard gelatin capsules containing a white to off-white powder. In addition to SAGE-217 Drug Substance, the 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. Subjects will take the assigned dose orally once daily in the evening (approximately 8:00 to 11:00 pm) with food.

Reference therapy, dosage and mode of administration (Part B only):

In Part B, placebo capsules are visually matched to the active capsules and are available as hard gelatin capsules containing only the excipients listed above for the active capsule treatment. Study drug will be administered orally once daily in the evening (approximately 8:00 to 11:00 pm) with food.

Duration of Treatment: 14 days

Statistical methods:

A separate statistical analysis plan (SAP) for each part (Parts A and B) will provide a detailed description of the analyses to be performed in the respective part of the study. The SAPs 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.

General:

The data from Parts A and B will be analyzed separately. For the purpose of all safety and efficacy analyses where applicable, baseline is defined as the last available measurement prior to the start of study drug administration.

Continuous endpoints will be summarized with 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:

Randomized set (Part B only) will be defined as all subjects who are randomized. This analysis set will be used of all data listings in Part B. Data listings for Part A will be based on Safety or Efficacy Set, as appropriate.

The Safety Set, defined as all subjects received at least 1 dose of study drug, will be used to provide descriptive summaries of safety data.

The Efficacy Set, defined as all subjects who are in Safety Set and have at least one post-baseline HAM-D evaluation, will be used to analyze efficacy data unless otherwise specified.

[redacted]

Safety Analysis:

The overall incidence of adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Data for vital signs, clinical laboratory measurements, ECG, and concomitant medication usage will also be summarized.

Safety data will be summarized and examined for possible relationships between subject characteristics and plasma SAGE-217 concentrations, as appropriate. Suicidality data collected using the C-SSRS and evaluation of mania collected using the YMRS at baseline and at each visit during the active Treatment Period will be listed for all subjects. Out-of-range safety endpoints may be categorized as low or high, where applicable. Subjects will be summarized according to treatment received for the purpose of safety.

Efficacy Analysis:

The primary endpoint in Part B, the change from baseline in HAM-D total score, will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include treatment, baseline HAM-D total score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be considered as fixed effects and the subject effect will be considered random in the model. All post-baseline time points will be included in the model. The primary comparison will be between SAGE-217 and matching placebo at Day 15. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported. An unstructured covariance structure will be used to model the within-subject errors. Other continuous endpoints will be analyzed using similar methods.

Other efficacy analyses, including those in Part A, will be specified in the SAP. In general, data will be analyzed using appropriate descriptive statistics or pre-specified statistical methods as applicable; subject listings will be provided for all efficacy data. Subjects will be analyzed according to randomized treatment for the purpose of efficacy unless otherwise specified.

[redacted]

Sample Size Calculation

Part A: The sample size of approximately 30 subjects was selected based on clinical and not statistical considerations.

Part B: Assuming a two-sided alpha level of 0.05, a sample size of 112 total evaluable subjects (56 per treatment group) would provide 80% power to detect a placebo-adjusted treatment difference of

approximately 4 points in the primary endpoint, change from baseline in HAM-D total score at Day 15, assuming standard deviation (SD) of 7.5 points.

Assuming a 15% dropout rate, approximately 132 total randomized subjects will be required to obtain a total of 112 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have a valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the drop-out rate is higher than 15%.

Table 1: Schedule of Events

Study Period	**Screening Period**	**Treatment Period**					**Follow-up Period[a]**			
Visit Day	**D-28 to D-1**	**D1**	**D3 (+1d)**	**D8 (±1d)**	**D12 (±1d)**	**D15 (±1d)/EOTa**	**D21 (±3d)**	**D28 (±3d)**	**D35 (±3d)**	**D42 (±3d)/ ET**
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Study Procedure										
Informed Consent	X									
Inclusion/Exclusion	X	X								
Demographics	X									
Medical/Family History	X									
SCID-5-CT	X									
MGH-ATRQ	X									
Serum FSH test	X									
Randomization (Part B only)		X								
Physical Examination	X	X				X				X
Body Weight/Height[c]	X					X (wt only)				X (wt only)
Clinical Laboratory Assessments[d]	X	X		X		X	X	X		X
Drug & Alcohol Screen[e]	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[f]	X	X				X		X		X
Hepatitis & HIV Screen	X									
[redacted]										
Vital Signs[i]	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[j]	X	X	X			X				X
C-SSRS[k]	X	X	X	X	X	X	X	X	X	X
HAM-D[l]	X	X	X	X	X	X	X	X	X	X
MADRS[l]		X	X	X	X	X	X	X	X	X
CGI-S		X	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X	X	X
YMRS[l]	X	X	X	X	X	X	X	X	X	X
[redacted]										

Table 1: Schedule of Events (Continued)

Study Period	**Screening Period**	**Treatment Period**					**Follow-up Period[a]**			
Visit Day	**D-28 to D-1**	**D1**	**D3 (+1d)**	**D8 (±1d)**	**D12 (±1d)**	**D15 (±1d)/EOT**Ta	**D21 (±3d)**	**D28 (±3d)**	**D35 (±3d)**	**D42 (±3d)/ ET**
[redacted]										
ISI		X		X		X	X	X		X
[redacted]										
Study Drug Dispensation[o]		X		X						
Study Drug Administration		X (Day 1-14)								
Study Drug Accountability/Return			X	X	X	X				
Adverse Events/Serious Adverse Events[p]	X									
Prior/Concomitant Medications/ Procedures[q]	X									

CGI-I = Clinical Global Impression - Improvement; CGI-S – Clinical Global Impression - Severity; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; EOT = end of treatment; ECG = electrocardiogram; ET = early termination; [redacted] FSH = follicle stimulating hormone; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; ISI = Insomnia Severity Index; MADRS = Montgomery-Åsberg Depression Rating Scale; MGH-ATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; O = optional; [redacted]; SCID-5-CT = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition for clinical trials; [redacted] YMRS = Young Mania Rating Scale

[a] Subjects who discontinue treatment early should return to the site for an EOT visit as soon as possible, preferably the day after treatment is discontinued. Follow-up visits should take place every 7 days after the last dose of treatment for a total of 4 follow-up visits. If at any time after the EOT visit, a subject decides to terminate the study, the subject should return for an ET visit. The EOT 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 both visits will be conducted.

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

[c] Height measured at screening only

[d] Safety laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis. Laboratory assessments are to be completed in the morning.

[e] Urine toxicology for selected drugs of abuse, and breath test for alcohol (as per the standard procedures at each site).

[f] For women of child-bearing potential, serum pregnancy test at screening and urine pregnancy test at all other scheduled timepoints.

[redacted]

[i] Vital signs include oral temperature (°C), respiratory rate, heart rate, pulse oximetry, 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 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.

[j] Triplicate 12-lead ECGs will be performed with the subject in the supine position. When ECG [redacted] sample collection occur during the same visit, ECGs will be collected first.

[k] The "Baseline/Screening" C-SSRS form will be completed at screening. The "Since Last Visit" C-SSRS form will be completed at any time of day at all subsequent time points.

[l] For MADRS, HAM-D, and YMRS, the "Since Last Evaluation" forms will be completed at all subsequent time points following the initial assessment.

[redacted]

[o] Additional unscheduled dispensation visits may be needed for dose reductions.

[p] AEs/SAEs will be collected starting at the time of informed consent and throughout the duration of the subject's participation in the study.

[q] Prior medications will be collected at Screening and concomitant medications will be collected at each subsequent visit. All medications taken within 30 days prior to Screening through the duration of the study will be recorded. In addition, all psychotropic medications taken within 6 months prior to Screening will be recorded.

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

LIST OF TABLES

LIST OF FIGURES

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
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CGI-I	Clinical Global Impression scale for improvement
CGI-S	Clinical Global Impression scale for severity
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
ET	early termination
[redacted]	[redacted]
FSH	follicle-stimulating hormone
GABA	γ-aminobutyric acid
HAM-D	Hamilton Depression Rating Scale
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ID	identification
IRT	interactive response technology
ISI	Insomnia Severity Index
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MDE	major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
MGH-ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire

Table 2: Abbreviations and specialist terms (Continued)

Abbreviation or specialist term	Explanation
MMRM	mixed effects model for repeated measures
PI	Principal Investigator; the investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
[redacted]	[redacted]
QTcF	QT corrected according to Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SCID-5-CT	Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition for clinical trials
SD	standard deviation
[redacted]	[redacted]
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
YMRS	Young Mania Rating Scale

5. INTRODUCTION

5.1. Background of Bipolar Disorders and Unmet Medical Need

Bipolar disorder is a chronic and episodic illness that is associated with significant disability worldwide (Sachs 2007). The Global Burden of Disease Study revealed that in 2013, there were 48.8 million cases of bipolar disorder globally (Ferrari 2016). Bipolar disorder accounted for 9.9 million disability-adjusted life years (DALYs) globally, explaining 0.4% of total DALYs and 1.3% of total years lived with disability.

There are subtypes of bipolar disorder; this study includes the bipolar I and II subtypes. Bipolar I is characterized by a manic episode, whereas bipolar II is characterized by a hypomanic episode. The difference in the severity of the manic features relies on functional impairment that is caused by these episodes (DSM-5). The National Comorbidity Survey estimate of the lifetime prevalence of bipolar disorder is 2.1% in the US population when bipolar I disorder and bipolar II Disorder are combined (Merikangas 2007).

While the manic or hypomanic episodes represent distinct departure from the baseline mood state and easily attract attention, evidence suggests that depressive episodes of both bipolar I and II are associated with more disability than any other aspect of the illness. A seminal long-term study of patients with bipolar I disorder demonstrated that over the 13-year follow-up period, patients were symptomatic about 47% of the time, and depressive symptoms were present in 32% of the follow-up weeks vs manic features, which were present in 9% (Judd 2002). A similar analysis in patients with bipolar II disorder with a longer follow up of up to 20 years found that patients were symptomatic more than half of the time (54%) where depressive symptoms dominated the course at 50% of the follow-up weeks versus 1.3% for the hypomanic symptoms (Judd 2003). A study in patients with unipolar depression found a prevalence of depressive symptoms 47% of the time (Judd 1998), suggesting a comparable time spent with depressive symptoms in the bipolar spectrum. These naturalistic studies have also found that about half the time patients reported taking psychotropic medications. In another large-scale study with a follow-up period of up to 2 years, 58% of nearly 1500 patients with bipolar disorder who were symptomatic at study entry achieved recovery (Perlis 2006). Similarly, during the follow-up period, 49% of these individuals experienced recurrent episodes, where depressive episodes (38%) outweighed manic, hypomanic, or mixed episodes combined (13.8%). In the Stanley Foundation Bipolar Network Study, in which year-long, daily clinician ratings were included, despite treatment with an average of 4.1 psychotropic medications, patients with bipolar disorder spent 3 times as much time with depressive symptoms as manic symptoms (Post 2003).

There are only 3 medications approved in the US for the treatment of bipolar depression, (lurasidone, olanzapine-fluoxetine combination, and quetiapine), all of which include atypical antipsychotics that are associated with significant adverse metabolic effects. None of the currently available antidepressants are indicated for bipolar depression due to their limited efficacy, and the possibility that their use may be associated with a manic switch and rapid cycling. While some studies reported varying levels of efficacy with antidepressants (Gijsman 2004), a large-scale, double-blind, placebo-controlled clinical trial sponsored by the National Institutes of Mental Health, The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), found that only 23.5% of patients with bipolar depression receiving a mood stabilizer and adjunctive antidepressants versus 27.3% of those receiving a

mood stabilizer and placebo experienced a durable recovery, confirming the lack of effectiveness of antidepressants in bipolar depression (Sachs 2007). The tolerability profile of the approved atypical antipsychotics and limited efficacy of available antidepressants highlight the critical unmet need in the treatment of bipolar depression.

In 1998, the lifetime cost of bipolar disorder in the US was estimated at $24 billion. The cost of a single manic episode was estimated at $11,720 to $624,785 for persons with nonresponsive/chronic episodes (Begley 1998); the cost of bipolar depression specifically, is less well studied, however, available estimates indicate a higher cost associated with bipolar depression than for mania (Bowden 2004).

Kessler has studied the impact of mood disorders on work performance in a representative sample of over 3,000 US workers (Kessler 2006). Bipolar disorder and major depressive disorder were associated with 65.5 and 27.2 lost workdays per worker per year, respectively. Moreover, it was found that the increase in bipolar disorder was attributable to depressive symptoms rather than manic episodes in bipolar disorder.

Taken together, these findings point to substantial predominance of depressive symptoms across the spectrum of bipolar disorder. In particular, they also highlight the importance of successful depressive symptom control, and an unmet need in the treatment of depressive episodes for both bipolar I and bipolar II disorder.

5.2. SAGE-217

SAGE-217 is a positive allosteric modulator of γ-aminobutyric acid $(GABA)_A$ 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 portion of the Phase 2a study of SAGE-217 administered to subjects with moderate to severe major depressive disorder (MDD) showed clinically significant improvements from baseline in depression scale scores (HAM-D, Montgomery-Åsberg Depression Rating Scale [MADRS], 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 (N=89) in which a rapid and substantial decrease in HAM-D scores was observed at Day 15 (primary endpoint), starting at Day 2. This response pattern was also observed with other efficacy scales, including MADRS and CGI-I. Statistically significant differences from the placebo group favoring the SAGE-217 arm were observed for 2 weeks in the follow-up period.

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 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.

5.3. 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 2 study of SAGE-217 in subjects with MDD and the current significant unmet need in the treatment of depressive episodes associated with bipolar I/II disorders, a favorable risk-benefit balance and investigation of SAGE-217 in patients with bipolar I/II disorders are justified.

5.4. Dose Justification

The dose of SAGE-217 to be administered in this study (30 mg) was determined based on the maximum tolerated dose in the multiple ascending dose study of SAGE-217 in healthy subjects, and is the same dose level that has been used and generally well tolerated in clinical studies in various patient populations, including patients with MDD. Due to the observed improved tolerability of sedation/somnolence effects when taken in the evening in previous clinical studies, SAGE-217 will be administered in the evening in this study as well.

With respect to the duration of treatment course, a 14-day study drug administration is planned. This is based on previous clinical trial data with SAGE-217, demonstrating substantial improvement in depressive symptoms in patients with MDD, starting within the first week of treatment.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Study Objective

6.1.1. Primary Objective

Part A

The primary objective of Part A of this study is to evaluate the safety and tolerability of SAGE-217 in subjects with bipolar I/II disorder with a current major depressive episode (MDE).

Part B

The primary objective of Part B of this study is to assess the efficacy of SAGE-217 in reducing depressive symptoms in subjects with bipolar I/II disorder with a current MDE.

6.1.2. Secondary Objectives

Part A

Secondary objectives of Part A of this study are:

- To assess the efficacy of SAGE-217 in reducing depressive symptoms in subjects with bipolar I/II disorder with a current MDE.
- To assess the effect of SAGE-217 on sleep.

Part B

Secondary objectives of Part B of this study are:

- To evaluate the safety and tolerability of SAGE-217 in subjects with bipolar I/II disorder with a current MDE.
- To assess the effect of SAGE-217 on sleep.

6.2. Endpoints

6.2.1. Primary Endpoint

Part A

The primary endpoint for Part A of this study is the safety and tolerability of SAGE-217, as assessed by the frequency and severity of adverse events (AEs); changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs); suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS); and mania using the Young Mania Rating Scale (YMRS).

Part B

The primary endpoint of Part B of this study is the reduction in depressive symptoms with SAGE-217 treatment, as assessed by the change from baseline in the 17-item HAM-D total score at Day 15.

6.2.2. Secondary Endpoints

Part A

Secondary endpoints of Part A of this study are:

- The reduction in depressive symptoms, as assessed by:
  - Change from baseline in the 17-item HAM-D total score at Day 15 and all other time points
  - HAM-D response at Day 15 and all other time points
  - HAM-D remission at Day 15 and all other time points
  - Change from baseline in the MADRS total score at Day 15 and all other time points
  - Change from baseline in HAM-D individual item scores at Day 15 and all other time points
  - The response to the CGI-S and CGI-I at Day 15 and all other time points.
- The reduction in insomnia severity as assessed by the Insomnia Severity Index (ISI).

Part B

Secondary endpoints of Part B of this study are:

- The reduction in depressive symptoms, as assessed by:
  - Change from baseline in total HAM-D score at all other time points
  - HAM-D response at Day 15 and all other time points
  - HAM-D remission at Day 15 and all other time points

  - Change from baseline in the MADRS total score at Day 15 and all other time points
  - Change from baseline in HAM-D individual item scores at Day 15 and all other time points
  - CGI-S and CGI-I response at Day 15 and all other time points.
- The safety and tolerability of SAGE-217 as assessed by the frequency and severity of AEs; changes from baseline in clinical laboratory measures, vital signs, and ECGs; and suicidal ideation and behavior using the C-SSRS, and the YMRS.
- The reduction in insomnia severity, as assessed by the ISI.

[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This study will be conducted in 2 sequential parts: Part A (open-label) and Part B (randomized, double-blind, placebo-controlled, parallel group). Part B will be initiated pending the review of Part A data.The methods of the 2 parts will be identical unless otherwise noted. The study is designed to assess the safety, tolerability, [redacted] and efficacy of SAGE-217 in adult subjects with bipolar I/II disorder, who are currently experiencing an MDE.

Screening begins with the signing of the informed consent form (ICF) at the Screening Visit. The diagnosis of bipolar I or II disorder will be made using the Structured Clinical Interview for DSM-5 for clinical trials (SCID-5-CT) performed by a qualified healthcare professional. Subjects on antidepressants or mood stabilizers (lamotrigine, lithium, and valproic acid only) that have been taken at the same dose for at least 60 days prior to Day 1 are to continue the stable dose throughout the treatment period.

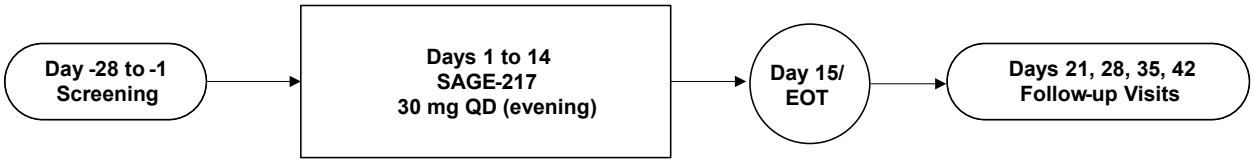
Subjects will return to the study center during the treatment and follow-up periods as outlined in the Schedule of Events (Table 1). All assessments to be performed are summarized in Table 1.

If at any time during the study, a subject has a YMRS score of ≥13, the Investigator will clinically assess the subject for a manic or hypomanic switch. If the clinical assessment is consistent with hypomania or mania, the subject will be discontinued from study drug and treated as clinically appropriate (see Section 8.3).

Part A

The study design for Part A is presented in Figure 1. In Part A, all subjects will receive SAGE-217. Beginning on Day 1, qualified subjects will self-administer 30-mg SAGE-217 once daily in the evening (approximately 8:00 to 11:00 pm) with food for 14 days. Dose adjustments based on study drug tolerability are permitted following the guidelines outlined in Section 7.4.

Figure 1: Study Design (Part A)



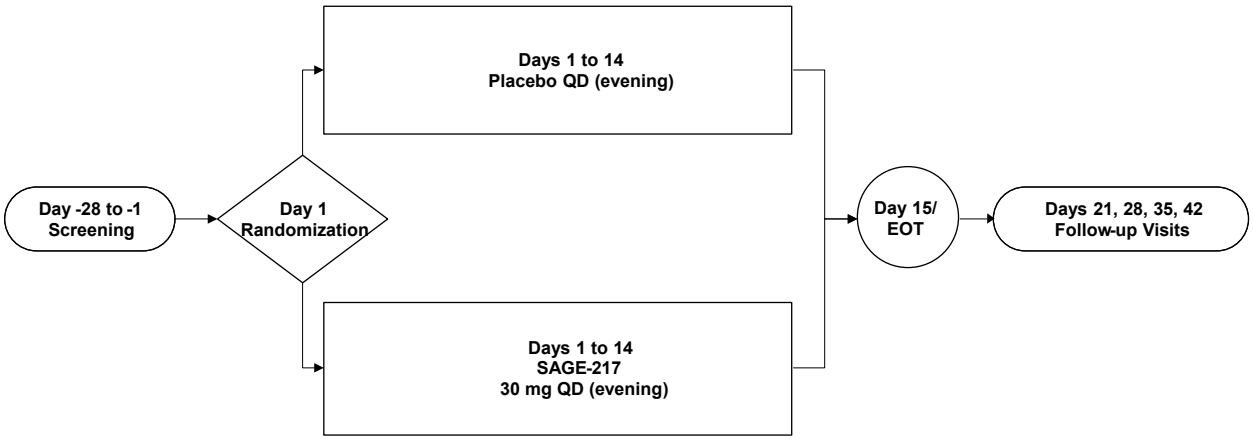
QD = once daily
A dose adjustment to 20-mg SAGE-217 is permitted if the 30-mg dose is not tolerated at any time.

Part B

The study design for Part B is presented in Figure 2. In Part B, subjects will be randomized in a 1:1 ratio to receive SAGE-217 or placebo; randomization will be stratified based on use of mood stabilizers (Y/N). Beginning on Day 1, qualified subjects will self-administer the study drug

(30 mg SAGE-217 or placebo) once daily in the evening (approximately 8:00 to 11:00 pm) with food for 14 days. Dose adjustments based on study drug tolerability are permitted following the guidelines outlined in Section 7.4.

Figure 2: Study Design (Part B)



QD = once daily
A dose adjustment to 20-mg SAGE-217 is permitted if the 30-mg dose is not tolerated at any time.

7.2. Number of Subjects

Part A

Approximately 30 subjects will be dosed in Part A.

Part B

After review of Part A data, approximately 132 subjects will be randomized and dosed in Part B to obtain a total of 112 evaluable subjects (see Section 13.8).

7.3. Treatment Assignment

Part A

In Part A, all subjects will receive SAGE-217 in an open-label manner.

Part B

In Part B, subjects will be randomized to a treatment group (SAGE-217 or placebo) in a 1:1 ratio; randomization will be stratified based on use of mood stabilizers (Y/N).

7.4. Dose Adjustment Criteria

If at any time, 30 mg is not tolerated, as assessed by the occurrence of a severe AE judged by the investigator to be related to study drug, the dose on the next day will be reduced to 20 mg and continued for the remainder of the treatment period. Dose adjustments related to moderate AEs will be judged by the Investigator. If a dose adjustment from 30 mg to 20 mg is deemed

necessary by the Investigator, the subject will return to the site for the adjusted dose to be dispensed. Subjects who cannot tolerate the 20-mg dose at any time will be discontinued from study drug (see Section 8.3).

7.5. Study Termination

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of 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 the conduct of any study-specific procedures.
2. Subject agrees to adhere to the study requirements, including use of prior, concomitant, and prohibited medications.
3. Subject is an ambulatory man or woman, aged 18 to 65 years, inclusive, at Screening.
4. 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.
5. Subject has a documented history of hypomanic or manic episode (verified by medical records and/or treating healthcare professional) and a diagnosis of bipolar I or bipolar II disorder with a current MDE as per DSM-5 SCID-5-CT.
6. Subject has a HAM-D score of ≥22 at Screening.
7. Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are 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 or bilateral oophorectomy):
    - 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 ligation/occlusion.
    - Vasectomized partner.
    - Sexual abstinence (no sexual intercourse).
8. 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. Acceptable methods of effective contraception for males includes sexual abstinence, 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 #7 for acceptable method of contraception for females).
9. 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.

8.2. Subject Exclusion Criteria

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

1. Subject has a history of suicide attempt within the last 2 years.
2. Subject has current suicidal ideation with plans based on Investigator clinical assessment and/or the C-SSRS response at Screening or Day 1.
3. Subject has a history of rapid cycling bipolar disorder as per DSM-5 SCID-5-CT.
4. Subject's current depressive episode meets the DSM-5 specifier criteria for mixed features.
5. Subject has ≥25% reduction in HAM-D score from Screening to Day 1.
6. 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.
7. Subject has abnormal liver function as shown by an abnormal liver function profile at screening (eg, repeated values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥2x the upper limit of normal).
8. Subject has a clinically significant abnormal 12-lead ECG at the Screening or Day 1 visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in male or >470 msec in female subjects will be the basis for exclusion from the study.
9. Subject has a YMRS score ≥13 at Screening or Day 1.
10. Subject presents for the study receiving a mood stabilizer other than lamotrigine, lithium, or valproic acid.
11. Subject presents for the study receiving psychotropic medications, which have not been taken at the same dose for at least 60 days prior to Day 1.
12. Subject that presents for the study receiving psychotropic medications and does not intend to continue the current treatment regimen during the treatment period.
13. Subject is taking typical or atypical antipsychotics, monoamine oxidase inhibitors (MAOIs), benzodiazepines or $GABA_A$ modulators other than the allowed mood stabilizers at the Screening Visit.
14. Subject has a history of severe rashes or Stevens-Johnson Syndrome associated with lamotrigine and is currently taking lamotrigine.
15. Subject's current depressive episode is treatment resistant; defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants from two different classes for an adequate amount of time (ie, at least 4 weeks of treatment). This will be assessed using the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.

16. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
17. Subject has a positive pregnancy test at the Screening Visit or on Day 1 (prior to administration of study drug) or, if she is breastfeeding at Screening or on Day 1 (prior to administration of study drug), she does not agree to temporarily cease giving breast milk to her child(ren) from just prior to receiving study drug on Day 1 until 7 days after the last dose of study drug.
18. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and HCV viral load, or human immunodeficiency virus (HIV) antibody at screening.
19. Subject has active psychosis per Investigator assessment.
20. Subject has a medical history of seizures.
21. Subject has a medical history schizophrenia, and/or schizoaffective disorder.
22. Subject has a history of mild, moderate, or severe substance use disorder diagnosed using DSM-5 criteria in the 12 months prior to screening.
23. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
24. Subject has had exposure to another investigational medication or device within 30 days prior to the Screening visit.
25. Subject has been previously treated or randomized in any study using SAGE-217. Subjects who participate in Part A are not eligible to participate in Part B.
26. Subject has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to receiving the first dose of study drug.
27. Subject has used CYP inducers, such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort, within 28 days prior to the first dose of study drug.
28. Subject plans to undergo elective surgery during participation in the study.

8.3. Subject Withdrawal Criteria

8.3.1. Withdrawal from the Study or Discontinuation of Study Drug

Subjects may discontinue study drug or withdraw from the study at any time for any reason. The Investigator may discontinue the subject from the study or study drug 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

In addition, if at any time during the study, a subject has a YMRS score of ≥13, the Investigator will clinically assess the subject for a manic or hypomanic switch. If the clinical assessment is consistent with hypomania or mania, the subject will be discontinued from study drug and treated as clinically appropriate. These incidents will be documented as AEs.

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has discontinued or been withdrawn for any reason.

Subjects who discontinue study drug early/withdraw during the treatment period should, if possible, have an end of treatment (EOT) visit, including the EOT assessments as summarized in the Schedule of Events (Table 1). The EOT visit should be scheduled as soon as possible, preferably the day after the subject's last dose. All details of the EOT visit should be recorded in the subject's medical source documents. For subjects that discontinue study drug early, follow-up visits should take place every 7 days for 28 days. If at any time after the EOT visit, a subject decides to terminate the study early, the subject should return for an early termination (ET) visit. The EOT 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 both visits will be conducted only once.

If the subject fails or refuses to return to the study center, an attempt must be made to contact the subject by telephone in order to assess as many safety and efficacy parameters as possible. All data collected over the telephone must be documented and kept in the subject's record. A subject will be deemed lost to follow-up after 3 attempts at contact have been made and it has been at least 1 month since the last subject contact. The third attempt at contact must be a certified letter accompanied by a survey inquiring the reason for study discontinuation. All attempts at contact will be documented.

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.

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.

8.3.2. Replacement of Subjects

Part A

In Part A, subjects will not be replaced.

Part B

In Part B, subjects will not be replaced. Additional subjects may be randomized if the drop-out rate is higher than anticipated (see Section 13.8).

9. TREATMENT OF SUBJECTS

9.1. Study Drug

Subjects will self-administer study drug orally once daily in the evening (approximately 8:00 to 11:00 pm) with food for 14 days as outlined in Section 7.1.

9.2. Prior Medications, Concomitant Medications, and Restrictions

9.2.1. Prior and Concomitant Medications and/or Supplements

The start and end dates, route of administration, 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 drugs taken within 6 months prior to Screening will be recorded.

Any concomitant medication determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study under the guidance outlined in these sections.

Antidepressants and mood stabilizers (lamotrigine, lithium, and valproic acid only) 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 throughout the treatment period.

Medications intended for contraception are permitted for female subjects (see Section 8.1):

9.2.2. Prohibited Medications

The following specific classes of medications are prohibited at any time during the treatment period:

- Benzodiazepines
- $GABA_A$ modulators other than the allowed mood stabilizers
- Typical or atypical antipsychotics
- MAOIs
- Any known strong inhibitors of CYP3A4
- Use of CYP inducers, such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort.

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 drugs of abuse and alcohol 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 1 until 7 days after the last dose of study drug following the treatment period.

9.3. Treatment Adherence

SAGE-217 (Parts A and B) or placebo (Part B only) will be self-administered by subjects once every evening (approximately 8:00 to 11:00 pm) with food. Sites will dispense study drug to the subjects to take at home with instructions for use (Section 10.4).

Administration of study drug will be monitored by a medication adherence monitoring platform used on smartphones to visually confirm medication ingestion. Subjects will receive a reminder within a predefined time window to take study drug while using the application. Subjects will follow a series of prescribed steps in front of the front-facing webcam to visually confirm their ingestion of the medication. The application will record the date and time of study drug administration by dose level, as well as missed doses.

In addition, the subject will be instructed to bring their dosing kit to each visit during the treatment period, at which time the Investigator or designee will be responsible for ensuring the kit contains sufficient doses until the next scheduled dispensation.

If the subject is persistently noncompliant with the study drug, the Investigator should discuss with Sage Therapeutics the potential discontinuation of the subject (Section 8.3). Dosing requirements will be reviewed with each subject during all study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.4. Randomization and Blinding

Part A

Part A is an open-label design in which all subjects will receive SAGE-217.

Part B

Part B is a randomized, double-blind, placebo-controlled, parallel group design. Subjects who meet the entrance criteria will be stratified based on use of mood stabilizers (Y/N) and randomly assigned within each stratum in a 1:1 ratio to receive SAGE-217 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 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.

During the study, the blind is to be broken only if the safety of a subject is at risk and the treatment plan is dependent on the study treatment received. See Section 12.6 for details of unblinding in the event of a medical emergency or pregnancy.

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.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Description of 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 10-mg, 20-mg, and 30-mg strengths to achieve the target dose of 20 mg or 30 mg. Subjects will be administered 2 capsules per dose in Part A. Subjects will be administered 1 capsule per dose in Part B.

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

10.2. Study Drug Packaging and Labeling

SAGE-217 and matched placebo will be provided to the clinic pharmacist and/or designated site staff responsible for dispensing the study drug in appropriately labeled, subject-specific kits each containing sealed unit doses. Each open-label unit dose for Part A consists of 2 capsules. Blinded unit doses for Part B will consist of 1 capsule each. 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 Code of Federal Regulations and Good Manufacturing Practices/Good Clinical Practices guidelines will be prepared by the clinical research organization.

10.3. Study Drug Storage

SAGE-217 and matched placebo are to be stored at room temperature, safely and separately from other drugs.

10.4. Study Drug Preparation

Not applicable.

10.5. Study Drug Administration

SAGE-217 is to be administered orally in the evening (approximately 8:00 to 11:00 pm) with food.

10.6. Study Drug Accountability

Upon receipt of study drug, the Investigator(s), or the responsible pharmacist or designee, will inspect the study drug and complete 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.

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. In the event of an unscheduled dose reduction (Section 7.4), a new subject-specific kit will be dispensed.

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 medication 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 within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

10.7. Study Drug Handling and Disposal

At the end of the study, all used and unused study drug will be reconciled and returned to Sage Therapeutics 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.

11. ASSESSMENT OF EFFICACY [redacted]

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

11.1. Efficacy Assessments

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

The primary outcome measure is the change from baseline in the 17-item HAM-D total score at Day 15.

The 17-item HAM-D will be used to rate the severity of depression in subjects who are identified as experiencing an MDE (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.

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

In addition to the primary efficacy endpoint of change from baseline in HAM-D total score, several secondary efficacy endpoints will be derived for the HAM-D. Hamilton Rating Scale for Depression subscale scores will be calculated as the sum of the items comprising each subscale. Hamilton Rating Scale for Depression response will be defined as having a 50% or greater reduction from baseline in HAM-D total score. Hamilton Rating Scale for Depression remission will be defined as having a HAM-D total score of ≤7.

The HAM-D subject interview may be audio-recorded for independent quality control purposes.

11.1.2. Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a 10-item diagnostic questionnaire used to measure the severity of depressive episodes in subjects with mood disorders. It was designed as an adjunct to the HAM-D that 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 will be calculated as the sum of the ten individual item scores.

The MADRS subject interview may be audio-recorded for independent quality control purposes.

11.1.3. Clinical Global Impression (CGI)

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.

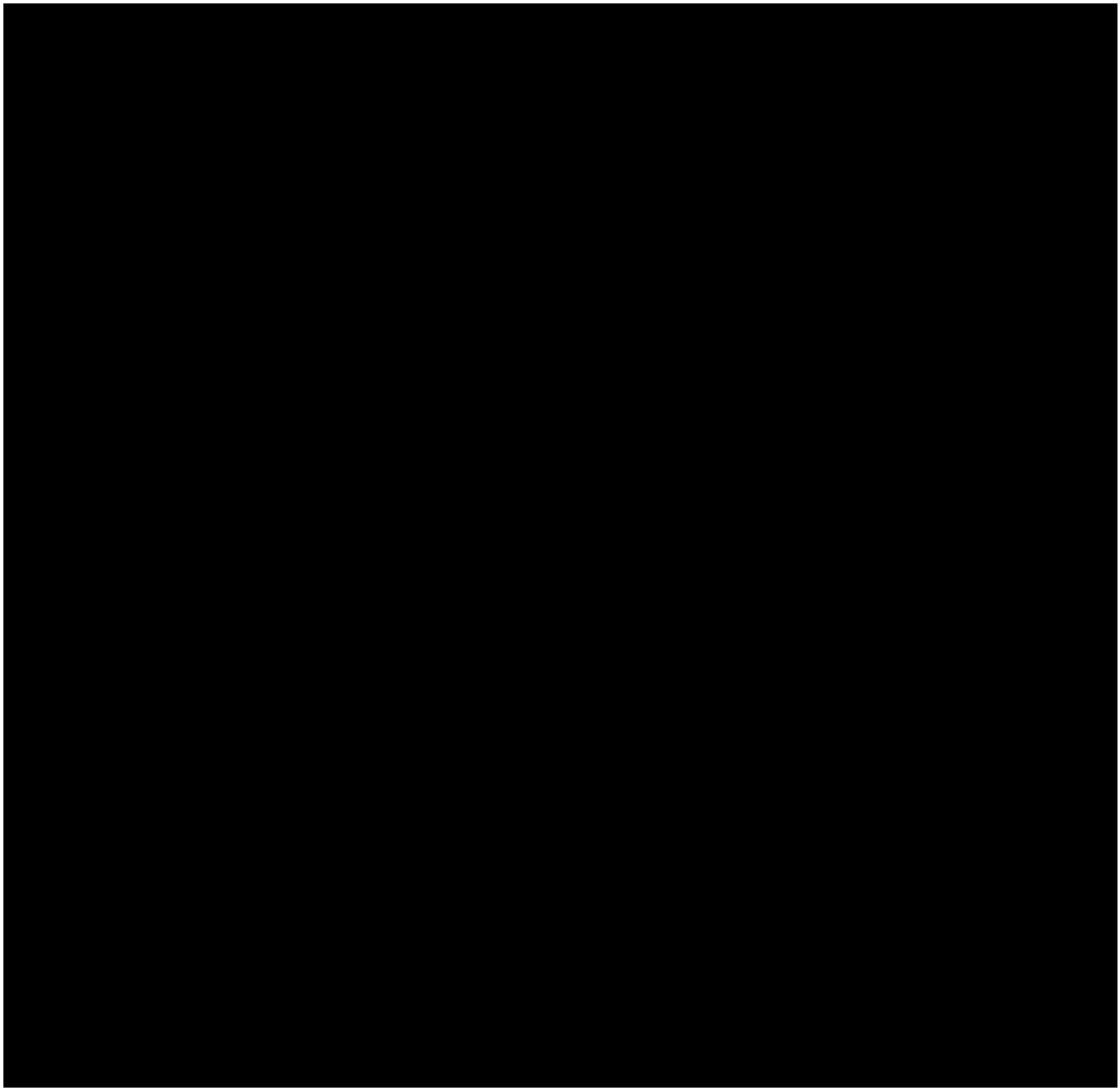
The Clinical Global Impression - Severity (CGI-S) uses a 7-point Likert scale to rate the severity of the subject's illness at the time of assessment, relative to the clinician's past experience with

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).

The Clinical Global Impression - Improvement (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."

11.1.4. Insomnia Severity Index (ISI)

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 (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)."



12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

The safety and tolerability of SAGE-217 will be assessed by the frequency and severity of AEs; changes from baseline in clinical laboratory measures, vital signs, and ECGs; suicidal ideation and behavior using the C-SSRS; and the YMRS. All assessments will be conducted according to the schedule of assessments (Table 1).

12.1.1. Demographic/Medical History

Demographic and baseline characteristics (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and a full medical history, including family psychiatric history, will be documented. The diagnosis of bipolar I or II disorder will be determined using the SCID-5-CT.

12.1.2. Weight and Height

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

12.1.3. Physical Examination

Physical examinations assessing body systems (eg, head, eye, ear, nose, and throat; heart; lungs; abdomen; and extremities), as well as cognitive and neurological examinations and mental status examinations will be conducted and documented. Whenever possible, the same individual is to perform all physical examinations for a given subject. Unscheduled brief 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 12.2.1.1.

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 in the standing position. Respiratory rate, pulse oximetry 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, with the blood sample collected as close to the scheduled time as possible.

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 12.2.1.1.

12.1.5. Electrocardiogram (ECG)

Supine 12-lead ECGs will be performed in triplicate. The standard intervals (heart rate, PR, QRS, QT, and QTcF) as well as any rhythm abnormalities will be recorded. When ECG [redacted] sample 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 12.2.1.1.

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 morphology	ALT Albumin Alkaline phosphatase AST Total bilirubin Direct bilirubin Indirect bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase GGT Potassium Sodium Lactate dehydrogenase Glucose Chloride Bicarbonate Calcium Phosphorus Triglycerides	pH Specific gravity Protein Glucose Red blood cells Nitrite Leukocyte esterase Ketones Bilirubin Urobilinogen	Activated partial thromboplastin time Prothrombin time International normalized ratio
Diagnostic Screening			
Serum	**Urine**	**Breathalyzer**	
Hepatitis B Hepatitis C HIV-1 and -2 Female subjects of child bearing potential: serum human chorionic gonadotropin Female subjects, if menopause is suspected and not surgically sterile: FSH	Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, and propoxyphene Female subjects of child bearing potential: urine human chorionic gonadotropin	Alcohol	

The central laboratory will perform laboratory tests for hematology, serum chemistry, and urinalysis. 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, 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 12.2.1.1. 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.

Follicle stimulating hormone testing 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]

12.1.6.1. Drugs of Abuse and Alcohol

Urine toxicology will be performed for selected drugs of abuse, and a breath test will be performed for alcohol (Table 1).

12.1.6.2. Pregnancy Screen

A serum pregnancy test in women of child-bearing potential will be conducted at Screening and a urine pregnancy test will be conducted at all other scheduled timepoints (Table 1).

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

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. Young Mania Rating Scale (YMRS)

Manic symptoms will be assessed during the study using the YMRS (Young 1978). The clinician-administered scale is based on 11 items of core symptoms of mania. Four of the items (irritability, speech, thought content, and disruptive/aggressive behavior) are graded on a scale of 0 to 8 (choices given as even numbers), with the remaining 7 items graded on a scale of 0 to 4. Scoring between the points given (whole or half points) is possible.

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 TEAE is an AE that occurs after the first administration of any study drug. The term study drug includes any Sage investigational product, a comparator, or a placebo administered in a clinical trial.

An abnormal laboratory value will be considered an AE if the value represents a clinically significant change from baseline as determined by the Investigator.

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

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 been enrolled and throughout the duration of the study, whether or not they are related to the study, must be recorded on the SAE form provided by Sage Therapeutics within 24 hours of first awareness (Section 12.5). All SAEs should to be followed until the event resolved, the condition stabilized, was no longer considered clinically significant or the subject was lost to follow-up.

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.

Should a pregnancy occur, it must be reported and recorded on the Sage Therapeutics pregnancy notification form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication or a complication relating to the pregnancy occurs (eg, spontaneous abortion, which requires reporting as an SAE). All pregnancies occurring during this study are to be reported in the same time frame as SAEs (eg, within 24 hours of the site becoming aware of the pregnancy).

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented on the Sage Therapeutics pregnancy outcome form even if the subject was discontinued from the study. Reports of congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs.

If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Sage Therapeutics, or designee. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. 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), the Investigator should follow the procedures for reporting an SAE.

12.5. Reporting Serious Adverse Events

All SAEs must be reported to Sage, 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 staff on the SAE report form. 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. Each site is responsible for notifying its ethics committee of these SUSARs. 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 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. The blinding of the study will be broken after the database has been locked. Electronic copies of the randomization code will be made available to the laboratory performing the bioanalytical analyses in order to allow for limited analysis of samples from subjects receiving placebo.

In the event of a medical emergency or pregnancy, the Investigator will discuss with the Medical Monitor if unblinding is warranted for medical management of the subject. If there is agreement to unblind treatment assignment, the unblinding procedure described in the Safety Management Plan for the study will be followed. If the Investigator is unable to contact the Medical Monitor in a medical emergency, and it is deemed clinically necessary by the Investigator, the treatment group for that subject may be unblinded in the IRT system.

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) for each part (Part A and B) will provide a detailed description of the analyses to be performed in the respective part of the study. The SAPs will be finalized and approved prior to database lock. Any deviations from or changes to the respective SAP following database lock will be described in detail in the clinical study report.

13.1. Data Analysis Sets

The Safety Set, defined as all subjects that received at least 1 dose of study drug, will be used to provide descriptive summaries of safety data.

The Efficacy Set, defined as all subjects in the Safety Set that have at least 1 post-baseline HAM-D evaluation, will be used to analyze efficacy data, unless otherwise specified.

[redacted]

Part B will also include a Randomized Set, defined as all subjects who are randomized. This analysis set will be used for all data listings in Part B.

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 sets, using all non-missing data available. No imputation process will be used to estimate missing data.

13.3. General Considerations

For the purpose of all primary and secondary analyses where applicable, baseline is defined as the last measurement prior to receipt of study drug.

Continuous endpoints will be summarized with number (n), mean, standard deviation (SD), 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 (Section 12.1.1) and baseline characteristics, such as height, weight, and body mass index, will be summarized using the Safety Set.

Pregnancy results will be listed but not summarized.

Medical history will be listed by subject.

13.5. Efficacy Analysis

The primary efficacy endpoint, the change from baseline in HAM-D total score, will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include center, treatment, baseline HAM-D total score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be considered as fixed

effects and the subject effect will be considered random in the model. All post-baseline time points will be included in the model. The primary comparison will be between SAGE-217 and matching placebo at Day 15. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p values) will be reported. An unstructured covariance structure will be used to model the within-subject errors. In case of convergence issues, other covariance structures will be considered; this will be detailed in the statistical analyses plan. Other continuous endpoints will be analyzed using similar methods.

Other efficacy analyses will be specified in the statistical analysis plan. In general, data will be analyzed using appropriate descriptive statistics or pre-specified statistical methods as applicable; subject listings will be provided for all efficacy data. Subjects will be analyzed according to randomized treatment for the purpose of efficacy unless otherwise specified.

13.6. Safety Analyses

Safety and tolerability of SAGE-217 will be assessed by the frequency and severity of AEs; changes from baseline in clinical laboratory measures, vital signs, and ECGs. Suicidal ideation and behavior will be evaluated using the C-SSRS. Mania will be evaluated using the YMRS. Safety data will be listed by subject and summarized by treatment group. All safety summaries will be performed on the Safety Set.

13.6.1. Adverse Events

The analysis of AEs 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 20.1 or higher, system organ class (SOC), and preferred term (PT). 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 (Section 13.6.1).

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

Clinical laboratory results will be listed by subject and timing of collection. Mean changes from baseline in clinical laboratory measures will be evaluated.

13.6.3. Physical Examinations

Physical examination data will be listed by subject, but not summarized.

13.6.4. Vital Signs

Vital sign results will be listed by subject and timing of collection. Mean changes from baseline in vital signs will be evaluated by time point.

13.6.5. 12-Lead Electrocardiogram

The following ECG parameters will be listed for each subject: heart rate, PR, QRS, QT, and QTcF. Any clinically significant abnormalities or changes in ECGs should be listed as an AE. 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.

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 will be summarized and 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. Young Mania Rating Scale

Mania data collected on the YMRS at baseline and by visit will be summarized and listed for all subjects.

[redacted]

13.8. Determination of Sample Size

13.8.1. Part A

For Part A, the sample size of approximately 30 subjects was selected based on clinical and not statistical considerations.

13.8.2. Part B

For Part B, assuming a two-sided alpha level of 0.05, a sample size of 112 total evaluable subjects (56 per treatment group) would provide 80% power to detect a placebo-adjusted treatment difference of approximately 4 points in the primary endpoint, change from baseline in HAM-D total score at Day 15, assuming standard deviation (SD) of 7.5 points.

Assuming a 15% dropout rate, approximately 132 total randomized subjects will be required to obtain a total of 112 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have a valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the drop-out rate is higher than 15%.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the study site guarantee access to source documents by Sage Therapeutics or sponsor's designee and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by Sage Therapeutics or sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

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. Protocol Deviations

Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the Sage Therapeutics or sponsor's designee (and IRB, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

14.4. 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 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 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.

19. LIST OF REFERENCES

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Protocol 217-BPD-201, Amendment 1

Date of Amendment: 13 September 2018

A 2-PART STUDY (OPEN-LABEL FOLLOWED BY DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUP) OF THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF SAGE-217 IN THE TREATMENT OF SUBJECTS WITH BIPOLAR I/II DISORDER WITH A CURRENT MAJOR DEPRESSIVE EPISODE

Rationale for Protocol Amendment

Protocol 217-BPD-201 has been amended to limit SAGE-217 treatment to 30 mg per day for 2 weeks, consistent with experience using the same dose level and duration in other unipolar depression studies. Accordingly, the 20-mg dose titrations prior to and following treatment with 30 mg have been removed, and endpoint assessments have been adjusted; for example, from Day 29 to Day 15 (Note: dose reduction to 20 mg dose during the treatment period are still allowed). A number of sections have been updated to reflect this change.

Additional changes were made as outlined below.

- Additional information (regarding prohibited medication) was added to Exclusion #13.
- Details related to breastfeeding were added to Exclusion #17.
- Clarification of Exclusion #27 regarding CYP inducers.
- Updated details regarding drug materials.
- Updated language regarding reporting adverse events and serious adverse events.
- Minor administrative changes have been made throughout the protocol to increase clarity on the procedures of the study including:
  - Alcohol testing to be conducted at each visit
  - All medications taken within 30 days prior to Screening through the duration of the study will be recorded
  - Insomnia Severity Index (ISI) scoring anchor error

A detailed summary of changes is provided in Table 1. Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting are not detailed.

Table 1: Protocol Amendment 1 Detailed Summary of Changes

The change in Protocol Amendment 1 is indicated. The corresponding related text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: Updated dosing duration, including removal of up- and down-titration.

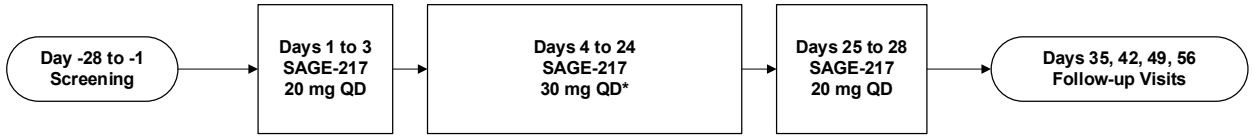
The primary change occurs in Section 7, Investigational Plan, and Table 1, Schedule of Events. This change is reflected throughout the document as the end of treatment visit occurs on Day 15 (rather than Day 28). As there are multiple references to the length of the study and duration of study drug treatment. For ease of review, this change has not been outlined in this table for every occurrence. A tracked changes version of the protocol is available noting all edits made to incorporate this change throughout the document.

Previous text:

Part A

The study design for Part A is presented in Figure 1. In Part A, all subjects will receive SAGE-217. Beginning on Day 1, qualified subjects will self-administer the study drug once daily in the evening with food for 28 days: 20 mg SAGE-217 for 3 days, 30 mg SAGE-217 for 21 days, and then 20 mg-SAGE-217 for 4 days. Dose adjustments based on study drug tolerability are permitted following the guidelines outlined in Section 7.4.

Figure 1: Study Design (Part A)

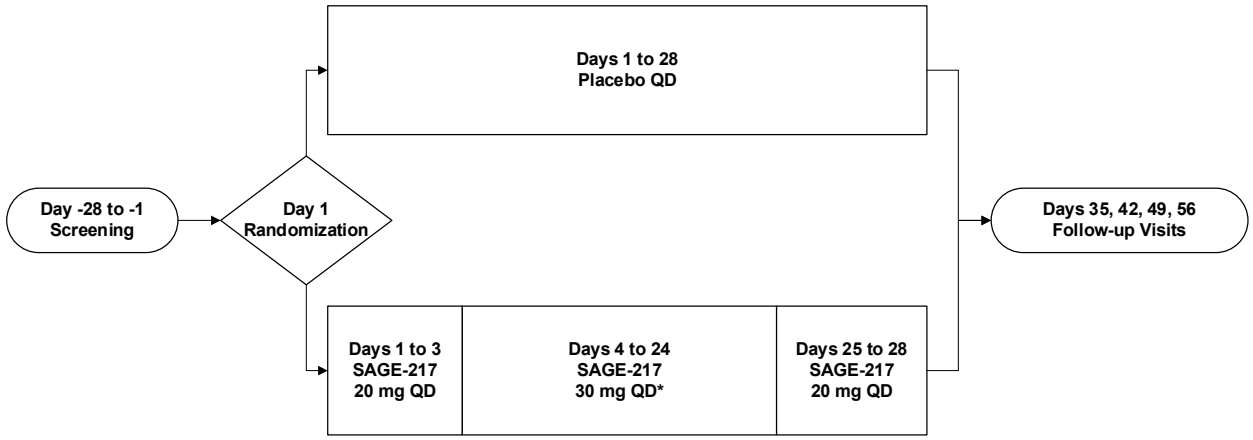


QD = once daily
*A dose adjustment to 20-mg SAGE-217 is permitted if the 30-mg dose is not tolerated at any time during Days 4 to 24.

Part B

The study design for Part B is presented in Figure 2. In Part B, subjects will be randomized in a 1:1 ratio to receive SAGE-217 or placebo; randomization will be stratified based on use of mood stabilizers (Y/N). Beginning on Day 1, qualified subjects will self-administer the study drug once daily in the evening with food for 28 days: 20 mg SAGE-217 for 3 days, 30 mg SAGE-217 for 21 days, and then 20 mg-SAGE-217 for 4 days. Dose adjustments based on study drug tolerability are permitted following the guidelines outlined in Section 7.4.

Figure 2: Study Design (Part B)



QD = once daily
*A dose adjustment to 20-mg SAGE-217 is permitted if the 30-mg dose is not tolerated at any time during Days 4 to 24.

New text:

Part A

The study design for Part A is presented in Figure 1. In Part A, all subjects will receive SAGE-217. Beginning on Day 1, qualified subjects will self-administer 30-mg SAGE-217 once daily in the evening with food for 14 days. Dose adjustments based on study drug tolerability are permitted following the guidelines outlined in Section 7.4.

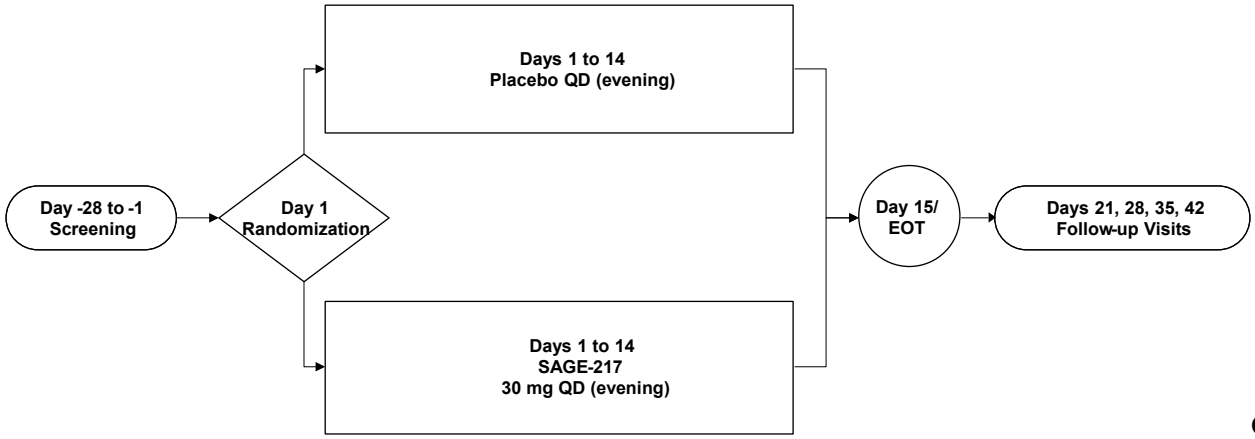
Figure 3: Study Design (Part A)

QD = once daily
A dose adjustment to 20-mg SAGE-217 is permitted if the 30-mg dose is not tolerated at any time.

Part B

The study design for Part B is presented in Figure 2. In Part B, subjects will be randomized in a 1:1 ratio to receive SAGE-217 or placebo; randomization will be stratified based on use of mood stabilizers (Y/N). Beginning on Day 1, qualified subjects will self-administer the study drug (30 mg SAGE-217 or placebo) once daily in the evening with food for 14 days. Dose adjustments based on study drug tolerability are permitted following the guidelines outlined in Section 7.4.

Figure 4: Study Design (Part B)



QD = once daily

A dose adjustment to 20-mg SAGE-217 is permitted if the 30-mg dose is not tolerated at any time.

Purpose: Details regarding prohibited medications were added to Exclusion Criteria #13.

The primary change occurs in Section 8.2, Subject Exclusion Criteria

Added text: *13. Subject is taking typical or atypical antipsychotics, MAOIs, and/or benzodiazepines at the Screening Visit.*

New text: *13. Subject is taking typical or atypical antipsychotics, monoamine oxidase inhibitors (MAOIs), benzodiazepines or GABA A modulators other than the allowed mood stabilizers at the Screening Visit.*

Sections also affected by this change:

- Synopsis
- Section 9.2.2, Prohibited Medications

Purpose: Details regarding breastfeeding were added to Exclusion Criteria #17.

The primary change occurs in Section 8.2, Subject Exclusion Criteria

Added text: *17. Subject has a positive pregnancy test at the Screening Visit or on Day 1 (prior to administration of study drug)* ***or, if she is breastfeeding at Screening or on Day 1 (prior to administration of study drug), she does not agree to temporarily cease giving breast milk to her child(ren) from just prior to receiving study drug on Day 1 until 7 days after the last dose of study drug.***

Sections also affected by this change:

- Synopsis
- Section 9.2.3, Other Restrictions

Purpose: Details regarding CYP inhibitors were added to Exclusion Criteria #27.

The primary change occurs in Section 8.2, Subject Exclusion Criteria

Previous text: *27. Subject has used ~~any~~ CYP inducer, such as such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort, within 28 days prior to the first dose of study drug.*

New text: *27. Subject has used CYP inducers, such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort, within 28 days prior to the first dose of study drug.*

Sections also affected by this change:

- Synopsis
- Section 9.2.3, Other Restrictions

Purpose: Updated details regarding drug materials.

The primary change occurs in Section 10, Study Drug Materials and Management

Added text:

10.1 Description of 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 10-mg, 20-mg, and 30-mg strengths to achieve the target dose of 20 mg or 30 mg. Subjects will be administered 2 capsules per dose* ***in Part A. Subjects will be administered 1 capsule per dose in Part B.***

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

10.2. Study Drug Packaging and Labeling

SAGE-217 and matched placebo will be provided to the clinic pharmacist and/or designated site staff responsible for dispensing the study drug in appropriately labeled, subject-specific kits each containing sealed unit doses. Each ***open-label*** *unit dose* ***for Part A*** *consists of 2 capsules.* ***Blinded unit doses for Part B will consist of 1 capsule each.***

Section also affected by this change:

- Synopsis

Purpose: Updated language regarding reporting serious adverse events.

The primary change occurs in Section 12.2.1.2, Serious Adverse Events (SAE).

Added text: All SAEs that occur after any subject has been enrolled and throughout the duration of the study, whether or not they are related to the study, must be recorded on the SAE form provided by Sage Therapeutics **within 24 hours of first awareness (Section 12.5). All SAEs should to be followed until the event resolved, the condition stabilized, was no longer considered clinically significant or the subject was lost to follow-up.**

Purpose: Adverse Event Language related to pregnancy was edited to align across program protocols.

The primary change occurs in Section 12.4, Recording Adverse Events.

Added text:

Should a pregnancy occur, it must be reported and recorded on the Sage Therapeutics pregnancy notification form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication ***or a complication relating to the pregnancy occurs (eg, spontaneous abortion, which requires reporting as an SAE). All pregnancies occurring during this study are to be reported in the same time frame as SAEs (eg, within 24 hours of the site becoming aware of the pregnancy).***

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented on the Sage Therapeutics pregnancy outcome form even if the subject was discontinued from the study. Reports of congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs.

If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Sage Therapeutics, or designee. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. 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), the Investigator should follow the procedures for reporting an SAE.

Sections also affected by this change:

- Section 12.5, Reprting Serious Adverse Events

A 2-PART STUDY (OPEN-LABEL FOLLOWED BY DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUP) OF THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF SAGE-217 IN THE TREATMENT OF SUBJECTS WITH BIPOLAR I/II DISORDER WITH A CURRENT MAJOR DEPRESSIVE EPISODE

PROTOCOL NUMBER: 217-BPD-201

Study Drug	SAGE-217
Clinical Phase	Phase 2
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted] Tel: [redacted] email: [redacted]
Sponsor Medical Monitor	[redacted] MD, MBA Tel: [redacted] email: [redacted]
Date of Original Protocol	Version 1.0, 03 JUL 2018
Date of Amendment 1	Version 2.0, 13 SEP 2018
Date of Amendment 2	Version 3.0, 18 OCT 2018

Protocol Number:	217-BPD-201
Study Drug:	SAGE-217
Study Phase:	Phase 2
Sponsor:	Sage Therapeutics, Inc.
Protocol Date:	Version 3.0, 18 Oct 2018

Sponsor Approval

[redacted] 18 OCT 2018
[redacted] MD, MBA Date (DD/MMM/YYYY)

[redacted] 18 OCT 2018
[redacted] RA Date (DD/MMM/YYYY)

[redacted] 18 Oct 2018
[redacted] MSHS Date (DD/MMM/YYYY)

[redacted] 18 Oct 2018
[redacted] PhD Date (DD/MMM/YYYY)

[redacted] 18 Oct 2018
[redacted] DVM, MS, MPH Date (DD/MMM/YYYY)
[redacted]

[redacted] 18 Oct 2018
[redacted] PhD Date (DD/MMM/YYYY)
[redacted]

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the 217-BPD-201 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 Month YYYY)

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics

Name of Investigational Product:
SAGE-217 Capsule

Name of Active Ingredient:
SAGE-217

Title of Study:
A 2-Part Study (Open-label followed by Double-blind, Randomized, Placebo-controlled, Parallel Group) of the Safety, Tolerability, Pharmacokinetics, and Efficacy of SAGE-217 in the Treatment of Subjects with Bipolar I/II Disorder with a Current Major Depressive Episode

Number of Sites and Study Location:
Part A: Approximately 10 sites in the United States
Part B: Approximately 40 sites in the United States

Phase of Development: 2

Planned Duration of participation: Up to 73 days (28-day Screening Period; 14-day Treatment Period, and 28-day [±3 days] Follow-up Period)

Objectives:
Part A Primary:

- To evaluate the safety and tolerability of SAGE-217 in subjects with bipolar I or II disorder with a current major depressive episode (MDE).

Part A Secondary:

- To assess the efficacy of SAGE-217 in reducing depressive symptoms in subjects with bipolar I/II disorder with a current MDE.
- To assess the effect of SAGE-217 on sleep.

Part B Primary:

- To assess the efficacy of SAGE-217 in reducing depressive symptoms in subjects with bipolar I/II disorder with a current MDE.

Part B Secondary:

- To evaluate the safety and tolerability of SAGE-217 in subjects with bipolar I/II disorder with a current MDE.
- To assess the effect of SAGE-217 on sleep.

[redacted]

Endpoints:

Part A Primary:

- The safety and tolerability of SAGE-217 as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and electrocardiogram (ECGs); and suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS); and mania using the Young Mania Rating Scale (YMRS).

Part A Secondary:

- The reduction in depressive symptoms, as assessed by:
  - Change from baseline in the 17-item Hamilton Depression Rating Scale (HAM-D) total score at Day 15 and all other time points
  - HAM-D response at Day 15 and all other time points
  - HAM-D remission at Day 15 and all other time points
  - Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Day 15 and all other time points
  - Change from baseline in HAM-D individual item scores at Day 15 and all other time points
  - The response to the Clinical Global Impression scale for severity and improvement (CGI-S and CGI-I, respectively) at Day 15 and all other time points.
- The reduction in insomnia severity, as assessed by Insomnia Severity Index (ISI).

Part B Primary:

- The primary endpoint in Part B is the reduction in depressive symptoms with SAGE-217 treatment, as assessed by the change from baseline in the HAM-D total score at Day 15.

Part B Secondary:

- The reduction in depressive symptoms, as assessed by:
  - Change from baseline in HAM-D total score at all other time points
  - HAM-D response at Day 15 and all other time points
  - HAM-D remission at Day 15 and all other time points
  - Change from baseline in the MADRS total score at Day 15 and all other time points
  - Change from baseline in HAM-D individual item scores at Day 15 and all other time points
  - CGI-S and CGI-I response at Day 15 and all other time points.
- The safety and tolerability of SAGE-217 as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and ECGs; and suicidal ideation and behavior using the C-SSRS; and mania using the YMRS.
- The reduction in insomnia severity, as assessed by ISI.
- [redacted]

Study Description:

This study will be conducted in 2 sequential parts: Part A (open-label) and Part B (randomized, double-blind, placebo-controlled, parallel group). Part B will be initiated pending the review of Part A data. The methods of the 2 parts will be identical unless otherwise noted. Subjects who participate in Part A will not be allowed to participate in Part B. The study is designed to assess the safety, tolerability, [redacted] and efficacy of SAGE-217 in adult subjects with bipolar I/II disorder, who are currently experiencing an MDE.

The assessments are summarized in the Schedule of Events (Table 1).

Screening begins with the signing of the informed consent form at the Screening Visit. The diagnosis of bipolar I or II disorder will be made using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) for clinical trials (SCID-5-CT) performed by a qualified healthcare professional.

Beginning on Day 1, qualified subjects will self-administer the study drug once daily in the evening with food for 14 days. In Part A, all subjects will receive SAGE-217. For Part B, subjects will be randomized in a 1:1 ratio to receive SAGE-217 or placebo; randomization will be stratified based on use of mood stabilizers (Y/N). Subjects on antidepressants or mood stabilizers (lamotrigine, lithium, and valproic acid only) that have been taken at the same dose for at least 60 days prior to Day 1 are to continue the stable dose throughout the treatment period.

If at any time, 30 mg is not tolerated, as assessed by the occurrence of a severe AE judged by the investigator to be related to study drug, the dose on the next day will be reduced to 20 mg and continued for the remainder of the treatment period. Dose adjustments related to moderate AEs will be judged by the Investigator. If a dose adjustment from 30 mg to 20 mg is deemed necessary by the Investigator, the subject will return to the site for the adjusted dose to be dispensed. Subjects who cannot tolerate the 20-mg dose at any time will be discontinued from study drug.

If at any time during the study, a subject has a YMRS score of ≥13, the Investigator will clinically assess the subject for a manic or hypomanic switch. If the clinical assessment is consistent with hypomania or mania, the subject will be discontinued from study drug and treated as clinically appropriate. These incidents will be documented as AEs.

Subjects will return to the study center during the treatment and follow-up periods as outlined in Table 1.

Number of Subjects (planned):

Part A: Approximately 30 subjects will be dosed.

Part B: Approximately 132 subjects will be randomized and dosed to obtain a total of 112 evaluable subjects.

Eligibility criteria:

Inclusion Criteria:

1. Subject has signed an informed consent form (ICF) prior to the conduct of any study-specific procedures.
2. Subject agrees to adhere to the study requirements, including use of prior, concomitant, and prohibited medications.
3. Subject is a man or woman, aged 18 to 65 years, inclusive, at Screening.
4. 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.
5. Subject has a documented history of hypomanic or manic episode (verified by medical records and/or treating healthcare professional) and a diagnosis of bipolar I or bipolar II disorder with a current MDE as per DSM-5 SCID-5-CT.
6. Subject has a HAM-D score of ≥22 at Screening.
7. Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are 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 or bilateral oophorectomy), or in sexual relationship(s) which do not carry a risk of pregnancy (eg, same-sex relationship(s)):
   - 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 ligation/occlusion.
   - Vasectomized partner.
   - Sexual abstinence (no sexual intercourse).
8. 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 is in sexual relationship(s) which do not carry a risk of pregnancy (eg, same-sex relationship(s)). Acceptable methods of effective contraception for males includes sexual abstinence, 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 #7 for acceptable method of contraception for females).
9. 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.

Exclusion Criteria:

1. Subject has a history of suicide attempt within the last 2 years.

2. Subject has current suicidal ideation with plans based on Investigator clinical assessment and/or the C-SSRS response at Screening or Day 1.
3. Subject has a history of rapid cycling bipolar disorder as per DSM-5 SCID-5-CT.
4. Subject's current depressive episode meets the DSM-5 specifier criteria for mixed features.
5. Subject has ≥25% reduction in HAM-D score from Screening to Day 1.
6. 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.
7. Subject has abnormal liver function as shown by an abnormal liver function profile at screening (eg, repeated values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥2x the upper limit of normal).
8. Subject has a clinically significant abnormal 12-lead ECG at the Screening or Day 1 visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in male or >470 msec in female subjects will be the basis for exclusion from the study.
9. Subject has a YMRS score ≥13 at Screening or Day 1.
10. Subject presents for the study receiving a mood stabilizer other than lamotrigine, lithium, or valproic acid.
11. Subject presents for the study receiving antidepressants and mood stabilizers, which have not been taken at the same dose for at least 60 days prior to Day 1.
12. Subject that presents for the study receiving psychotropic medications and does not intend to continue the current treatment regimen during the treatment period.
13. Subject is taking benzodiazepines or $GABA_A$ modulators/GABA-containing agents (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28.
14. Subject has a history of severe rashes or Stevens-Johnson Syndrome associated with lamotrigine and is currently taking lamotrigine.
15. Subject's current depressive episode is treatment resistant; defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants from two different classes for an adequate amount of time (ie, at least 4 weeks of treatment). This will be assessed using the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.
16. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
17. Subject has a positive pregnancy test at the Screening Visit or on Day 1 (prior to administration of study drug) or, if she is breastfeeding at Screening or on Day 1 (prior to administration of study drug), she does not agree to temporarily cease giving breast milk to her child(ren) from just prior to receiving study drug on Day 1 until 7 days after the last dose of study drug.

18. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and HCV viral load, or human immunodeficiency virus (HIV) antibody at screening.
19. Subject has active psychosis per Investigator assessment.
20. Subject has a medical history of seizures.
21. Subject has a medical history schizophrenia, and/or schizoaffective disorder.
22. Subject has a history of mild, moderate, or severe substance use disorder diagnosed using DSM-5 criteria in the 12 months prior to screening.
23. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
24. Subject has had exposure to another investigational medication or device within 30 days prior to the Screening visit.
25. Subject has been previously treated or randomized in any study using SAGE-217. Subjects who participate in Part A are not eligible to participate in Part B.
26. Subject has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to receiving the first dose of study drug.
27. Subject has used CYP inducers, such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort, within 28 days prior to the first dose of study drug.
28. Subject plans to undergo elective surgery during participation in the study.
29. Subject is taking non-GABA anti-insomnia medications (eg, melatonin, Benadryl [anti-histamines], trazodone, low-dose quetiapine, mirtazapine, etc) at Day -14 .

SAGE-217 dosage and mode of administration:

SAGE-217 is available as hard gelatin capsules containing a white to off-white powder. In addition to SAGE-217 Drug Substance, the 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. Subjects will take the assigned dose orally once daily in the evening with food.

Reference therapy, dosage and mode of administration (Part B only):

In Part B, placebo capsules are visually matched to the active capsules and are available as hard gelatin capsules containing only the excipients listed above for the active capsule treatment. Study drug will be administered orally once daily in the evening with food.

Duration of Treatment: 14 days

Statistical methods:

A separate statistical analysis plan (SAP) for each part (Parts A and B) will provide a detailed description of the analyses to be performed in the respective part of the study. The SAPs 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.

General:

The data from Parts A and B will be analyzed separately. For the purpose of all safety and efficacy analyses where applicable, baseline is defined as the last available measurement prior to the start of study drug administration.

Continuous endpoints will be summarized with 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:

Randomized set (Part B only) will be defined as all subjects who are randomized. This analysis set will be used of all data listings in Part B. Data listings for Part A will be based on Safety or Efficacy Set, as appropriate.

The Safety Set, defined as all subjects received at least 1 dose of study drug, will be used to provide descriptive summaries of safety data.

The Efficacy Set, defined as all subjects who are in Safety Set and have at least one post-baseline HAM-D evaluation, will be used to analyze efficacy data unless otherwise specified.

[redacted]

Safety Analysis:

The overall incidence of adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Data for vital signs, clinical laboratory measurements, ECG, and concomitant medication usage will also be summarized.

Safety data will be summarized and examined for possible relationships between subject characteristics and plasma SAGE-217 concentrations, as appropriate. Suicidality data collected using the C-SSRS and evaluation of mania collected using the YMRS at baseline and at each visit during the active Treatment Period will be listed for all subjects. Out-of-range safety endpoints may be categorized as low or high, where applicable. Subjects will be summarized according to treatment received for the purpose of safety.

Efficacy Analysis:

The primary endpoint in Part B, the change from baseline in HAM-D total score, will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include treatment, baseline HAM-D total score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be considered as fixed effects and the subject effect will be considered random in the model. All post-baseline time points will be included in the model. The primary comparison will be between SAGE-217 and matching placebo at Day 15. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported. An unstructured covariance structure will be used to model the within-subject errors. Other continuous endpoints will be analyzed using similar methods.

Other efficacy analyses, including those in Part A, will be specified in the SAP. In general, data will be analyzed using appropriate descriptive statistics or pre-specified statistical methods as applicable;

subject listings will be provided for all efficacy data. Subjects will be analyzed according to randomized treatment for the purpose of efficacy unless otherwise specified.

[redacted]

Sample Size Calculation

Part A: The sample size of approximately 30 subjects was selected based on clinical and not statistical considerations.

Part B: Assuming a two-sided alpha level of 0.05, a sample size of 112 total evaluable subjects (56 per treatment group) would provide 80% power to detect a placebo-adjusted treatment difference of approximately 4 points in the primary endpoint, change from baseline in HAM-D total score at Day 15, assuming standard deviation (SD) of 7.5 points.

Assuming a 15% dropout rate, approximately 132 total randomized subjects will be required to obtain a total of 112 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have a valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the drop-out rate is higher than 15%.

Table 1: Schedule of Events

Study Period	**Screening Period**	**Treatment Period**					**Follow-up Period[a]**			
Visit Day	**D-28 to D-1**	**D1**	**D3 (+1d)**	**D8 (±1d)**	**D12 (±1d)**	**D15 (±1d)/EOT[a]**	**D21 (±3d)**	**D28 (±3d)**	**D35 (±3d)**	**D42 (±3d)/ ET**
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Study Procedure										
Informed Consent	X									
Inclusion/Exclusion	X	X								
Demographics	X									
Medical/Family History	X									
SCID-5-CT	X									
MGH-ATRQ	X									
Serum FSH test	X									
Randomization (Part B only)		X								
Physical Examination	X	X				X				X
Body Weight/Height[c]	X					X (wt only)				X (wt only)
Clinical Laboratory Assessments[d]	X	X		X		X	X	X		X
Drug & Alcohol Screen[e]	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[f]	X	X				X		X		X
Hepatitis & HIV Screen	X									
[redacted]										
Vital Signs[i]	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[j]	X	X	X			X				X
C-SSRS[k]	X	X	X	X	X	X	X	X	X	X
HAM-D[l]	X	X	X	X	X	X	X	X	X	X
MADRS[l]		X	X	X	X	X	X	X	X	X
CGI-S		X	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X	X	X
YMRS[l]	X	X	X	X	X	X	X	X	X	X
[redacted]										
ISI		X		X		X	X	X		X

Study Period	**Screening Period**	**Treatment Period**					**Follow-up Period[a]**			
Visit Day	**D-28 to D-1**	**D1**	**D3 (+1d)**	**D8 (±1d)**	**D12 (±1d)**	**D15 (±1d)/EOT[a]**	**D21 (±3d)**	**D28 (±3d)**	**D35 (±3d)**	**D42 (±3d)/ ET**
[redacted]										
Study Drug Dispensation[o]		X		X						
Study Drug Administration		X (Day 1-14)								
Study Drug Accountability/Return			X	X	X	X				
Adverse Events/Serious Adverse Events[p]	X									
Prior/Concomitant Medications/ Procedures[q]	X									

CGI-I = Clinical Global Impression - Improvement; CGI-S – Clinical Global Impression - Severity; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; EOT = end of treatment; ECG = electrocardiogram; ET = early termination; [redacted] FSH = follicle stimulating hormone; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; ISI = Insomnia Severity Index; MADRS = Montgomery-Åsberg Depression Rating Scale; MGH-ATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; O = optional; [redacted] SCID-5-CT = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition for clinical trials; [redacted] YMRS = Young Mania Rating Scale

[a] Subjects who discontinue treatment early should return to the site for an EOT visit as soon as possible, preferably the day after treatment is discontinued. Follow-up visits should take place every 7 days after the last dose of treatment for a total of 4 follow-up visits. If at any time after the EOT visit, a subject decides to terminate the study, the subject should return for an ET visit. The EOT 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 both visits will be conducted.

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

[c] Height measured at screening only

[d] Safety laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis. Laboratory assessments are to be completed in the morning.

[e] Urine toxicology for selected drugs of abuse, and breath test for alcohol (as per the standard procedures at each site).

[f] For women of child-bearing potential, serum pregnancy test at screening and urine pregnancy test at all other scheduled timepoints.

[redacted]

[i] Vital signs include oral temperature (°C), respiratory rate, heart rate, pulse oximetry, 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 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.

[j] Triplicate 12-lead ECGs will be performed with the subject in the supine position. When ECG [redacted] sample collection occur during the same visit, ECGs will be collected first.

[k] The "Baseline/Screening" C-SSRS form will be completed at screening. The "Since Last Visit" C-SSRS form will be completed at any time of day at all subsequent time points.

[l] For MADRS, HAM-D, and YMRS, the "Since Last Evaluation" forms will be completed at all subsequent time points following the initial assessment.

[redacted]

[o] Additional unscheduled dispensation visits may be needed for dose reductions.
[p] AEs/SAEs will be collected starting at the time of informed consent and throughout the duration of the subject's participation in the study.
[q] Prior medications will be collected at Screening and concomitant medications will be collected at each subsequent visit. All medications taken within 30 days prior to Screening through the duration of the study will be recorded. In addition, all psychotropic medications taken within 6 months prior to Screening will be recorded.

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

LIST OF TABLES

LIST OF FIGURES

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
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CGI-I	Clinical Global Impression scale for improvement
CGI-S	Clinical Global Impression scale for severity
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
ET	early termination
[redacted]	[redacted]
FSH	follicle-stimulating hormone
GABA	γ-aminobutyric acid
HAM-D	Hamilton Depression Rating Scale
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ID	identification
IRT	interactive response technology
ISI	Insomnia Severity Index
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MDE	major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
MGH-ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire

Table 2: Abbreviations and specialist terms (Continued)

Abbreviation or specialist term	Explanation
MMRM	mixed effects model for repeated measures
PI	Principal Investigator; the investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
[redacted]	[redacted]
QTcF	QT corrected according to Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SCID-5-CT	Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition for clinical trials
SD	standard deviation
[redacted]	[redacted]
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
YMRS	Young Mania Rating Scale

5. INTRODUCTION

5.1. Background of Bipolar Disorders and Unmet Medical Need

Bipolar disorder is a chronic and episodic illness that is associated with significant disability worldwide (Sachs 2007). The Global Burden of Disease Study revealed that in 2013, there were 48.8 million cases of bipolar disorder globally (Ferrari 2016). Bipolar disorder accounted for 9.9 million disability-adjusted life years (DALYs) globally, explaining 0.4% of total DALYs and 1.3% of total years lived with disability.

There are subtypes of bipolar disorder; this study includes the bipolar I and II subtypes. Bipolar I is characterized by a manic episode, whereas bipolar II is characterized by a hypomanic episode. The difference in the severity of the manic features relies on functional impairment that is caused by these episodes (DSM-5). The National Comorbidity Survey estimate of the lifetime prevalence of bipolar disorder is 2.1% in the US population when bipolar I disorder and bipolar II Disorder are combined (Merikangas 2007).

While the manic or hypomanic episodes represent distinct departure from the baseline mood state and easily attract attention, evidence suggests that depressive episodes of both bipolar I and II are associated with more disability than any other aspect of the illness. A seminal long-term study of patients with bipolar I disorder demonstrated that over the 13-year follow-up period, patients were symptomatic about 47% of the time, and depressive symptoms were present in 32% of the follow-up weeks vs manic features, which were present in 9% (Judd 2002). A similar analysis in patients with bipolar II disorder with a longer follow up of up to 20 years found that patients were symptomatic more than half of the time (54%) where depressive symptoms dominated the course at 50% of the follow-up weeks versus 1.3% for the hypomanic symptoms (Judd 2003). A study in patients with unipolar depression found a prevalence of depressive symptoms 47% of the time (Judd 1998), suggesting a comparable time spent with depressive symptoms in the bipolar spectrum. These naturalistic studies have also found that about half the time patients reported taking psychotropic medications. In another large-scale study with a follow-up period of up to 2 years, 58% of nearly 1500 patients with bipolar disorder who were symptomatic at study entry achieved recovery (Perlis 2006). Similarly, during the follow-up period, 49% of these individuals experienced recurrent episodes, where depressive episodes (38%) outweighed manic, hypomanic, or mixed episodes combined (13.8%). In the Stanley Foundation Bipolar Network Study, in which year-long, daily clinician ratings were included, despite treatment with an average of 4.1 psychotropic medications, patients with bipolar disorder spent 3 times as much time with depressive symptoms as manic symptoms (Post 2003).

There are only 3 medications approved in the US for the treatment of bipolar depression, (lurasidone, olanzapine-fluoxetine combination, and quetiapine), all of which include atypical antipsychotics that are associated with significant adverse metabolic effects. None of the currently available antidepressants are indicated for bipolar depression due to their limited efficacy, and the possibility that their use may be associated with a manic switch and rapid cycling. While some studies reported varying levels of efficacy with antidepressants (Gijsman 2004), a large-scale, double-blind, placebo-controlled clinical trial sponsored by the National Institutes of Mental Health, The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), found that only 23.5% of patients with bipolar depression receiving a mood stabilizer and adjunctive antidepressants versus 27.3% of those receiving a

mood stabilizer and placebo experienced a durable recovery, confirming the lack of effectiveness of antidepressants in bipolar depression (Sachs 2007). The tolerability profile of the approved atypical antipsychotics and limited efficacy of available antidepressants highlight the critical unmet need in the treatment of bipolar depression.

In 1998, the lifetime cost of bipolar disorder in the US was estimated at $24 billion. The cost of a single manic episode was estimated at $11,720 to $624,785 for persons with nonresponsive/chronic episodes (Begley 1998); the cost of bipolar depression specifically, is less well studied, however, available estimates indicate a higher cost associated with bipolar depression than for mania (Bowden 2004).

Kessler has studied the impact of mood disorders on work performance in a representative sample of over 3,000 US workers (Kessler 2006). Bipolar disorder and major depressive disorder were associated with 65.5 and 27.2 lost workdays per worker per year, respectively. Moreover, it was found that the increase in bipolar disorder was attributable to depressive symptoms rather than manic episodes in bipolar disorder.

Taken together, these findings point to substantial predominance of depressive symptoms across the spectrum of bipolar disorder. In particular, they also highlight the importance of successful depressive symptom control, and an unmet need in the treatment of depressive episodes for both bipolar I and bipolar II disorder.

5.2. SAGE-217

SAGE-217 is a positive allosteric modulator of γ-aminobutyric acid $(GABA)_A$ 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 portion of the Phase 2a study of SAGE-217 administered to subjects with moderate to severe major depressive disorder (MDD) showed clinically significant improvements from baseline in depression scale scores (HAM-D, Montgomery-Åsberg Depression Rating Scale [MADRS], 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 (N=89) in which a rapid and substantial decrease in HAM-D scores was observed at Day 15 (primary endpoint), starting at Day 2. This response pattern was also observed with other efficacy scales, including MADRS and CGI-I. Statistically significant differences from the placebo group favoring the SAGE-217 arm were observed for 2 weeks in the follow-up period.

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 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.

5.3. 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 2 study of SAGE-217 in subjects with MDD and the current significant unmet need in the treatment of depressive episodes associated with bipolar I/II disorders, a favorable risk-benefit balance and investigation of SAGE-217 in patients with bipolar I/II disorders are justified.

5.4. Dose Justification

The dose of SAGE-217 to be administered in this study (30 mg) was determined based on the maximum tolerated dose in the multiple ascending dose study of SAGE-217 in healthy subjects, and is the same dose level that has been used and generally well tolerated in clinical studies in various patient populations, including patients with MDD. Due to the observed improved tolerability of sedation/somnolence effects when taken in the evening in previous clinical studies, SAGE-217 will be administered in the evening in this study as well.

With respect to the duration of treatment course, a 14-day study drug administration is planned. This is based on previous clinical trial data with SAGE-217, demonstrating substantial improvement in depressive symptoms in patients with MDD, starting within the first week of treatment.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Study Objective

6.1.1. Primary Objective

Part A

The primary objective of Part A of this study is to evaluate the safety and tolerability of SAGE-217 in subjects with bipolar I/II disorder with a current major depressive episode (MDE).

Part B

The primary objective of Part B of this study is to assess the efficacy of SAGE-217 in reducing depressive symptoms in subjects with bipolar I/II disorder with a current MDE.

6.1.2. Secondary Objectives

Part A

Secondary objectives of Part A of this study are:

- To assess the efficacy of SAGE-217 in reducing depressive symptoms in subjects with bipolar I/II disorder with a current MDE.
- To assess the effect of SAGE-217 on sleep.

Part B

Secondary objectives of Part B of this study are:

- To evaluate the safety and tolerability of SAGE-217 in subjects with bipolar I/II disorder with a current MDE.
- To assess the effect of SAGE-217 on sleep.

6.2. Endpoints

6.2.1. Primary Endpoint

Part A

The primary endpoint for Part A of this study is the safety and tolerability of SAGE-217, as assessed by the frequency and severity of adverse events (AEs); changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs); suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS); and mania using the Young Mania Rating Scale (YMRS).

Part B

The primary endpoint of Part B of this study is the reduction in depressive symptoms with SAGE-217 treatment, as assessed by the change from baseline in the 17-item HAM-D total score at Day 15.

6.2.2. Secondary Endpoints

Part A

Secondary endpoints of Part A of this study are:

- The reduction in depressive symptoms, as assessed by:
  - Change from baseline in the 17-item HAM-D total score at Day 15 and all other time points
  - HAM-D response at Day 15 and all other time points
  - HAM-D remission at Day 15 and all other time points
  - Change from baseline in the MADRS total score at Day 15 and all other time points
  - Change from baseline in HAM-D individual item scores at Day 15 and all other time points
  - The response to the CGI-S and CGI-I at Day 15 and all other time points.
- The reduction in insomnia severity as assessed by the Insomnia Severity Index (ISI).

Part B

Secondary endpoints of Part B of this study are:

- The reduction in depressive symptoms, as assessed by:
  - Change from baseline in total HAM-D score at all other time points
  - HAM-D response at Day 15 and all other time points
  - HAM-D remission at Day 15 and all other time points

  - Change from baseline in the MADRS total score at Day 15 and all other time points
  - Change from baseline in HAM-D individual item scores at Day 15 and all other time points
  - CGI-S and CGI-I response at Day 15 and all other time points.
- The safety and tolerability of SAGE-217 as assessed by the frequency and severity of AEs; changes from baseline in clinical laboratory measures, vital signs, and ECGs; and suicidal ideation and behavior using the C-SSRS, and the YMRS.
- The reduction in insomnia severity, as assessed by the ISI.

[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This study will be conducted in 2 sequential parts: Part A (open-label) and Part B (randomized, double-blind, placebo-controlled, parallel group). Part B will be initiated pending the review of Part A data.The methods of the 2 parts will be identical unless otherwise noted. The study is designed to assess the safety, tolerability, [redacted] and efficacy of SAGE-217 in adult subjects with bipolar I/II disorder, who are currently experiencing an MDE.

Screening begins with the signing of the informed consent form (ICF) at the Screening Visit. The diagnosis of bipolar I or II disorder will be made using the Structured Clinical Interview for DSM-5 for clinical trials (SCID-5-CT) performed by a qualified healthcare professional. Subjects on antidepressants or mood stabilizers (lamotrigine, lithium, and valproic acid only) that have been taken at the same dose for at least 60 days prior to Day 1 are to continue the stable dose throughout the treatment period.

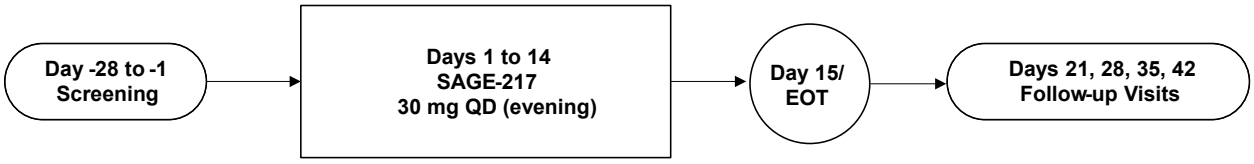
Subjects will return to the study center during the treatment and follow-up periods as outlined in the Schedule of Events (Table 1). All assessments to be performed are summarized in Table 1.

If at any time during the study, a subject has a YMRS score of ≥13, the Investigator will clinically assess the subject for a manic or hypomanic switch. If the clinical assessment is consistent with hypomania or mania, the subject will be discontinued from study drug and treated as clinically appropriate (see Section 8.3).

Part A

The study design for Part A is presented in Figure 1. In Part A, all subjects will receive SAGE-217. Beginning on Day 1, qualified subjects will self-administer 30-mg SAGE-217 once daily in the evening with food for 14 days. Dose adjustments based on study drug tolerability are permitted following the guidelines outlined in Section 7.4.

Figure 1: Study Design (Part A)



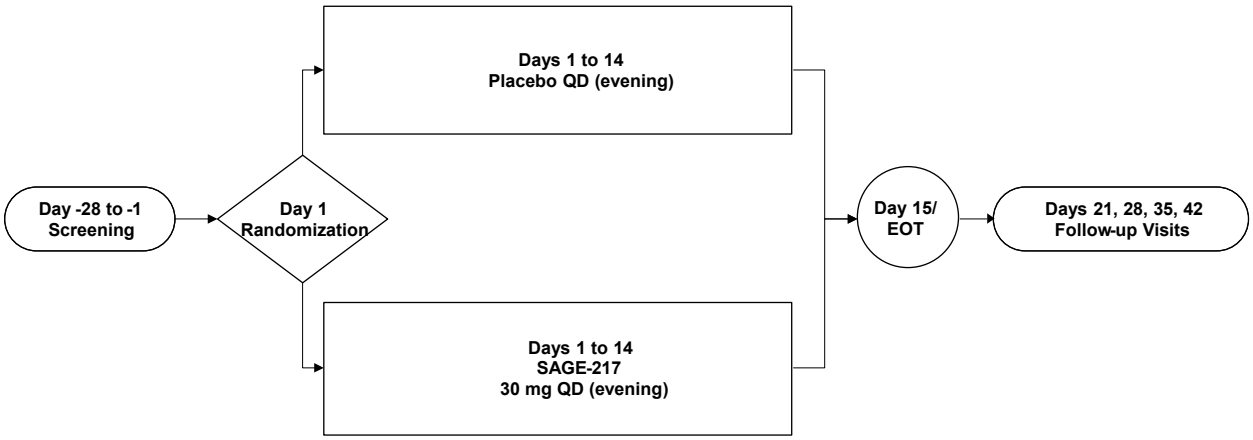
QD = once daily
A dose adjustment to 20-mg SAGE-217 is permitted if the 30-mg dose is not tolerated at any time.

Part B

The study design for Part B is presented in Figure 2. In Part B, subjects will be randomized in a 1:1 ratio to receive SAGE-217 or placebo; randomization will be stratified based on use of mood stabilizers (Y/N). Beginning on Day 1, qualified subjects will self-administer the study drug

(30 mg SAGE-217 or placebo) once daily in the evening with food for 14 days. Dose adjustments based on study drug tolerability are permitted following the guidelines outlined in Section 7.4.

Figure 2: Study Design (Part B)



QD = once daily
A dose adjustment to 20-mg SAGE-217 is permitted if the 30-mg dose is not tolerated at any time.

7.2. Number of Subjects

Part A

Approximately 30 subjects will be dosed in Part A.

Part B

After review of Part A data, approximately 132 subjects will be randomized and dosed in Part B to obtain a total of 112 evaluable subjects (see Section 13.8).

7.3. Treatment Assignment

Part A

In Part A, all subjects will receive SAGE-217 in an open-label manner.

Part B

In Part B, subjects will be randomized to a treatment group (SAGE-217 or placebo) in a 1:1 ratio; randomization will be stratified based on use of mood stabilizers (Y/N).

7.4. Dose Adjustment Criteria

If at any time, 30 mg is not tolerated, as assessed by the occurrence of a severe AE judged by the investigator to be related to study drug, the dose on the next day will be reduced to 20 mg and continued for the remainder of the treatment period. Dose adjustments related to moderate AEs will be judged by the Investigator. If a dose adjustment from 30 mg to 20 mg is deemed

necessary by the Investigator, the subject will return to the site for the adjusted dose to be dispensed. Subjects who cannot tolerate the 20-mg dose at any time will be discontinued from study drug (see Section 8.3).

7.5. Study Termination

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of 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 the conduct of any study-specific procedures.
2. Subject agrees to adhere to the study requirements, including use of prior, concomitant, and prohibited medications.
3. Subject is a man or woman, aged 18 to 65 years, inclusive, at Screening.
4. 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.
5. Subject has a documented history of hypomanic or manic episode (verified by medical records and/or treating healthcare professional) and a diagnosis of bipolar I or bipolar II disorder with a current MDE as per DSM-5 SCID-5-CT.
6. Subject has a HAM-D score of ≥22 at Screening.
7. Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are 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 or bilateral oophorectomy), or in sexual relationship(s) which do not carry a risk of pregnancy (eg, same-sex relationship(s)):
   - 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 ligation/occlusion.
   - Vasectomized partner.
   - Sexual abstinence (no sexual intercourse).
8. 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 is in sexual relationship(s) which do not carry a risk of pregnancy (eg, same-sex relationship(s)). Acceptable methods of effective contraception for males includes sexual abstinence, 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 #7 for acceptable method of contraception for females).

9. 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.

8.2. Subject Exclusion Criteria

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

1. Subject has a history of suicide attempt within the last 2 years.
2. Subject has current suicidal ideation with plans based on Investigator clinical assessment and/or the C-SSRS response at Screening or Day 1.
3. Subject has a history of rapid cycling bipolar disorder as per DSM-5 SCID-5-CT.
4. Subject's current depressive episode meets the DSM-5 specifier criteria for mixed features.
5. Subject has ≥25% reduction in HAM-D score from Screening to Day 1.
6. 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.
7. Subject has abnormal liver function as shown by an abnormal liver function profile at screening (eg, repeated values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥2x the upper limit of normal).
8. Subject has a clinically significant abnormal 12-lead ECG at the Screening or Day 1 visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in male or >470 msec in female subjects will be the basis for exclusion from the study.
9. Subject has a YMRS score ≥13 at Screening or Day 1.
10. Subject presents for the study receiving a mood stabilizer other than lamotrigine, lithium, or valproic acid.
11. Subject presents for the study receiving psychotropic medications, which have not been taken at the same dose for at least 60 days prior to Day 1.
12. Subject that presents for the study receiving psychotropic medications and does not intend to continue the current treatment regimen during the treatment period.
13. Subject is taking benzodiazepines or $GABA_A$ modulators/GABA-containing agents (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28.
14. Subject has a history of severe rashes or Stevens-Johnson Syndrome associated with lamotrigine and is currently taking lamotrigine.
15. Subject's current depressive episode is treatment resistant; defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants from two different classes for an adequate amount of time (ie, at least 4 weeks of treatment). This

will be assessed using the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.

16. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
17. Subject has a positive pregnancy test at the Screening Visit or on Day 1 (prior to administration of study drug) or, if she is breastfeeding at Screening or on Day 1 (prior to administration of study drug), she does not agree to temporarily cease giving breast milk to her child(ren) from just prior to receiving study drug on Day 1 until 7 days after the last dose of study drug.
18. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and HCV viral load, or human immunodeficiency virus (HIV) antibody at screening.
19. Subject has active psychosis per Investigator assessment.
20. Subject has a medical history of seizures.
21. Subject has a medical history schizophrenia, and/or schizoaffective disorder.
22. Subject has a history of mild, moderate, or severe substance use disorder diagnosed using DSM-5 criteria in the 12 months prior to screening.
23. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
24. Subject has had exposure to another investigational medication or device within 30 days prior to the Screening visit.
25. Subject has been previously treated or randomized in any study using SAGE-217. Subjects who participate in Part A are not eligible to participate in Part B.
26. Subject has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to receiving the first dose of study drug.
27. Subject has used CYP inducers, such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort, within 28 days prior to the first dose of study drug.
28. Subject plans to undergo elective surgery during participation in the study.
29. Subject is taking non-GABA anti-insomnia medications (eg, melatonin, Benadryl [anti-histamines], trazodone, low dose quetiapine, mirtazapine, etc) at Day -14.

8.3. Subject Withdrawal Criteria

8.3.1. Withdrawal from the Study or Discontinuation of Study Drug

Subjects may discontinue study drug or withdraw from the study at any time for any reason. The Investigator may discontinue the subject from the study or study drug 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

In addition, if at any time during the study, a subject has a YMRS score of ≥13, the Investigator will clinically assess the subject for a manic or hypomanic switch. If the clinical assessment is consistent with hypomania or mania, the subject will be discontinued from study drug and treated as clinically appropriate. These incidents will be documented as AEs.

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has discontinued or been withdrawn for any reason.

Subjects who discontinue study drug early/withdraw during the treatment period should, if possible, have an end of treatment (EOT) visit, including the EOT assessments as summarized in the Schedule of Events (Table 1). The EOT visit should be scheduled as soon as possible, preferably the day after the subject's last dose. All details of the EOT visit should be recorded in the subject's medical source documents. For subjects that discontinue study drug early, follow-up visits should take place every 7 days for 28 days. If at any time after the EOT visit, a subject decides to terminate the study early, the subject should return for an early termination (ET) visit. The EOT 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 both visits will be conducted only once.

If the subject fails or refuses to return to the study center, an attempt must be made to contact the subject by telephone in order to assess as many safety and efficacy parameters as possible. All data collected over the telephone must be documented and kept in the subject's record. A subject will be deemed lost to follow-up after 3 attempts at contact have been made and it has been at least 1 month since the last subject contact. The third attempt at contact must be a certified letter accompanied by a survey inquiring the reason for study discontinuation. All attempts at contact will be documented.

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.

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.

8.3.2. Replacement of Subjects

Part A

In Part A, subjects will not be replaced.

Part B

In Part B, subjects will not be replaced. Additional subjects may be randomized if the drop-out rate is higher than anticipated (see Section 13.8).

9. TREATMENT OF SUBJECTS

9.1. Study Drug

Subjects will self-administer study drug orally once daily in the evening with food for 14 days as outlined in Section 7.1. Practical options include taking within 1 hour of dinner, or taking later in the evening with solid food.

9.2. Prior Medications, Concomitant Medications, and Restrictions

9.2.1. Prior and Concomitant Medications and/or Supplements

The start and end dates, route of administration, 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 drugs taken within 6 months prior to Screening will be recorded.

Any concomitant medication determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study under the guidance outlined in these sections.

Antidepressants and mood stabilizers (lamotrigine, lithium, and valproic acid only) 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 throughout the treatment period.

Medications intended for contraception are permitted for female subjects (see Section 8.1):

- 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

9.2.2. Prohibited Medications

The following specific classes of medications are prohibited at any time during the treatment period:

- Initiation of new psychotropic medications at any time during the study
- Initiation of new antidepressant therapy from 60 days prior to Day 1 through the duration of the study
- Use of any benzodiazepines, $GABA_A$ modulators, $GABA_A$-like acting drugs, or GABA-containing agents from Day -28 through the duration of the study
- Use of any non-GABA anti-insomnia medications (eg, melatonin, Benadryl [anti-histamines], trazodone, low dose quetiapine, mirtazapine, etc) from Day -14 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
- Any known strong inhibitors of CYP3A4 from Day -28 or 5 half-lives prior to Day 1 (whichever is longer) through the duration of the study
- Use of any CYP inducer, such as such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort from Day -28 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 drugs of abuse and alcohol 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 1 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.

9.3. Treatment Adherence

SAGE-217 (Parts A and B) or placebo (Part B only) will be self-administered by subjects once every evening with food. Sites will dispense study drug to the subjects to take at home with instructions for use (Section 10.4).

Administration of study drug will be monitored by a medication adherence monitoring platform used on smartphones to visually confirm medication ingestion. Subjects will receive a reminder within a predefined time window to take study drug while using the application. Subjects will follow a series of prescribed steps in front of the front-facing webcam to visually confirm their ingestion of the medication. The application will record the date and time of study drug administration by dose level, as well as missed doses.

In addition, the subject will be instructed to bring their dosing kit to each visit during the treatment period, at which time the Investigator or designee will be responsible for ensuring the kit contains sufficient doses until the next scheduled dispensation.

If the subject is persistently noncompliant with the study drug, the Investigator should discuss with Sage Therapeutics the potential discontinuation of the subject (Section 8.3). Dosing requirements will be reviewed with each subject during all study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.4. Randomization and Blinding

Part A

Part A is an open-label design in which all subjects will receive SAGE-217.

Part B

Part B is a randomized, double-blind, placebo-controlled, parallel group design. Subjects who meet the entrance criteria will be stratified based on use of mood stabilizers (Y/N) and randomly assigned within each stratum in a 1:1 ratio to receive SAGE-217 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 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.

During the study, the blind is to be broken only if the safety of a subject is at risk and the treatment plan is dependent on the study treatment received. See Section 12.6 for details of unblinding in the event of a medical emergency or pregnancy.

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.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Description of 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 10-mg, 20-mg, and 30-mg strengths to achieve the target dose of 20 mg or 30 mg.

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

10.2. Study Drug Packaging and Labeling

SAGE-217 and matched placebo will be provided to the clinic pharmacist and/or designated site staff responsible for dispensing the study drug in appropriately labeled, subject-specific kits each containing sealed unit doses. Part A is open-label and Part B is blinded. 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 Code of Federal Regulations and Good Manufacturing Practices/Good Clinical Practices guidelines will be prepared by the clinical research organization.

10.3. Study Drug Storage

SAGE-217 and matched placebo are to be stored at room temperature, safely and separately from other drugs.

10.4. Study Drug Preparation

Not applicable.

10.5. Study Drug Administration

SAGE-217 is to be administered orally in the evening with food. Practical options include taking within 1 hour of dinner, or taking later in the evening with solid food.

10.6. Study Drug Accountability

Upon receipt of study drug, the Investigator(s), or the responsible pharmacist or designee, will inspect the study drug and complete 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.

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. In the event of an unscheduled dose reduction (Section 7.4), a new subject-specific kit will be dispensed.

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 medication 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 within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

10.7. Study Drug Handling and Disposal

At the end of the study, all used and unused study drug will be reconciled and returned to Sage Therapeutics 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.

11. ASSESSMENT OF EFFICACY [redacted]

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

11.1. Efficacy Assessments

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

The primary outcome measure is the change from baseline in the 17-item HAM-D total score at Day 15.

The 17-item HAM-D will be used to rate the severity of depression in subjects who are identified as experiencing an MDE (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.

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

In addition to the primary efficacy endpoint of change from baseline in HAM-D total score, several secondary efficacy endpoints will be derived for the HAM-D. Hamilton Rating Scale for Depression subscale scores will be calculated as the sum of the items comprising each subscale. Hamilton Rating Scale for Depression response will be defined as having a 50% or greater reduction from baseline in HAM-D total score. Hamilton Rating Scale for Depression remission will be defined as having a HAM-D total score of ≤7.

The HAM-D subject interview may be audio-recorded for independent quality control purposes.

11.1.2. Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a 10-item diagnostic questionnaire used to measure the severity of depressive episodes in subjects with mood disorders. It was designed as an adjunct to the HAM-D that 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 will be calculated as the sum of the ten individual item scores.

The MADRS subject interview may be audio-recorded for independent quality control purposes.

11.1.3. Clinical Global Impression (CGI)

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.

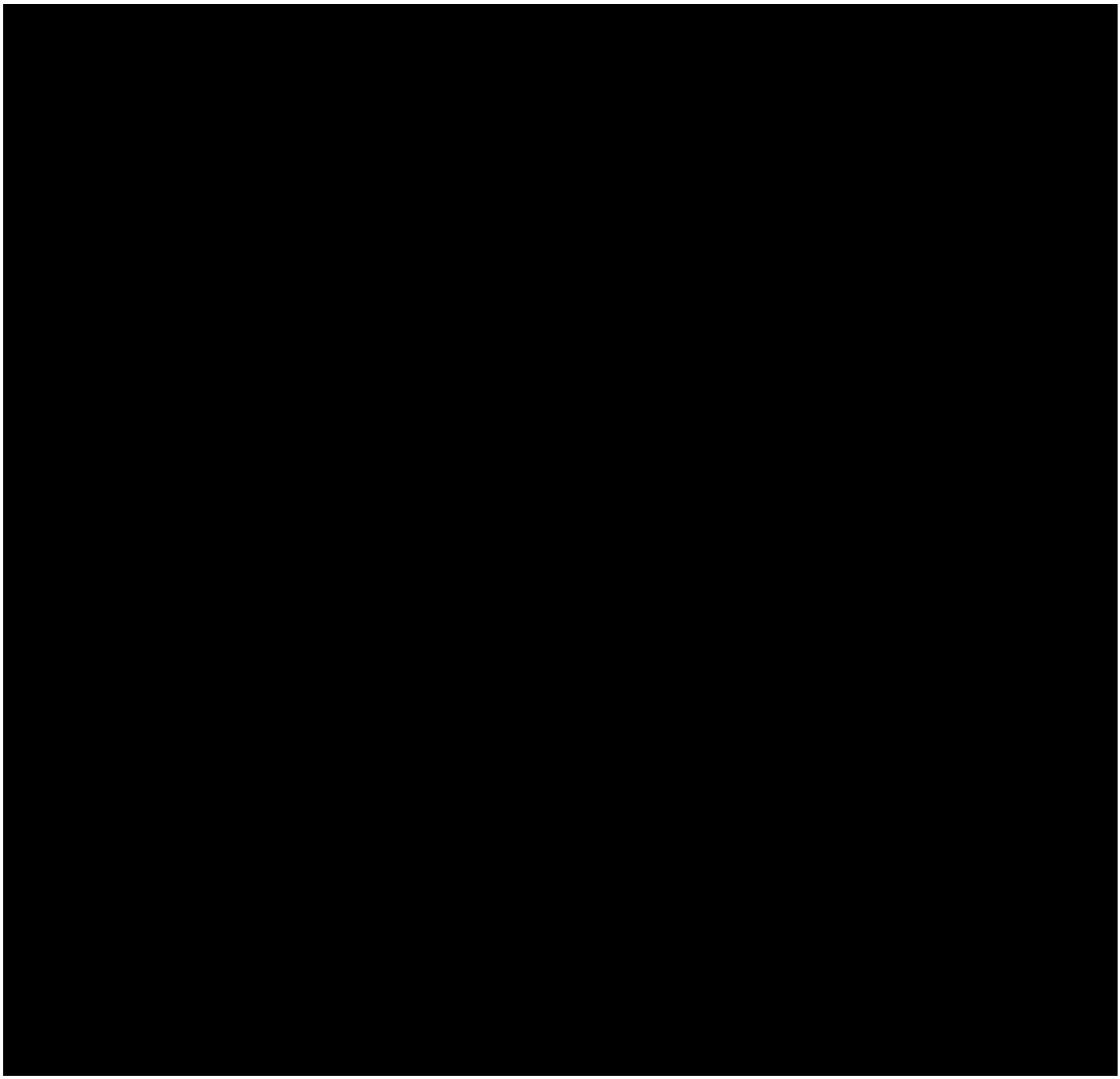
The Clinical Global Impression - Severity (CGI-S) uses a 7-point Likert scale to rate the severity of the subject's illness at the time of assessment, relative to the clinician's past experience with

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).

The Clinical Global Impression - Improvement (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."

11.1.4. Insomnia Severity Index (ISI)

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 (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)."



12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

The safety and tolerability of SAGE-217 will be assessed by the frequency and severity of AEs; changes from baseline in clinical laboratory measures, vital signs, and ECGs; suicidal ideation and behavior using the C-SSRS; and the YMRS. All assessments will be conducted according to the schedule of assessments (Table 1).

12.1.1. Demographic/Medical History

Demographic and baseline characteristics (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and a full medical history, including family psychiatric history, will be documented. The diagnosis of bipolar I or II disorder will be determined using the SCID-5-CT.

12.1.2. Weight and Height

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

12.1.3. Physical Examination

Physical examinations assessing body systems (eg, head, eye, ear, nose, and throat; heart; lungs; abdomen; and extremities), as well as cognitive and neurological examinations and mental status examinations will be conducted and documented. Whenever possible, the same individual is to perform all physical examinations for a given subject. Unscheduled brief 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 12.2.1.1.

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 in the standing position. Respiratory rate, pulse oximetry 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, with the blood sample collected as close to the scheduled time as possible.

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 12.2.1.1.

12.1.5. Electrocardiogram (ECG)

Supine 12-lead ECGs will be performed in triplicate. The standard intervals (heart rate, PR, QRS, QT, and QTcF) as well as any rhythm abnormalities will be recorded. When ECG [redacted] sample 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 12.2.1.1.

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 morphology	ALT Albumin Alkaline phosphatase AST Total bilirubin Direct bilirubin Indirect bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase GGT Potassium Sodium Lactate dehydrogenase Glucose Chloride Bicarbonate Calcium Phosphorus Triglycerides	pH Specific gravity Protein Glucose Red blood cells Nitrite Leukocyte esterase Ketones Bilirubin Urobilinogen	Activated partial thromboplastin time Prothrombin time International normalized ratio

Table 3: Clinical Laboratory Tests (Continued)

Diagnostic Screening			
Serum	**Urine**	**Breathalyzer**	
Hepatitis B Hepatitis C HIV-1 and -2 Female subjects of child bearing potential: serum human chorionic gonadotropin Female subjects, if menopause is suspected and not surgically sterile: FSH	Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, and propoxyphene Female subjects of child bearing potential: urine human chorionic gonadotropin	Alcohol	

The central laboratory will perform laboratory tests for hematology, serum chemistry, and urinalysis. 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, 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 12.2.1.1. 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.

Follicle stimulating hormone testing 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]

12.1.6.1. Drugs of Abuse and Alcohol

Urine toxicology will be performed for selected drugs of abuse, and a breath test will be performed for alcohol (Table 1).

12.1.6.2. Pregnancy Screen

A serum pregnancy test in women of child-bearing potential will be conducted at Screening and a urine pregnancy test will be conducted at all other scheduled timepoints (Table 1).

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

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. Young Mania Rating Scale (YMRS)

Manic symptoms will be assessed during the study using the YMRS (Young 1978). The clinician-administered scale is based on 11 items of core symptoms of mania. Four of the items (irritability, speech, thought content, and disruptive/aggressive behavior) are graded on a scale of 0 to 8 (choices given as even numbers), with the remaining 7 items graded on a scale of 0 to 4. Scoring between the points given (whole or half points) is possible.

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 TEAE is an AE that occurs after the first administration of any study drug. The term study drug includes any Sage investigational product, a comparator, or a placebo administered in a clinical trial.

An abnormal laboratory value will be considered an AE if the value represents a clinically significant change from baseline as determined by the Investigator.

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

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 been enrolled and throughout the duration of the study, whether or not they are related to the study, must be recorded on the SAE form provided by Sage Therapeutics within 24 hours of first awareness (Section 12.5). All SAEs should to be followed until the event resolved, the condition stabilized, was no longer considered clinically significant or the subject was lost to follow-up.

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 the 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 the sponsor.

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 or a complication relating to the pregnancy occurs (eg, spontaneous abortion). 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 Serious Adverse Events

All SAEs must be reported to Sage, 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 staff on the SAE report form. 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. Each site is responsible for notifying its ethics committee of these SUSARs. 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 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. The blinding of the study will be broken after the database has been locked. Electronic copies of the randomization code will be made available to the laboratory performing the bioanalytical analyses in order to allow for limited analysis of samples from subjects receiving placebo.

In the event of a medical emergency or pregnancy, the Investigator will discuss with the Medical Monitor if unblinding is warranted for medical management of the subject. If there is agreement to unblind treatment assignment, the unblinding procedure described in the Safety Management Plan for the study will be followed. If the Investigator is unable to contact the Medical Monitor in a medical emergency, and it is deemed clinically necessary by the Investigator, the treatment group for that subject may be unblinded in the IRT system.

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) for each part (Part A and B) will provide a detailed description of the analyses to be performed in the respective part of the study. The SAPs will be finalized and approved prior to database lock. Any deviations from or changes to the respective SAP following database lock will be described in detail in the clinical study report.

13.1. Data Analysis Sets

The Safety Set, defined as all subjects that received at least 1 dose of study drug, will be used to provide descriptive summaries of safety data.

The Efficacy Set, defined as all subjects in the Safety Set that have at least 1 post-baseline HAM-D evaluation, will be used to analyze efficacy data, unless otherwise specified.

[redacted]

Part B will also include a Randomized Set, defined as all subjects who are randomized. This analysis set will be used for all data listings in Part B.

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 sets, using all non-missing data available. No imputation process will be used to estimate missing data.

13.3. General Considerations

For the purpose of all primary and secondary analyses where applicable, baseline is defined as the last measurement prior to receipt of study drug.

Continuous endpoints will be summarized with number (n), mean, standard deviation (SD), 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 (Section 12.1.1) and baseline characteristics, such as height, weight, and body mass index, will be summarized using the Safety Set.

Pregnancy results will be listed but not summarized.

Medical history will be listed by subject.

13.5. Efficacy Analysis

The primary efficacy endpoint, the change from baseline in HAM-D total score, will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include center, treatment, baseline HAM-D total score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be considered as fixed

effects and the subject effect will be considered random in the model. All post-baseline time points will be included in the model. The primary comparison will be between SAGE-217 and matching placebo at Day 15. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p values) will be reported. An unstructured covariance structure will be used to model the within-subject errors. In case of convergence issues, other covariance structures will be considered; this will be detailed in the statistical analyses plan. Other continuous endpoints will be analyzed using similar methods.

Other efficacy analyses will be specified in the statistical analysis plan. In general, data will be analyzed using appropriate descriptive statistics or pre-specified statistical methods as applicable; subject listings will be provided for all efficacy data. Subjects will be analyzed according to randomized treatment for the purpose of efficacy unless otherwise specified.

13.6. Safety Analyses

Safety and tolerability of SAGE-217 will be assessed by the frequency and severity of AEs; changes from baseline in clinical laboratory measures, vital signs, and ECGs. Suicidal ideation and behavior will be evaluated using the C-SSRS. Mania will be evaluated using the YMRS. Safety data will be listed by subject and summarized by treatment group. All safety summaries will be performed on the Safety Set.

13.6.1. Adverse Events

The analysis of AEs 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 20.1 or higher, system organ class (SOC), and preferred term (PT). 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 (Section 13.6.1).

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

Clinical laboratory results will be listed by subject and timing of collection. Mean changes from baseline in clinical laboratory measures will be evaluated.

13.6.3. Physical Examinations

Physical examination data will be listed by subject, but not summarized.

13.6.4. Vital Signs

Vital sign results will be listed by subject and timing of collection. Mean changes from baseline in vital signs will be evaluated by time point.

13.6.5. 12-Lead Electrocardiogram

The following ECG parameters will be listed for each subject: heart rate, PR, QRS, QT, and QTcF. Any clinically significant abnormalities or changes in ECGs should be listed as an AE. 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.

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 will be summarized and 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. Young Mania Rating Scale

Mania data collected on the YMRS at baseline and by visit will be summarized and listed for all subjects.

[redacted]

13.8. Determination of Sample Size

13.8.1. Part A

For Part A, the sample size of approximately 30 subjects was selected based on clinical and not statistical considerations.

13.8.2. Part B

For Part B, assuming a two-sided alpha level of 0.05, a sample size of 112 total evaluable subjects (56 per treatment group) would provide 80% power to detect a placebo-adjusted treatment difference of approximately 4 points in the primary endpoint, change from baseline in HAM-D total score at Day 15, assuming standard deviation (SD) of 7.5 points.

Assuming a 15% dropout rate, approximately 132 total randomized subjects will be required to obtain a total of 112 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have a valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the drop-out rate is higher than 15%.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the study site guarantee access to source documents by Sage Therapeutics or sponsor's designee and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by Sage Therapeutics or sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

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. Protocol Deviations

Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the Sage Therapeutics or sponsor's designee (and IRB, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

14.4. 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 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 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.

19. LIST OF REFERENCES

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Protocol 217-BPD-201, Amendment 2

Date of Amendment: 18 October 2018

A 2-Part Study (Open-label followed by Double-blind, Randomized, Placebo-controlled, Parallel Group) of the Safety, Tolerability, Pharmacokinetics, and Efficacy of SAGE-217 in the Treatment of Subjects with Bipolar I/II Disorder with a Current Major Depressive Episode

Rationale for Protocol Amendment

The primary purpose for this protocol amendment is as follows:

- Define exclusionary period for use of benzodiazepines and $GABA_A$ modulators/GABA-containing agents to avoid confounding by the natural resolution of prolonged mild GABAergic withdrawal symptoms
- Removed number of capsules at each dose to allow for difference manufacturing processes. Specific instructions will be provided in the pharmacy manual.

Additional changes are being implemented as outlined below:

- Exclude subjects that have taken non-GABA anti-insomnia medications (eg melatonin, Benadryl [anti-histamines], trazodone, low dose quetiapine, mirtazapine, etc) within 14 days of initition of study drug.
- Remove criterion that subjects must be ambulatory.
- Include exception to contraception criteria for subjects in same-sex relationship(s) which do not carry a risk of pregnancy.
- Remove specific timing of dosing and offer practical options for taking study drug with food in the evening
- Reiterate exclusion criterion prohibiting elective surgeries.
- Define timeframes for each type of prohibited medication.

A detailed summary of changes is provided in Table 1. Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting are not detailed.

Table 1: Protocol Amendment 2 Detailed Summary of Changes

The primary section of the protocol affected by the changes in Protocol Amendment 2 is indicated. The corresponding related text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: Remove criterion that subjects must be ambulatory.

The primary change occurs in Section 8.1 Subject Inclusion Criteria

Changed text: 3. Subject is a~~n ambulatory~~ male or female between 18 and 65 years of age, inclusive, at Screening.

Sections also affected by this change:

- Synopsis

Purpose: Include exception to contraception criteria for subjects in same-sex relationship(s) which do not carry a risk of pregnancy.

The primary change occurs in Section 8.1. Subject Inclusion Criteria

Changed text:

7. Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle stimulating hormone [FSH] >40 mIU/mL) and/or surgically sterile (hysterectomy or bilateral oophorectomy)**, or in sexual relationship(s) which do not carry a risk of pregnancy (eg, same-sex relationship(s))**:
   - 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 ligation/occlusion.
   - Vasectomized partner.
   - Sexual abstinence (no sexual intercourse).
8. 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 is in sexual relationship(s) which do not carry a risk of pregnancy (eg, same-sex relationship(s))**. Acceptable methods of effective contraception for males includes sexual abstinence, 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 #7 for acceptable contraception methods).

Sections also affected by this change:

- Synopsis

Purpose: Define exclusionary period for use of benzodiazepines and $GABA_A$ modulators/GABA-containing agents to avoid confounding by the natural resolution of prolonged mild GABAergic withdrawal symptoms.

The primary change occurs in Section 8.2 Subject Exclusion Criteria

Changed text: 13. Subject is taking ~~typical or atypical antipsychotics, monoamine oxidase inhibitors (MAOIs),~~ benzodiazepines or $GABA_A$ modulators/**GABA-containing agents (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28** ~~other than the allowed mood stablizers at the Screening Visit~~.

Sections also affected by this change:

- Synopsis, 9.2.2 Prohibited Medications

Purpose: Exclude subjects that have taken non-GABA anti-insomnia medications (eg, melatonin, Benadryl [anti-histamines], trazodone, low dose quetiapine, mirtazapine, etc) within 14 days of initition of study drug.

The primary change occurs in Section 8.2 Subject Exclusion Criteria

Added text: **29. Subject is taking non-GABA anti-insomnia medications (eg, melatonin, Benadryl [anti-histamines], trazodone, low dose quetiapine, mirtazapine, etc) at Day -14.**

Sections also affected by this change:

- Synopsis, 9.2.2 Prohibited Medications

Purpose: Offer practical options for taking study drug with food in the evening.

The primary change occurs in Section 10.5 Study Drug Administration

Added text: SAGE-217 is to be administered orally once daily in the evening with food. **Practical options include taking SAGE-217 within 1 hour of dinner or taking SAGE-217 later in the evening with solid food.** If a subject misses a dose, the subject should skip that dose (ie, they should not take the dose in the morning) and take the next scheduled dose in the evening the next day.

Sections also affected by this change:

- Synopsis and Section 9.1 Study Drug

Purpose: Remove specific timing of dosing.

The primary change occurs in Section 9.1 Study Drug

Deleted text: ~~(approximately 8:00 to 11:00 pm)~~

Sections also affected by this change:

- Synopsis, Section 7.1 Overall Study Design, 9.3 Treatment Adherence, 10.5 Study Drug Administration

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Purpose: Define timeframes for each type of prohibited medication.

The primary change occurs in Section 9.2.2 Prohibited Medications

Changed text:

The following specific classes of medications are prohibited at any time during the treatment period:

- Initiation of new psychotropic medications at any time during the study
- Initiation of new antidepressant therapy from 60 days prior to Day 1 through the duration of the study
- Use of any benzodiazepines, $GABA_A$ modulators, $GABA_A$-like acting drugs, or GABA-containing agents from Day -28 through the duration of the study
- Use of any non-GABA anti-insomnia medications (eg, melatonin, Benadryl [anti-histamines], trazodone, low dose quetiapine, mirtazapine, etc) from Day -14 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
- Any known strong inhibitors of CYP3A4 from Day -28 or 5 half-lives prior to Day 1 (whichever is longer) through the duration of the study
- Use of any CYP inducer, such as such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort from Day -28 through the duration of the study.
- ~~Benzodiazepines~~
- ~~$GABA_A$ modulators other than the allowed mood stabilizers~~
- ~~Typical or atypical antipsychotics~~
- ~~MAOIs~~

- ~~Any known strong inhibitors of CYP3A4~~
- ~~Use of CYP inducers, such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort.~~

Sections also affected by this change:

- Not applicable

Purpose: Reiterate exclusion criterion prohibiting elective surgeries.

The primary change occurs in Section 9.2.3 Other Restriction

Added text: **Elective surgeries or procedures are prohibited during participation in the study.**

Sections also affected by this change:

- Not applicable

Purpose: Removed number of capsules at each dose.

The primary change occurs in Section 10.1 Description of Study Drug

Deleted text: ~~Subjects will be administered 2 capsules per dose in Part A. Subjects will be administered 1 capsule per dose in Part B.~~

Sections also affected by this change:

- Section 10.2 Study Drug Packaging and Labeling

Purpose: *Correct typographical errors, punctuation, grammar, abbreviations, and formatting.*

These changes are not listed individually.

November 8, 2018

217-BPD-201 Protocol Memo to Sites

Study title: A 2-Part Study (Open-label Followed by Double-Blind, Randomized, Placebo-Controlled, Parallel Group) of the Safety, Tolerability, Pharmacokinetics, and Efficacy of SAGE-217 in the Treatment of Subjects with Bipolar I/II Disorder with a Current Major Depressive Episode

This memo is to inform you of additional changes regarding subject eligibility and prior medications following the finalization of Protocol v3.0, Amendment 2 dated 18-Oct-2018. An amendment incorporating these changes will be forthcoming. Any questions in the meantime can be directed to the CST.

1. Modification of exclusion criteria #13.

   From:

   13. Subject is taking benzodiazepines or GABAA modulators/GABA-containing agents (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28.

   To:

   13. Subject is taking benzodiazepines, barbiturates, or $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28, or subjects have been using these agents on a daily or near-daily (≥4 times per week) for more than one year.

   Rationale: Per FDA feedback, to avoid confounding effects of potential withdrawal that might result from discontinuation of GABAergic drugs after long-term exposure.

   Sections also affected by this change: Synopsis, Prior Medications, Concomitant Medications, and Restrictions

2. Modification of Section 9.2.1: Prior and Concomitant Medications and/or Supplements

   From:

   In addition, psychotropic drugs taken within 6 months prior to Screening will be recorded.

   To:

   In addition, psychotropic drugs taken within 12 months prior to Screening will be recorded.

   Rationale: Per FDA feedback, to avoid confounding effects of potential withdrawal that might result from discontinuation of GABAergic drugs after long-term exposure.

3. Addition of exclusion criteria # 30.

   Added:

   30. Subject has been taking psychostimulants (eg, methylphenidate, amphetamine) or opioids regularly or as needed, at Day -28.

   Rationale: To avoid any confounding antidepressant effects of stimulants, as well as potential pharmacodynamic interactions with opioids.

   Sections also affected by this change: Synopsis, Prohibited Medications

4. Modification to Section 9.2.2: Prohibited Medications

   Added:

   Use of psychostimulants (eg, methylphenidate, amphetamine) or opioids regularly or as needed, from Day -28 through the duration of the study.

   Rationale: To avoid any confounding antidepressant effects of stimulants, as well as potential pharmacodynamic interactions with opioids.

[redacted]
[redacted] MD, MBA
[redacted]
Sage Therapeutics

A 2-PART STUDY (OPEN-LABEL FOLLOWED BY DOUB E-BLI D, RANDOMIZED, PLACEBO-CONTROLLED, PARALLE GROUP) OF T E SAFETY, TOLERABI ITY, PHARMACOKI ETICS, A D EFFICACY OF SAGE-217 I T E TREATME T OF SUBJECTS WIT BIPOLAR I/II DISORDER WITH A CURRENT MAJOR DEPRESSI E EPISODE

PROTOCOL UMBER: 217-BPD-201

Study Drug	SAGE-217
Clinical Phase	Phase 2
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted] Tel: [redacted] email: [redacted]
Sponsor Medical Monitor	[redacted] MD, MBA Tel: [redacted] email: [redacted]
Date of Original Protocol	Version 1.0, 03 JUL 2018
Date of Amendment 1	Version 2.0, 13 SEP 2018
Date of Amendment 2	Version 3.0, 18 OCT 2018
Date of Amendment 3	Version 4.0, 16 JAN 2019

Protocol Number:	217-BPD-201
Study Drug:	SAGE-217
Study Phase:	Phase 2
Sponsor:	Sage Therapeutics, Inc.
Protocol Date:	Version 4.0, 16 Jan 2019

Sponsor Approval

[redacted] 18JAN2019

[redacted] MD, MBA Date (DD/MMM/YYYY)

[redacted] 16JAN2019

[redacted] AC Date (DD/MMM/YYYY)

[redacted] 16Jan2019

Date (DD/MMM/YYYY)

[redacted] 16 JAN 2019

[redacted] PhD Date (DD/MMM/YYYY)

[redacted] 16 JAN 2019

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

[redacted] 16 Jan 2019

[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-BPD-201 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 Month YYYY)

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics

Name of Investigational Product:
SAGE-217 Capsule

Name of Active Ingredient:
SAGE-217

Title of Study:
A 2-Part Study (Open-label followed by Double-blind, Randomized, Placebo-controlled, Parallel Group) of the Safety, Tolerability, Pharmacokinetics, and Efficacy of SAGE-217 in the Treatment of Subjects with Bipolar I/II Disorder with a Current Major Depressive Episode

Number of Sites and Study Location:
Part A: Approximately 10 sites in the United States
Part B: Approximately 40 sites in the United States

Phase of Development: 2

Planned Duration of participation: Up to 73 days (28-day Screening Period; 14-day Treatment Period, and 28-day [±3 days] Follow-up Period)

Objectives:
Part A Primary:

- To evaluate the safety and tolerability of SAGE-217 in subjects with bipolar I or II disorder with a current major depressive episode (MDE).

Part A Secondary:

- To assess the efficacy of SAGE-217 in reducing depressive symptoms in subjects with bipolar I/II disorder with a current MDE.
- To assess the effect of SAGE-217 on sleep.

Part B Primary:

- To assess the efficacy of SAGE-217 in reducing depressive symptoms in subjects with bipolar I/II disorder with a current MDE.

Part B Secondary:

- To evaluate the safety and tolerability of SAGE-217 in subjects with bipolar I/II disorder with a current MDE.
- To assess the effect of SAGE-217 on sleep.

[redacted]

Endpoints:

Part A Primary:

- The safety and tolerability of SAGE-217 as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and electrocardiogram (ECGs); and suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS); and mania using the Young Mania Rating Scale (YMRS).

Part A Secondary:

- The reduction in depressive symptoms, as assessed by:
  - Change from baseline in the 17-item Hamilton Depression Rating Scale (HAM-D) total score at Day 15
  - HAM-D response at Day 15
  - HAM-D remission at Day 15
  - Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Day 15
  - The response to the Clinical Global Impression scale for severity and improvement (CGI-S and CGI-I, respectively) at Day 15
- The reduction in insomnia severity, as assessed by Insomnia Severity Index (ISI) at Day 15

Part B Primary:

- The primary endpoint in Part B is the reduction in depressive symptoms with SAGE-217 treatment, as assessed by the change from baseline in the HAM-D total score.

Part B Secondary:

- The reduction in depressive symptoms, as assessed by:
  - Change from baseline in HAM-D total score at Day 15
  - HAM-D response at Day 15
  - HAM-D remission at Day 15
  - Change from baseline in the MADRS total score at Day 15
  - CGI-S and CGI-I response at Day 15
- The safety and tolerability of SAGE-217 as assessed by the frequency and severity of adverse events; changes from baseline in clinical laboratory measures, vital signs, and ECGs; and suicidal ideation and behavior using the C-SSRS; and mania using the YMRS.
- The reduction in insomnia severity, as assessed by ISI at Day 15

[redacted]

Study Description:

This study will be conducted in 2 sequential parts: Part A (open-label) and Part B (randomized, double-blind, placebo-controlled, parallel group). Part B will be initiated pending the review of Part A data. The methods of the 2 parts will be identical unless otherwise noted. Subjects who participate in Part A will not be allowed to participate in Part B. The study is designed to assess the safety, tolerability, [redacted] and efficacy of SAGE-217 in adult subjects with bipolar I/II disorder, who are currently experiencing an MDE.

The assessments are summarized in the Schedule of Events (Table 1).

Screening begins with the signing of the informed consent form at the Screening Visit. The diagnosis of bipolar I or II disorder will be made using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) for clinical trials (SCID-5-CT) performed by a qualified healthcare professional.

Beginning on Day 1, qualified subjects will self-administer the study drug once daily in the evening with food for 14 days. In Part A, all subjects will receive SAGE-217. For Part B, subjects will be randomized in a 1:1 ratio to receive SAGE-217 or placebo; randomization will be stratified based on use of mood stabilizers (Y/N). Subjects on antidepressants or mood stabilizers (lamotrigine, lithium, and valproic acid only) that have been taken at the same dose for at least 60 days prior to Day 1 are to continue the stable dose throughout the treatment period.

If at any time, 30 mg is not tolerated, as assessed by the occurrence of a severe AE judged by the investigator to be related to study drug, the dose on the next day will be reduced to 20 mg and continued for the remainder of the treatment period. Dose adjustments related to moderate AEs will be judged by the Investigator. If a dose adjustment from 30 mg to 20 mg is deemed necessary by the Investigator, the subject will return to the site for the adjusted dose to be dispensed. Subjects who cannot tolerate the 20-mg dose at any time will be discontinued from study drug.

If at any time during the study, a subject has a YMRS score of ≥13, the Investigator will clinically assess the subject for a manic or hypomanic switch. If the clinical assessment is consistent with hypomania or mania, the subject will be discontinued from study drug and treated as clinically appropriate. These incidents will be documented as AEs.

Subjects will return to the study center during the treatment and follow-up periods as outlined in Table 1.

Number of Subjects (planned):

Part A: Approximately 30 subjects will be dosed.

Part B: Approximately 132 subjects will be randomized and dosed to obtain a total of 112 evaluable subjects.

Eligibility criteria:

Inclusion Criteria:

1. Subject has signed an informed consent form (ICF) prior to the conduct of any study-specific procedures.
2. Subject agrees to adhere to the study requirements, including use of prior, concomitant, and prohibited medications.
3. Subject is a man or woman, aged 18 to 65 years, inclusive, at Screening.
4. 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.
5. Subject has a documented history of hypomanic or manic episode (verified by medical records and/or treating healthcare professional) and a diagnosis of bipolar I or bipolar II disorder with a current MDE as per DSM-5 SCID-5-CT.
6. Subject has a HAM-D score of ≥22 at Screening.
7. Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are 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 or bilateral oophorectomy), or does not engage in sexual relation(s) which carry a risk of pregnancy:
   - 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 ligation/occlusion.
   - Vasectomized partner.
   - Sexual abstinence (no sexual intercourse).
8. 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 relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception for males includes sexual abstinence, 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 #7 for acceptable method of contraception for females).
9. 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.

Exclusion Criteria:

1. Subject has a history of suicide attempt within the last 2 years.

2. Subject has current suicidal ideation with plans based on Investigator clinical assessment and/or the C-SSRS response at Screening or Day 1.
3. Subject has a history of rapid cycling bipolar disorder as per DSM-5 SCID-5-CT.
4. Subject's current depressive episode meets the DSM-5 specifier criteria for mixed features.
5. Subject has ≥25% reduction in HAM-D score from Screening to Day 1.
6. 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.
7. Subject has abnormal liver function as shown by an abnormal liver function profile at screening (eg, repeated values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥2x the upper limit of normal).
8. Subject has a clinically significant abnormal 12-lead ECG at the Screening or Day 1 visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in male or >470 msec in female subjects will be the basis for exclusion from the study.
9. Subject has a YMRS score ≥13 at Screening or Day 1.
10. Subject presents for the study receiving a mood stabilizer other than lamotrigine, lithium, or valproic acid.
11. Subject presents for the study receiving antidepressants and mood stabilizers, which have not been taken at the same dose for at least 60 days prior to Day 1.
12. Subject that presents for the study receiving psychotropic medications and does not intend to continue the current treatment regimen during the treatment period.
13. Subject is taking benzodiazepines, barbituates, or $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28, or subject has been using these agents on a daily or near-daily (≥4 times per week) for more than one year.
14. Subject has a history of severe rashes or Stevens-Johnson Syndrome associated with lamotrigine and is currently taking lamotrigine.
15. Subject's current depressive episode is treatment resistant; defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants from two different classes for an adequate amount of time (ie, at least 4 weeks of treatment). This will be assessed using the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.
16. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
17. Subject has a positive pregnancy test at the Screening Visit or on Day 1 (prior to administration of study drug) or, if she is breastfeeding at Screening or on Day 1 (prior to administration of study drug), she does not agree to temporarily cease giving breast milk to her child(ren) from just prior to receiving study drug on Day 1 until 7 days after the last dose of study drug.

18. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and HCV viral load, or human immunodeficiency virus (HIV) antibody at screening.
19. Subject has active psychosis per Investigator assessment.
20. Subject has a medical history of seizures.
21. Subject has a medical history schizophrenia, and/or schizoaffective disorder.
22. Subject has a history of mild, moderate, or severe substance use disorder diagnosed using DSM-5 criteria in the 12 months prior to screening.
23. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
24. Subject has had exposure to another investigational medication or device within 30 days prior to the Screening visit.
25. Subject has been previously treated or randomized in any study using SAGE-217. Subjects who participate in Part A are not eligible to participate in Part B.
26. Subject has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to receiving the first dose of study drug.
27. Subject has used strong CYP3A inducers, such as carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, or St Johns Wort within 28 days prior to the first dose of study drug.
28. Subject plans to undergo elective surgery during participation in the study.
29. Subject is taking non-GABA anti-insomnia medications (eg, melatonin, Benadryl [anti-histamines], trazodone, low-dose quetiapine, mirtazapine, etc) at Day -14 .
30. Subject has been taking psychostimulants (eg, methylphenidate, amphetamine) or opioids regularly or as needed, at Day -28.

SAGE-217 dosage and mode of administration:

SAGE-217 (30 mg) will be administered orally once daily in the evening with food.

Reference therapy, dosage and mode of administration (Part B only):

Placebo capsules will only be used for Part B. Study drug placebo will be administered orally once daily in the evening with food.

Duration of Treatment: 14 days

Statistical methods:

A separate statistical analysis plan (SAP) for each part (Parts A and B) will provide a detailed description of the analyses to be performed in the respective part of the study. The SAPs 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.

General:

The data from Parts A and B will be analyzed separately. For the purpose of all safety and efficacy analyses where applicable, baseline is defined as the last available measurement prior to the start of study drug administration.

Continuous endpoints will be summarized with 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:

Randomized set (Part B only) will be defined as all subjects who are randomized. This analysis set will be used of all data listings in Part B. Data listings for Part A will be based on Safety or Efficacy Set, as appropriate.

The Safety Set, defined as all subjects received at least 1 dose of study drug, will be used to provide descriptive summaries of safety data.

The Efficacy Set, defined as all subjects who are in Safety Set and have at least one post-baseline HAM-D evaluation, will be used to analyze efficacy data unless otherwise specified.

[redacted]

Safety Analysis:

The overall incidence of adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Data for vital signs, clinical laboratory measurements, ECG, and concomitant medication usage will also be summarized.

Safety data will be summarized and examined for possible relationships between subject characteristics and plasma SAGE-217 concentrations, as appropriate. Suicidality data collected using the C-SSRS and evaluation of mania collected using the YMRS at baseline and at each visit during the active Treatment Period will be listed for all subjects. Out-of-range safety endpoints may be categorized as low or high, where applicable. Subjects will be summarized according to treatment received for the purpose of safety.

Efficacy Analysis:

The primary endpoint in Part B, the change from baseline in HAM-D total score, will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include treatment, baseline HAM-D total score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be considered as fixed effects and the subject effect will be considered random in the model. All post-baseline time points will be included in the model. The primary comparison will be between SAGE-217 and matching placebo at Day 15. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p-values) will be reported. An unstructured covariance structure will be used to model the within-subject errors. Other continuous endpoints will be analyzed using similar methods.

Other efficacy analyses, including those in Part A, will be specified in the SAP. In general, data will be analyzed using appropriate descriptive statistics or pre-specified statistical methods as applicable;

subject listings will be provided for all efficacy data. Subjects will be analyzed according to randomized treatment for the purpose of efficacy unless otherwise specified.

[redacted]

Sample Size Calculation

Part A: The sample size of approximately 30 subjects was selected based on clinical and not statistical considerations.

Part B: Assuming a two-sided alpha level of 0.05, a sample size of 112 total evaluable subjects (56 per treatment group) would provide 80% power to detect a placebo-adjusted treatment difference of approximately 4 points in the primary endpoint, change from baseline in HAM-D total score at Day 15, assuming standard deviation (SD) of 7.5 points.

Assuming a 15% dropout rate, approximately 132 total randomized subjects will be required to obtain a total of 112 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have a valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the drop-out rate is higher than 15%.

Table 1: Schedule of Events

Study Period	**Screening Period**	**Treatment Period**					**Follow-up Period[a]**			
Visit Day	**D-28 to D-1**	**D1**	**D3 (+1d)**	**D8 (±1d)**	**D12 (±1d)**	**D15 (±1d)/ EOT[a]**	**D21 (±3d)**	**D28 (±3d)**	**D35 (±3d)**	**D42 (±3d)/ ET**
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Study Procedure										
Informed Consent	X									
Inclusion/Exclusion	X	X								
Demographics	X									
Medical/Family History	X									
SCID-5-CT	X									
MGH-ATRQ	X									
Serum FSH test[b]	X									
Randomization (Part B only)		X								
Physical Examination	X	X				X				X
Body Weight/Height[c]	X					X (wt only)				X (wt only)
Clinical Laboratory Assessments[d]	X	X		X		X	X	X		X
Drug & Alcohol Screen[e]	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[f]	X	X				X		X		X
Hepatitis & HIV Screen	X									
[redacted]										
Vital Signs[i]	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[j]	X	X	X			X				X
C-SSRS[k]	X	X	X	X	X	X	X	X	X	X
HAM-D[l]	X	X	X	X	X	X	X	X	X	X
MADRS[l]		X	X	X	X	X	X	X	X	X
CGI-S		X	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X	X	X
YMRS[l]	X	X	X	X	X	X	X	X	X	X
[redacted]										

Study Period	**Screening Period**	**Treatment Period**					**Follow-up Period[a]**			
Visit Day	**D-28 to D-1**	**D1**	**D3 (+1d)**	**D8 (±1d)**	**D12 (±1d)**	**D15 (±1d)/ EOT[a]**	**D21 (±3d)**	**D28 (±3d)**	**D35 (±3d)**	**D42 (±3d)/ ET**
ISI		X		X		X	X	X		X
[redacted]										
Study Drug Dispensation[o]		X		X						
Study Drug Administration		X (Day 1-14)								
Study Drug Accountability/Return			X	X	X	X				
Adverse Events/Serious Adverse Events[p]	X									
Prior/Concomitant Medications/ Procedures[q]	X									

CGI-I = Clinical Global Impression - Improvement; CGI-S – Clinical Global Impression - Severity; C-SSRS = Columbia Suicide Severity Rating Scale; D = day; EOT = end of treatment; ECG = electrocardiogram; ET = early termination; [redacted] FSH = follicle stimulating hormone; HAM-D = Hamilton Rating Scale for Depression, 17-item; HIV = human immunodeficiency virus; ISI = Insomnia Severity Index; MADRS = Montgomery-Åsberg Depression Rating Scale; MGH-ATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; O = optional; [redacted] SCID-5-CT = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition for clinical trials; [redacted] YMRS = Young Mania Rating Scale

[a] Subjects who discontinue treatment early should return to the site for an EOT visit as soon as possible, preferably the day after treatment is discontinued. Follow-up visits should take place every 7 days after the last dose of treatment for a total of 4 follow-up visits. If at any time after the EOT visit, a subject decides to terminate the study, the subject should return for an ET visit. The EOT 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 both visits will be conducted.

[b] A serum follicle stimulating hormone test will be conducted for female subjects at Screening to confirm whether a female subject with ≥12 months of spontaneous amenorrhea and not surgically sterile meets the protocol-defined criteria for being post-menopausal.

[c] Height measured at screening only

[d] Safety laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis. Laboratory assessments are to be completed in the morning.

[e] Urine toxicology for selected drugs of abuse, and breath test for alcohol (as per the standard procedures at each site).

[f] For women of child-bearing potential, serum pregnancy test at screening and urine pregnancy test at all other scheduled timepoints.

[redacted]

[i] Vital signs include oral temperature (°C), respiratory rate, heart rate, pulse oximetry, 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 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.

[j] Triplicate 12-lead ECGs will be performed with the subject in the supine position. When ECG [redacted] sample collection occur during the same visit, ECGs will be collected first.

[k] The "Baseline/Screening" C-SSRS form will be completed at screening. The "Since Last Visit" C-SSRS form will be completed at any time of day at all subsequent time points.

[l] For MADRS, HAM-D, and YMRS, the "Since Last Evaluation" forms will be completed at all subsequent time points following the initial assessment.

[redacted]

[o] Additional unscheduled dispensation visits may be needed for dose reductions.

[p] AEs/SAEs will be collected starting at the time of informed consent and throughout the duration of the subject's participation in the study.

[q] Prior medications will be collected at Screening and concomitant medications will be collected at each subsequent visit. All medications taken within 30 days prior to Screening through the duration of the study will be recorded. In addition, all psychotropic medications taken within 12 months prior to Screening will be recorded.

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

LIST OF TABLES

LIST OF FIGURES

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
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CGI-I	Clinical Global Impression scale for improvement
CGI-S	Clinical Global Impression scale for severity
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
ET	early termination
[redacted]	[redacted]
FSH	follicle-stimulating hormone
GABA	γ-aminobutyric acid
HAM-D	Hamilton Depression Rating Scale
HCV	**hepatitis C virus**
HIV	human immunodeficiency virus
ICF	informed consent form
ID	identification
IRT	interactive response technology
ISI	Insomnia Severity Index
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MDE	major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or specialist term	Explanation
MGH-ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
MMRM	mixed effects model for repeated measures
PI	Principal Investigator; the investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
[redacted]	[redacted]
QTcF	QT corrected according to Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SCID-5-CT	Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition for clinical trials
SD	standard deviation
[redacted]	[redacted]
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
YMRS	Young Mania Rating Scale

5. INTRODUCTION

5.1. Background of Bipolar Disorders and Unmet Medical Need

Bipolar disorder is a chronic and episodic illness that is associated with significant disability worldwide (Sachs 2007). The Global Burden of Disease Study revealed that in 2013, there were 48.8 million cases of bipolar disorder globally (Ferrari 2016). Bipolar disorder accounted for 9.9 million disability-adjusted life years (DALYs) globally, explaining 0.4% of total DALYs and 1.3% of total years lived with disability.

There are subtypes of bipolar disorder; this study includes the bipolar I and II subtypes. Bipolar I is characterized by a manic episode, whereas bipolar II is characterized by a hypomanic episode. The difference in the severity of the manic features relies on functional impairment that is caused by these episodes (DSM-5). The National Comorbidity Survey estimate of the lifetime prevalence of bipolar disorder is 2.1% in the US population when bipolar I disorder and bipolar II Disorder are combined (Merikangas 2007).

While the manic or hypomanic episodes represent distinct departure from the baseline mood state and easily attract attention, evidence suggests that depressive episodes of both bipolar I and II are associated with more disability than any other aspect of the illness. A seminal long-term study of patients with bipolar I disorder demonstrated that over the 13-year follow-up period, patients were symptomatic about 47% of the time, and depressive symptoms were present in 32% of the follow-up weeks vs manic features, which were present in 9% (Judd 2002). A similar analysis in patients with bipolar II disorder with a longer follow up of up to 20 years found that patients were symptomatic more than half of the time (54%) where depressive symptoms dominated the course at 50% of the follow-up weeks versus 1.3% for the hypomanic symptoms (Judd 2003). A study in patients with unipolar depression found a prevalence of depressive symptoms 47% of the time (Judd 1998), suggesting a comparable time spent with depressive symptoms in the bipolar spectrum. These naturalistic studies have also found that about half the time patients reported taking psychotropic medications. In another large-scale study with a follow-up period of up to 2 years, 58% of nearly 1500 patients with bipolar disorder who were symptomatic at study entry achieved recovery (Perlis 2006). Similarly, during the follow-up period, 49% of these individuals experienced recurrent episodes, where depressive episodes (38%) outweighed manic, hypomanic, or mixed episodes combined (13.8%). In the Stanley Foundation Bipolar Network Study, in which year-long, daily clinician ratings were included, despite treatment with an average of 4.1 psychotropic medications, patients with bipolar disorder spent 3 times as much time with depressive symptoms as manic symptoms (Post 2003).

There are only 3 medications approved in the US for the treatment of bipolar depression, (lurasidone, olanzapine-fluoxetine combination, and quetiapine), all of which include atypical antipsychotics that are associated with significant adverse metabolic effects. None of the currently available antidepressants are indicated for bipolar depression due to their limited efficacy, and the possibility that their use may be associated with a manic switch and rapid cycling. While some studies reported varying levels of efficacy with antidepressants (Gijsman 2004), a large-scale, double-blind, placebo-controlled clinical trial sponsored by the National Institutes of Mental Health, The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), found that only 23.5% of patients with bipolar depression receiving a mood stabilizer and adjunctive antidepressants versus 27.3% of those receiving a

mood stabilizer and placebo experienced a durable recovery, confirming the lack of effectiveness of antidepressants in bipolar depression (Sachs 2007). The tolerability profile of the approved atypical antipsychotics and limited efficacy of available antidepressants highlight the critical unmet need in the treatment of bipolar depression.

In 1998, the lifetime cost of bipolar disorder in the US was estimated at $24 billion. The cost of a single manic episode was estimated at $11,720 to $624,785 for persons with nonresponsive/chronic episodes (Begley 1998); the cost of bipolar depression specifically, is less well studied, however, available estimates indicate a higher cost associated with bipolar depression than for mania (Bowden 2004).

Kessler has studied the impact of mood disorders on work performance in a representative sample of over 3,000 US workers (Kessler 2006). Bipolar disorder and major depressive disorder were associated with 65.5 and 27.2 lost workdays per worker per year, respectively. Moreover, it was found that the increase in bipolar disorder was attributable to depressive symptoms rather than manic episodes in bipolar disorder.

Taken together, these findings point to substantial predominance of depressive symptoms across the spectrum of bipolar disorder. In particular, they also highlight the importance of successful depressive symptom control, and an unmet need in the treatment of depressive episodes for both bipolar I and bipolar II disorder.

5.2. SAGE-217

SAGE-217 is a positive allosteric modulator of γ-aminobutyric acid $(GABA)_A$ 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 portion of the Phase 2a study of SAGE-217 administered to subjects with moderate to severe major depressive disorder (MDD) showed clinically significant improvements from baseline in depression scale scores (HAM-D, Montgomery-Åsberg Depression Rating Scale [MADRS], 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 (N=89) in which a rapid and substantial decrease in HAM-D scores was observed at Day 15 (primary endpoint), starting at Day 2. This response pattern was also observed with other efficacy scales, including MADRS and CGI-I. Statistically significant differences from the placebo group favoring the SAGE-217 arm were observed for 2 weeks in the follow-up period.

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 AEs were reported as mild or moderate in intensity. As of the Investigator's Brochure cut-off date (24 September 2018), 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.

5.3. 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 2 study of SAGE-217 in subjects with MDD and the current significant unmet need in the treatment of depressive episodes associated with bipolar I/II disorders, a favorable risk-benefit balance and investigation of SAGE-217 in patients with bipolar I/II disorders are justified.

5.4. Dose Justification

The dose of SAGE-217 to be administered in this study (30 mg) was determined based on the maximum tolerated dose in the multiple ascending dose study of SAGE-217 in healthy subjects, and is the same dose level that has been used and generally well tolerated in clinical studies in various patient populations, including patients with MDD. Due to the observed improved tolerability of sedation/somnolence effects when taken in the evening in previous clinical studies, SAGE-217 will be administered in the evening in this study as well.

With respect to the duration of treatment course, a 14-day study drug administration is planned. This is based on previous clinical trial data with SAGE-217, demonstrating substantial improvement in depressive symptoms in patients with MDD, starting within the first week of treatment.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Study Objective

6.1.1. Primary Objective

Part A

The primary objective of Part A of this study is to evaluate the safety and tolerability of SAGE-217 in subjects with bipolar I/II disorder with a current major depressive episode (MDE).

Part B

The primary objective of Part B of this study is to assess the efficacy of SAGE-217 in reducing depressive symptoms in subjects with bipolar I/II disorder with a current MDE.

6.1.2. Secondary Objectives

Part A

Secondary objectives of Part A of this study are:

- To assess the efficacy of SAGE-217 in reducing depressive symptoms in subjects with bipolar I/II disorder with a current MDE.
- To assess the effect of SAGE-217 on sleep.

Part B

Secondary objectives of Part B of this study are:

- To evaluate the safety and tolerability of SAGE-217 in subjects with bipolar I/II disorder with a current MDE.
- To assess the effect of SAGE-217 on sleep.

6.2. Endpoints

6.2.1. Primary Endpoint

Part A

The primary endpoint for Part A of this study is the safety and tolerability of SAGE-217, as assessed by the frequency and severity of adverse events (AEs); changes from baseline in clinical laboratory measures, vital signs, and electrocardiograms (ECGs); suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS); and mania using the Young Mania Rating Scale (YMRS).

Part B

The primary endpoint of Part B of this study is the reduction in depressive symptoms with SAGE-217 treatment, as assessed by the change from baseline in the 17-item HAM-D total score.

6.2.2. Secondary Endpoints

Part A

Secondary endpoints of Part A of this study are:

- The reduction in depressive symptoms, as assessed by:
  - Change from baseline in the 17-item HAM-D total score at Day 15
  - HAM-D response at Day 15
  - HAM-D remission at Day 15
  - Change from baseline in the MADRS total score at Day 15
  - The response to the CGI-S and CGI-I at Day 15
- The reduction in insomnia severity as assessed by the Insomnia Severity Index (ISI) at Day 15

Part B

Secondary endpoints of Part B of this study are:

- The reduction in depressive symptoms, as assessed by:
  - Change from baseline in total HAM-D score at Day 15
  - HAM-D response at Day 15
  - HAM-D remission at Day 15
  - Change from baseline in the MADRS total score at Day 15
  - CGI-S and CGI-I response at Day 15

- The safety and tolerability of SAGE-217 as assessed by the frequency and severity of AEs; changes from baseline in clinical laboratory measures, vital signs, and ECGs; and suicidal ideation and behavior using the C-SSRS, and the YMRS.
- The reduction in insomnia severity, as assessed by the ISI at Day 15

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This study will be conducted in 2 sequential parts: Part A (open-label) and Part B (randomized, double-blind, placebo-controlled, parallel group). Part B will be initiated pending the review of Part A data.The methods of the 2 parts will be identical unless otherwise noted. The study is designed to assess the safety, tolerability, [redacted] and efficacy of SAGE-217 in adult subjects with bipolar I/II disorder, who are currently experiencing an MDE.

Screening begins with the signing of the informed consent form (ICF) at the Screening Visit. The diagnosis of bipolar I or II disorder will be made using the Structured Clinical Interview for DSM-5 for clinical trials (SCID-5-CT) performed by a qualified healthcare professional. Subjects on antidepressants or mood stabilizers (lamotrigine, lithium, and valproic acid only) that have been taken at the same dose for at least 60 days prior to Day 1 are to continue the stable dose throughout the treatment period.

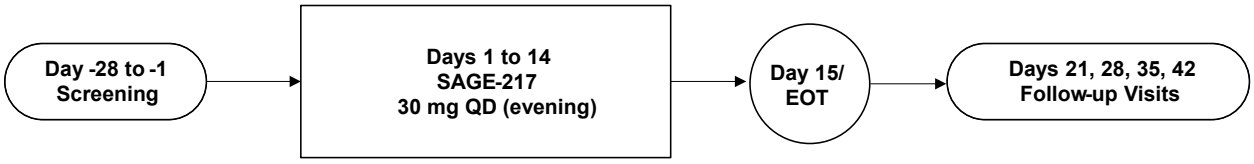
Subjects will return to the study center during the treatment and follow-up periods as outlined in the Schedule of Events (Table 1). All assessments to be performed are summarized in Table 1.

If at any time during the study, a subject has a YMRS score of ≥13, the Investigator will clinically assess the subject for a manic or hypomanic switch. If the clinical assessment is consistent with hypomania or mania, the subject will be discontinued from study drug and treated as clinically appropriate (see Section 8.3).

Part A

The study design for Part A is presented in Figure 1. In Part A, all subjects will receive SAGE-217. Beginning on Day 1, qualified subjects will self-administer 30-mg SAGE-217 once daily in the evening with food for 14 days. Dose adjustments based on study drug tolerability are permitted following the guidelines outlined in Section 7.4.

Figure 1: Study Design (Part A)



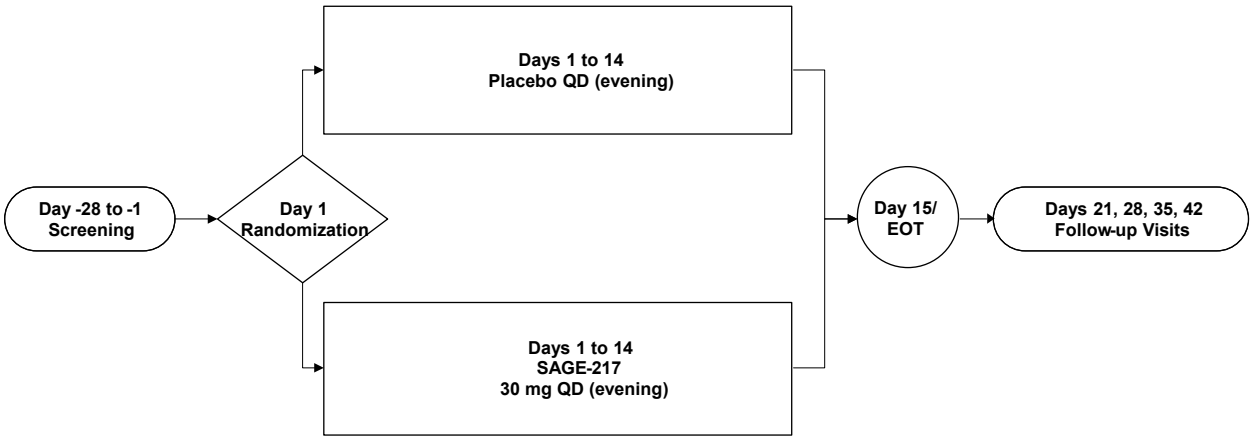
QD = once daily
A dose adjustment to 20-mg SAGE-217 is permitted if the 30-mg dose is not tolerated at any time.

Part B

The study design for Part B is presented in Figure 2. In Part B, subjects will be randomized in a 1:1 ratio to receive SAGE-217 or placebo; randomization will be stratified based on use of mood stabilizers (Y/N). Beginning on Day 1, qualified subjects will self-administer the study drug

(30 mg SAGE-217 or placebo) once daily in the evening with food for 14 days. Dose adjustments based on study drug tolerability are permitted following the guidelines outlined in Section 7.4.

Figure 2: Study Design (Part B)



QD = once daily
A dose adjustment to 20-mg SAGE-217 is permitted if the 30-mg dose is not tolerated at any time.

7.2. Number of Subjects

Part A

Approximately 30 subjects will be dosed in Part A.

Part B

After review of Part A data, approximately 132 subjects will be randomized and dosed in Part B to obtain a total of 112 evaluable subjects (see Section 13.8).

7.3. Treatment Assignment

Part A

In Part A, all subjects will receive SAGE-217 in an open-label manner.

Part B

In Part B, subjects will be randomized to a treatment group (SAGE-217 or placebo) in a 1:1 ratio; randomization will be stratified based on use of mood stabilizers (Y/N).

7.4. Dose Adjustment Criteria

If at any time, 30 mg is not tolerated, as assessed by the occurrence of a severe AE judged by the investigator to be related to study drug, the dose on the next day will be reduced to 20 mg and continued for the remainder of the treatment period. Dose adjustments related to moderate AEs will be judged by the Investigator. If a dose adjustment from 30 mg to 20 mg is deemed

necessary by the Investigator, the subject will return to the site for the adjusted dose to be dispensed. Subjects who cannot tolerate the 20-mg dose at any time will be discontinued from study drug (see Section 8.3).

7.5. Study Termination

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of 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 the conduct of any study-specific procedures.
2. Subject agrees to adhere to the study requirements, including use of prior, concomitant, and prohibited medications.
3. Subject is a man or woman, aged 18 to 65 years, inclusive, at Screening.
4. 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.
5. Subject has a documented history of hypomanic or manic episode (verified by medical records and/or treating healthcare professional) and a diagnosis of bipolar I or bipolar II disorder with a current MDE as per DSM-5 SCID-5-CT.
6. Subject has a HAM-D score of ≥22 at Screening.
7. Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are 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 or bilateral oophorectomy), or does not engage in sexual relation(s) which carry a risk of pregnancy:
   - 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 ligation/occlusion.
   - Vasectomized partner.
   - Sexual abstinence (no sexual intercourse).
8. 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 relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception for males includes sexual abstinence, 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 #7 for acceptable method of contraception for females).

9. 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.

8.2. Subject Exclusion Criteria

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

1. Subject has a history of suicide attempt within the last 2 years.
2. Subject has current suicidal ideation with plans based on Investigator clinical assessment and/or the C-SSRS response at Screening or Day 1.
3. Subject has a history of rapid cycling bipolar disorder as per DSM-5 SCID-5-CT.
4. Subject's current depressive episode meets the DSM-5 specifier criteria for mixed features.
5. Subject has ≥25% reduction in HAM-D score from Screening to Day 1.
6. 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.
7. Subject has abnormal liver function as shown by an abnormal liver function profile at screening (eg, repeated values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥2x the upper limit of normal).
8. Subject has a clinically significant abnormal 12-lead ECG at the Screening or Day 1 visits. NOTE: mean QT interval calculated using the Fridericia method (QTcF) of >450 msec in male or >470 msec in female subjects will be the basis for exclusion from the study.
9. Subject has a YMRS score ≥13 at Screening or Day 1.
10. Subject presents for the study receiving a mood stabilizer other than lamotrigine, lithium, or valproic acid.
11. Subject presents for the study receiving psychotropic medications, which have not been taken at the same dose for at least 60 days prior to Day 1.
12. Subject that presents for the study receiving psychotropic medications and does not intend to continue the current treatment regimen during the treatment period.
13. Subject is taking benzodiazepines, barbituates, or $GABA_A$ modulators (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28, or subject has been using these agents on a daily or near-daily (≥4 times per week) for more than one year.
14. Subject has a history of severe rashes or Stevens-Johnson Syndrome associated with lamotrigine and is currently taking lamotrigine.
15. Subject's current depressive episode is treatment resistant; defined as persistent depressive symptoms despite treatment with adequate doses of antidepressants from two different classes for an adequate amount of time (ie, at least 4 weeks of treatment). This

will be assessed using the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.

16. Subject has a known allergy to SAGE-217, allopregnanolone, or related compounds.
17. Subject has a positive pregnancy test at the Screening Visit or on Day 1 (prior to administration of study drug) or, if she is breastfeeding at Screening or on Day 1 (prior to administration of study drug), she does not agree to temporarily cease giving breast milk to her child(ren) from just prior to receiving study drug on Day 1 until 7 days after the last dose of study drug.
18. Subject has detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) and HCV viral load, or human immunodeficiency virus (HIV) antibody at screening.
19. Subject has active psychosis per Investigator assessment.
20. Subject has a medical history of seizures.
21. Subject has a medical history schizophrenia, and/or schizoaffective disorder.
22. Subject has a history of mild, moderate, or severe substance use disorder diagnosed using DSM-5 criteria in the 12 months prior to screening.
23. Subject has a positive drug and/or alcohol screen at screening or on Day 1 prior to dosing.
24. Subject has had exposure to another investigational medication or device within 30 days prior to the Screening visit.
25. Subject has been previously treated or randomized in any study using SAGE-217. Subjects who participate in Part A are not eligible to participate in Part B.
26. Subject has used any known strong inhibitors of cytochrome P450 (CYP)3A4 within 28 days or five half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, or Seville oranges, or products containing these within 14 days prior to receiving the first dose of study drug.
27. Subject has used strong CYP3A inducers, such as carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, or St Johns Wort within 28 days prior to the first dose of study drug.
28. Subject plans to undergo elective surgery during participation in the study.
29. Subject is taking non-GABA anti-insomnia medications (eg, melatonin, Benadryl [anti-histamines], trazodone, low dose quetiapine, mirtazapine, etc) at Day -14.
30. Subject has been taking psychostimulants (eg, methylphenidate, amphetamine) or opioids regularly or as needed, at Day -28.

8.3. Subject Withdrawal Criteria

8.3.1. Withdrawal from the Study or Discontinuation of Study Drug

Subjects may discontinue study drug or withdraw from the study at any time for any reason. The Investigator may discontinue the subject from the study or study drug 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

In addition, if at any time during the study, a subject has a YMRS score of ≥13, the Investigator will clinically assess the subject for a manic or hypomanic switch. If the clinical assessment is consistent with hypomania or mania, the subject will be discontinued from study drug and treated as clinically appropriate. These incidents will be documented as AEs.

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has discontinued or been withdrawn for any reason.

Subjects who discontinue study drug early/withdraw during the treatment period should, if possible, have an end of treatment (EOT) visit, including the EOT assessments as summarized in the Schedule of Events (Table 1). The EOT visit should be scheduled as soon as possible, preferably the day after the subject's last dose. All details of the EOT visit should be recorded in the subject's medical source documents. For subjects that discontinue study drug early, follow-up visits should take place every 7 days for 28 days. If at any time after the EOT visit, a subject decides to terminate the study early, the subject should return for an early termination (ET) visit. The EOT 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 both visits will be conducted only once.

If the subject fails or refuses to return to the study center, an attempt must be made to contact the subject by telephone in order to assess as many safety and efficacy parameters as possible. All data collected over the telephone must be documented and kept in the subject's record. A subject will be deemed lost to follow-up after 3 attempts at contact have been made and it has been at least 1 month since the last subject contact. The third attempt at contact must be a certified letter accompanied by a survey inquiring the reason for study discontinuation. All attempts at contact will be documented.

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.

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.

8.3.2. Replacement of Subjects

Part A

In Part A, subjects will not be replaced.

Part B

In Part B, subjects will not be replaced. Additional subjects may be randomized if the drop-out rate is higher than anticipated (see Section 13.8).

9. TREATMENT OF SUBJECTS

9.1. Study Drug

Subjects will self-administer study drug orally once daily in the evening with food for 14 days as outlined in Section 7.1. Practical options include taking within 1 hour of dinner, or taking later in the evening with solid food.

9.2. Prior Medications, Concomitant Medications, and Restrictions

9.2.1. Prior and Concomitant Medications and/or Supplements

The start and end dates, route of administration, 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 drugs taken within 12 months prior to Screening will be recorded.

Any concomitant medication determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study under the guidance outlined in these sections.

Antidepressants and mood stabilizers (lamotrigine, lithium, and valproic acid only) 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 throughout the treatment period.

Medications intended for contraception are permitted for female subjects (see Section 8.1):

- 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

9.2.2. Prohibited Medications

The following specific classes of medications are prohibited at any time during the treatment period:

- Initiation of new antidepressant therapy from 60 days prior to Day 1 through the end of treatment period
- Use of any benzodiazepines, $GABA_A$ modulators, $GABA_A$-like acting drugs, or GABA-containing agents from Day -28
- Use of any non-GABA anti-insomnia medications (eg, melatonin, Benadryl [anti-histamines], trazodone, low dose quetiapine, mirtazapine, etc) from Day -14
- Exposure to another investigational medication or device from 30 days prior to Screening (throughout the treatment and follow-up periods).

- Any known strong inhibitors of CYP3A4 from Day -28 or 5 half-lives prior to Day 1 (whichever is longer)
- Use of strong CYP3A inducers, such as carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, or St Johns Wort within 28 days prior to the first dose of study drug or 5 half-lives prior to Day 1 (whichever is longer)
- Use of psychostimulants (eg, methylphenidate, amphetamine) or opioids regularly or as needed, from Day -28.

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 drugs of abuse and alcohol 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 1 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.

9.3. Treatment Adherence

SAGE-217 (Parts A and B) or placebo (Part B only) will be self-administered by subjects once every evening with food. Sites will dispense study drug to the subjects to take at home with instructions for use (Section 10.4).

Administration of study drug will be monitored by a medication adherence monitoring platform used on smartphones to visually confirm medication ingestion. Subjects will receive a reminder within a predefined time window to take study drug while using the application. Subjects will follow a series of prescribed steps in front of the front-facing webcam to visually confirm their ingestion of the medication. The application will record the date and time of study drug administration by dose level, as well as missed doses.

In addition, the subject will be instructed to bring their dosing kit to each visit during the treatment period, at which time the Investigator or designee will be responsible for ensuring the kit contains sufficient doses until the next scheduled dispensation.

If the subject is persistently noncompliant with the study drug, the Investigator should discuss with Sage Therapeutics the potential discontinuation of the subject (Section 8.3). Dosing requirements will be reviewed with each subject during all study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.4. Randomization and Blinding

Part A

Part A is an open-label design in which all subjects will receive SAGE-217.

Part B

Part B is a randomized, double-blind, placebo-controlled, parallel group design. Subjects who meet the entrance criteria will be stratified based on use of mood stabilizers (Y/N) and randomly assigned within each stratum in a 1:1 ratio to receive SAGE-217 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 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.

During the study, the blind is to be broken only if the safety of a subject is at risk and the treatment plan is dependent on the study treatment received. See Section 12.6 for details of unblinding in the event of a medical emergency or pregnancy.

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.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Description of 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 10-mg, 20-mg, and 30-mg strengths to achieve the target dose of 20 mg or 30 mg.

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

10.2. Study Drug Packaging and Labeling

SAGE-217 and matched placebo will be provided to the clinic pharmacist and/or designated site staff responsible for dispensing the study drug in appropriately labeled, subject-specific kits each containing sealed unit doses. Part A is open-label and Part B is blinded. 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 Code of Federal Regulations and Good Manufacturing Practices/Good Clinical Practices guidelines will be prepared by the clinical research organization.

10.3. Study Drug Storage

SAGE-217 and matched placebo are to be stored at room temperature, safely and separately from other drugs.

10.4. Study Drug Preparation

Not applicable.

10.5. Study Drug Administration

SAGE-217 is to be administered orally in the evening with food. Practical options include taking within 1 hour of dinner, or taking later in the evening with solid food.

10.6. Study Drug Accountability

Upon receipt of study drug, the Investigator(s), or the responsible pharmacist or designee, will inspect the study drug and complete 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.

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. In the event of an unscheduled dose reduction (Section 7.4), a new subject-specific kit will be dispensed.

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 medication 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 within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

10.7. Study Drug Handling and Disposal

At the end of the study, all used and unused study drug will be reconciled and returned to Sage Therapeutics 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.

11. ASSESSMENT OF EFFICACY [redacted]

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

11.1. Efficacy Assessments

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

The primary outcome measure is the change from baseline in the 17-item HAM-D total score at Day 15.

The 17-item HAM-D will be used to rate the severity of depression in subjects who are identified as experiencing an MDE (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.

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

In addition to the primary efficacy endpoint of change from baseline in HAM-D total score, several secondary efficacy endpoints will be derived for the HAM-D. Hamilton Rating Scale for Depression subscale scores will be calculated as the sum of the items comprising each subscale. Hamilton Rating Scale for Depression response will be defined as having a 50% or greater reduction from baseline in HAM-D total score. Hamilton Rating Scale for Depression remission will be defined as having a HAM-D total score of ≤7.

The HAM-D subject interview may be audio-recorded for independent quality control purposes.

11.1.2. Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a 10-item diagnostic questionnaire used to measure the severity of depressive episodes in subjects with mood disorders. It was designed as an adjunct to the HAM-D that 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 will be calculated as the sum of the ten individual item scores.

The MADRS subject interview may be audio-recorded for independent quality control purposes.

11.1.3. Clinical Global Impression (CGI)

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.

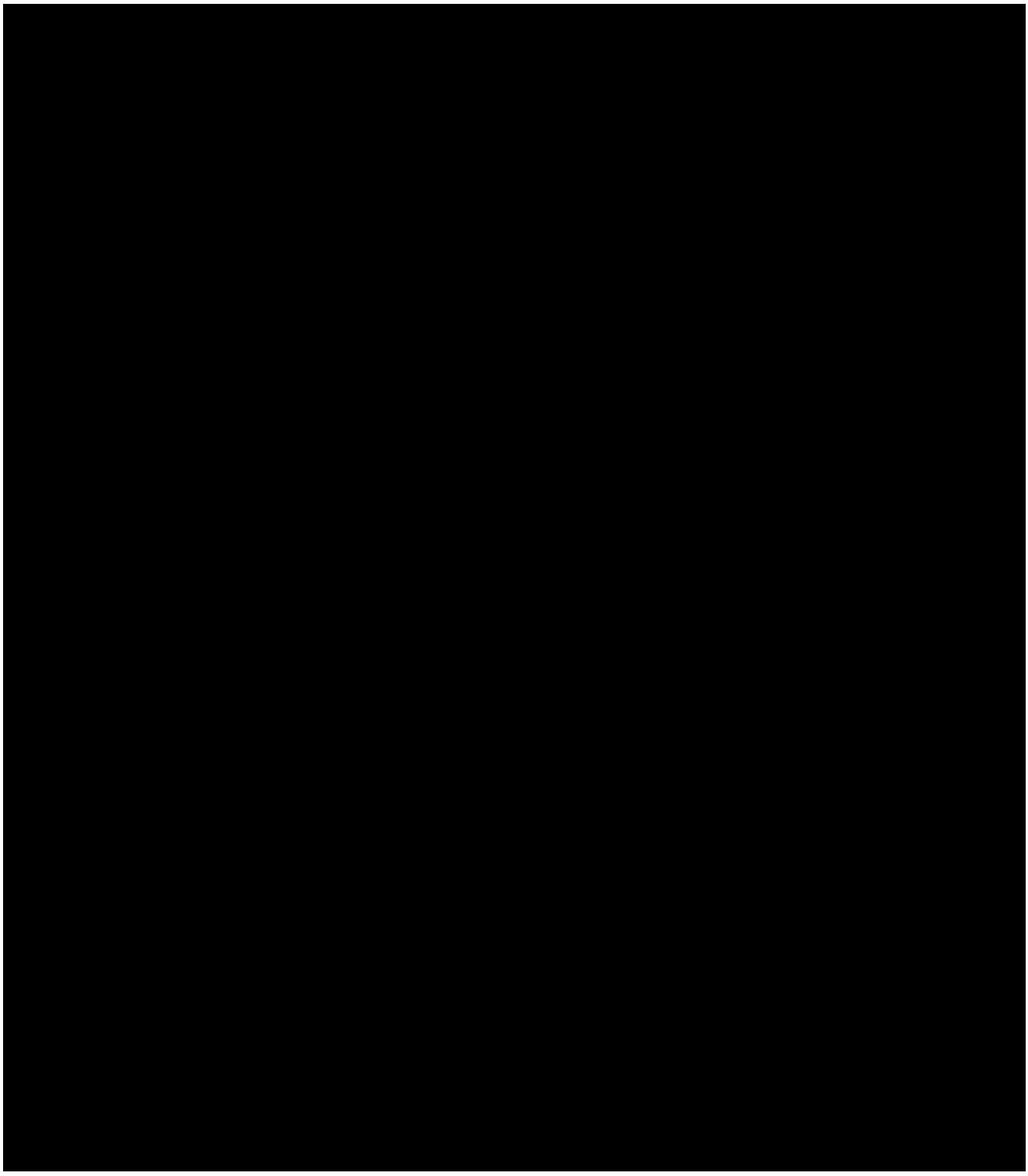
The Clinical Global Impression - Severity (CGI-S) uses a 7-point Likert scale to rate the severity of the subject's illness at the time of assessment, relative to the clinician's past experience with

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).

The Clinical Global Impression - Improvement (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."

11.1.4. Insomnia Severity Index (ISI)

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 (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)."



12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

The safety and tolerability of SAGE-217 will be assessed by the frequency and severity of AEs; changes from baseline in clinical laboratory measures, vital signs, and ECGs; suicidal ideation and behavior using the C-SSRS; and the YMRS. All assessments will be conducted according to the schedule of assessments (Table 1).

12.1.1. Demographic/Medical History

Demographic and baseline characteristics (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and a full medical history, including family psychiatric history, will be documented. The diagnosis of bipolar I or II disorder will be determined using the SCID-5-CT.

12.1.2. Weight and Height

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

12.1.3. Physical Examination

Physical examinations assessing body systems (eg, head, eye, ear, nose, and throat; heart; lungs; abdomen; and extremities), as well as cognitive and neurological examinations and mental status examinations will be conducted and documented. Whenever possible, the same individual is to perform all physical examinations for a given subject. Unscheduled brief 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 12.2.1.1.

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 in the standing position. Respiratory rate, pulse oximetry 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, with the blood sample collected as close to the scheduled time as possible.

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 12.2.1.1.

12.1.5. Electrocardiogram (ECG)

Supine 12-lead ECGs will be performed in triplicate. The standard intervals (heart rate, PR, QRS, QT, and QTcF) as well as any rhythm abnormalities will be recorded. When ECG [redacted] sample 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 12.2.1.1.

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 morphology	ALT Albumin Alkaline phosphatase AST Total bilirubin Direct bilirubin Indirect bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase GGT Potassium Sodium Lactate dehydrogenase Glucose Chloride Bicarbonate Calcium Phosphorus Triglycerides	pH Specific gravity Protein Glucose Red blood cells Nitrite Leukocyte esterase Ketones Bilirubin Urobilinogen	Activated partial thromboplastin time Prothrombin time International normalized ratio
Diagnostic Screening			
Serum	**Urine**	**Breathalyzer**	
Hepatitis B Hepatitis C HIV-1 and -2 Female subjects of child bearing potential: serum human chorionic gonadotropin	Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, and propoxyphene	Alcohol	

Female subjects, if menopause is suspected and not surgically sterile: FSH	Female subjects of child bearing potential: urine human chorionic gonadotropin		

The central laboratory will perform laboratory tests for hematology, serum chemistry, and urinalysis. 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, 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 12.2.1.1. 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.

Follicle stimulating hormone testing will be conducted at Screening to confirm whether a female subject with ≥12 months of spontaneous amenorrhea and not surgically sterile meets the protocol-defined criteria for being post-menopausal (Section 8.1).

[redacted]

12.1.6.1. Drugs of Abuse and Alcohol

Urine toxicology will be performed for selected drugs of abuse, and a breath test will be performed for alcohol (Table 1).

12.1.6.2. Pregnancy Screen

A serum pregnancy test in women of child-bearing potential will be conducted at Screening and a urine pregnancy test will be conducted at all other scheduled timepoints (Table 1).

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

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. Young Mania Rating Scale (YMRS)

Manic symptoms will be assessed during the study using the YMRS (Young 1978). The clinician-administered scale is based on 11 items of core symptoms of mania. Four of the items (irritability, speech, thought content, and disruptive/aggressive behavior) are graded on a scale of 0 to 8 (choices given as even numbers), with the remaining 7 items graded on a scale of 0 to 4. Scoring between the points given (whole or half points) is possible.

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 TEAE is an AE that occurs after the first administration of any study drug. The term study drug includes any Sage investigational product, a comparator, or a placebo administered in a clinical trial.

An abnormal laboratory value will be considered an AE if the value represents a clinically significant change from baseline as determined by the Investigator.

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

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 been enrolled and throughout the duration of the study, whether or not they are related to the study, must be recorded on the SAE form provided by Sage Therapeutics within 24 hours of first awareness (Section 12.5). All SAEs should to be followed until the event resolved, the condition stabilized, was no longer considered clinically significant or the subject was lost to follow-up.

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 the 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 the sponsor.

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 or a complication relating to the pregnancy occurs (eg, spontaneous abortion). 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 Serious Adverse Events

All SAEs must be reported to Sage, 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 staff on the SAE report form. 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. Each site is responsible for notifying its ethics committee of these SUSARs. 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 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. The blinding of the study will be broken after the database has been locked. Electronic copies of the randomization code will be made available to the laboratory performing the bioanalytical analyses in order to allow for limited analysis of samples from subjects receiving placebo.

In the event of a medical emergency or pregnancy, the Investigator will discuss with the Medical Monitor if unblinding is warranted for medical management of the subject. If there is agreement to unblind treatment assignment, the unblinding procedure described in the Safety Management Plan for the study will be followed. If the Investigator is unable to contact the Medical Monitor in a medical emergency, and it is deemed clinically necessary by the Investigator, the treatment group for that subject may be unblinded in the IRT system.

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) for each part (Part A and B) will provide a detailed description of the analyses to be performed in the respective part of the study. The SAPs will be finalized and approved prior to database lock. Any deviations from or changes to the respective SAP following database lock will be described in detail in the clinical study report.

13.1. Data Analysis Sets

The Safety Set, defined as all subjects that received at least 1 dose of study drug, will be used to provide descriptive summaries of safety data.

The Efficacy Set, defined as all subjects in the Safety Set that have at least 1 post-baseline HAM-D evaluation, will be used to analyze efficacy data, unless otherwise specified.

[redacted]

Part B will also include a Randomized Set, defined as all subjects who are randomized. This analysis set will be used for all data listings in Part B.

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 sets, using all non-missing data available. No imputation process will be used to estimate missing data.

13.3. General Considerations

For the purpose of all primary and secondary analyses where applicable, baseline is defined as the last measurement prior to receipt of study drug.

Continuous endpoints will be summarized with number (n), mean, standard deviation (SD), 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 (Section 12.1.1) and baseline characteristics, such as height, weight, and body mass index, will be summarized using the Safety Set.

Pregnancy results will be listed but not summarized.

Medical history will be listed by subject.

13.5. Efficacy Analysis

The primary efficacy endpoint, the change from baseline in HAM-D total score at Day 15, will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include center, treatment, baseline HAM-D total score, stratification factor, assessment time point, and time point-by-treatment as explanatory variables. All explanatory variables will be

considered as fixed effects and the subject effect will be considered random in the model. All post-baseline time points will be included in the model. The primary comparison will be between SAGE-217 and matching placebo at Day 15. Model-based point estimates (ie, least squares [LS] means, 95% confidence intervals, and p values) will be reported. An unstructured covariance structure will be used to model the within-subject errors. In case of convergence issues, other covariance structures will be considered; this will be detailed in the statistical analyses plan. Other continuous endpoints will be analyzed using similar methods.

Other efficacy analyses will be specified in the statistical analysis plan. In general, data will be analyzed using appropriate descriptive statistics or pre-specified statistical methods as applicable; subject listings will be provided for all efficacy data. Subjects will be analyzed according to randomized treatment for the purpose of efficacy unless otherwise specified.

13.6. Safety Analyses

Safety and tolerability of SAGE-217 will be assessed by the frequency and severity of AEs; changes from baseline in clinical laboratory measures, vital signs, and ECGs. Suicidal ideation and behavior will be evaluated using the C-SSRS. Mania will be evaluated using the YMRS. Safety data will be listed by subject and summarized by treatment group. All safety summaries will be performed on the Safety Set.

13.6.1. Adverse Events

The analysis of AEs 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 20.1 or higher, system organ class (SOC), and preferred term (PT). 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 (Section 13.6.1).

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

Clinical laboratory results will be listed by subject and timing of collection. Mean changes from baseline in clinical laboratory measures will be evaluated.

13.6.3. Physical Examinations

Physical examination data will be listed by subject, but not summarized.

13.6.4. Vital Signs

Vital sign results will be listed by subject and timing of collection. Mean changes from baseline in vital signs will be evaluated by time point.

13.6.5. 12-Lead Electrocardiogram

The following ECG parameters will be listed for each subject: heart rate, PR, QRS, QT, and QTcF. Any clinically significant abnormalities or changes in ECGs should be listed as an AE. 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.

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 will be summarized and 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. Young Mania Rating Scale

Mania data collected on the YMRS at baseline and by visit will be summarized and listed for all subjects.

[redacted]

13.8. Determination of Sample Size

13.8.1. Part A

For Part A, the sample size of approximately 30 subjects was selected based on clinical and not statistical considerations.

13.8.2. Part B

For Part B, assuming a two-sided alpha level of 0.05, a sample size of 112 total evaluable subjects (56 per treatment group) would provide 80% power to detect a placebo-adjusted treatment difference of approximately 4 points in the primary endpoint, change from baseline in HAM-D total score at Day 15, assuming standard deviation (SD) of 7.5 points.

Assuming a 15% dropout rate, approximately 132 total randomized subjects will be required to obtain a total of 112 evaluable subjects. Evaluable subjects are defined as those randomized subjects who receive study drug and have a valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the drop-out rate is higher than 15%.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the study site guarantee access to source documents by Sage Therapeutics or sponsor's designee and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by Sage Therapeutics or sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

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. Protocol Deviations

Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the Sage Therapeutics or sponsor's designee (and IRB, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

14.4. 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 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 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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Protocol 217-BPD-201, Amendment 3

Date of Amendment: 16 January 2019

A 2-Part Study (Open-label followed by Double-blind, Randomized, Placebo-controlled, Parallel Group) of the Safety, Tolerability, Pharmacokinetics, and Efficacy of SAGE-217 in the Treatment of Subjects with Bipolar I/II Disorder with a Current Major Depressive Episode

Rationale for Protocol Amendment

The primary purpose for this protocol amendment is as follows:

- Updated Inclusion/Exclusion criteria to keep consistency within the SAGE-217 program. This includes contraception use by subjects (and partners of subjects), clarification of use of benzodiazepines and $GABA_A$ modulator agents, and use of CYP3A inducers.
- Addition of the following Exclusion criterion: Subject has been taking psychostimulants (eg, methylphenidate, amphetamine) or opioids regularly or as needed, at Day -28.

Additional changes are being implemented as outlined below:

- Updated sponsor contact
- Updated secondary endpoints to be specific to one timepoint
- Updated description of SAGE-217 and reference therapy dosage and mode of administration.
- Changed collection period of prior psychotropic medications (from 6 to 12 months).
- Added cut-off date for SAEs in SAGE-217 program.
- Clarified details in the "Prohibited Medications" section for consistency with Inclusion/Exclusion criteria.
- Added "or surgically sterile" regarding FSH assessment.

A detailed summary of changes is provided in Table 1. Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting are not detailed.

Table 1: Protocol Amendment 3 Detailed Summary of Changes

The primary section of the protocol affected by the changes in Protocol Amendment 3 is indicated. The corresponding related text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: Updated Inclusion/Exclusion criteria to keep consistency within the SAGE-217 program. This includes contraception use by subjects (and partners of subjects), clarification of use of benzodiazepines and $GABA_A$ modulator agents, and use of CYP3A inducers.

The primary change occurs in Section 8.1 Subject Inclusion Criteria and 8.2 Subject Exclusion Criteria

Changed text:

From Inclusion:

7. Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are 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 or bilateral oophorectomy), or **does not engage** in sexual relation**(s)**~~ship(s)~~ which ~~do not~~ carry a risk of pregnancy ~~(eg, same-sex relationship(s)).~~

   - 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 ligation/occlusion.
   - Vasectomized partner.
   - Sexual abstinence (no sexual intercourse).

8. 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** ~~is~~ sexual relation~~ship~~(s) which ~~do not~~ carry a risk of pregnancy ~~(eg, same-sex relationship(s))~~. Acceptable methods of effective contraception for males includes sexual abstinence, 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 #7 for acceptable method of contraception for females).

From Exclusion Criteria:

13. Subject is taking benzodiazepines**, barbiturates,** or $GABA_A$ modulators~~/GABA-containing agents~~ (eg, eszopiclone, zopiclone, zaleplon, and zolpidem) at Day -28**, or subject has been using these agents on a daily or near-daily (≥4 times per week) for more than one year**.

27. Subject has used **strong CYP3A inducers, such as carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, or St Johns wort within 28 days prior to the first dose of study drug.**~~CYP inducers, such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort, within 28 days prior to the first dose of study drug~~

Sections also affected by this change:

- Synopsis

Purpose: Added exclusion related to psychostimulants and opioids.

The primary change occurs in Section 8.2. Subject Exclusion Criteria

Added text:

30. Subject has been taking psychostimulants (eg, methylphenidate, amphetamine) or opioids regularly or as needed, at Day -28.

Sections also affected by this change:

- Synopsis

Purpose: Updated sponsor contact.

The primary change occurs on the Title Pahe

Changed text:

[redacted]
~~Tel:~~ [redacted]
~~email:~~ [redacted]

[redacted]
Tel: [redacted]
email: [redacted]

Purpose: Timing of assessments was removed as these will be defined in the Statistical Analysis Plan.

The primary change occurs in Section 6.2 Endpoints

Changed text:

Part A Secondary:

- The reduction in depressive symptoms, as assessed by:
  - Change from baseline in the 17-item Hamilton Depression Rating Scale (HAM-D) total score at Day 15~~ and all other time points~~
  - HAM-D ~~response at Day 15 and all other time points~~
  - HAM-D remission at Day 15~~ and all other time points~~
  - ~~o~~ Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score ~~at Day 15 and all other time points~~
  - ~~o Change from baseline in HAM-D individual item scores at Day 15 and all other time points~~
  - The response to the Clinical Global Impression scale for severity and improvement (CGI-S and CGI-I, respectively) at Day 15~~ and all other time points.~~

Part B Secondary:

- The reduction in depressive symptoms, as assessed by:
  - Change from baseline in HAM-D total score **at Day 15** ~~at all other time points~~
  - HAM-D response at Day 15 ~~and all other time points~~
  - HAM-D remission at Day 15 ~~and all other time points~~
  - Change from baseline in the MADRS total score at Day 15~~ and all other time points~~
  - ~~Change from baseline in HAM-D individual item scores~~ ~~at Day 15 and all other time points~~
  - CGI-S and CGI-I response at Day 15~~ and all other time points~~

Sections also affected by this change:

- Synopsis

Purpose: Update description of SAGE-217 and reference therapy dosage and mode of administration.

The primary change occurs in the synopsis

Changed text:

SAGE-217 dosage and mode of administration:

~~SAGE-217 is available as hard gelatin capsules containing a white to off-white powder. In addition to SAGE-217 Drug Substance, the 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. Subjects will take the assigned dose~~ **SAGE-217 (30 mg) will be administered** orally once daily in the evening with food.

Reference therapy, dosage and mode of administration (Part B only): ~~In Part B, placebo capsules are visually matched to the active capsules and are available as hard gelatin capsules containing only the excipients listed above for the active capsule treatment~~ **Placebo capsules will only be used for Part B.** Study drug **placebo** will be administered orally once daily in the evening with food.

Purpose: Changed collection period of prior psychotropic medications (from 6 to 12 months).

The change occurs in Schedule of Events and Section 9.2.1 Prior and Concomitant Medications and/or Supplements

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Purpose: Added cut-off date for SAEs in SAGE-217 program to align with IB.

The primary change occurs in Section 5.2 SAGE-217

Changed text:

As of the IB cut-off date (24 September 2018), 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.

Purpose: Clarified details in the "Prohibited Medications" section for consistency with Inclusion/Exclusion criteria.

The primary change occurs in Section 9.2.2 Prohibited Medications

Changed text:

The following specific classes of medications are prohibited at any time during the treatment period:

- ~~Initiation of new psychotropic medications at any time during the study~~
- Initiation of new antidepressant therapy from 60 days prior to Day 1 through the ~~duration of the study~~ **end of treatment period**
- Use of any benzodiazepines, $GABA_A$ modulators, $GABA_A$-like acting drugs, or GABA-containing agents from Day -28. ~~through the duration of the study~~
- Use of any non-GABA anti-insomnia medications (eg, melatonin, Benadryl [anti-histamines], trazodone, low dose quetiapine, mirtazapine, etc) from Day -14 ~~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~~ **(throughout the treatment and follow-up periods)**
- Any known strong inhibitors of CYP3A4 from Day -28 or 5 half-lives prior to Day 1 (whichever is longer) ~~through the duration of the study~~
- **Use of strong CYP3A inducers, such as carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, or St Johns Wort within 28 days prior to the first dose of study drug** ~~Use of any CYP inducer, such as such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital and St John's Wort from Day -28 through the duration of the study.~~ **or 5 half-lives prior to Day 1 (whichever is longer)** ~~through the duration of the study~~
- **Use of psychostimulants (eg, methylphenidate, amphetamine) or opioids regularly or as needed, from Day -28.**

Purpose: Added "or surgically sterile" from FSH assessment.

The primary change occurs in Section 12.1.6 Laboratory Assessments

Changed text: Follicle stimulating hormone testing will be conducted at Screening to confirm whether a female subject with ≥12 months of spontaneous amenorrhea **and not surgically sterile** meets the protocol-defined criteria for being post-menopausal**.**

Sections also affected by this change:

- Schedule of Events

Purpose: *Correct typographical errors, punctuation, grammar, abbreviations, and formatting.*

These changes are not listed individually.
