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
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9. DOCUMENTATION OF STATISTICAL METHODS

Statistical Analysis Plan

SAGE THERAPEUTICS INCORPORATED

Statistical Analysis Plan

Methods

Protocol Number SAGE-217-BPD-201

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

Author of SAP: [redacted]

Version: Version 1.0

Version Date of SAP: 12 JUN 2019

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Authorization Signature Page

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

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2 LIST OF ABBREVIATIONS

Abbreviation or specialist term	Explanation
ADaM	Analysis Data Model
AE	adverse event
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical Classification
BLQ	Below the Limit of Quantitation
BUN	Blood urea nitrogen
C	Celsius
CGI-I	Clinical Global Impression scale for improvement
CGI-S	Clinical Global Impression scale for severity
C-SSRS	Columbia Suicide Severity Rating Scale
ECG	Electrocardiogram
EOT	end of treatment
ET	early termination
[redacted]	[redacted]
FSH	follicle stimulating hormone
GGT	Gamma Glutamyl Transferase
HAM-D	Hamilton Rating Scale for Depression, 17-item
HIV	human immunodeficiency virus
ICF	informed consent form
ISI	Insomnia Severity Index
LFT	Liver function tests
LLOQ	Lower Limit of Quantification
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
PCS	potentially clinically significant
PCSC	potentially clinically significant change
[redacted]	[redacted]
PT	Preferred term
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]
SDTM	Study Data Tabulation Model
[redacted]	[redacted]
SI	International System of Units
SOC	System organ class
SpO_2	Pulse oximetry
TEAE	treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell count
WHO-DD	World Health Organization-Drug dictionary
YMRS	Young Mania Rating Scale

3 INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis and is based on the approved clinical study protocol, 217-BPD-201, dated 16 Jan 2019, version 4.0.

Protocol 217-BPD-201 is an umbrella protocol that describes methods for two parts, referred to as Parts A and B (hereafter referred to as Study 217-BPD-201A and Study 217-BPD-201B, respectively). These two parts will be conducted as two separate studies and will be analyzed and reported as such: Study 217-BPD-201A and Study 217-BPD-201B.

The purpose of the SAP is to describe in detail the statistical methodology and the statistical analyses to be conducted for the above-mentioned protocol for Study 217-BPD-201A. The SAP will be approved and finalized before Part A database lock.

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of Study 217-BPD-201A is to evaluate the safety and tolerability of SAGE-217 in subjects with bipolar I/II disorder with a current major depressive episode (MDE).

4.2 Secondary Objective

The secondary objectives of Study 217-BPD-201A 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.

[redacted]

5 STUDY ENDPOINTS

5.1 Primary Endpoint

- The primary endpoint for Study 217-BPD-201A 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).

5.2 Secondary Endpoints

Secondary endpoints of this study are:

- 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
    - Change from baseline in HAM-D individual item scores at Day 15
    - The response to the Clinical Global Impression scale for severity (CGI-S) and improvement (CGI-I) at Day 15.
- The reduction in insomnia severity, as assessed by Insomnia Severity Index (ISI) at Day 15.

[redacted]

6 STUDY DESIGN

6.1 Overall Design

Study 217-BPD-201A 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 Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition 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 (Appendix A). All assessments to be performed are summarized in Appendix A.

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 Clinical Protocol Section 8.3).

The study design for 217-BPD-201A is presented in Figure 1. 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 Clinical Protocol Section 7.4.

Figure 1: Study Design (217-BPD-201A)

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

6.2 Sample Size and Power

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

6.3 Randomization

Study 217-BPD-201A is an open-label design, hence randomization does not apply.

6.4 Blinding and Unblinding

All subjects who receive any study drug in this part of the study, 217-BPD-201A, will receive SAGE-217 in an open-label manner, hence blinding/unblinding does not apply.

7 MODIFICATIONS

7.1 Modifications to the Approved Clinical Study Protocol

There are no modifications from the clinical study protocol (version 4.0, dated 16 JAN 2019).

7.2 Modifications to the Approved Statistical Analysis Plan

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

7.3 Modifications to the Approved DMC Charter

Not applicable.

8 ANALYSIS SETS

8.1 Safety Set

The Safety Set is defined as all subjects that received at least 1 dose of study drug.

8.2 Efficacy Set

The Efficacy Set is defined as all subjects in the Safety Set that have at least 1 post-baseline HAM-D evaluation.

[redacted]

[redacted]

8.5 Modified Safety Set

The Modified Safety Set is defined as all subjects in the Safety Set who have taken at least 14 capsules over the first 7 days of planned treatment period for profill patients and at least 7 capsules over the first 7 days of planned treatment period for autofill patients. [Profill and autofill patients are identified by the kit type used (Pro Kit Type for profill patients and Auto Kit Type for autofill patients).]

8.6 Modified Efficacy Set

The Modified Efficacy Set is defined as all subjects in the Efficacy Set who have taken at least 14 capsules over the first 7 days of planned treatment period for profill patients and at least 7 capsules over the first 7 days of planned treatment period for autofill patients.

9 STATISTICAL ANALYSIS

9.1 General Considerations

Unless otherwise specified, continuous endpoints will be summarized with n, mean, standard deviation (SD), median, minimum (min) and maximum (max). If the measurements in the source (raw) data are integers, then the corresponding mean and median will be presented to 1 decimal place and the SD to 2 decimal places; if the measurements are obtained to 1 decimal place, then the mean and median will be presented to 2 decimal places and the SD to 3 decimal places; and so forth. Minimum and maximum will be displayed as reported in the source (raw) data. In addition, change from baseline values (visit value – baseline value) will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages. Percentages will be presented to 1 decimal place unless otherwise specified; the denominator of percentages will be the number of subjects in the analysis set used unless specified otherwise.

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

All subject data, including those derived, to support tables and figures will be presented in the subject data listings. In general, the subject data listings will be sorted by subject number and assessment visit and date (and time, if applicable). The summary tables will be presented descriptively in a pooled group for the analysis population.

For the purpose of all safety and efficacy analyses, baseline is defined as the last non-missing measurement prior to the first dose of study drug.

Last value on treatment is derived as the last value after the first dose of study drug and on or before last dose of study drug +1 day. Last value on study is derived as the last value after the first dose of study drug.

9.1.1 Study Day Definition

Study day will be defined as follows:

- The day of subject receiving the first dose of study drug is designated as Day 1.

- For visit days after Day 1, study day = visit date – Day 1 date + 1.
- For visit days prior to Day 1, study day = visit date – Day 1 date. Thus, study days for screening visit are negative numbers. There is no "Day 0".

9.1.2 Missing Data

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis sets, using all non-missing data available. No imputation process will be used to estimate missing data. Imputation of missing data in scoring of questionnaires are discussed in respective sections below. Handling of missing or incomplete dates have been discussed in Section 12.3, Appendix B.

9.2 Background Characteristics

9.2.1 Subject Disposition

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

The summaries of subject disposition will include the number and percentage of subjects who received study drug, who completed the study, who prematurely withdrawn from the study, primary reasons for not completing the study, who discontinued treatment, and primary reasons for discontinuing treatment. In addition, the number and percentage of subjects who underwent a dose reduction to 20mg will be provided. A completer for the study is defined as one who completed the final follow up visit (Day 42), and is derived from the study conclusion CRF page with completion question answered Yes. A subject who is marked as discontinuing treatment prematurely in the treatment discontinuation CRF page is considered prematurely discontinuing treatment; the main reason is provided in the same CRF page.

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

A separate data listing will be provided for all subjects who prematurely discontinued treatment or prematurely withdrew from the study with reasons, number of days on study drug, the number of days in each dose of study drug, etc.

A data listing of screen failure subjects with date of informed consent, demographic information, any AE/serious adverse event (SAE) and eligibility criteria information will be provided.

9.2.2 Protocol Deviations

Protocol deviation analyses will use the Safety Set.

Protocol deviations identified during site monitoring in consultation with Medical Monitor will be captured in a protocol deviation log and categorized as major and minor deviations. These deviations will be summarized by major-efficacy, major-safety, major-GCP, and minor.

9.2.3 Demographics and Baseline Characteristics

The following analyses will use the Safety Set.

Demographic data (age, race, gender, ethnicity, employment status, highest education level, marital/civil status) and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized. Highest education level will be categorized in the summary tables as follows:

Less than 12^{th} grade
12^{th} grade diploma or GED
Some college but no degree
Associate degree

Bachelor's degree
Master's degree
Professional degree
Doctoral degree

Baseline subgroups will be summarized for the following categories:

- Race (Black or African American, White, Other)
- Age group (18-24, 25-50, 51-65 years)
- Baseline antidepressant use (Yes, No)
- Baseline use of mood stabilizer (Yes – Lamotrigine, Lithium, Valproic acid, No)
- BMI ($\leq$18.4, 18.5-24.9, 25-29.9, $\geq$30 kg/m^2)

Pregnancy results will be listed but not summarized.

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

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

9.2.4 Medical/Surgical History

The following analyses will use the Safety Set.

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

Medical/surgical history data will be summarized by system organ class (SOC) and preferred term (PT).

Detailed history of bipolar (type of bipolar, date of initial diagnosis, type of episode, etc.) will be collected. Type of bipolar, years since initial diagnosis of bipolar, anti-depressant usage, etc. will be summarized. Other psychiatric disorders (excluding bipolar) status and history will be listed and summarized separately from bipolar. Family history of psychiatric disorders will be summarized. Years since initial diagnosis of bipolar, anti-depressant usage, etc. will be calculated using: First dose date of the study drug – Date of interest. For imputation of incomplete dates in disease history, please see section 12.2.3.

9.2.5 Prior and Concomitant Medications / Concomitant Procedures

The following analyses will use the Safety Set.

All medications taken and procedures undergone during the study will be recorded; in addition, psychotropic medications taken within 6 months prior to screening, and non-psychotropic medications taken within 30 days prior to screening will also be collected. All medications will be coded using World Health Organization-Drug dictionary (WHO-DD) March 2018 or later.

Medications will be presented according to whether they are being taken prior to and/or during the study (concomitant). Prior medications are defined as those taken prior to the initiation of the start of study drug. Concomitant medications are defined as 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. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

- Concomitant medications will be further divided by usage period as follows (if time is missing, the date will be used for this algorithm): On treatment concomitant medications are those that have been used any time from start of first dose to the last dose of study drug.
- Post-treatment concomitant medications are those that have been started after the last dose of study drug.

Prior and concomitant non-psychotropic medication summaries will be performed by anatomical therapeutic chemical (ATC) level 1 and Generic Term. Similar summary tables will be provided for psychotropic medications.

Screening criteria for this study requires that if the patient is using a mood stabilizer before the first dose of the study drug, this must be one of the following three medications – Lamotrigine, Lithium, Valproic acid. If the patient started a mood stabilizer before the first dose of the study drug and continued the same dose after first dose, they will be considered as baseline users. Anti-depressant use is permitted for entry into the study as long as it is at stable dose for 60 days prior to the first dose of study. Anti-depressant medications are identified by ATC3 level code of N06A. If the patient started anti-depressant medications prior to first dose of the study drug and continued after first dose, they will be considered as baseline users. A summary of anti-depressant use at baseline versus use of different mood stabilizers at baseline will be provided. In addition, any change in these medications post-baseline (including the follow up period) will be summarized.

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

9.2.6 Study Drug Exposure

The following analyses will use the Safety Set

Total drug exposure (in mg) is defined as the total study drug in mg that were taken during the study. Subjects on Profill capsules will be administered 2 capsules per dose. If the subject takes one capsule instead of 2 in a day, the dose taken on that day is considered 30mg if this happened within Day 1 and Day 14 (both inclusive) without any dose reduction to 20mg before this day; otherwise the dose taken on that day is considered 10mg. Subjects on Autofill capsules will be administered 1 capsule per dose. If the patient skips dose on any of the days, the dose taken is 0mg.

Total exposure duration to study drug (in days) is defined as total number of days treated with study drug during the study: Date of last dose – date of first dose + 1.

Percent of planned exposure received is defined as the total drug exposure, divided by planned exposure, times 100. For subjects who complete the treatment period, planned exposure is 14 days of treatment planned, times 30 mg. For subjects who discontinue the treatment early, the planned exposure is (Last dose date – First dose date + 1), times 30 mg.

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

9.2.7 Study Drug Adherence

The following analyses will use the Efficacy Set.

Study drug adherence (%) is defined as the total number of capsules taken divided by total number of planned capsules, times 100. For autofill patients, planned dose is one capsule per day; for profill patients, planned dose is two capsules per day. Number of planned capsules for study drug intake is defined as follows:

1. If the subject discontinues treatment within Day 2 and Day 14 (both inclusive), the planned number of capsules is the last dose day of study drug if the subject took autofill capsules, and the last dose day of study drug, times 2, if the subject took profill capsules.

2. If the subject does not discontinue treatment, the planned number of capsules is 14 for autofill subjects and 28 for profill subjects.

Study drug adherence will be descriptively summarized.

9.3 Efficacy Analysis

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

9.3.1 Definition of Efficacy Variables

The efficacy variables are defined as follows:

9.3.1.1 Hamilton Rating Scale for Depression (HAM-D)

The 17-item HAM-D will be used to rate the severity of depression in subjects who are identified as experiencing an MDE. HAM-D is collected during the clinic visit at Screening, Days 1, 3, 8, 12, 15, 21, 28, 35, 42.The 17-item HAM-D comprises individual ratings related to the following symptoms: depressed mood (sadness, hopeless, helpless, worthless), feelings of guilt, suicide, insomnia (early, middle, late), work and activities, retardation (slowness of thought and speech; impaired ability to concentrate; decreased motor activity), agitation, anxiety (psychic and somatic), somatic symptoms (gastrointestinal and general), genital symptoms, hypochondriasis, loss of weight, and insight. Each item is scored in a range of 0 to 2 or 0 to 4, with higher scores indicating a greater degree of depression. The score for each item will be summed to compute a total score, which ranges from 0 to 52. If more than 3 individual items are missing, the HAM-D total score will not be calculated and will be left as missing. If less than or equal to 3 individual item scores are missing, the missing item scores will be imputed by the mean of all other available item scores, or the maximum possible values for the missing responses, whichever is smaller, to calculate the HAM-D total score.

HAM-D Response will be defined as a 50% or greater reduction from baseline in HAM-D total score. HAM-D Remission will be defined as a HAM-D total score of ≤7. The Core Subscale score is the sum of the following symptom scores: depressed mood, feelings of guilt, suicide, work and activities, and retardation. The Anxiety Subscale score is the sum of the following symptom scores: anxiety (psychic and somatic), somatic symptoms (gastrointestinal and general), hypochondriasis, and loss of weight. The Bech-6 Subscale score is the sum of the following symptom scores: depressed mood,

feelings of guilt, work and activities, retardation, anxiety psychic, and somatic symptoms general. The Meier Subscale score is the sum of the following symptom scores: depressed mood, feelings of guilt, work and activities, retardation, agitation, and anxiety psychic.

9.3.1.2 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. MADRS is collected during the clinic visit on Days 1, 3, 8, 12, 15, 21, 28, 35, and 42.

Each MADRS item ranges from 0 to 6; higher MADRS scores indicate more severe depression. The MADRS total score will be calculated as the sum of the 10 individual item scores, which ranges from 0 to 60. If more than two individual items are missing, the MADRS total score will not be calculated and will be left as missing. If less than or equal to two individual item scores are missing, the missing item scores will be imputed by the mean of all other available item scores, to calculate the MADRS total score.

9.3.1.3 Clinical Global Impression – Severity (CGI-S)

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. CGI-S is collected during the clinic visit on Days 1, 3, 8, 12, 15, 21, 28, 35, and 42.

9.3.1.4 Clinical Global Impression – Improvement (CGI-I)

The Clinical Global Impression - Improvement (CGI-I) employs a 7-point Likert scale to measure the overall improvement in the subject's condition post-treatment. The Investigator will rate the subject's total improvement. Response choices include: 0=not assessed, 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse. The CGI-I is only rated at post-treatment assessments on Days 3, 8, 12, 15, 21, 28, 35, 42. By definition, all CGI-I assessments are evaluated against baseline conditions. CGI-I response will be defined as having a CGI-I score of "very much improved" or "much improved." Missing CGI-I at the visit will not be evaluated for response.

9.3.1.5 Insomnia Severity Index (ISI)

The ISI is a validated, 7-item questionnaire designed to assess the nature, severity, and impact of insomnia. It is collected during the clinic visit on Days 1, 8, 15, 21, 28, 42. The ISI uses a 5-point Likert Scale to measure various aspects of insomnia severity (0 = none, 1 = mild, 2 = moderate; 3 = severe; 4 = very severe), satisfaction with current sleep pattern (0 = very satisfied, 1 = satisfied, 2 =neutral, 3 = dissatisfied, 4 = very dissatisfied), and various aspects of the impact of insomnia on daily functioning (0 = not at all, 1 = a little, 2 = somewhat, 3 = much, 4 = very much). The total score is derived as the sum of item scores. If more than 1 individual items are missing, the ISI total score will not be calculated and will be left as missing. If less than or equal to 1 individual item scores are missing, the missing item scores will be imputed by the mean of all other available item scores to calculate the ISI total score. Total score is categorized as: 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)." Improvement since baseline is defined as a shift to a lower category compared to baseline.

9.3.2 Visit Windows

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

Once analysis visit windows are assigned, all visits, including scheduled visits, unscheduled visits, and EOT/ET visits will be eligible for being flagged as the "analyzed record" within the analysis window, a subject's individual analysis visit window could potentially contain more than 1 visit. In the event of multiple visits falling within an analysis window or in case of a tie, the following rules will be used in sequence to determine the "analyzed record" for the analysis visit window:

- If there is a scheduled visit/day for the analysis visit window, then the scheduled visit/day data will be used.
- If there is no scheduled visit/day for the analysis visit window, the data closest to the scheduled day/time will be used.
- If there is no scheduled visit/day for the analysis visit window and there is a tie between the data in the number of days/hours before and after the scheduled day, the later data will be used.

The summary by visit will use "analyzed records" only ---at most one per subject. However, any time post-baseline PCS values or last value on treatment/study will use all analyzed records as well as any other record available in the respective time frame.

An unscheduled visit that does not fall under any window (e.g. in case one is available after Day 45) will remain in the database and will be included in the listings. The data not flagged as the "analyzed record" will be included in subject listings. Table 1 displays windows for efficacy analysis.

Table 1: Visit Windows for Efficacy Analysis

Scheduled Visit	Study Day of Expected Visit	Study Day Window for Visit
Screening	Day -1	Days (-28) to (-1)
First Dose	Day 1 (pre-dose)	Day 1 (pre-dose)
Day 3 (+1 day)	Day 3	Day 2 - Day 5
Day 8 (±1 day)	Day 8	Day 6- Day 9
Day 12 (±1 day)	Day 12	Day 10 - Day 13
Day 15 (±1 day)	Day 15	Day 14 - Day 17
Day 21/last dose +7 days (±3 day)	Day 21/ (last dose +7 days)	Day 18 - Day 24 (last dose day+4 days, +10 days)
Day 28/last dose +14 days (±3 day)	Day 28/ (last dose +14 days)	Day 25 - Day 31(last dose day +11days, +17 days)
Day 35/last dose +21 days (±3 days)	Day 35(/last dose +21 days)	Day 32 – 38 (last dose date+ 18 days, +24 days)

Day 42/last dose+28 days (±3 days)	Day 42(/last dose+28 days)	Day 39 – 45 (last dose date+25 days, +31 days)

Note: Parenthesized study day and study day window are for unscheduled, EOT or ET visits that occur at least 4 days after the last dose date.

9.3.3 Analysis of Efficacy Variable(s)

The Efficacy Set will be used for all efficacy summary tables.

The following efficacy endpoints will be summarized descriptively by scheduled assessment time point (including last value on treatment and last value on study, separately):

- HAM-D total score – observed, change from baseline, percent change from baseline
- HAM-D individual item score -– observed, change from baseline, percent change from baseline
- MADRS total score – observed, change from baseline, percent change from baseline -
- MADRS individual item score – observed, change from baseline, percent change from baseline
- ISI total score – observed (including categories) including any shift toward improvement from baseline
- CGI-I score – observed
- CGI-S score – observed and change from baseline
- HAM-D response
- HAM-D remission
- CGI-I response

If the Modified Efficacy Set is less than 90% of the Efficacy Set, a sensitivity analysis of the HAM-D change from baseline in total score, response and remission, and MADRS change from baseline in total score will be performed on the Modified Efficacy Set.

The HAM-D change from baseline in total score, response and remission, and MADRS change from baseline total score will be presented by the subgroups of the following variable (subgroup definitions are provided in Section 9.2.3):

1. Age group
2. Race
3. Gender
4. Baseline antidepressant use
5. Baseline use of mood stabilizer

Change from baseline in HAM-D and MADRS total score over time will be presented graphically.

9.4 Safety Analysis

The primary objective is to evaluate 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. Safety analyses will be conducted using the Safety Set, unless specified otherwise.

The safety endpoints and variables considered in the summary tables for this study are summarized in Table 2.

Table 2: Safety endpoints and variables in the summary tables

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

Note: PCS criteria are outlined in sections 9.4.2-9.4.4

X = to be summarized in tables

Z = to be presented in listings only

The visit windows used for safety endpoints are the same as the visit windows used for efficacy endpoints, as outlined in Table 1, in Section 9.3.2.

9.4.1 Adverse Events

Adverse events are collected starting at the time of informed consent and throughout the duration of a subject's participation in the study. A treatment-emergent adverse event (TEAE) is defined as an adverse event with onset after the start of study drug.

An on-treatment TEAE is defined as an adverse event with onset after the start of study drug but on or before 7 days since the last dose of study drug. A post-treatment TEAE is defined as an adverse event with onset after 7 days from the last dose of study drug.

If the date of an adverse event is incomplete and an unambiguous determination could not be made with respect to its onset time versus the first dose of study drug and/or last dose of study drug, the adverse event will be assumed to be a TEAE and on-treatment. For imputation of missing AE dates, please refer to Appendix B.

All adverse events will be coded using MedDRA version 21.0 or higher. An overview summary table of AEs will present the number and percentage of subjects as well as the number of events for the following:

- TEAE
- On-treatment TEAE and Post-treatment TEAE
- TEAEs by maximum severity (severe>moderate>mild)
- TEAE leading to discontinuation of study drug
- TEAE leading to withdrawal from the study
- Death
- SAE

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

- TEAEs
- On-treatment TEAE
- Post-treatment TEAE
- TEAEs by maximum Severity
- TEAEs by relationship to study drug
- Serious TEAEs
- TEAEs leading to discontinuation of study drug
- TEAEs leading to withdrawal from the study
- TEAEs leading to dose reduction (from 30mg to 20mg)
- TEAEs leading to dose interruption of the study drug

Most common TEAEs are defined as those, which occur in more than 5% of the safety population. A summary of most common TEAE by preferred term where the incidence is more than 5% will be provided, sorted by decreasing frequency.

For maximum severity, subjects will be counted only once within each SOC and PT at the maximum severity in the following order: severe> moderate> mild; an AE with missing severity will be omitted from severity presentation. For relationship to study drug, subjects will be counted only once within each SOC and PT at the strongest relationship to study drug in the following order: probably related > possibly related > not related. 'Related' is defined as relationship being "possible" or "probable" or missing. The incidences will be presented by descending frequency of SOC and then, within a SOC, by descending frequency of PT based on the subject count, and in alphabetical order of PT if the incidence within a PT is a tie. Adverse events with onset before the first dose of study drug will be provided in a separate listing. Separate data listing for deaths and non-fatal SAEs will be provided.

TEAEs will be classified by the last dose taken before the onset of AE. A summary of TEAEs by SOC/PT and by last dose taken before the onset of AE will be provided.

If the Modified Safety Set is less than 90% of the Safety Set, a summary of TEAE by SOC/PT for the Modified Safety Set will be provided. TEAE summary by SOC/PT will also be presented by the following subgroups (subgroup definitions are provided in Section 9.2.3):

1. Age group
2. Race
3. Gender
4. Baseline antidepressant use
5. Baseline use of mood stabilizer

9.4.2 Clinical Laboratory

The clinical laboratory tests to be performed for monitoring of safety are listed in Table 3. They are collected during the clinic visits at Screening, Days 1, 8, 15, 21, 28, and 42.

Table 1: 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	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Total bilirubin Direct bilirubin Indirect bilirubin Total protein Creatinine Blood urea nitrogen (BUN) Creatine kinase Gamma Glutamyl Transferase (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 labs as outlined in the protocol are excluded from safety analysis; the results will be listed by subject for safety population as part of baseline characteristics.

All parameters will be converted to consistent units according to the International System of Units (SI) before summarization. Listing will provide the results in SI units; the results reported in original unit will reside in the database. For the laboratory results that is "< or <= x", where x is a number as collected in the data, the numeric part of the result will be used in calculation in the summary tables. Same is true if the result is presented as BLQ and a LLOQ value is provided – LLOQ value will be used for calculation in the summary tables. The actual results as collected will be displayed in the listings.

Summary tables on safety will include descriptive statistics for the observed values and changes from baseline by scheduled assessment timepoint (as well as for last value on treatment and last value on study) in hematology, serum chemistry, coagulation and quantitative urinalysis test results. If a normal range is provided for the parameter, out-of-range values will be flagged as low or high, where applicable, in the subject data listings. A shift table for these parameters from baseline to each scheduled assessment time point will be provided. This table will also include the shift from normal to high or low at any time during treatment (>Day 1, <= last day of treatment), any time post-baseline during the study and at the end of study (i.e. the last available value in the database).

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

Laboratory Parameter	**Gender**	**Units**	**Criteria for PCS Values (Observed values)**	
			High	Low
Hematology				
Hemoglobin	Male	g/L	>185	<115
	Female	g/L	>170	<100
Hematocrit	Male	Fraction of 1	>0.55	<0.385
	Female	Fraction of 1	>0.49	<0.345
Platelet count		10^9/L	>600	<125
WBC		10^9/L	>15	<2.5
Basophils		10^9/L	>0.5	NA
Eosinophils		10^9/L	>1.5	NA
Neutrophils		10^9/L	NA	<1.5
Lymphocytes		10^9/L	>6.0	<0.5
Monocytes		10^9/L	>1.4	NA
Serum Chemistry				
Albumin		g/L	>70	<28
Blood urea nitrogen		mmol/L	>10.71	
Calcium		mmol/L	>2.75	<2.0
Creatinine		μmol/L	>3 x ULN or >3 x Baseline	NA
Phosphorus		mmol/L	>1.94	<0.61
Sodium		mmol/L	>150	<132
Bicarbonate		mmol/L	>34	<18
Potassium		mmol/L	>5.4	<3.3
Chloride		mmol/L	>120	<90
Protein		g/L		<45
Glucose		mmol/L	>13.9	<2.8
GGT			>3 x ULN	
Liver Function Tests (LFT)				
Bilirubin		μ/L	>2xULN	NA
Aspartate Aminotransferase		U/L	>3xULN	NA
Alanine Aminotransferase		U/L	>3xULN	NA
Alkaline Phosphatase		U/L	>1.5xULN	NA

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

Alanine Aminotransferase: >3xULN, >5xULN, >10xULN
Aspartate Aminotransferase: >3xULN, >5xULN, >10xULN

Alanine Aminotransferase or Aspartate Aminotransferase: >3xULN, >5xULN, >10xULN
Alkaline Phosphatase: >1.5xULN, >2xULN
Total Bilirubin: >1.5xULN, >2xULN
Total Bilirubin > 2xULN **AND** (Alanine Aminotransferase or Aspartate Aminotransferase >3xULN)
Total Bilirubin >2xULN **AND** Alkaline Phosphatase >2xULN **AND** (Alanine Aminotransferase or Aspartate Aminotransferase >3xULN)
Any lab results considered clinically significant by the investigator will be captured as adverse events, hence will show up in AE displays.

9.4.3 Vital Signs

Vitals for the following parameters - respiratory rate (breaths/minute), oral temperature (degrees C), supine heart rate (beats/minute), supine systolic blood pressure (mmHg), supine diastolic blood pressure (mmHg), standing heart rate (beats/minute), standing systolic blood pressure (mmHg), standing diastolic blood pressure (mmHg), and pulse oximetry (SpO_2, %) – are collected during the clinic visits at Screening, Days 1, 3, 8, 12, 15, 21, 28, 35, 42. Descriptive summaries of observed values and changes from baseline will be provided for vital sign parameters - by scheduled assessment time point as well as for last value on treatment and last value on study

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

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

Orthostatic BP = Supine - Standing

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

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

9.4.4 Electrocardiogram

Supine 12-lead ECGs will be performed in triplicate, and are collected during the clinic visits at Screening, Days 1, 3, 15, and 42. The following ECG parameters will be listed for each subject: heart rate (beats per minute), PR (msec), QRS (msec), QT (msec), and QTcF (msec).

The average of the triplicate values will be used in the summary, including baseline ECG values. The observed value at each time point and change from baseline at each post-baseline scheduled time point will be summarized. Each ECG is evaluated as 'normal', 'abnormal, not clinically significant' and 'abnormal, clinically significant'; the number and percentage of subjects with at least one of the triplicate values in the categories of 'abnormal, clinically significant' and 'abnormal, not clinically significant' will be provided at baseline and each post-baseline scheduled assessment time point. ECG vendor information on normal/abnormal/clinically significant/not clinically significant will reside in the database, but will not be summarized or listed.

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

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

9.4.5 Physical Examination

Physical examination is scheduled for Screening, Days 1, 15, 42. Only clinically significant abnormalities are captured in the database – for post-baseline observations, these will be reported as adverse events, hence these will be included in AE displays; for pre-baseline observations, these will be reported as medical history, hence these will be included in Medical History displays. No further display for physical examination will be provided.

9.4.6 Columbia Suicide Severity Rating Scale (C-SSRS)

Suicidality data collected on the C-SSRS is collected during the clinical visits at Screening, Days 1, 3, 8, 12, 15, 21, 28, 35, and 42. 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 subject's non-suicidal self-injurious behaviors is also assessed separately as part of C-SSRS. 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.

The assessments for suicidal ideation is ranked as follows with 5 being the worst:

1. Wish to be dead
2. Non-specific active suicidal thoughts
3. Active suicidal ideation with any methods
4. Active suicidal ideation with some intent
5. Active suicidal ideation with specific plan

The assessments for suicidal behavior is ranked as follows with 5 being the worst:

1. Preparatory acts or behavior
2. Aborted attempt
3. Interrupted attempt
4. Actual attempt (non-fatal)
5. Completed suicide

Suicidal behavior is considered worse than suicidal ideation.

Baseline for each question is defined as the worst of the assessments done before the first dose of study drug, excluding the lifetime version. This will typically include the 'past 24-month 'version from screening and 'since last visit version' from Day 1; any Yes will make the baseline value as Yes.

Summary of shift from baseline in C-SSRS suicidal ideation and suicidal behavior will be presented for the following categories (no suicidal ideation/behavior, suicidal ideation, suicidal behavior) for each scheduled assessment time point. If the answer to all 5 assessments in suicidal ideation and all 5 assessments in suicidal behavior is 'No' then the category for the table is considered as 'No suicidal ideation/behavior'. If any of the assessments in suicidal behavior is Yes, the category is considered as 'Suicidal behavior'. If any of the assessments in suicidal ideation is Yes but all assessments in suicidal behavior is No, the category is considered as 'Suicidal ideation'.

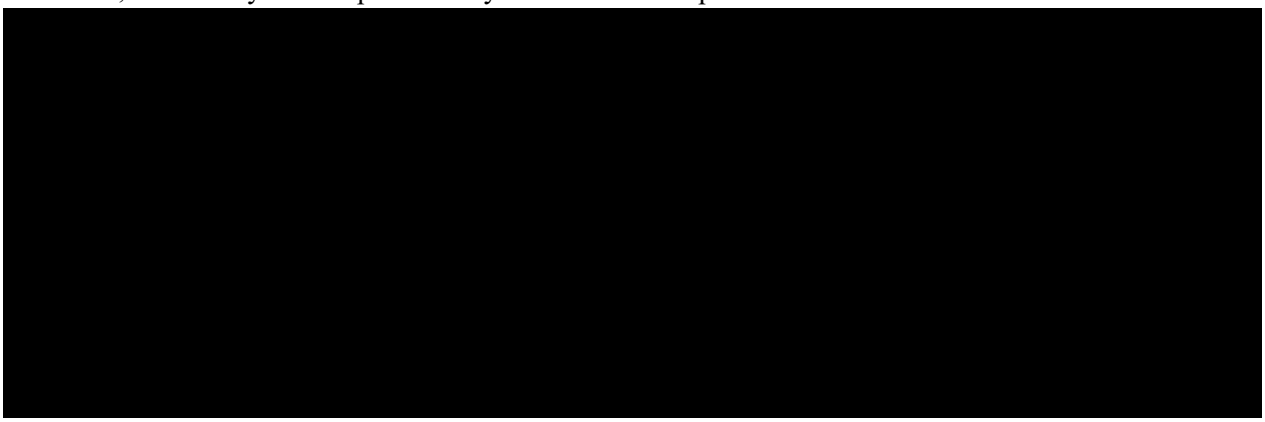
The number and percentage of subjects with at least one response of 'Yes' to any C-SSRS suicidal ideation or suicidal behavior item, as well as for Subject's non-suicidal self-injurious behavior, will be summarized for baseline and any time post-baseline.

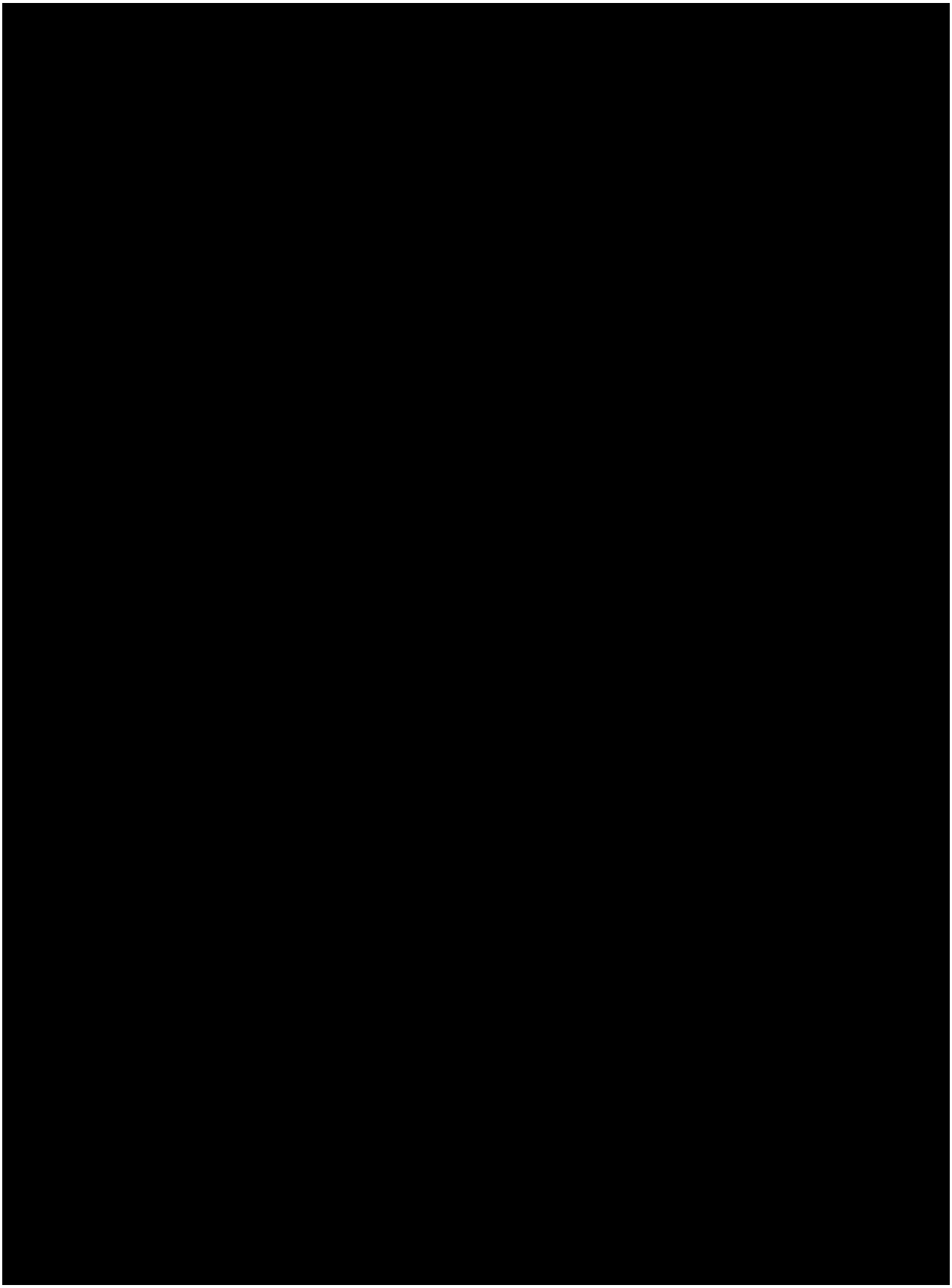
In addition, summary of shift in suicidal ideation from baseline maximum rank score for any time post-baseline maximum rank score will be presented. Maximum score 0 refers to all No for all assessments in the desired period for all 5 questions on suicidal ideation.

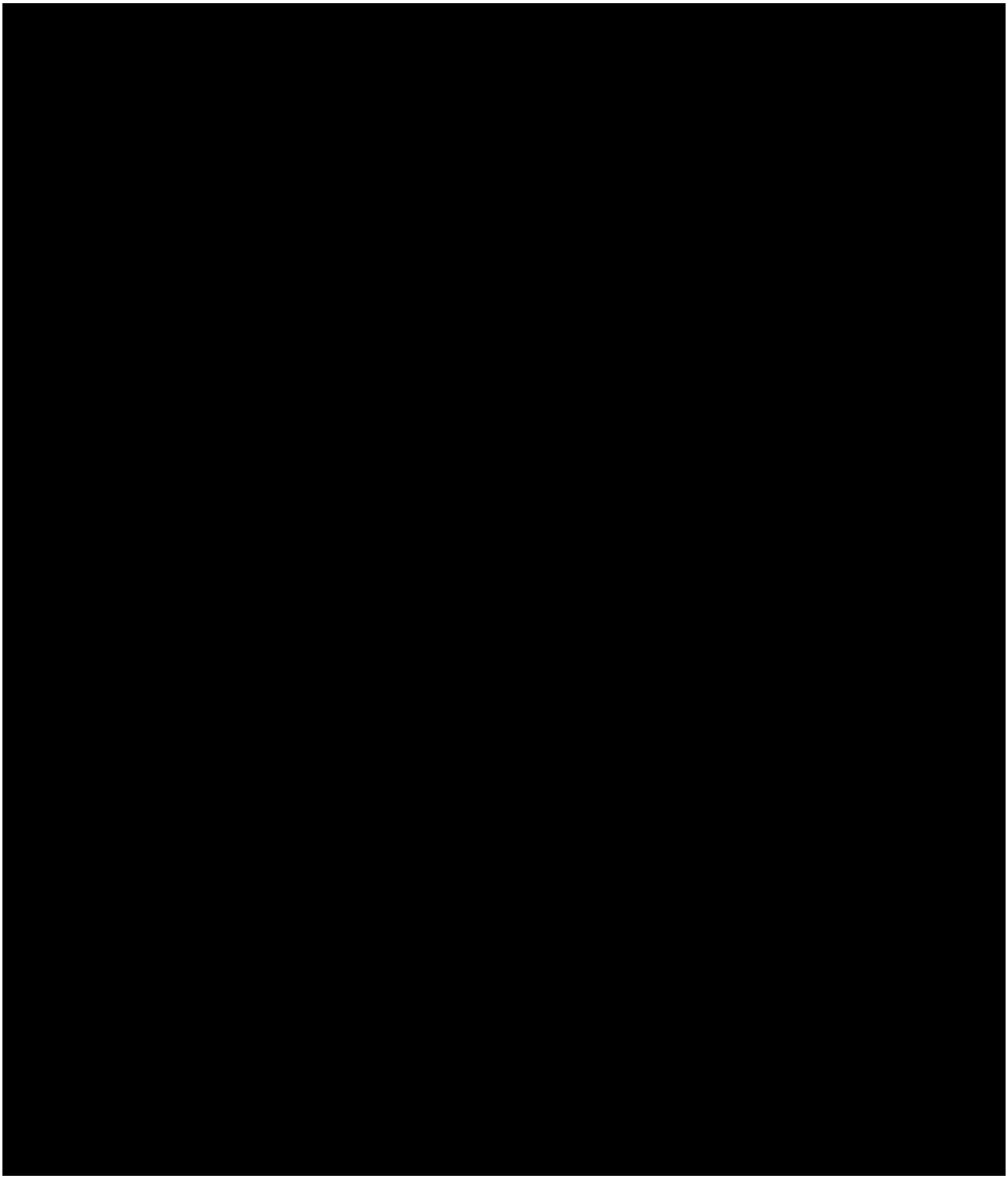
9.4.7 Young Mania Rating Scale (YMRS)

YMRS is collected during the clinical visits at Screening, Days 1, 3, 8, 12, 15, 21, 28, 35, and 42. 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. The total score ranges from 0 to 60. If more than 2 individual items are missing, the YMRS total score will not be calculated and will be left as missing. If less than or equal to 2 individual item scores are missing, the missing item scores will be imputed by the mean of all other available item scores or the maximum possible values for the missing responses, whichever is smaller, to calculate the YMRS total score. A higher total score indicates a greater degree of mania.

Observed values and changes from baseline will be summarized for YMRS total score by each scheduled assessment time point (as well as the last value on treatment and last value on study). In addition, a summary will be provided by the use of antidepressant and mood stabilizer at baseline.







10 SUMMARY OF INTERIM AND DMC ANALYSES

Not applicable

11 REFERENCES

Clinical Study Protocol: Version 4.0 (16 January 2019), Company: Sage Therapeutics Inc.

12 LIST OF APPENDICES

12.1 Appendix A: Schedule of Assessments

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]										

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
[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
[redacted]										
Study Drug Dispensation[o]		X		X						
Study Drug Administration		X (Day 1 – Day 14)								
Study Drug Accountability/Return			X	X	X	X				
Adverse Events/Serious Adverse Events[p]	X									
Prior/Concomitant Medications/	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**
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Procedures[q]										

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.

12.2 Appendix B: Handling of Missing Dates

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

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

12.2.1 Adverse Events

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

For partial AE start dates:

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

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

- If the year of AE onset > the year of initiation of the treatment, then the day will be set to the 1st day of month.
  - If the imputed AE onset date is after the AE stop date, then the onset date will be set to the stop date.

- When the year and day are present and the month is missing, treat it as if the day is missing, and only year is present. Follow the imputation rules for "year is known, but the month and day is unknown".
- When the year is missing, but the month and/or day is known, treat this date as missing; do not impute.

12.2.2 Prior and Concomitant Medications

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

For the partial start date of medication:

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

For the partial end date of medication:

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

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

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

12.3 Appendix D: List of Displays

12.3.1 Index of Tables

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