

Official Title: A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-217 in the Treatment of Adult Female Subjects With Severe Postpartum Depression

NCT Number: NCT02978326

Document Date: Protocol Version 9.0: 02 July 2018



PROTOCOL NUMBER: 217-PPD-201

**A MULTICENTER, RANDOMIZED, DOUBLE-BLIND,
PARALLEL-GROUP, PLACEBO-CONTROLLED STUDY
EVALUATING THE EFFICACY, SAFETY, AND
PHARMACOKINETICS OF SAGE-217 IN THE TREATMENT
OF ADULT FEMALE SUBJECTS WITH SEVERE
POSTPARTUM DEPRESSION**

IND NUMBER: 132,131

Investigational Product	SAGE-217
Clinical Phase	3
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Medical Monitor & Sponsor Contact	[REDACTED], MD, MBA Phone: [REDACTED]
Date of Original Protocol	Version 1.0, 18 October 2016
Date of Amendment 1	Version 2.0, 13 December 2016
Date of Amendment 2	Version 3.0, 17 March 2017
Date of Amendment 3	Version 4.0, 06 June 2017
Date of Amendment 4	Version 5.0, 31 August 2017
Date of Amendment 5	Version 6.0, 01 December 2017
Date of Amendment 6	Version 7.0, 15 February 2018
Date of Amendment 7	Version 8.0, 14 June 2018
Date of Amendment 8	Version 9.0, 02 July 2018

Confidentiality Statement

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from Sage Therapeutics.

PROTOCOL SIGNATURE PAGE

Protocol Number: 217-PPD-201
Product: SAGE-217
IND No.: 132,131
Study Phase: 3
Sponsor: Sage Therapeutics
Date of Amendment 7, Version 8.0: 02 July 2018

Sponsor Approval

[REDACTED]	<u>03 Jul 2018</u>
[REDACTED] MD, MBA	Date (DD/MMM/YYYY)
[REDACTED]	<u>02 Jul 2018</u>
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[REDACTED]	<u>02 Jul 2018</u>
[REDACTED] MSHS	Date (DD/MMM/YYYY)
[REDACTED]	<u>02 JUL 2018</u>
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[REDACTED]	<u>02 JUL 2018</u>
[REDACTED]	Date (DD/MMM/YYYY)

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the Clinical Protocol 217-PPD-201 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

CONTACTS IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Telephone Number
Clinical Research Organization	Premier Research	512-686-1256

2. SYNOPSIS

Name of Sponsor: Sage Therapeutics 215 First Street Cambridge, MA 02142	
Protocol No. 217-PPD-201	Phase: 3
Name of Investigational Product: SAGE-217 Capsules	
Name of Active Ingredient: SAGE-217	
Title of the Protocol: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF SAGE-217 IN THE TREATMENT OF ADULT FEMALE SUBJECTS WITH SEVERE POSTPARTUM DEPRESSION	
Study Sites: Approximately 60 sites in the United States	
Primary Efficacy Objective: To determine if treatment with SAGE-217 reduces depressive symptoms in subjects with severe postpartum depression (PPD) compared to placebo as assessed by the change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at Day 15.	
Secondary Efficacy Objectives: <ul style="list-style-type: none">• To determine if treatment with SAGE-217 Capsules 30 mg QD reduces depressive symptoms in subjects with severe PPD compared to placebo as assessed by the change from baseline in the HAM-D total score at all other time points.• To determine if treatment with SAGE-217 Capsules 30 mg QD reduces depressive symptoms compared to placebo as assessed by HAM-D response, HAM-D remission, change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score, Clinical Global Impression – Improvement (CGI-I) response, and changes from baseline in HAM-D subscales and individual item scores at Day 15 and all other time points.• To determine if treatment with SAGE-217 Capsules 30 mg QD reduces anxiety symptoms compared to placebo as assessed by changes from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score Day 15 and all other time points.	
Safety Objective: <ul style="list-style-type: none">• To evaluate the safety and tolerability of SAGE-217 compared to placebo as assessed by the incidence of adverse events, vital sign measurements, clinical laboratory evaluations, electrocardiogram (ECG) parameters, and the Columbia Suicide Severity Rating Scale (C-SSRS).	

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take the study drug with food. Study drug will be self-administered by subjects in the evening (8:00 pm \pm 30 min) on an outpatient basis for the entire 14-day Treatment Period. Study drug administration will be monitored via a follow-up call from the site each evening (within approximately 1 hour following the scheduled evening dose) on Days 1 to 14. Subjects will not be allowed to initiate psychotropic medications or other medications that may potentially have an impact on efficacy or safety endpoints within 30 days prior to informed consent until completion of the Day 15 assessments. Psychotropic medications initiated at least 30 days prior to informed consent must remain at a stable dose until completion of the Day 15 assessments. Efficacy and safety assessments will be performed periodically during the study, and blood samples may be collected for analysis of SAGE-217 and metabolites of SAGE-217 as outlined in the Schedule of Events. [REDACTED]	
Follow-up Period: The Follow-up Period assessments will be conducted on an outpatient basis on Day 21 \pm 1 day and Day 45 \pm 3 days after the initiation of study drug administration.	
Number of Subjects: Approximately 140 subjects will be randomized in a 1:1 ratio for approximately 70 subjects per treatment group. Additional subjects may be enrolled in order to ensure there are 130 evaluable subjects. Evaluable subjects are defined as those randomized subjects receiving study drug with valid baseline and at least 1 post-baseline HAM-D assessment.	
Inclusion Criteria: The following inclusion criteria must be met for individuals to be eligible for the study. <ol style="list-style-type: none">1. Subject has signed an ICF prior to any study-specific procedures being performed.2. Subject is an ambulatory female between 18 and 45 years of age, inclusive.3. 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.4. Subject agrees to adhere to the study requirements.5. Subject either must have ceased lactating at screening or, if still lactating or actively breastfeeding at screening, must agree to temporarily cease giving breast milk to her infant(s) from just prior to receiving study drug through Day 21, allowing for a 7-day washout after the last dose of study drug.6. Subject must have a negative pregnancy test at screening and Day 1 prior to the start of study drug administration.7. Subject has had a major depressive episode that began no earlier than the third trimester and no later than the first 4 weeks following delivery, and meets criteria for major depressive episode	

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<p>per DSM-5, diagnosed by Structured Clinical Interview for (DSM-5) Axis I Disorders (SCID-I).</p> <ol style="list-style-type: none">8. Subject has a HAM-D total score of ≥ 26 at screening and Day 1 (prior to randomization).9. Subject is ≤ 6 months postpartum.10. Subject is willing to delay start of other antidepressant or anxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics, until after the Treatment Period ends and all Day 15 assessments have been completed.11. Subject has no detectable hepatitis B surface antigen (HBsAg), no detectable anti-hepatitis C virus (HCV), detectable anti-HCV but negative viral load, and no detectable human immunodeficiency virus (HIV) antibody at screening.12. Subject agrees to use 1 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 surgically sterile:<ul style="list-style-type: none">• Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation.• Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation.• Intrauterine device.• Intrauterine hormone-releasing system.• Bilateral tubal occlusion.• Vasectomized partner.	
Exclusion Criteria: Subjects will be excluded if they meet any of the following exclusion criteria. <ol style="list-style-type: none">1. 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 participate in or complete this clinical study.2. Subject has a known allergy to SAGE-217 Capsule or its excipients.3. Subject has active psychosis per Investigator assessment.4. Subject has attempted suicide associated with the current episode of PPD.5. Subject has a medical history of seizures.	

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<ol style="list-style-type: none">6. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.7. Subject has a history of active alcoholism or drug addiction (including benzodiazepines) in the 12 months prior to screening.8. Subject has had exposure to another investigational medication or device within 30 days prior to screening.9. Subject has prior participation in any SAGE-547 or SAGE-217 clinical study.10. Subject who presents for the study while currently receiving psychotropic medications that are used with the intent to treat depressive symptoms such as antidepressants, atypical antipsychotics, etc., which have not been taken at the same dose for at least 30 days prior to Day 1. (Subjects presenting for the study who have stopped taking these medications within the 30 days prior to the start day of study drug may be eligible if they will be off of the medications for longer than 5 half-lives until the start day of study drug).11. Use of any known strong inhibitors of cytochrome P450 (CYP)3A4 within 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or products containing these within 14 days prior to receiving the first dose of study drug and throughout the study.12. Subject has a positive urine drug test at the screening visit.13. Use of any CYP inducers, such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital or St John's Wort, within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study drug and throughout the study.14. Subject plans to undergo elective surgery during participation in the study.	
Investigational Product, Dosage, and Mode of Administration: SAGE-217 Capsules are 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 in order to provide treatment doses of 20 mg and 30 mg. Subjects will be administered 2 capsules per dose.	
Reference Therapy, Dosage, and Mode of Administration: Matched placebo capsules containing only the above-listed capsule excipients will be provided. Subjects will be administered 2 placebo capsules per day, to maintain blinding.	
Duration of Participation: Up to 76 days (14 days of treatment)	
Randomization: Subjects will be randomized to receive SAGE 217 or matching placebo in a 1:1 ratio.	

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Subjects, clinicians, and the study team will be blinded to treatment allocation. Randomization will be performed centrally via an interactive response technology (IRT) system.	
Dose Adjustment for Safety/Tolerability Reasons: During the Treatment Period, subjects will be able to receive study drug as long as there are no dose-limiting safety/tolerability concerns. Dose adjustment criteria are described in Section 9.3 of the protocol.	
Criteria for Evaluation: <u>Primary Efficacy Endpoint</u> The primary efficacy endpoint will be the change from baseline in HAM-D total score at the end of the Treatment Period (Day 15). The HAM-D total score will be calculated as the sum of the 17 individual item scores. <u>Secondary Efficacy Endpoints</u> Secondary endpoints will include: <ul style="list-style-type: none">• Change from baseline in the HAM-D total score at all time points other than Day 15;• HAM-D response defined as a 50% or greater reduction from baseline in HAM-D total score;• HAM-D remission defined as a HAM-D total score of ≤ 7;• Change from baseline in MADRS total score at Day 15 and other time points;• CGI-I response defined as “very much improved” or “much improved”;• Change from baseline in HAM-A total score at Day 15 and other time points;• Changes from baseline in HAM-D subscales and individual item scores at Day 15 and other time points Safety Endpoints <ul style="list-style-type: none">• Safety and tolerability of study drug will be evaluated by frequency of adverse events; severity, relatedness, and seriousness of adverse events; clinical laboratory measures, vital signs, ECGs; and concomitant medication usage. Suicidality will be monitored using the C-SSRS. <p>Concomitant medications: The doses of all psychotropic medications will be recorded throughout the study. No changes and/or additions to antidepressant or anxiolytic medicine will be allowed during the Treatment Period.</p> <div style="background-color: black; width: 100%; height: 100px; margin-top: 10px;"></div>	

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[REDACTED]	
Statistical Methods: General: For the purpose of all safety, efficacy, and other analyses where applicable, baseline is defined as the last measurement prior to the start of blinded study drug administration. Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages. Analysis Sets and Methods: The All Randomized Set, defined as all subjects who have been randomized, will be used for subject disposition, demographics, and baseline characteristic summaries. Subjects will be classified according to randomized treatment. The Safety Set, defined as all subjects administered study drug, will be used to provide descriptive summaries of safety data. Subjects will be summarized according to treatment received. The Efficacy Set, defined as all subjects in the All Randomized Set who complete at least 1 day of study drug and have a valid baseline and at least 1 post-baseline efficacy assessment, will be used to analyze efficacy data. Efficacy data will be analyzed using appropriate descriptive statistics and pre-specified statistical methods, as well as other data presentation methods where applicable; subject listings will be provided for all efficacy data. Subjects will be analyzed according to randomized treatment. [REDACTED] 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, assessment time point, and time point-by-treatment as explanatory variables. All post-baseline time points will be included in the model. The primary comparison will be between SAGE-217 and placebo at the 15-day time point. 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. Continuous secondary and other variables will be analyzed using similar methods.	

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<p>Binary efficacy endpoints, including responder and remission endpoints, will be summarized and analyzed using the generalized estimating equation method.</p> <p>Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA™) Version 19.1 or higher. The overall incidence of adverse events will be displayed by System Organ Class, preferred term, and treatment. The incidence of adverse events will also be presented by maximum severity and relationship to study drug. Vital signs, clinical laboratory measures, ECG, concomitant medication usage, and C-SSRS data will be summarized by treatment, where applicable. Out-of-range safety endpoints may be categorized as low or high, where applicable. 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 at baseline and at each visit during the active Treatment Period will be listed for all subjects. The C-SSRS listings will include behavior type and/or category for suicidal ideation and suicidal behavior of the C-SSRS.</p>	
<u>Sample Size Calculation:</u> <p>Assuming a 2-sided test at an alpha level of 0.05, a sample size of approximately 65 subjects per treatment group would provide 90% 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 points.</p> <p>Assuming a 10% dropout and a 1:1 randomization ratio, approximately 72 randomized subjects per treatment group will be required to obtain 130 evaluable subjects. Evaluable subjects are defined as those randomized subjects who received study drug and have a valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the dropout rate is higher than 10%.</p>	

Table 2: Schedule of Events

Study Procedure	Study Period / Visit						
	Screening Period	Treatment Period ^a				Follow-up Period	
	D-28 to -1	D1*	D3 (+1d)	D8	D15	D21/ET (±1d)	D45 (±3d)
Clinic Visit	X	X	X	X	X	X	X
Informed Consent	X						
Inclusion/Exclusion	X	X					
SCID-I	X						
Demographics	X						
Medical/Family History ^b	X						
Physical Examination	X			X ^c	X ^c	X	
Body Weight/Height	X				X ^{c, d}	X ^d	
Clinical Laboratory Assessments ^e	X			X ^c	X ^c	X	
Drug & Alcohol Screen ^f	X	X					
Pregnancy Test ^g	X	X				X (ET only)	X
Hepatitis & HIV Screen	X						
Hormone Sample ^h	O			O ^c	O ^c		
Genetic Sample ⁱ	O						
Vital Signs ^j	X	X	X	X	X ^c	X	X
12-Lead ECG ^k	X	X		X	X	X	
C-SSRS ^l	X	X	X	X	X ^c	X	X
CGI-I			X	X	X	X ^c	X ^c
CGI-S	X	X	X	X	X	X ^c	X ^c
HAM-A		X	X	X	X	X ^c	X ^c
HAM-D ^m	X	X	X	X	X	X ^c	X ^c
MADRS	X	X	X	X	X	X ^c	X ^c
Dispense Study Drug ⁿ		X		X			

Study Procedure	Study Period / Visit						
	Screening Period	Treatment Period ^a				Follow-up Period	
	D-28 to -1	D1*	D3 (+1d)	D8	D15	D21/ET (±1d)	D45 (±3d)
Study Drug Administration ^f		X (QD until Day 14 - inclusive)					
Treatment Compliance Call ^g		X (QD until Day 14 - inclusive)					
Adverse Events				X			
Prior/Concomitant Medications ^t				X			

██████████; CGI-I = Clinical Global Impression of Improvement; CGI-S – Clinical Global Impression - Severity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; ██████████; ██████████; ET = early termination; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression, 17-item; ██████████; HIV = human immunodeficiency virus; MADRS = -Montgomery-Åsberg- Depression Rating Scale; O = Optional; ██████████; ██████████; QD = once daily; SCID-I = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders Axis I Disorders; ██████████

*All D1 procedures are to be completed prior to dosing

^a An unscheduled visit may be needed if a dose adjustment is deemed necessary by the Investigator at any time during the treatment period in order for any remaining current dose to be returned and for the adjusted dose to be dispensed.

^b Subjects will be specifically asked about the depression and anxiety diagnoses listed in [Appendix 1](#).

^c To be performed/collected in the morning at the clinic.

^d Weight only.

^e Safety laboratory tests will include hematology, serum chemistry, coagulation, select hormone parameters, and urinalysis.

^f Urine toxicology for selected drugs of abuse and serum (screening only) or breath test for alcohol.

^g Serum pregnancy test at screening and urine pregnancy test at Day 1 and Day 45. A urine pregnancy test will also be collected as part of the early termination assessments for subjects who discontinue the study early.

^h An optional blood sample for stress hormone levels, kynurenine biochemistry, and markers of inflammation, where consent is given.

ⁱ An optional genetic sample for biomarker testing, where consent is given.

^j Vital signs include respiratory rate, oral temperature, and supine (for at least 5 minutes prior to the measurement) and standing systolic and diastolic blood pressure and heart rate. Vital signs may be repeated at the discretion of the Investigator as clinically indicated.

^k Performed at screening and within ±60 minutes of the scheduled time point at 9:00 AM.

^l The “Baseline/Screening” C-SSRS form will be completed at screening. The “Since Last Visit” C-SSRS form will be completed at all subsequent time points.

^m HAM-D to be completed at the scheduled clinic visits 12 hours (±1 hour) following the evening dose.

ⁿ

^q Per investigator discretion, an additional visit to dispense study drug may occur. The only planned procedure for this visit will be study drug dispensation.

^r Dosing will occur daily at 8:00 PM ±30 minutes with food. If the dose is not administered within <60 minutes after the scheduled dose, the subject will skip the dose and take the next scheduled dose on the following day (a dose occurring >30 minutes but <60 minutes before/after the scheduled time will be considered a protocol deviation).

^s A treatment compliance call will be made within approximately 1 hour following the scheduled evening dose on Days 1 to 14.

^t To include those taken prior to the first dose of study drug and throughout the study, as well as history of antidepressant medications and treatment listed in [Appendix 2](#).

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

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 3: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	adverse event
BMI	body mass index
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
C _{max}	maximum plasma concentration
CS	clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
ECG	electrocardiogram
eCRF	electronic case report form
GABA	γ-aminobutyric- acid
GABA _A	γ-aminobutyric- acid-ligand gated chloride channel
GCP	Good Clinical Practice
GEE	generalized estimating equation
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Rating Scale for Depression
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board

Abbreviation or Specialist Term	Explanation
LS	least squares
MADRS	Montgomery-Åsberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effects model for repeated measures
MTD	maximum tolerated dose
NCS	not clinically significant
NF	National Formulary
PPD	postpartum depression
QD	once daily
QTcF	QT interval calculated using the Fridericia method
SAD	single ascending dose
SCID-I	Structured Clinical Interview for DSM-5 Axis I Disorders
SD	standard deviation
SOC	System Organ Class
SSRIs	serotonin reuptake inhibitors
SUSAR	suspected, unexpected, serious, adverse reaction
TEAE	treatment-emergent adverse event
t_{\max}	time at maximum (peak) plasma concentration
WHO-DD	World Health Organization-Drug dictionary

5. INTRODUCTION

5.1. Background of Postpartum Depression and Unmet Medical Need

Postpartum depression (PPD) is defined as the occurrence of major depressive episode within 4 weeks of delivery (DSM-IV 1994) or up to a year after giving birth (Okun 2013). In Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the onset specifier includes the entire pregnancy as well as 4 weeks following delivery (DSM-5 2013). There are 2 entry criteria for the diagnosis of depression (depressed mood and/or loss of interest) and 7 associated symptoms of depression (appetite problems, sleep problems, motor problems, lack of concentration, loss of energy, poor self-esteem, and suicidality). To be diagnosed with severe PPD, women must present at least 5 symptoms of depression (DSM-5 2013). Most women experience onset of symptoms within the first 3 months following delivery, and PPD is most prevalent at 10 to 14 weeks following childbirth (Okun 2013). The overall incidence of PPD is estimated at around 15% to 20%, with up to 10% being considered severe (Edge 2007; O'Hara 2014). Although frequently recognized in the postpartum period, depressive episodes can also begin in the last trimester or earlier during pregnancy (Meltzer-Brody 2011).

Converging preclinical and clinical evidence (Luscher 2011) implicates deficits in GABAergic neurotransmission in the pathophysiology of depressive disorders including PPD. Furthermore, several pieces of experimental data implicate deficiencies in the normal regulation of endogenous neuroactive steroid in depressive disorders (Maguire 2008; Maguire 2009). It is thought that the large increase in progesterone-derived neurosteroids during pregnancy and their precipitous decrease at parturition may have considerable effects on γ -aminobutyric acid-gated chloride channel (GABA_A) receptors during pregnancy and postpartum leading to PPD. The dynamic trafficking of extrasynaptic (δ -containing) GABA_A receptors may be an important compensatory mechanism to changing neurosteroid levels during healthy pregnancies, and this trafficking pattern may be disrupted in PPD (Maguire 2008; Maguire 2009). In a preclinical model of PPD, mice lacking GABA_A receptor δ -subunits (Gabrd^{-/-} mice) exhibit postpartum-specific phenotypes including reduced tonic inhibition, neuronal hyperexcitability, depressive-like behaviors, and profound deficits in maternal care (Maguire 2008; Maguire 2009). In this model, the onset of depression-like behaviors occurred only in the postpartum period and included a significant increase in pup mortality due to maternal neglect and cannibalism, analogous to the increase in infanticide observed in human women with PPD. These data suggest that augmenting extrasynaptic GABA_A receptor function may provide a therapeutic benefit in PPD.

Current standard of care for severe PPD comprises cautious use of pharmacological therapies in nursing mothers combined with other interventions. Evidence for efficacy of tricyclic antidepressants and/or selective serotonin reuptake inhibitors (SSRIs) is based on use in the general population rather than any extensive studies in PPD (Austin 2013), and SSRIs tend to be preferred due to better data on safety while breastfeeding (Altshuler 2001). Based on the level of evidence for antidepressants in major depressive disorder (Kirsch 2008; Fournier 2010), there is a considerable need for improved pharmacological therapy for PPD.

Drugs may be combined with a number of counseling, behavioral, and other nonpharmacological therapy approaches, which are generally used as the first-line therapy in less severe PPD (Altshuler 2001). Urgent referral and potentially admission are recommended for mothers at risk

of self-harm, with their infants, if such facilities exist ([Austin 2013](#)). Therapeutic options in severe PPD are currently limited, and it is not clear whether the current standard of care impacts the natural history of the disease, although most women recover within a year.

5.2. SAGE-217

SAGE-217 is a synthetic neuroactive steroid and a positive allosteric modulator of GABA_A receptors, the major class of inhibitory neurotransmitter receptors in the brain and representing the most highly expressed synaptic and extrasynaptic inhibitory receptors in the mammalian brain. Consistent with the actions of other GABA_A receptor potentiators ([Rudolph and Knoflach 2011](#)), SAGE-217 exhibits potent anticonvulsant, anxiolytic, and sedative activity when administered in vivo and pharmacological data provide evidence that SAGE-217 is a potent and efficacious neuroactive steroid and potentiator of multiple subtypes of GABA_A receptors.

To date, the safety, tolerability, efficacy, and pharmacokinetics (PK) of SAGE-217 (Oral Solution and Capsules) have been evaluated in Phase 1 studies and in Phase 2 studies (either complete or ongoing) in subjects with Essential Tremor, Parkinson's Disease, Postpartum Depression and Major Depressive Disorder. The maximum tolerated dose (MTD) was 30 mg SAGE-217 Oral Solution in the Phase 1 multiple-ascending dose study and is the target therapeutic dose in clinical development with the capsule formulation. Based on a Phase 1 relative bioavailability study of SAGE-217 Oral Solution and Capsules, exposures with SAGE-217 Capsules were lower than or equal to exposures observed at the same dose with SAGE-217 Oral Solution.

SAGE-217 has been generally well tolerated to date, based on available data from the Phase 1 and 2 studies. The most common treatment-emergent adverse events were sedation, somnolence, and dizziness. Most adverse events were reported as mild or moderate in intensity and resolved by the end of the study. A single suspected, unexpected, serious, adverse reaction (SUSAR) has been reported to date: an event of transient confusion leading to discontinuation of study drug in a subject with essential tremor who received the SAGE-217 Oral Solution.

Refer to the [Investigator's Brochure](#) for detailed background information on SAGE-217.

5.3. Potential Benefits and Risks

Protocol 217-PPD-201 is the first clinical study of SAGE-217 evaluating the efficacy, safety, and pharmacokinetics in subjects with PPD. Thus, the potential benefits in this population are unknown, although the risks are likely to be similar to those noted in the [Investigator's Brochure](#). Known risks of severe PPD include maternal suicide, infanticide, decreased maternal bonding with the infant, resulting in poor attachment ([Lindahl 2005](#); [McLearn 2006](#); [Austin 2007](#); [Meltzer-Brody 2014](#)). It has also been demonstrated that effects of PPD extend to the paternal mood and, as a result, negatively impact the functioning of the entire family ([Paulson 2010](#)).

In order to mitigate risks associated with this study, dose adjustments based on tolerability are allowed in the protocol.

In the 217-CLP-103 study, SAGE-217 was found to be generally well-tolerated with no serious adverse events (AEs) reported during the treatment and follow-up periods. The most frequent AE

observed was sedation that was mild, transient, and occurred within 1 to 4 hours and generally dissipated by 8 hours.

In conclusion, the known safety profile, coupled with exclusion of high-risk patients with attempted suicide associated with the current episode of depression, are expected to place this protocol at a favorable benefit to risk ratio.

5.4. Dose Justification

5.4.1. Safety Measures

SAGE-217 has been generally well tolerated to date (see [Section 5.2](#)).

Dose reductions are permitted during the study. During the treatment period, subjects will receive study drug as long as there are no dose-limiting safety/tolerability concerns. Dose adjustments should be made according to the process outlined in [Section 9.3](#).

In addition, as SAGE-217 is a central nervous system-active compound, the Columbia Suicide Severity Rating Scale (C-SSRS) will be used to monitor emergence or regression of suicidal ideation as means of detecting adverse effects on mood.

5.4.2. Safety Instructions

The study will be conducted on an outpatient basis. All doses will be self-administered by the subject at home. Adverse events will be collected throughout the subject's participation. If safety concerns arise, the Investigator may hospitalize the subjects as clinically indicated.

Instructions to the subject must include warnings about avoiding activities for which sedative effects of the study drug may impair performance, such as interactions with the infant, driving a motor vehicle, and operating machinery.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Efficacy Objective

To determine if treatment with SAGE-217 reduces depressive symptoms in subjects with severe PPD compared to placebo as assessed by the change from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score at Day 15.

6.2. Secondary Efficacy Objectives

The secondary objectives of the study are:

- To determine if treatment with SAGE-217 Capsules 30 mg QD reduces depressive symptoms in subjects with severe PPD compared to placebo as assessed by the change from baseline in the HAM-D total score at all other time points.
- To determine if treatment with SAGE-217 Capsules 30 mg QD reduces depressive symptoms compared to placebo as assessed by the HAM-D response, HAM-D remission, change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score, Clinical Global Impression – Improvement (CGI-I) response, and changes from baseline in HAM-D subscales and individual item scores at Day 15 and all other time points.
- To determine if treatment with SAGE-217 Capsules 30 mg QD reduces anxiety symptoms compared to placebo as assessed by changes from baseline in Hamilton Anxiety Rating Scale (HAM-A) total score at Day 15 and all other time points.

6.3. Safety Objectives

- To evaluate the safety and tolerability of SAGE-217 compared to placebo as assessed by the incidence of adverse events, vital sign measurements, clinical laboratory evaluations, electrocardiogram (ECG) parameters, and the C-SSRS.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the efficacy, safety, and PK of SAGE-217 in adult subjects diagnosed with severe PPD.

The study will be conducted in 2 parts. One subject was enrolled and dosed in Part A before it was closed to enrollment (see Protocol Amendment 2, Version 3.0); the current amendment describes Part B only.

The study will consist of an up to 28-day Screening Period (Day -28 to -1), 14-day Treatment Period (Day 1 to Day 14), and Follow-up Period (through Day 45).

During the Screening Period, after signing the informed consent form (ICF), subjects will be assessed for study eligibility and the severity of each subject's PPD will be evaluated using HAM-D. Eligible subjects will be admitted to the clinical study unit on Day 1.

If applicable, standard of care data collected prior to obtaining informed consent may also be included as screening data, if appropriate, such as laboratory tests, ECG, physical examination, and vital signs conducted within the preceding 48 hours, as long as the requirement for the screening assessment to be collected retrospectively is met in full. If applicable, to ensure protocol compliance, any standard of care data eligible for inclusion as screening data must include the precise nature and timing of data collection.

Eligible subjects will be randomized to active study drug or placebo on a 1:1 basis. The end of the Screening Period coincides with the beginning of the Treatment Period.

SAGE-217 or placebo will be self-administered by the subject on an outpatient basis, with subjects instructed to take the study drug each evening at 8:00 PM \pm 30 minutes. Compliance with study drug administration will be monitored via a follow-up call from the site each evening (within approximately 1 hour following the scheduled evening dose) on Days 1 to 14.

Efficacy and safety assessments will be performed periodically during the study, [REDACTED]

Subjects will be monitored for safety during the Treatment and Follow-up Periods (through Study Day 45 [\pm 3 days]) including monitoring for adverse events/serious adverse events, routine clinical laboratory assessments, physical examination, vital signs, and ECG.

During the Treatment Period, subjects will be able to receive study drug as long as there are no dose-limiting safety/tolerability concerns. Dose adjustments should be made according to the process outlined in [Section 9.3](#).

7.2. Blinding and Randomization

Subjects who meet the entrance criteria will be randomly assigned in a 1:1 ratio to receive SAGE-217 or placebo on Day 1. 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.

In the event of a medical emergency, the pharmacist and/or designated pharmacy staff may reveal actual study drug contents to the Investigator, who should also alert Sage of the emergency (see [Section 13.6](#) for more details related to unblinding). 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 electronic case report form (eCRF). If the subject or study center personnel (other than pharmacist and/or designated pharmacy staff) have been unblinded, the subject will be terminated from the study.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the study.

1. Subject has signed an ICF prior to any study-specific procedures being performed.
2. Subject is an ambulatory female between 18 and 45 years of age, inclusive.
3. 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.
4. Subject agrees to adhere to the study requirements.
5. Subject either must have ceased lactating at screening or, if still lactating or actively breastfeeding at screening, must agree to temporarily cease giving breast milk to her infant(s) from just prior to receiving study drug through Day 21, allowing for a 7-day washout after the last dose of study drug.
6. Subject must have a negative pregnancy test at screening and Day 1 prior to the start of study drug administration.
7. Subject has had a major depressive episode that began no earlier than the third trimester and no later than the first 4 weeks following delivery, and meets criteria for major depressive episode per DSM-5, diagnosed by Structured Clinical Interview for (DSM-5) Axis I Disorders (SCID-I).
8. Subject has a HAM-D total score of ≥ 26 at screening and Day 1 (prior to randomization).
9. Subject is ≤ 6 months postpartum.
10. Subject is willing to delay start of other antidepressant or anxiety medications and any new pharmacotherapy regimens, including as-needed benzodiazepine anxiolytics, until after the Treatment Period ends and all Day 15 assessments have been completed.
11. Subject has no detectable hepatitis B surface antigen (HBsAg), no detectable anti-hepatitis C virus (HCV), detectable anti-HCV but negative viral load, and no detectable human immunodeficiency virus (HIV) antibody at screening.
12. Subject agrees to use 1 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 surgically sterile:
 - Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation.
 - Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
 - Intrauterine device.
 - Intrauterine hormone-releasing system.
 - Bilateral tubal occlusion.

- Vasectomized partner.

8.2. Subject Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria.

1. 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 participate in or complete this clinical study.
2. Subject has a known allergy to SAGE-217 Capsule or its excipients.
3. Subject has active psychosis per Investigator assessment.
4. Subject has attempted suicide associated with the current episode of PPD.
5. Subject has a medical history of seizures.
6. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
7. Subject has a history of active alcoholism or drug addiction (including benzodiazepines) in the 12 months prior to screening.
8. Subject has had exposure to another investigational medication or device within 30 days prior to screening.
9. Subject has prior participation in any SAGE-547 or SAGE-217 clinical study.
10. Subject who presents for the study while currently receiving psychotropic medications that are used with the intent to treat depressive symptoms such as antidepressants, atypical antipsychotics, etc., which have not been taken at the same dose for at least 30 days prior to Day 1. (Subjects presenting for the study who have stopped taking these medications within the 30 days prior to the start day of study drug may be eligible if they will be off of the medications for longer than 5 half-lives until the start day of study drug).
11. Use of any known strong inhibitors of cytochrome P450 (CYP)3A4 within 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or products containing these within 14 days prior to receiving the first dose of study drug and throughout the study.
12. Subject has a positive urine drug test at the screening visit.
13. Use of any CYP inducers, such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital or St John's Wort, within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study drug and throughout the study.
14. Subject plans to undergo elective surgery during participation in the study.

8.3. Subject Withdrawal Criteria

If there is an adverse event or medical reason for the withdrawal, the subject should be followed medically until the condition has either resolved or is stable. Details of the reason for withdrawal should be recorded in the subject's eCRF.

Subjects who withdraw should, if possible, complete the Early Termination Visit, including a physical examination, the appropriate investigations, vital signs, clinical laboratory tests [REDACTED] [REDACTED] as outlined for the Day 21 visit (Table 2). All details of the Early Termination Visit should be recorded in the subject's medical source documents.

8.3.1. Study Drug Withdrawal

Participation in the study is strictly voluntary. Subjects are free to discontinue the study at any time without giving their reason(s).

A subject must be withdrawn from the study treatment in the event of any of the following:

- Withdrawal of the subject's consent;
- New onset of a condition that would have met exclusion criterion, is clinically relevant and affects the subject's safety, and discontinuation is considered necessary by the Investigators or Sage;
- Occurrence of intolerable adverse events;
- Intake of nonpermitted concomitant medication;
- Subject noncompliance;
- Significant protocol deviation determined in consultation with the Medical Monitor.

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.

Subjects may be withdrawn from the study if there is concern for the subject's safety or it is determined that the subject is no longer a qualified participant.

Subjects who withdraw or are withdrawn from the study will be replaced only if they withdraw prior to dosing. Subjects who are withdrawn from the study, fail to return or are no longer qualified will not be replaced.

8.3.2. Criteria for Study Termination

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons, including the occurrence of adverse events 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 Institutional Review Board (IRB) and initiate withdrawal procedures for participating subjects.

9. TREATMENT OF SUBJECTS

9.1. Number of Subjects

Approximately 140 subjects with severe PPD will be randomized in a 1:1 ratio for approximately 70 subjects per treatment group. Additional subjects may be enrolled in order to ensure there are 130 evaluable subjects. Evaluable subjects are defined as those randomized subjects receiving study drug with valid baseline and at least 1 post-baseline HAM-D assessment.

9.2. Treatment Assignment

This is a double-blind study. Eligible subjects will be randomly assigned to receive SAGE-217 or matched placebo on a 1:1 basis. Subjects, clinicians, and study team will be blinded to treatment allocation.

Dose adjustments will only be allowed as described in [Section 9.3](#).

9.3. Dose Adjustment Criteria

During the Treatment Period, subjects will be able to receive study drug as long as there are no dose-limiting safety/tolerability concerns. Subjects who cannot tolerate 30 mg QD will receive 20 mg QD for the remainder of the Treatment Period. Subjects who experience intolerable AEs at the 20 mg QD dose level may be discontinued from study treatment at the discretion of the Investigator.

Dose adjustments will be made based on tolerability as assessed by occurrence of a severe AE or a moderate AE of special interest (sedation, somnolence, dizziness, euphoric mood, confusion, drowsiness, inebriation (feeling drunk), or fatigue) judged by the investigator to be related to study drug. If a dose adjustment is deemed necessary by the Investigator at any time during the treatment period, the subject will return to the site to return any remaining current dose and for the adjusted dose to be dispensed.

9.4. Prior/Concomitant Medications and Restrictions

9.4.1. Prior/Concomitant Medications

In this study, psychotropic medications refer to central nervous system active medications taken to help depressive symptoms, and include antidepressants, benzodiazepines, and hypnotic agents. Subjects presenting to the study on psychotropic medications may be eligible to participate if the same dose of the medications has been taken at least 30 days prior to Day 1; these subjects must remain at their same dose until completion of the Day 15 assessments. Those subjects on benzodiazepines and hypnotic agents may be considered for eligibility based on specific discussions between the Investigator and Sage to ensure safety. Subjects on other psychotropic medications, including stimulants, antipsychotics (if used for the purpose of treating psychotic symptoms), and mood stabilizers, are not eligible to participate in this study. Atypical antipsychotic use may be approved if it has been prescribed to augment the effects of antidepressants.

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

Section 9.4.2. All medications taken from 3 months prior to informed consent through the Day 45 visit should be recorded on the eCRF. Prior medications (ie, those taken prior to signing of ICF) that required washout for study entry will also be documented.

9.4.2. Restricted Medications

Restrictions on specific classes of medications include the following:

- Initiation of new antidepressant therapy is prohibited upon admission to the study center for those eligible subjects who desire study participation. Those subjects already taking an antidepressant at the time of study entry (and meeting all study inclusion criteria) will be permitted to remain on the pre-existing antidepressant at their current dose if they were taking this dose at least 30 days prior to Day 1.
- Benzodiazepines are to be avoided as much as possible. Eligible subjects taking a stable dose of benzodiazepine at least 30 days prior to Day 1 will be discussed on a case-by-case basis with Sage to determine eligibility. Subjects may be permitted to continue to take their current dose of the benzodiazepine (to prevent acute withdrawal), but no new benzodiazepine use will be permitted during the course of the study.
- The use of hypnotics for sleep/insomnia such as Ambien[®] and trazodone is to be avoided; use of hypnotics will be discussed on a case-by-case basis with Sage.
- Anticonvulsants are prohibited. Atypical antipsychotics are allowed only if the indication has been for the treatment of the depressive episode and not for treatment of psychotic symptoms.
- Use of any known strong inhibitors of cytochrome P450 (CYP)3A4 within 14 days or 5 half-lives (whichever is longer) prior to receiving the first dose of study drug and throughout the study.
- Use of any CYP inducers, such as rifampin, carbamazepine, ritonavir, enzalutamide, efavirenz, nevirapine, phenytoin, phenobarbital or St John's Wort, within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study drug and throughout the study.

9.4.3. Other Restrictions

The consumption of grapefruit juice, grapefruit, Seville oranges, or products containing these within 14 days prior to receiving the first dose of study drug and throughout the study is prohibited.

Subjects are prohibited from giving their breast milk to infant(s) from just prior to receiving study drug through Day 21, allowing for a 7-day washout after the last dose of study drug.

Subjects are prohibited from undergoing elective surgery during participation in the study.

9.5. Treatment Compliance

Study drug will be dispensed by the site. Study drug administration will be monitored via a follow-up call from the site each evening (within approximately 1 hour following the scheduled evening dose) on Days 1-14. Any reasons for noncompliance will be documented, including:

- Missed visits;
- Interruptions in the schedule of administration; and
- Nonpermitted medications.

The time at which study procedures are conducted should follow the protocol timelines as closely as possible.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

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. Capsules will be available in 10-mg, 20-mg, and 30-mg strengths in order to provide treatment doses of 20 mg and 30 mg. Subjects will be administered 2 capsules per dose.

Matching placebo capsules are hard gelatin capsules for oral administration containing only the excipients listed above for the active capsule treatment. Subjects will receive 2 placebo capsules per dose.

10.2. Batch Formula for SAGE-217 Capsules

In addition to SAGE-217 Drug Substance, the SAGE-217 Capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose, and sodium stearyl fumarate as excipients.

Matching placebo capsules contain only the excipients listed above for the active capsule treatment.

10.3. Study Drug Packaging and Labeling

The composition and pharmaceutical quality of the investigational product will be maintained according to the current Good Manufacturing Practice and Good Clinical Practice (GCP) guidelines and available for review in the study medication documentation. All study drug will be labeled conforming to the applicable Code of Federal Regulations guidelines. SAGE-217 Capsules and matched placebo capsules will be provided to the sites in subject-specific kits containing appropriately labeled bottles. Study drug will be dispensed by the appropriate site staff per the Pharmacy Manual.

10.4. Study Drug Storage

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

The study drug may not be used for any purpose other than the present study. After the study is completed, all unused study drug must be retained, returned as directed, or destroyed on site per Sage's instructions.

10.5. Administration

Subjects will self-administer study drug (30 mg SAGE-217 or placebo) daily for 14 days on an outpatient basis. Subjects will be instructed to take the study drug each evening with food at 8:00 PM \pm 30 minutes. If dosing occurs >30 minutes but <60 minutes before/after the scheduled time, this would constitute a protocol deviation. If the dose is not administered within <60 minutes after the scheduled dose, the subject will skip the dose and take the next scheduled dose on the

following day. Compliance with study drug administration will be monitored via a follow-up phone call from the site each evening (within approximately 1 hour following the scheduled evening dose) on Days 1-14. Subjects who tolerate 30 mg QD will receive this dose for the rest of the Treatment Period. Those subjects who cannot tolerate the 30 mg QD dose will have a dose reduction and receive 20 mg QD for the rest of the Treatment Period (see [Section 9.3](#) for dose adjustment criteria).

10.6. Study Drug Accountability

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

The study drug provided is for use only as directed in this protocol. The Investigator or designee must maintain a record of all study drug received, used, and discarded. It must be clear from the records which subject received which kit of active or placebo treatment.

If a dose adjustment is deemed necessary by the Investigator at any time during the treatment period (see [Section 9.3](#) for dose adjustment criteria), the subject will be instructed to return to the site to return any remaining current dose and for the adjusted dose to be dispensed.

Sage or designee 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 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 administered 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

For all efficacy assessments, the baseline values will be calculated as the last recorded value prior to the start of randomized study drug administration. Change from baseline values will be calculated as the assessment score minus the baseline value. Change from baseline values will be calculated for each item and total score.

Subject-rated and clinician-rated scales are to be completed according to the Schedule of Events (Table 2).

11.1. Primary Efficacy Outcome Measure - Hamilton Rating Scale for Depression (HAM-D)

The primary outcome measure will be the change from baseline in 17-item HAM-D total score at the end of the Treatment Period (Day 15).

The 17-item HAM-D will be used to rate the severity of depression in subjects who are already diagnosed as depressed (Hamilton 1960). 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. The HAM-D assessments are to be completed at the scheduled clinic visits 12 hours \pm 1 hour following the evening dose. 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 .

11.2. Secondary Efficacy Outcome Measures

Secondary efficacy assessments include evaluation of depressive and anxiety symptom severity by the MADRS (Section 11.2.1), CGI (Section 11.2.2), and HAM-A (Section 11.2.3).

11.2.1. Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a ten-item diagnostic questionnaire that psychiatrists use 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 to the changes brought on by antidepressants and other forms of treatment than the Hamilton Scale.

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 (McDowell 2006; Müller-Thomsen 2005).

The questionnaire includes questions on the following symptoms: apparent sadness; reported sadness; inner tension; reduced sleep; reduced appetite; concentration difficulties; lassitude; inability to feel; pessimistic thoughts; and suicidal thoughts. The MADRS total score will be calculated as the sum of the ten individual item scores.

11.2.2. 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.

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

11.2.3. Hamilton Anxiety Rating Scale (HAM-A)

The 14-item HAM-A will be used to rate the severity of symptoms of anxiety ([Hamilton 1959](#)). Each of the 14 items is defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Scoring for HAM-A is calculated by assigning scores of 0 (not present) to 4 (very severe), with a total score range of 0 to 56, where ≤ 17 indicates mild severity, 18 to 24 mild to moderate severity, and 25 to 30 moderate to severe severity.

The HAM-A total score will be calculated as the sum of the 14 individual item scores.

[REDACTED]

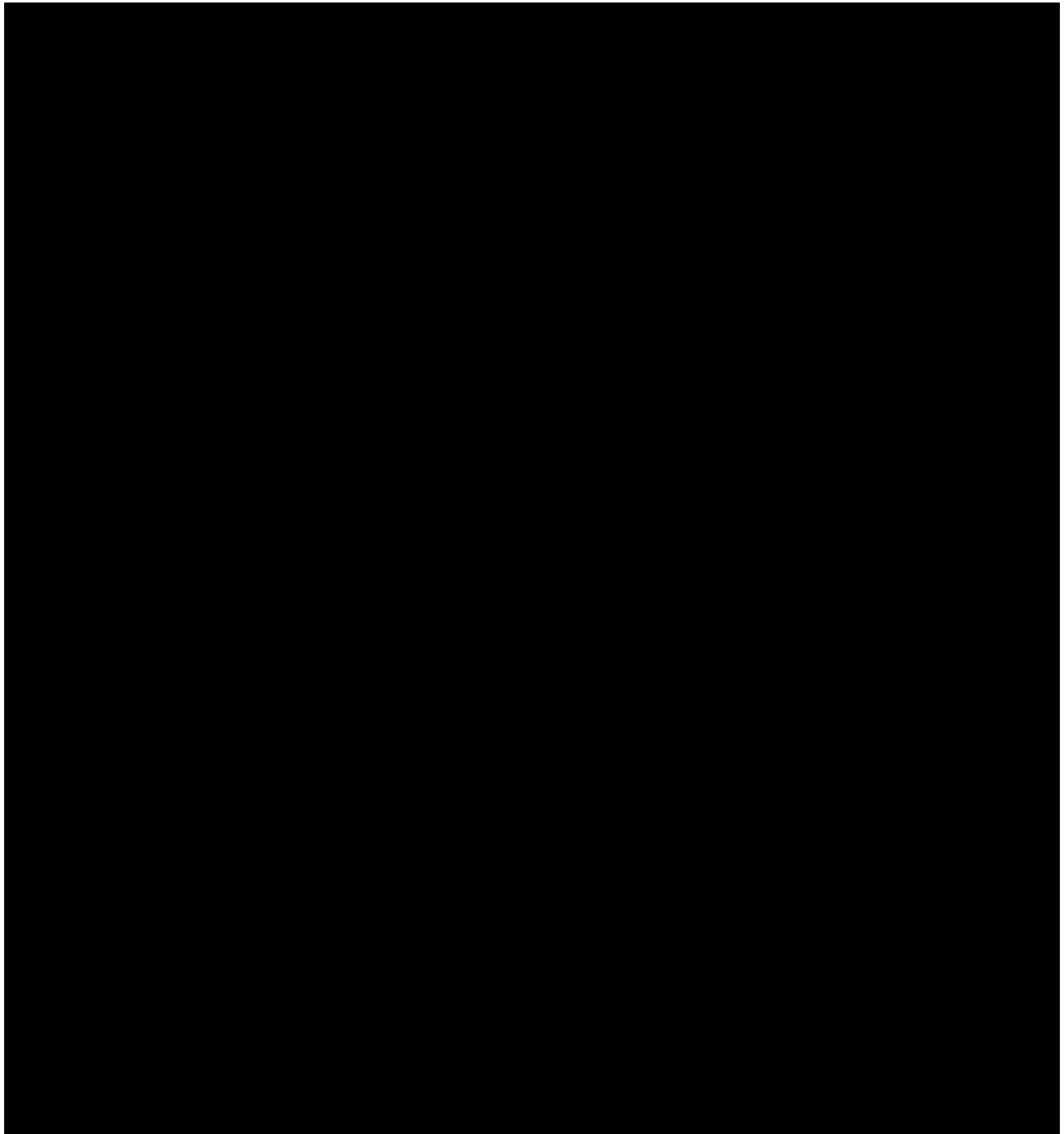
[REDACTED]

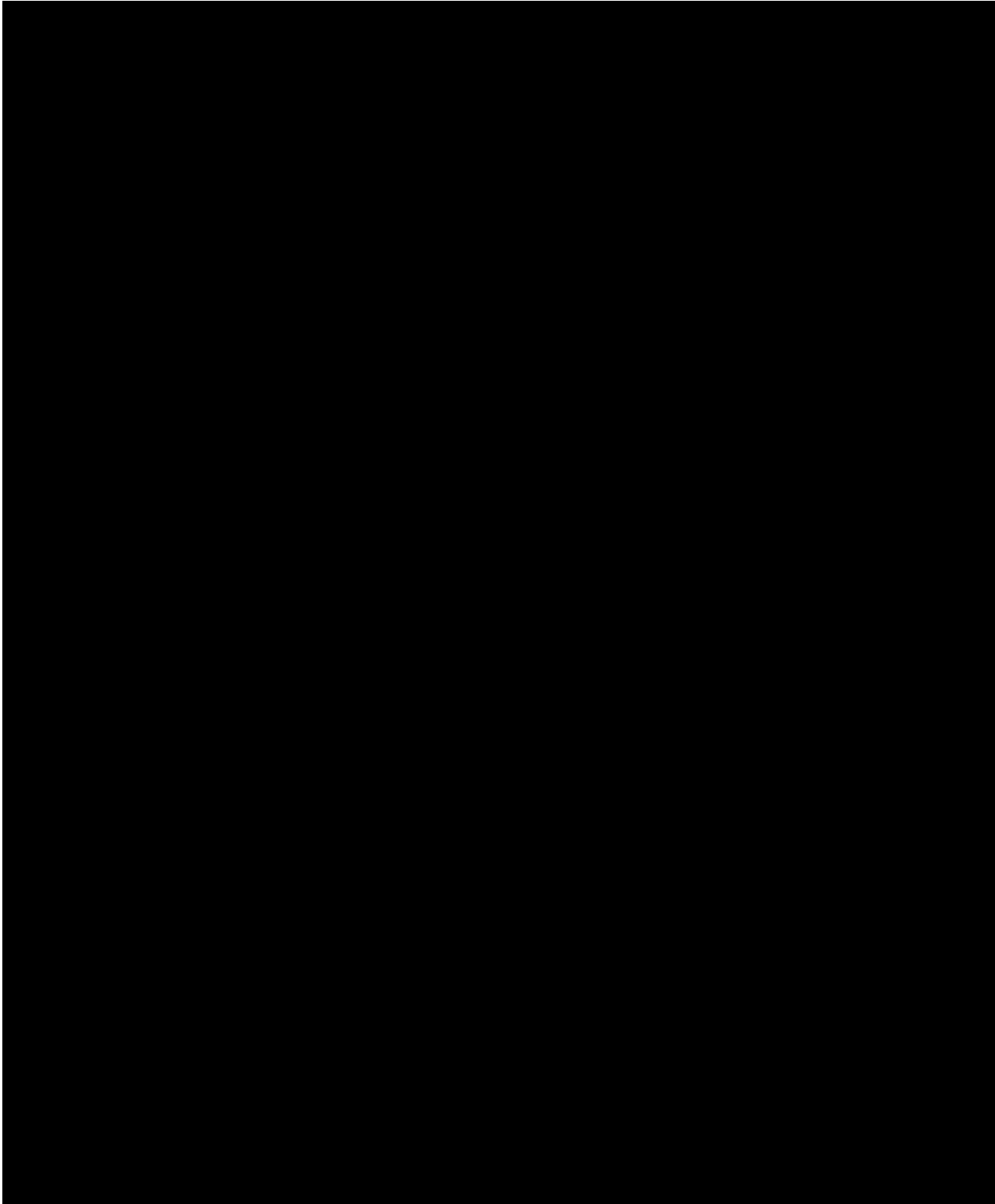
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]





13. ASSESSMENT OF SAFETY

The study will be conducted on an outpatient basis. Subjects will be instructed to self-administer the study drug with food each evening. Adverse events will be collected throughout the subject's participation. If safety concerns arise, the Investigator may hospitalize the patients as clinically indicated. Instructions to the subject must include warnings about avoiding activities for which sedative effects of the study drug may impair performance, such as interactions with the infant, driving a motor vehicle, and operating machinery.

If daily monitoring calls reveal AEs, the PI will be notified and the subjects may be brought in for evaluation at the PI's discretion. During these visits, if the PI determines that dose adjustment is needed, subjects will be dispensed the lower dose (20 mg) for the remaining dosing period.

13.1. Safety and Tolerability Parameters

Safety and tolerability of study drug will be evaluated by vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, and adverse event reporting. All safety and tolerability parameters will be assessed according to the Schedule of Events ([Table 2](#)).

13.1.1. Demographic/Medical History

Age, race, and ethnic origin will be recorded at the Screening visit. The diagnosis of depression will be determined using the SCID-I. A full medical and family history, including recording of depression and anxiety diagnoses and all major depression episodes (and for the subject, depression and anxiety treatment history [medication, hospitalization]), other Axis I and Axis II disorders, and postpartum depression episodes in immediate female family members (siblings, parents, and grandparents), will be recorded at the Screening visit. Subjects will be specifically asked about the depression or anxiety diagnoses listed in [Appendix 1](#) and use of antidepressants listed in [Appendix 2](#).

13.1.2. Vital Signs

Vital signs include respiratory rate, oral temperature, and supine (for at least 5 minutes prior to the measurement) and standing systolic and diastolic blood pressure and heart rate. Vital signs may be repeated at the discretion of the Investigator as clinically indicated.

13.1.3. Weight and Height

Body weight and height will be measured at the Screening visit; weight will also be measured on Days 15 and 21.

13.1.4. Physical Examination

A physical examination of all major body systems will be undertaken and recorded.

13.1.5. Electrocardiogram (ECG)

A 12-lead ECG will be assessed; the standard intervals as well as any abnormalities will be recorded.

13.1.6. Laboratory Assessments

Blood and urine samples will be collected for hematology, serum chemistry, coagulation, select hormone parameters, and urinalysis. Where consent is given, an optional blood sample for hormone and exploratory biochemistry testing and optional genetic sample for biomarker testing will be collected at the Screening visit, Day 8 and Day 15.

Serum and urine samples for pregnancy tests will also be collected. These assessments should be performed as outlined below.

All samples will be analyzed at the central laboratory. Subjects may be considered eligible for the study based on local laboratory results; however, screening samples must also be sent to the central laboratory. Both local and central screening labs must adhere to the visit window provided in the Schedule of Events.

All clinical laboratory test results outside the reference range will be interpreted by the Investigator as abnormal, not clinically significant (NCS) or abnormal, clinically significant (CS). Screening results considered abnormal, CS recorded at the Screening visit may make the subject ineligible for the study pending review by the Medical Monitor. Clinical laboratory results that are abnormal, CS during the study but within normal range at baseline and/or indicate a worsening from baseline will be considered adverse events, assessed according to [Section 13.2.1](#), and recorded in the eCRF.

13.1.6.1. Hematology

Hematology tests will include complete blood count, including red blood cells, white blood cells with differentiation, hemoglobin, hematocrit, reticulocytes, and platelets. The coagulation panel will include activated partial thromboplastin time, prothrombin time, and international normalized ratio.

13.1.6.2. Blood Chemistry

Serum chemistry tests will include serum electrolytes; glucose; renal function tests, including creatinine, blood urea nitrogen, bicarbonate or total carbon dioxide; liver function tests, including alkaline phosphatase, total bilirubin, aspartate aminotransferase, and alanine aminotransferase; total protein; albumin; and thyroid stimulating hormone.

13.1.6.3. Urinalysis

Urinalysis will include assessment of protein, hemoglobin, glucose, ketones, bilirubin, urobilinogen, leukocyte esterase, nitrites, color, turbidity, pH, and specific gravity.

13.1.6.4. Virus Serology

Subjects will be screened for hepatitis (HBsAg and anti-HCV) and HIV prior to being enrolled in the study. If subjects are positive for anti-HCV, reflex RNA testing (viral load) for HCV should be conducted; those subjects with positive anti-HCV may be enrolled only if the viral load is negative.

13.1.6.5. Hormones and Exploratory Biochemistry

Optional blood samples will be collected and may be analyzed for stress hormone levels, kynurenine biochemistry, and markers of inflammation. Future research may suggest other biochemical pathways as candidates for influencing not only response to SAGE-217 but also susceptibility to disorders for which SAGE-217 may be evaluated. Thus, the exploratory biochemistry may involve study of additional unnamed molecular pathways, but only as related to disease susceptibility and drug action.

13.1.6.6. Pregnancy Test

Women of childbearing potential will be tested for pregnancy by serum pregnancy test at the Screening visit and by urine pregnancy test on Day 1 (predose), and at the follow-up visit. A urine pregnancy test will also be performed as part of the early termination assessments for subjects who discontinue the study early. If a subject becomes pregnant during the study, the process for reporting the pregnancy and guidance for collection of information related to the pregnancy is outlined in the Safety Management Plan.

13.1.6.7. Genetic Testing

Where consent is given, an optional genetic sample for biomarker testing will be collected at the Screening visit.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (ie, distribution, safety, tolerability, and efficacy) to SAGE-217. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (eg, cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of SAGE-217 (eg, AKR1C4 [3 α -hydroxysteroid dehydrogenase]), genes associated with the GABA receptor (eg, GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3), and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-217 but also susceptibility to disorders for which SAGE-217 may be evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

13.1.6.8. Drugs of Abuse and Alcohol

A urine sample for assessment of selected drugs of abuse (including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and phencyclidine) and a serum (screening) or breath sample (predose on Day 1) for alcohol screen will be collected. Use of benzodiazepines at screening is not necessarily exclusionary, as subjects will be allowed to take psychotropics at a stable dose that have been initiated within 30 days prior to informed consent (see [Section 9.4](#)).

13.1.7. 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 2](#).

13.2. Adverse and Serious Adverse Events

13.2.1. Definition of Adverse Events

13.2.1.1. Adverse Event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. In clinical studies, an adverse event can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

13.2.1.2. Suspected Adverse Reaction

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of Investigational New Drug safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

13.2.1.3. Serious Adverse Event

A serious adverse event is an adverse event occurring during any study phase and at any dose of the investigational product, comparator or placebo, that fulfills 1 or more of the following:

- It results in death
- It is immediately life-threatening
- It requires inpatient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- It results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent 1 of the outcomes listed above.

All serious adverse events that occur after any subject has been enrolled, whether or not they are related to the study, must be recorded for the duration of the study on the SAE form provided by Sage Therapeutics or designee.

13.3. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product 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 “related.”

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 to be related to the investigational product for the purposes of expedited regulatory reporting.

13.4. 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. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as adverse events unless they prompt corrective medical action by the Investigator, constitute a serious adverse event, or lead to discontinuation of administration of study drug.

Information about adverse events will be collected from the signing of the ICF until the final visit of the study for that subject. Adverse events that occur after the first administration of study drug will be denoted as treatment-emergent adverse events (TEAEs).

All adverse events regardless of Investigator-determined causality, should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant.

The adverse event term should be reported in standard medical terminology when possible. For each adverse event, the Investigator will evaluate and report the onset (date and time), resolution or clinical plateau (date and time), severity, causality, action taken, outcome, and whether or not it caused the subject to discontinue the study.

Severity 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)

13.5. Reporting Adverse Events

All serious adverse events (regardless of causality) will be recorded from the signing of the ICF until the Day 45 Follow-up visit. Any serious adverse events considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All serious adverse events must be reported to Sage or Sage's designee immediately in writing within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the serious adverse event form, verify the accuracy of the information recorded on the serious adverse event form with the corresponding source documents, and send a copy to Sage Therapeutics or designee.

Additional follow-up information, if required or available, should be sent to Sage Therapeutics or designee within 24 hours of receipt; a follow-up serious adverse event form should be completed and placed with the original serious adverse event information and kept with the appropriate section of the eCRF and/or study file.

Sage Therapeutics or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB of all serious adverse events that occur at his or her site if applicable per the IRB's requirements. Investigators will also be notified of all unexpected, serious, drug-related events (7-/15-Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB of these additional serious adverse events.

13.6. 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 interactive response technology system.

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


14. STATISTICS

14.1. Data Analysis Sets

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

The Safety Set, defined as all subjects administered study drug, will be used to provide descriptive summaries of all safety data; subjects will be classified according treatment received.

The Efficacy Set, defined as all subjects in the All Randomized Set who complete at least 1 day of study drug and have a valid baseline and at least 1 post-baseline efficacy assessment, will be used to analyze all efficacy data; subjects will be analyzed according to randomized treatment.



14.2. 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. A sensitivity analysis method will be used to investigate the impact of missing data if $\geq 5\%$ of subjects have missing data.

14.3. General Considerations

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

Continuous endpoints will be summarized with 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.

14.4. Demographics and Baseline Characteristics

Demographic data, such as age, race, and ethnicity, and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized using the Randomized Set.

Hepatitis, HIV, drug and alcohol, and pregnancy screening results will be listed, but not summarized as they are considered part of the inclusion/exclusion criteria.

Medical/family history will be listed by subject.

14.5. Primary Efficacy Endpoint

Change from baseline to each assessment 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, assessment time point, and time point-by-treatment as explanatory variables. Center will be treated as a random effect while all other explanatory variables will be treated as

fixed effects. All post-baseline time points will be included in the model. The primary comparison will be between SAGE-217 Capsule and placebo at the 15-day time point. Model-based point estimates (ie, least squares [LS] means), 95% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. Compound symmetry covariance structure will be used if there is a convergence issue with the unstructured covariance model.

14.6. Secondary Efficacy Endpoints

14.6.1. Efficacy Analyses

Similar to those methods described for the primary endpoint in [Section 14.5](#), MMRM will be used for the analysis of the following variables: changes from baseline in MADRS total score, HAM-A total score, [REDACTED], and select individual item and subscale scores. For each model, the comparison of interest will be between SAGE-217 capsule and placebo at the 15-day time point. Model-based point estimates (ie, LS means), 95% confidence intervals, and p-values will be reported.

Generalized estimating equation (GEE) methods will be used for the analysis of the following binary variables: HAM-D response (define as $\geq 50\%$ reduction from baseline in HAM-D total score), HAM-D remission (defined as ≤ 7.0 HAM-D total score), and CGI-I response. Generalized estimating equation models will include terms for center, treatment, baseline score, assessment time point, and time point-by-treatment as explanatory variables. The comparison of interest will be the difference between SAGE-217 Capsules and placebo at the 15-day time point. Model-based point estimates (ie, odds ratios), 95% confidence intervals, and p-values will be reported. For the CGI-I response analysis, baseline CGI-S score will be included in the model.

Descriptive statistics for all scores, change from baseline values, and response variables will be presented by treatment and assessment time point. Summaries will include n, mean, SD, median, minimum, and maximum.

14.6.2. Safety Analyses

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

14.6.2.1. Adverse Events

The analysis of adverse events will be based on the concept of TEAEs. A TEAE is defined as an adverse event with onset after the start of study drug, or any worsening of a pre-existing medical condition/adverse event with onset after the start of study drug and until 7 days after the last dose. The incidence of TEAEs will be summarized overall and by Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 or higher System Organ Class (SOC) and preferred term. Incidences will be presented in order of decreasing frequency for the SAGE-217 treatment group. In addition, summaries will be provided by severity (mild, moderate, severe) and by causality (related, not related) to study drug (see [Section 13.3](#)).

Treatment-emergent adverse events leading to discontinuation and serious adverse events (see [Section 13.2.1.3](#) for definition) with onset after the start of randomized study drug will also be summarized.

All adverse events and serious adverse events (including those with onset or worsening before the start of randomized study drug) through the Day 45 Follow-up visit will be listed.

14.6.2.2. 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 summarized.

14.6.2.3. Physical Examinations

Any clinically significant change in physical examination compared to those observed at screening should be noted as an adverse event.

14.6.2.4. Vital Signs

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

14.6.2.5. 12-Lead Electrocardiogram

The following ECG parameters will be listed for each subject: heart rate, PR, QRS, QT, QTc, and QT interval calculated using the Fridericia method (QTcF). Any clinically significant abnormalities or changes in ECGs should be listed as an adverse event. Electrocardiogram findings will be listed by subject and visit.

14.6.2.6. 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 2016, 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 first dose 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.

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

14.6.2.7. Columbia Suicide Severity Rating Scale

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

[REDACTED]

14.8. Determination of Sample Size

Assuming a 2-sided test at an alpha level of 0.05, a sample size of approximately 65 subjects per treatment group would provide 90% 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 points.

Assuming a 10% dropout and a 1:1 randomization ratio, approximately 72 randomized subjects per treatment group will be required to obtain 130 evaluable subjects. Evaluable subjects are defined as those randomized subjects who received study drug and have a valid baseline and at least 1 post-baseline HAM-D assessment. Additional subjects may be randomized if the dropout rate is higher than 10%.

14.9. Changes from Protocol Specified Analyses

Any changes from the analytical methods outlined in the protocol will be documented in the final statistical analysis plan.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

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

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

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

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

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

15.2. Audits and Inspections

Authorized representatives of Sage Therapeutics, a regulatory authority, an Independent Ethics Committee (IEC) or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sage Therapeutics or designee 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, GCP guidelines of the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and any applicable regulatory requirements. The Investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency about an inspection.

15.3. Institutional Review Board (IRB)

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

16. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator and institution will permit study-related monitoring, audits, IRB review, and regulatory inspections as requested by the Food and Drug Administration, Sage, or Sage's designee, including direct access to source data/documents (ie, original medical records, laboratory reports, hospital documents, progress reports, signed ICFs) in addition to eCRFs.

Quality assurance and quality-control systems with written standard operating procedures will be followed to ensure this study will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality-assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements made by Sage with the Investigator/institution and any other parties involved with the clinical study will be in writing in a separate agreement.

17. ETHICS

17.1. Ethics Review

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

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC 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 or designee will provide this information to the Principal Investigator.

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

17.2. 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 its most recent amendment (2008) and are consistent with ICH/GCP and other applicable regulatory requirements.

17.3. Written Informed Consent

The Principal Investigator 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 before signing the ICF.

As additional assessments, the ICF will contain provisions for optional consent for the collection of blood samples for hormone and biomarker testing during screening and the collection of breast milk for biobanking [REDACTED] purposes. The ICF, as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

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 ICF. A copy of the signed ICF must be given to the subject.

18. DATA HANDLING AND RECORDKEEPING

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

Electronic CRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, adverse events, and subject status.

The Investigator will have access to the electronic data capture system and will receive a copy of the subject eCRF data at the end of the study. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

18.1. Inspection of Records

Sage Therapeutics or designee will be allowed to conduct site visits to the investigational 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 related to study conduct.

18.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuation 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.

18.3. Confidentiality

To maintain subject privacy, all eCRFs, study reports, and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from Sage or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Sage. It is understood that there is an obligation to provide Sage with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

19. 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.

20. LIST OF REFERENCES

- Altshuler LL, Cohen LS, Moline ML, et al. Treatment of depression in women: a summary of the expert consensus guidelines. *J Psychiatr Pract.* 2001;7(3):185-208.
- Austin MP, Kildea S, Sullivan E. Maternal mortality and psychiatric morbidity in the perinatal period: challenges and opportunities for prevention in the Australian setting. *Med J Aust.* 2007;186:36–47.
- Austin MP, Middleton P, Reilly NM, Hight NJ. Detection and management of mood disorders in the maternity setting: the Australian Clinical Practice Guidelines. *Women Birth.* 2013;26(1):2-9.
- Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry.* 1987;150:782-6.
- DSM-IV. Diagnostic and statistical manual of mental disorders (4th ed.). American Psychiatric Association 1994. Arlington, VA: American Psychiatric Association Publishing.
- DSM-5. Diagnostic and statistical manual of mental disorders (5th ed). American Psychiatric Association 2013. Arlington, VA: American Psychiatric Publishing.
- Edge D. Ethnicity, psychosocial risk, and perinatal depression—a comparative study among inner-city women in the United Kingdom. *J Psychosom Res.* 2007;63(3):291-5.
- Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity—a patient-level meta-analysis. *JAMA.* 2010;303:47-53.
- Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol.* 1959;32:50-5.
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23:56-62.
- Kirsch I, Deacon BJ, Huedo-Medina TB, et al. Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration. *PLoS Med.* 2008; 5(2): e45.
- Lindahl V, Pearson JL, Colpe L. Prevalence of suicidality during pregnancy and the postpartum. *Arch Womens Ment Health.* 2005;8:77–87.
- Luscher B, Shen Q, Sahir N. The GABAergic deficit hypothesis of major depressive disorder. *Mol Psychiatry.* 2011;16(4):383-406.
- Maguire J, Mody I. GABA(A)R plasticity during pregnancy: Relevance to postpartum depression. *Neuron.* 2008;59(2):207-13.
- Maguire J, Ferando I, Simonsen C, Mody I. Excitability changes related to GABAA receptor plasticity during pregnancy. *J Neurosci.* 2009;29(30):9592-601.
- McDowell, I. *Measuring Health: A guide to rating scales and questionnaires.* 2006: 3rd Ed. New York: Oxford University Press.
- McLearn KT, Minkovitz CS, Strobino DM, et al. Maternal depressive symptoms at 2 to 4 months post partum and early parenting practices. *Arch Pediatr Adolesc Med.* 2006;160:279-84.

Meltzer-Brody S. New insights into perinatal depression: pathogenesis and treatment during pregnancy and postpartum. *Dialogues Clin Neurosci.* 2011;13(1):89-100.

Meltzer-Brody S, Stuebe A. The long-term psychiatric and medical prognosis of perinatal mental illness. *Best Pract Res Clin Obstet Gynaecol.* 2014 Jan;28(1):49-60.

Müller-Thomsen T, Arlt S, Mann U, et al. Detecting depression in Alzheimer's disease: evaluation of four different scales. *Archives of Clinical Neuropsychology* 2005;20:271-6.

O'Hara MW, Wisner KL. Perinatal mental illness: definition, description and aetiology. *Best Pract Res Clin Obstet Gynaecol.* 2014;28(1):3-12.

Okun ML. Postpartum depression. In: *Encyclopedia of Behavioral Medicine* 2013. Ed. Gellman MD and Turner JR; Springer Science and Business Media, New York: 1518-1520. 10.1007/978-1-4419-1005-9_826.

Paulson JF, Dauber S, Leiferman JA. Individual and combined effects of postpartum depression in mothers and fathers on parenting behavior. *Pediatrics.* 2006;118:659–68.

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry.* 2011;168(12):1266-77.

Rudolph U, Knoflach F. Beyond classical benzodiazepines: novel therapeutic potential of GABAA receptor subtypes. *Nat Rev Drug Discov.* 2011 Jul 29;10(9):685-97.



21. APPENDICES

APPENDIX 1. DEPRESSION AND ANXIETY DISORDERS LIST

Purpose: It is important to have a complete medical history of the subjects' prior diagnoses for depression or anxiety. Please review this list with each subject and record any medical history on the appropriate case report form.

Generalized Anxiety Disorder
Obsessive-Compulsive Disorder
Panic Disorder
Posttraumatic Stress Disorder
Major Depressive Disorder
Persistent Depressive Disorder
Bipolar Disorder
Seasonal Affective Disorder
Psychotic Depression
Premenstrual Dysphoric Disorder
Situational Depression
Atypical Depression
Schizophrenia
Postpartum Depression

APPENDIX 2. PRIOR AND CONCOMITANT ANTIDEPRESSANT MEDICATION LIST

Purpose: It is important to have a complete history of the subjects' prior therapies for depression. Please review the following list of examples of common therapies for depression with each subject and record any experience with these or any therapies for depression on the appropriate case report form.

Celexa (citalopram)

Prozac, Sarafem (fluoxetine)

Zoloft (sertraline)

Cymbalta (duloxetine)

Effexor XR (venlafaxine)

Wellbutrin (bupropion)

Elavil (amitriptyline)

Pamelor (nortriptyline)

Lexapro (escitalopram)

Luvox (fluvoxamine)

Oleptro, Desyrel (trazodone)

Paxil, Pexeva, Brisdell (paroxetine)

Remeron, Remeron Soltab (mirtazapine)