1. PROTOCOL AND AMENDMENTS

Version Number	Date	Title
Amendment 4	16 March 2017	A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects With Severe Postpartum Depression and Adult Female Subjects with Moderate Postpartum Depression
Amendment 3	31 January 2017	A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects With Severe Postpartum Depression and Adult Female Subjects with Moderate Postpartum Depression
Amendment 2	30 June 2016	A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects With Severe Postpartum Depression and Adult Female Subjects with Moderate Postpartum Depression
Amendment 1	22 December 2015	A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects With Severe Postpartum Depression
Original	18 September 2015	A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects With Severe Postpartum Depression

Administrative Letter – 01 June 2017

Administrative Letter – 30 June 2017

Administrative Letter – 01 August 2017

Table 1: Summary of Amendment Changes

Version	Date
Amendment 1	22 December 2015
Amendment 2	30 June 2016
Amendment 3	02 February 2017
Amendment 4	16 March 2017

Administrative Letter

DATE: 1Aug2017

To: 547-PPD-202 Investigative Sites

FROM: [redacted] Sage [redacted]

PROTOCOL: A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects with Severe Postpartum Depression and Adult Female Subjects with Moderate Postpartum Depression

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The purpose of this Administrative Letter is to clarify the number of subjects to be randomized in Part B and Part C of 547-PPD-202. In the Number of Subjects section within the synopsis (page 6) it states:

> *Up to 32 subjects will be randomized in Part A, up to 120 subjects will be randomized in Part B, and up to 100 subjects will be randomized in Part C.*

In the Sample Size Calculation section within the synopsis (page 10) and in section 13.6 Determination of Sample Size (page 65) it states:

> *… For Part B, a sample size of 40 evaluable subjects per group (120 total) would provide 90% power… For Part C, a sample size of 50 evaluable subjects per group (100 total) would provide 90% power…*

As described in section 13.6 Determination of Sample Size, the intent of the study is to have 120 evaluable subjects in Part B and 100 evaluable subjects in Part C. Evaluable subjects are defined as those who are randomized and initiate treatment. Due to operational considerations, some subjects may be randomized and never initiate treatment.

Thus, this letter is to clarify that enrollment for Part B and Part C of 547-PPD-202 will remain open until at least 120 subjects randomize and initiate treatment in Part B and at least 100 subjects randomize and initiate treatment in Part C.

[redacted]

Sage [redacted]

Administrative Letter

DATE: 30June2017

To: 547-PPD-202 Investigative Sites

FROM: [redacted], MD, Sage [redacted]

PROTOCOL: A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects with Severe Postpartum Depression and Adult Female Subjects with Moderate Postpartum Depression

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The purpose of this Administrative Letter is to clarify the assessment windows as defined in Footnote i of the Schedule of Events (Table 1) of the in Version 5.0 16 March 2017 of the above-named protocol:

Footnote i in the Schedule of Events (Table 1) states that the following assessments: HAM-D, MADRS, BIMF, EPDS, GAD-7, and PHQ-9 are "To be completed within ±30 minutes of the scheduled time point during the Treatment Period." This memo is to clarify that the assessment window for the administration of the HAM-D is meant to be within ±30 minutes and specifically for the H0 (pre-dosing) assessment within 30 minutes prior to dosing. All of the other pre-dosing assessments with footnote i should be completed within 2 hours prior to dosing.

[redacted], MD

[redacted], MD

Sage [redacted]

Administrative Letter

DATE: 1June2017

To: 547-PPD-202 Investigative Sites

FROM: [redacted], MD, Sage [redacted]

PROTOCOL: A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects with Severe Postpartum Depression and Adult Female Subjects with Moderate Postpartum Depression

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The purpose of this Administrative Letter is to clarify the following inconsistency in Version 5.0 16 March 2017 of the above-named protocol:

Section 7.1, page 38 states: "Subjects will attend the clinic for safety follow-up assessment at 1 week (7±1d), 12 days (Part A), 2 weeks (14±2d [Part B and C]), 3 weeks (21±1d [Part B and C]), and 1 month (30d±3d) after the initiation of the study drug infusion."

The window surrounding the 3-week follow-up visit is intended to be ±3d not ±1d as indicated on page 38. The schedule of events (Table 1 in Section 2. Synopsis) and Section 12.3.2 correctly state the intended 21d±3d window for the 3-week follow-up visit.

This Administrative Letter will also clarify that the new CRO Medical Monitor contact information listed on the cover page and in Section 14.2.4 is:

[redacted]
24/7 Hotline: [redacted]
Email: [redacted]

Lastly, this administrative letter will correct the Study Design schema for Part A (Figure 1. in Section 7.1, page 35). Study Part A has concluded enrollment however it should be noted that the dose of SAGE-547/placebo that was administered was 90 µg/kg/hr not 30 µg/kg/hr as printed in the protocol.

Please refer to the corrections above when performing the 3-week follow-up visit and/or contacting the CRO Medical Monitor.

[redacted] MD

Sage [redacted], MD

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF SAGE-547 INJECTION IN THE TREATMENT OF ADULT FEMALE SUBJECTS WITH SEVERE POSTPARTUM DEPRESSION AND ADULT FEMALE SUBJECTS WITH MODERATE POSTPARTUM DEPRESSION

NUMBER: 547-PPD-202 / NCT02942004
IND NUMBER: 122,279
EUDRA CT NUMBER: 2016-005137-68

Investigational Product:	SAGE-547 Injection (allopregnanolone)
Clinical Phase:	3
Sponsor:	Sage Therapeutics 215 First Street Cambridge, MA 02142
Sponsor Contact:	Helen Colquhoun, M.D. Senior Medical Director Phone: [redacted]
Sponsor Medical Monitor:	[redacted], M.D., FAAP Study Medical Lead Phone: [redacted]
CRO Medical Monitor:	[redacted], M.D. [redacted] Phone: [redacted] 24/7 Hotline: [redacted]
Date of Original Protocol:	Version 1.0, 18 September 2015
Date of Amendment 1:	Version 2.0, 22 December 2015
Date of Amendment 2:	Version 3.0, 30 June 2016
Date of Amendment 3:	Version 4.0, 31 January 2017
Date of Amendment 4:	Version 5.0, 16 Mar 2017

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 the Sponsor.

1. SIGNATURE PAGE

Title of protocol:	A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects with Severe Postpartum Depression and Adult Female Subjects with Moderate Postpartum Depression
Protocol No:	547-PPD-202
IND No.:	122,279
Eudra CT No.:	2016-005137-68
Study Phase:	3
Sponsor:	Sage Therapeutics

Sponsor Approval

[redacted] 21 MAR 2017

Helen Colquhoun, M.D.
Senior Medical Director
Sage Therapeutics

Date (dd/mmm/yyyy)

[redacted] 21 MAR 2017

[redacted], M.P.H.
Sage Therapeutics

Date (dd/mmm/yyyy)

[redacted] 21 MAR 2017

Sage Therapeutics

Date (dd/mmm/yyyy)

[redacted] 21 MAR 2017

[redacted], Ph.D.
Sage Therapeutics

Date (dd/mmm/yyyy)

Investigator Agreement

By signing this page, I attest that I have read and understand the contents of Clinical Protocol 547-PPD-202 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: _____

Investigator's Name: _____

Institution: _____

Date (dd/mmm/yyyy): _____

2. SYNOPSIS

Name of Sponsor:

Sage Therapeutics
215 First Street
Cambridge, MA 02142

Protocol No. 547-PPD-202	**Phase:** 3

Name of Investigational Product:

SAGE-547 Injection

Name of Active Ingredient:

Allopregnanolone

Title of the Protocol:

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects With Severe Postpartum Depression and Adult Female Subjects with Moderate Postpartum Depression

Study Sites: Up to 100 global sites

Duration of Subject Participation: Up to 37 days

Primary Objective:

- To determine if SAGE-547 Injection infused intravenously for 60 hours at up to 90 μg/kg/h reduces depressive symptoms in subjects with severe postpartum depression (PPD) compared to placebo injection as assessed by the change from baseline in Hamilton Rating Scale for Depression (HAM-D) total score. This objective applies to both Parts A and B.

Secondary Objectives (unless otherwise specified, these objectives apply to Parts A, B, and C):

- To determine if SAGE-547 infusion at up to 60 μg/kg/h for 60 hours reduces depressive symptoms in subjects with severe PPD compared to placebo injection as assessed by the change from baseline in HAM-D total score. This objective applies to Part B.
- To determine if SAGE-547 Injection infused intravenously at up to 90 μg/kg/h for 60 hours reduces depressive symptoms in subjects with moderate PPD compared to placebo injection as assessed by the change from baseline in HAM-D total score. This objective applies to Part C.
- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms compared to placebo injection as assessed by HAM-D response, HAM-D remission, change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score, Clinical Global Impression – Improvement (CGI-I) response, and changes from baseline in HAM-D subscale and individual item scores.

- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces other mood symptoms compared to placebo injection as assessed by changes from baseline in the Generalized Anxiety Disorder 7-Item Scale (GAD-7) total score.
- To evaluate the safety and tolerability of SAGE-547 Injection compared with placebo as assessed by the incidence of adverse events (AEs), vital sign measurement, clinical laboratory evaluations, electrocardiogram (ECG) parameters, and the Columbia Suicide Severity Rating Scale (C-SSRS).

Other Objectives:

- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces subject-reported depressive symptoms compared to placebo injection as assessed by the change from baseline in Edinburgh Postnatal Depression Scale (EPDS) total score and the change from baseline in Patient Health Questionnaire (PHQ-9) total score.
- To determine if SAGE-547 Injection infused intravenously for 60 hours improves maternal behaviors compared to placebo injection as assessed by the change from baseline in Barkin Index of Maternal Functioning (BIMF) total and sub-scale scores.
- To determine if SAGE-547 Injection infused intravenously for 60 hours improves the general health status compared to placebo as assessed by the change from baseline in the Short Form-36 (SF-36) total score at Day 7 and Day 30.

Pharmacokinetic Objective:

To assess the pharmacokinetic (PK) profile of SAGE-547, metabolites of SAGE-547, and betadex sulfobutyl ether sodium (SBECD).

Study Design and Methodology:

This protocol comprises three multicenter, randomized, double-blind, parallel-group, placebo-controlled studies of the efficacy, safety, and PK of SAGE-547 Injection in adult female subjects diagnosed with severe or moderate PPD. Each study will be independently conducted, analyzed, and reported. In this protocol, Study 547-PPD-202A is hereafter referred to as Part A; Study 547-PPD-202B is hereafter referred to as Part B; and Study 547-PPD-202C is hereafter referred to as Part C. In Parts A and C, subjects will be randomized to one of two treatment groups (SAGE-547 90 µg/kg/hour or placebo) on a 1:1 basis. In Part B, subjects will be randomized to one of three treatment groups (SAGE-547 60 µg/kg/hour, SAGE-547 90 µg/kg/hour, or placebo) on a 1:1:1 basis. In each part, the continuous IV infusions of blinded study drug will increase and then taper. Subjects must remain as inpatients during the study Treatment Period, which is approximately 72 hours/3 days in duration (60 hours of treatment and an additional 12 hours for completion of 72-hour assessments). The Screening Period assessments may be conducted on an inpatient or an outpatient basis. The Follow-up Period assessments are conducted on an outpatient basis.

Screening Period: The Screening Period begins with the signature of the informed consent form (ICF). Eligibility is determined by applying the inclusion/exclusion criteria. The diagnosis of PPD must be by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). A full medical and family history will be taken from the subject, including recording of all depression, other Axis I and Axis II disorders, and postpartum depression episodes in primary probands.

Treatment Period: In Parts A and C, once subjects are confirmed as eligible for the study, they will be randomized to one of two treatment groups (SAGE-547 or placebo) on a 1:1 basis. Continuous intravenous (IV) infusions of blinded study drug will be administered, with a new bag hung at least

every 24 hours during the 60-hour infusion. Infusion rates will increase and then taper, with subjects in the SAGE-547 group receiving 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24-52 hours), followed by 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours). Placebo subjects will receive infusion rates equivalent to SAGE-547 90 µg/kg/hour. In Part B, once subjects are confirmed as eligible for the study, they will be randomized to one of three treatment groups (SAGE-547 60 µg/kg/hour, SAGE-547 90 µg/kg/hour, or placebo) on a 1:1:1 basis. For the 60 µg/kg/hour group, subjects will receive 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-56 hours), and 30 µg/kg/hour (56-60 hours). For the 90 µg/kg/hour group, subjects will receive 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24-52 hours), followed by 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours). Subjects in the placebo group will randomly receive infusion rates equivalent to either the 60 µg/kg/hour or 90 µg/kg/hour group. Parts B and C will run concurrently.

In all parts, subjects may be discharged after the 72-hour assessments have been completed (12 hours after completion of the study drug infusion). If their clinical condition does not allow discharge, normal standard of care will be employed in their ongoing management.

Initiation of benzodiazepines, narcotics, antibiotics, neuroleptics, and other anti-anxiety medications will not be allowed between screening and completion of the 72-hour assessments. Doses of psychotropics, which must have been initiated at least 14 days prior to screening, must remain at a stable dose until completion of the 72-hour assessments. If at the 72-hour assessment there has been no treatment response (HAM-D total score remains above 13), treatment with antidepressant medication may be optimized prior to discharge, and the subject may remain in the unit or be followed at an outpatient clinic, as clinically indicated.

Efficacy and safety assessments will be performed periodically during the study, and blood samples will be collected for analysis of SAGE-547, metabolites of SAGE-547, and SBECD concentrations, as outlined in the Schedule of Events (Table 1). Blood samples will be collected, and outcome measures will be obtained at pre-specified times over 72 hours during the Treatment Period.

Follow-up Period: For Part A, Follow-up Visits will be conducted one week (7±1 day), approximately two weeks (12±2 days), and one month (30±3 days) after the initiation of the study drug infusion. For Parts B and C, Follow-up Visits will be conducted one week (7±1 day), two weeks (14±2 days), three weeks (21±3 days), and one month (30±3 days) after the initiation of the study drug infusion. The blind will be maintained through the Follow-up period.

Number of Subjects:

Up to 32 subjects will be randomized in Part A, up to 120 subjects will be randomized in Part B, and up to 100 subjects will be randomized in Part C.

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 aged 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 breast feeding at screening, must agree to temporarily cease giving breastmilk to their infant(s) from just prior to receiving study drug through 4 days (Study Day 7) after the end of infusion.

6. Subject must have a negative pregnancy test at screening and Day 1 prior to the start of study drug infusion
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, as diagnosed by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)
8. For Part A and B, subject has a HAM-D total score of ≥26 at screening and Day 1 (prior to dosing). For Part C, subject has a HAM-D total score of ≥20 and ≤25 at screening and Day 1 (prior to dosing)
9. Subject is ≤6 months postpartum at screening
10. Subject is willing at screening to delay the start of any new pharmacotherapy regimens, including antidepressant or anti-anxiety medication, until the study drug infusion and 72-hour assessments have been completed; if the subject is taking psychotropic medications, these must be at a stable dose from 14 days prior to screening until the 72-hour assessments have been completed.
11. (Removed)
12. Subject must use one of the following methods of birth control during participation in the study and for 30 days following the end of the study drug infusion:
    - Total abstinence (no sexual intercourse)
    - Hormonal contraceptives (birth control) including birth control pills, implantable or injectable contraceptives (Norplant® or Depo-Provera®)
    - A barrier form of contraception such as a condom or occlusive cap with a spermicide
    - An intrauterine device

Exclusion Criteria:

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

1. Subject has renal failure requiring dialysis or fulminant hepatic failure or is anemic (hemoglobin ≤10 g/dL)
2. Known allergy to progesterone or allopregnanolone
3. Active psychosis per Investigator assessment
4. Attempted suicide associated with index case of postpartum depression
5. (Removed)
6. Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
7. History of active alcoholism or drug abuse (including benzodiazepines) in the 12 months prior to screening. A positive urine drug screen (except benzodiazepines under certain circumstances [see Section 10.3.3 and Section 11.1.2.6]) is exclusionary.
8. Exposure to another investigational medication or device within 30 days prior to screening
9. (Removed)
10. Subject has previously participated in this study or any other study employing SAGE-547
11. Administration of electroconvulsive therapy (ECT) within 14 days prior to screening and/or plans to administer ECT before the Study Day 7 Visit

Investigational Product, Dosage, and Mode of Administration:

SAGE-547 Injection, IV administration: SAGE-547 Injection is a sterile, clear, colorless 5 mg/mL solution of SAGE-547 (allopregnanolone) and 250 mg/mL SBECD buffered with 10 mM citrate at a pH of 6.0, supplied in single-use 20 mL vials for IV administration. As supplied, SAGE-547 Injection, which is hypertonic, requires further dilution with Sterile Water for Injection (SWFI) to render it isotonic for IV infusion. The specific infusion dose of SAGE-547 Injection will be calculated based on weight for each subject at screening and administered according to the randomization schedule. Infusion bags will be changed at least every 24 hours. Details about the preparation and administration of the study drug infusions will be included in the Pharmacy Manual.

Part A and Part C:

	Infusion Rate (µg/kg/hour)				
SAGE-547 Dose	**Day 1 0-4 hours**	**Day 1 4-24 hours**	**Day 2-3 24-52 hours**	**Day 3 52-56 hours**	**Day 3 56-60 hours**
90 µg	30	60	90	60	30

Part B:

	Infusion Rate (µg/kg/hour)				
SAGE-547 Dose	**Day 1 0-4 hours**	**Day 1 4-24 hours**	**Day 2-3 24-52 hours**	**Day 3 52-56 hours**	**Day 3 56-60 hours**
60 µg	30	60	60	60	30
90 µg	30	60	90	60	30

Reference Therapy, Dosage, and Mode of Administration:

An identical placebo IV infusion will be prepared for IV administration consisting of the same formulation without allopregnanolone. For each part of the study, the placebo infusion rate will match that of the SAGE-547 rate(s) used in that part.

Randomization:

Randomization will be stratified by antidepressant use at baseline and will follow the computer-generated randomization schedule. Subjects will be randomized within stratum to receive SAGE-547 Injection or placebo; subjects, clinicians, and study team will be blinded to treatment allocation. The pharmacist, who will prepare the infusion bags according to the randomization schedule, will be unblinded. In Parts A and C, the infusion rates are the same for all subjects within a particular dosing period (0-4 hours, 4-24 hours, etc.) regardless of randomized treatment. In Part B, the infusion rates will vary according to the randomized dose group.

Criteria for Evaluation:

Primary Endpoint

The primary outcome measure will be the 17-item Hamilton Rating Scale for Depression (HAM-D). The HAM-D will be administered before, during, and after the infusion of blinded study drug. The HAM-D total score will be calculated as the sum of the 17 individual item scores. The change from baseline in HAM-D total score at +60 hours will be the primary efficacy endpoint with comparison between the SAGE-547 and placebo treatment groups used to evaluate the efficacy of SAGE-547 in treating the depressive symptoms of PPD.

For Part A and Part C, the primary comparison will be between 90 μg SAGE-547 and placebo at the 60-hour assessment. For Part B, the primary comparison will be between 90 μg SAGE-547 and placebo at the 60-hour assessment; if this comparison is significant at the 0.05 level, then the 60 μg group will be compared to placebo at the 0.04 level of significance. More details will be provided in the statistical analysis plans (SAPs) regarding strong control of overall level of significance for multiple testing, including testing of key secondary endpoints.

Secondary Endpoints

The change from baseline in HAM-D total score at Day 30 will be included in the secondary endpoints. Additional measures of depressive symptom severity will be administered, including the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinical Global Impression (CGI) scale. Total scores and changes from baseline will be calculated where applicable. Changes from baseline at +60 hours and other time points will be evaluated as secondary efficacy endpoints with comparisons between the two treatment groups used to support the efficacy of SAGE-547 in treating the depressive symptoms of PPD. In addition to the above scales, the individual item scores and subscale scores from the HAM-D scale will also evaluated as secondary efficacy endpoints. GAD-7 will also be administered, and scores from these scales will be evaluated to assess the efficacy in other mood disorder and anxiety symptoms.

Safety and tolerability of SAGE-547 Injection will be evaluated by summarization of AEs by frequency, severity, and seriousness; clinical laboratory measures, vital signs, and ECGs (including changes from baseline); and concomitant medication usage. Suicidality will be monitored using the C-SSRS.

The doses of all anti-depressant medications will be recorded throughout the study. No changes and/or additions to antidepressant or anxiolytic medicine will be allowing during the dosing period. An analysis of time to starting/increasing the dose/decreasing the dose of each different anti-depressant medication will be undertaken for subjects discharged.

Plasma will be collected to assay for concentrations of SAGE-547, SAGE-547 metabolites, and SBECD. The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve (AUC) from time zero to 60 hours ($AUC_{0\text{-}60}$), AUC from time zero to infinity (AUC_{∞}), maximum (peak) plasma concentration (C_{max}), time at maximum (peak) plasma concentration (t_{max}), steady-state drug concentration in the plasma during constant-rate infusion (C_{ss}), and average drug concentration in the plasma at steady state during a dosing interval (C_{avg}).

Other Endpoints

Additional measures of symptoms and function related to the current episode of postpartum depression severity will be administered, including the EPDS, PHQ-9, BIMF, and SF-36.

Subscale and total scores and changes from baseline will be calculated where applicable. Changes from baseline at +60 hours and other time points will be evaluated as secondary efficacy endpoints with comparisons between the two treatment groups used to support the efficacy of SAGE-547 in treating the depressive symptoms of PPD. In addition to the above scales, the individual item scores will also be evaluated as other endpoints.

Statistical Methods:

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 infusion.

Interim Analysis

In Part A, an interim analysis will be conducted by an independent statistician for sample size re-estimation purposes when at least 16 subjects have completed efficacy assessments through 60 hours. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis for sample size re-estimation will be included in the statistical analysis plan.

There will be no interim analysis for Parts B or C.

Sample Size Calculation

Using a two-sided t-test at an alpha level of 0.05, a sample size of 10 evaluable subjects per group for Part A would provide 70% power to detect an effect size of 1.2 between the SAGE-547 and placebo groups with regard to the primary outcome variable of change from baseline in HAM-D total score. An effect size of 1.2 corresponds to a placebo-adjusted difference of 12 points in the change from baseline in HAM-D total score at 60 hours with an assumed standard deviation of 10 points. By including two treatment groups and using a 1:1 randomization ratio, a total of 20 evaluable subjects are required for Part A.

Based on the results of the interim analysis, the sample size in Part A could be increased to a maximum of 32 randomized subjects. This adjustment to the sample size would allow for an effect size of 1.0 to be detected.

For Part B, a sample size of 40 evaluable subjects per group (120 total) would provide 90% power to detect a treatment difference of 9.0 between the SAGE-547 and placebo groups and a common standard deviation of 12 points (for an effect size of 0.75) using a two-sided t-test at an alpha level of 0.05.

For Part C, a sample size of 50 evaluable subjects per group (100 total) would provide 90% power to detect a treatment difference of 8.0 between the SAGE-547 and placebo groups and a common standard deviation of 12 points (for an effect size of 0.667) using a two-sided t-test at an alpha level of 0.05.

Efficacy Analysis

The Efficacy Population will include all subjects who start the infusion of study drug and have a valid baseline HAM-D assessment and at least one post-baseline HAM-D assessment. Subjects will be classified and summarized by randomized treatment. Separate summaries will be produced for each part of the study.

For efficacy analysis purposes, centers with fewer than 15 subjects per center for Part B or 10 subjects per center for Part C will be pooled within regions (eg, North America region centers will be pooled separately those in Europe). For each part, the change from baseline in HAM-D total score will be analyzed using a mixed effects model for repeated measures; the model will include center (pooled), treatment, baseline score, visit time point, and visit time point-by-treatment terms as explanatory variables. Center and all other explanatory variables will be treated as fixed effects. The primary comparison between each SAGE-547 dose and placebo will be at the 60-hour time point. Comparisons at other time points, including the Day 30 time point, will be conducted to support the findings for the primary comparison. To account for multiple testing in Part B, (90 µg vs placebo and 60 µg vs placebo), the 90 µg group will be compared to placebo first. If this dose comparison is significant at the 0.05 level, then the 60 µg group will be compared to placebo at the 0.04 level. More details will be provided in the SAPs regarding strong control of overall level of significance for multiple testing, including testing of key secondary endpoints.

Changes from baseline in other rating scale scores will be analyzed with methods similar to the primary endpoint. Dichotomous response variables will be analyzed using Generalized Estimating Equation (GEE) method for repeated binary responses.

In addition to formal analysis, efficacy rating scale scores (including recorded and change from baseline values) will be summarized by descriptive statistics, including n, mean, standard deviation (SD), median, and minimum and maximum values. Categorical efficacy endpoints (including HAM-D, MADRS, and CGI-I response variables) will be summarized by frequency and percentage.

Safety Analysis

The Safety Population is defined as all randomized subjects who start the infusion of study drug. Subjects will be classified and summarized by actual treatment. Separate summaries will be produced for each part of the study.

Safety will be assessed using AEs, vital signs, ECG, clinical laboratory tests, C-SSRS, and concomitant medication data. Continuous safety data (including absolute and change from baseline values) will be summarized by descriptive statistics, including n, mean, standard deviation (SD), median, and minimum and maximum values. Categorical endpoints will be summarized by frequency and percentage.

Safety data will be examined for possible relationships between subject characteristics and plasma allopregnanolone concentrations, as appropriate.

Table 1: Schedule of Events

	Screening Period	Treatment Period Clinic Period (Day 1 to Day 3)															Follow-up Period			
Visit Days / Hours	**Screening D-7[a] to -1**	**D1 H0***	**D1 H2**	**D1 H4**	**D1 H8**	**D1 H12**	**D1 H18**	**D1 H24**	**D2 H30**	**D2 H36**	**D2 H42**	**D2 H48**	**D3 H54**	**D3 H60**	**D3 H66**	**D3 H72**	**D7/ET (±1d)**	**D14[a] (+2d)**	**D21[a] (+3d)**	**D30 (±3d)**
Study Procedure																				
Informed Consent	X																			
Inclusion/Exclusion Criteria	X	X																		
Randomization		X																		
Demographics	X																			
Medical/Family History	X																			
Physical Examination	X															X	X			
Body Weight/Height	X																			
Clinical Lab Assessments[b]	X															X	X			
Urinalysis[b]	X																X			
Drug & Alcohol Screen[c]	X	X																		
Pregnancy Test[d]	X	X																		X
Genetic Sample[e]	O																			
Vital Signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
12-Lead ECG[g]	X											X					X			
C-SSRS[h]		X						X						X		X	X	X	X	X
Confinement		X																		
CGI-I[i]			X	X		X		X		X		X		X		X	X	X	X	X
CGI-S	X	X																		
SCID-I	X																			
HAM-D[i]	X	X	X	X	X	X		X		X		X		X		X	X	X	X	X
MADRS[i]	X	X						X				X		X		X	X	X	X	X
BIMF[i]		X															X	X	X	X

Visit Days / Hours	Screening Period	Treatment Period Clinic Period (Day 1 to Day 3)															Follow-up Period			
	Screening D-7[a] to -1	D1 H0*	D1 H2	D1 H4	D1 H8	D1 H12	D1 H18	D1 H24	D2 H30	D2 H36	D2 H42	D2 H48	D3 H54	D3 H60	D3 H66	D3 H72	D7/ET (±1d)	D14[a] (+2d)	D21[a] (+3d)	D30 (±3d)
Study Procedure																				
EPDS[i]		X												X			X	X	X	X
GAD-7[i]		X												X			X	X	X	X
PHQ-9[i]		X												X			X	X	X	X
SF-36 (acute version)		X															X	X	X	X
HCRU	X	X																		
Plasma PK[J]		X		X	X	X		X	X	X		X		X		X				
Instructions for Lactating Subjects[k]		X							X				X							
Study Drug Infusion		X																		
Adverse Events		X																		
Prior/Concomitant Medications[l]		X																		

BIMF = Barkin Index of Maternal Functioning; CGI-I = Clinical Global Impression of Improvement; C-SSRS = Columbia Suicide Severity Rating Scale; D = Day; ECG = electrocardiogram; EPDS = Edinburgh Postnatal Depression Scale; GAD-7 = Generalized Anxiety Disorder 7-Item Scale; HAM-D = Hamilton Rating Scale for Depression, 17-item; HCRU = Health Care Resource Utilization; MADRS = Montgomery-Asberg Depression Rating Scale; PHQ-9 = Patient Health Questionnaire; PK = pharmacokinetic; SF-36 = Short Form-36; SCID-I = Structured Clinical Interview for DSM-IV Axis I Disorders.
O = optional; * = All H0 procedures to be completed prior to dosing

[a] The screening period for Part A is from Day -5 to Day -1. Follow-up Visits for Part A are on Days 7, 12, and 30.
[b] Safety laboratory tests will include hematology, serum chemistry, coagulation, and select hormone parameters. The urine test will include a urinalysis. Lab assessments are to be completed within ±30 minutes of the scheduled time point.
[c] Urine for selected drugs of abuse and alcohol (serum or breath)
[d] Serum at screening and urine for all other time points; lactation status (ie, subject is breastfeeding, subject is lactating but not breastfeeding, or subject is not lactating) will be recorded at screening
[e] A blood sample for genetic testing, where consent is given
[f] Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). Vital signs will be obtained within ±30 minutes of the scheduled time point, unless the subject is asleep between the hours of 23.00h and 06.00h.
[g] Performed within ±30 minutes of the scheduled time point on Day 2.
[h] The "Baseline/Screening" C-SSRS form will be completed on Day 1. The "Since Last Visit" C-SSRS form will be completed at all subsequent time points.
[i] To be completed within ±30 minutes of the scheduled time point during the Treatment Period.

[j] Blood samples for PK analysis will be collected at pre-infusion and at 4 (before change in infusion rate, if applicable), 8, 12, 24 (before change in infusion rate, if applicable), 30, 36, 48, 60 (before end of infusion), and 72 hours after the start of the infusion. PK blood draws after the start of infusion will have a window of ±10 minutes. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.

[k] Breast milk will be pumped and discarded by subjects who are lactating. On Day 3, subjects who are lactating will be reminded that they must continue to pump and discard breast milk through Day 7 of the study.

[l] To include those taken within 60 days prior to signing the informed consent through the Day 30 visit.

Note: In Part A only, SSS is completed within ±15 minutes of each time point through the 72-hour assessments, unless the subject is asleep between 23.00h and 06.00h.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALLO	allopregnanolone
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{∞}	area under the concentration-time curve from time zero to infinity
$AUC_{0\text{-}60}$	area under the concentration-time curve from time zero to 60 hours
BIMF	Barkin Index of Maternal Functioning
BMI	body mass index
BUN	blood urea nitrogen
C_{avg}	average drug concentration in the plasma at steady-state during a dosing interval
CBC	complete blood count
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression–Improvement
CGI-S	Clinical Global Impression–Severity
cGMP	Current Good Manufacturing Practice
C_{max}	maximum (peak) plasma concentration of the drug
CNS	central nervous system
CRF	case report form
CS	clinically significant
CSF	cerebrospinal fluid
CSR	clinical study report
C_{ss}	steady-state drug concentration in the plasma during constant-rate infusion
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EEG	electroencephalography
EFF	Efficacy Population
Ph. Eur.	European Pharmacopeia
EPDS	Edinburgh Postnatal Depression Scale
ERα	estrogen receptor alfa

Abbreviation	Definition
ERß	estrogen receptor beta
ET	early termination
GABA	gamma-aminobutyric acid
$GABA_A$	gamma-aminobutyric acid–gated chloride channel
GAD-7	Generalized Anxiety Disorder 7-Item Scale
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
GGT	gamma glutamyl transferase
h	hour
HAM-D	Hamilton Rating Scale for Depression, 17-item
hCG	human chorionic gonadotropin
HCRU	Healthcare Resource Utilization
Hct	hematocrit
HEENT	head, eyes, ears, nose, and throat
Hgb	hemoglobin
ICF	informed consent form
ICH	International Council on Harmonisation
ID	identification
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	intravenous
MADRS	Montgomery-Asberg Depression Rating Scale
MCH	mean corpuscular hemoglobin
MCS	mental component summary
MCV	mean corpuscular volume
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
NCS	not clinically significant
PCS	physical component summary
PHQ-9	Patient Health Questionnaire
PK	pharmacokinetic(s)
PKP	Pharmacokinetic Population
PMID	PubMed identification
PP	Per-Protocol Population
PPD	postpartum depression

Abbreviation	Definition
PR	progesterone receptor
PT/INR	prothrombin time/international normalized ratio
RBC	red blood cell
RSE	refractory status epilepticus
SAE	serious adverse event
SAP	statistical analysis plan
SBECD	betadex sulfobutyl ether sodium
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SD	standard deviation
SF-36	Short Form-36
SOC	system organ class
SOP	standard operating procedure
SRSE	super refractory status epilepticus
SSRI	selective serotonin reuptake inhibitors
SSS	Stanford Sedation Scale
SWFI	sterile water for injection
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximum (peak) plasma concentration
TSH	thyroid stimulating hormone
US	United States
USP	United States Pharmacopeia
VAS	visual analogue scale
V_d	volume of distribution
WBC	white blood cell

4. INTRODUCTION AND RATIONALE

This study is designed to evaluate the efficacy, safety, and pharmacokinetics (PK) of SAGE-547 (allopregnanolone) as a treatment for women with severe or moderate postpartum depression (PPD), an area of high unmet medical need.

PPD is considered to be moderate to severe depression in women who have recently given birth, otherwise defined as the occurrence of major depressive disorder (MDD) within 4 weeks of delivery (DSM-V 2013) or up to a year after giving birth (Okun 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-V 2013), although this diagnosis may be confounded by the relative frequency of symptoms such as sleep disturbance or appetite problems in pregnant and postpartum women. 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).

During pregnancy, estradiol and progesterone levels increase dramatically but then rapidly decline in the acute postpartum period (Gavin 2005). The onset of PPD symptoms coincides with the rapid decrease of the gonadal steroids postpartum. The duration of a PPD episode has been estimated as shorter than depressive episodes in the general population (approximately 5 months), while other studies indicate time to remission is approximately the same (Chaudron 2003).

PPD is common and has devastating consequences for the woman and for her family (Fihrer 2009, Verbeek 2012). Perinatal depression is reported to be the most underdiagnosed obstetric complication in America (Earls 2010). Furthermore, it is the most common psychiatric illness to occur in the puerperium (O'Hara 2014). A meta-analysis of 30 studies (Gaynes 2005) found that the point prevalence of major and minor depression ranged between 6.5% and 12.9% at different times during the first postpartum year. Overall incidence is estimated at around 15% to 20% with up to 10% being considered severe (Edge 2007, O'Hara 2014).

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 non-pharmacological 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.

4.1. Role of Allopregnanolone in Affective Disturbances

The neurosteroid metabolite of progesterone, allopregnanolone, acutely regulates neuronal function (Gangisetty 2010) and appears to play a significant role in affective disturbances that occur with changes in reproductive endocrine function, such as during the postpartum period (Amin 2006, Nappi 2001, Epperson 2006).

Neurosteroids are metabolites of cholesterol-derived steroid hormones that are synthesized in the brain and nervous system; they modulate the major inhibitory and excitatory central nervous system (CNS) neurotransmitter systems: γ-aminobutyric acid (GABA) and glutamate, respectively. Neurosteroids are among the most potent and effective modulators of $GABA_A$ receptors and augment GABAergic inhibition (Belelli 2005). The powerful anxiolysis that accompanies this potentiation of $GABA_A$ receptors has led to the speculation that neurosteroid dysregulation plays a central role in the etiology of affective disorders, including reproductive mood disorders, such as PPD (Amin 2006).

There is increasing evidence supporting the role of neurosteroids in affective dysregulation. Allopregnanolone and pregnanolone have been shown to modulate the GABA receptor positively (Majewska 1986). Several groups have demonstrated decreased allopregnanolone levels in MDD, with an increase seen in both plasma and cerebrospinal fluid (CSF) following successful antidepressant treatment (Uzunova 1998, Romeo 1998, Ströhle 1999, Schüle 2006, Eser 2006, Schüle 2007). In addition, allopregnanolone has demonstrated anxiolytic effects in several animal anxiety models (Bitran 1991; Wieland 1991; Bitran 1993).

Allopregnanolone may also exert antidepressant effects by reducing the physiological impact of stress, promoting neuroprotection, and protecting against the pro-inflammatory immune activation and cytokine hypersecretion associated with MDD. In animals, allopregnanolone increases in response to stress, reduces pain sensitivity, and is thought to restore physiologic homeostasis following stress (Frye 1994, Morrow 1995). Allopregnanolone also exerts neuroprotective effects by reducing the expression of pro-apoptotic proteins and apoptotic DNA fragmentation (Djebaili 2005, Sayeed 2009), thereby reducing the cell death and gliosis associated with depression (Glantz 2010, Shelton 2011). Neuroprotection is mediated by immune regulation in depression (Licinio 1999), and allopregnanolone reduces the expression of the pro-inflammatory cytokine TNF-α (He 2004), which is elevated in depressed individuals (Dowlati 2010). Thus, allopregnanolone modulates biological processes dysregulated in MDD.

4.1.1. Rationale for Allopregnanolone Treatment of PPD

Genetic susceptibility to affective dysregulation may be unmasked during periods of reproductive hormone change such as during pregnancy and postpartum (Maguire 2008). Maguire and Mody demonstrated that a GABA receptor subunit mutation was behaviorally silent until the animal was exposed to pregnancy and the postpartum state, at which time the dams showed depressive-like behaviors and cannibalized their offspring (Maguire 2008). During pregnancy, the expression of the $GABA_A$ receptor δ-subunit is down-regulated as allopregnanolone levels increase, and at parturition, the expression of the $GABA_A$ receptor δ-subunit is recovered in response to rapidly declining neurosteroid levels (Maguire 2009). In contrast, the $GABA_A$ receptor δ-subunit-deficient mice fail to adapt to the dramatic

changes in allopregnanolone and experience depression-like and anxiety-like behavior and abnormal maternal behaviors, which are reversed by administration of allopregnanolone (Maguire 2008). This model provides compelling support for the hypothesis that changes in neurosteroid concentrations during pregnancy and postpartum are capable of provoking affective dysregulation, particularly in those with a genetically-determined susceptibility. The capacity of changes in neurosteroids, such as allopregnanolone, to function as behavioral switches suggests a potentially important treatment role of this hormone metabolite in reproductive endocrine-related mood disorders such as PPD.

The onset of PPD symptoms coincides with the rapid decrease of the gonadal steroids postpartum and has been reproduced in a pivotal clinical study (Bloch 2000). The authors investigated the possible role of changes in gonadal steroid levels in PPD by simulating 2 hormonal conditions related to pregnancy and parturition in euthymic women, 8 with and 8 without a history of PPD. They induced hypogonadism with leuprolide, adding back supra-physiologic doses of estradiol and progesterone for 8 weeks to simulate pregnancy. They then withdrew both steroids under double-blind conditions to mimic the rapid decrease of sex steroids upon delivery. Five of the 8 women with a history of postpartum depression (62.5%) and 0% of the comparison group developed significant mood symptoms typical of PPD during the withdrawal period.

Although progesterone levels were measured in this study, allopregnanolone was not. However, since allopregnanolone is the major active metabolite of progesterone, it can be assumed that the decrease in progesterone would cause a similar precipitate drop in allopregnanolone levels, as observed in the postpartum period (Gilbert Evans 2005, Paoletti 2006, Nappi 2001). These data provide direct evidence in support of the involvement of progesterone and its metabolites in the development of postpartum depression in a subgroup of women. Further, they suggest that women with a history of postpartum depression are differentially sensitive to mood-destabilizing effects of gonadal steroids (Bloch 2000).

Additional details regarding the role of allopregnanolone in the etiology of affective disorders and its nonclinical pharmacology and PK are presented in the Investigator's Brochure.

4.2. SAGE-547 Injection (Allopregnanolone)

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex, and CNS (Holzbauer 1985, Ottander 2005, Paul 1992). Allopregnanolone is a metabolite of progesterone created by the actions of 5-α reductase and 3-α hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic $GABA_A$ receptors.

SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), United States Pharmacopeia (USP), and 250 mg/mL betadex sulfobutyl ether sodium buffered with 10 mM citrate at a pH of 6.0, and will be administered intravenously. SAGE-547 Injection is also being developed for the treatment of adult patients with refractory status epilepticus (RSE), inclusive of super refractory status epilepticus (SRSE), who have not responded to standard treatment regimens, and investigated for the treatment of adults with essential tremor.

4.3. Summary of Nonclinical and Clinical Experience with SAGE-547

4.3.1. Nonclinical Pharmacology

The primary pharmacological effects of allopregnanolone or SAGE-547 are described earlier in the rationale (Section 4.1 and Section 4.1.1). Secondary pharmacologic effects comprise mainly the binding and consequent increased activity of steroid hormone receptors (androgen receptor [(AR], progesterone receptor [PR], and estrogen receptor beta [ERß]), with some evidence of inhibition at the highest doses (AR and estrogen receptor alfa [ERα]). These non-target effects may yield some adverse events (AEs) in the clinic.

Nonclinical toxicology studies largely illustrate the sedative and anesthetic effects of allopregnanolone and/or SAGE-547 at higher equivalent doses than the proposed dose for the current study. PK data in animals indicate a short half-life ($t_{½}$) and rapid clearance with a moderate volume of distribution and cerebral levels higher than plasma. Refer to the SAGE-547 Investigator's Brochure for more details.

4.3.2. Clinical Experience

The clinical PK data with intravenous (IV) administration of allopregnanolone in healthy women, men, and women on oral contraceptives confirmed the PK observations in animals of C_{max} achievable at approximately third trimester levels (150 nM), rapid clearance and moderate volume of distribution (V_d). Refer to the SAGE-547 Investigator's Brochure for more details.

An open-label, proof-of-concept study (547-PPD-201) evaluating the safety, tolerability, PK, and efficacy of SAGE-547 Injection in the treatment of adult female subjects with severe postpartum depression was started in 2014. This was the first study in this indication. Four women experienced significant improvement in depressive symptoms within 24 hours after administration of open-label IV SAGE-547. During the SAGE-547 Treatment Period, all four subjects rapidly achieved remission, as measured by the HAM-D total score. All four subjects also demonstrated consistent improvement as measured by the CGI-I score. SAGE-547 was well-tolerated in all subjects treated with no serious adverse events (SAEs) observed during therapy or during the 30-day Follow-up Period. A total of 14 AEs were reported in four subjects. The only AE reported in more than one subject was sedation, observed in two subjects. This study was initially planned to enroll ten women; however, due to the observed clinical activity, Study 547-PPD-201 was stopped early with the plan to initiate a placebo-controlled clinical study as rapidly as possible.

There are six reported studies of allopregnanolone, mainly in healthy individuals and none in PPD (Timby 2006, Timby 2011a and 2011b, van Broekhoven 2007, Kask 2008, Kask 2009, Navarro 2003). Data indicate that normal physiological allopregnanolone levels in women vary during the menstrual cycle up to a maximum of 6 to 10 nM, with lower levels present post-menopause (Genazzani 1998). The highest physiological levels observed are in the third trimester of pregnancy, up to around 160 nM at time of delivery (Luisi 2000). Levels drop precipitously to baseline (<10 nM) with removal of the placenta (Klak 2003).

One study demonstrated subjective improvements in contentedness in women (van Broekhoven 2007). The clinical safety data are presented below in the Risks and Benefits section (Section 4.4).

4.4. Potential Risks and Benefits

In the open-label clinical study of SAGE-547 in PPD (547-PPD-201), a total of 14 AEs were reported in four subjects. The only AE reported in more than one subject was sedation, observed in two subjects.

In the recently completed 547-PPD-202A, there were no SAEs or discontinuations due to AEs. Out of 10 subjects who received SAGE-547, four reported AEs, and of 11 subjects who received placebo, eight reported AEs (Table 2). Three subjects in each treatment group reported dizziness, sedation or somnolence. Psychiatric disorder AEs, including abnormal dreams, insomnia and anxiety, were all reported in the group that received placebo. Three subjects in the placebo group and one in the SAGE-547 group reported nausea. Other AEs reported by more than one subject were infusion site pain and headache, all reported on placebo. One subject did not tolerate 60 µg/kg/hour due to sedation, thought to be associated with concomitant administration of a high dose of benzodiazepine, so the dose was reduced to 30 µg/kg/hour from 12 to 24 hours. The subject received 60 µg/kg/hour from 24 to 30 hours and 30 µg/kg/hour from 30 to 60 hours and completed the study.

Table 2: Adverse Events That Occurred in More than One Subject

	Placebo (n=11)		SAGE-547 (n=10)	
	No. of Subjects[a] n (%)	No of Events	No. of Subjects[a] n (%)	No of Events
Subjects with at least 1 TEAE	8 (72.7)	23	4 (40.0)	17
Dizziness	3 (27.3)	3	2 (20.0)	3
Somnolence	--	--	2 (20.0)	3
Nausea	3 (27.3)	3	1 (10.0)	1
Infusion Site Pain	2 (18.2)	3	--	--
Headache	2 (18.2)	2	--	--
Abnormal Dreams	2 (18.2)	2	--	--
Insomnia	2 (18.2)	2	--	--

Source: 547-PPD-202A, Table 14.3.2.2

[a] Subjects who have more than 1 AE per preferred term are counted only once

Consistent with these observations, published reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, vertigo, mild nausea, impaired episodic memory, and mild headache (Timby 2006, 2011a, and 2001b; van Broekhoven 2007). One subject experienced what was potentially a withdrawal effect, an anxiety attack (Timby 2011b). No SAEs were reported in the six clinical studies conducted to date (Timby 2006, Timby 2011a and 2011b, van Broekhoven 2007, Kask 2008, Kask 2009, Navarro 2003).

There is also a potential risk of synergistic sedative effects with other drugs interacting with the $GABA_A$ receptor, such as benzodiazepines and anti-epileptic medications (Norberg 1999); therefore, the Investigator is advised to avoid co-medication if possible and to exercise caution with these drug classes.

In 547-PPD-202A, the primary endpoint of the mean change from baseline in HAM-D total score at 60 hours compared with placebo [LS mean treatment difference of 12.2] was highly significant (p=0.008). In addition, the significant separation between the active and placebo groups was evident at 24 hours, and remained so at subsequent time points through 72 hours, 7 days, and 30 days after initiation of treatment.

In view of the limited nature of the demonstrated risks of exogenous allopregnanolone infusion and the potential for benefit in PPD, there is a favorable benefit-risk evaluation for the continued conduct of the present study.

4.5. Study No. 547-PPD-202

4.5.1. Study Population

This study will evaluate the efficacy, safety, and PK of SAGE-547 Injection in the treatment of adult female subjects diagnosed with severe or moderate postpartum depression.

Parts A and B of this study will study women with severe PPD, and Part C will study women with moderate PPD (Parts B and C will run concurrently). Moderate severity level will be studied because the pathogenesis of severe postpartum depression may not be generalized to those patients with a less severe form of illness. For example, outside of postpartum depression, findings suggest that patient's treatment-resistant depression may respond more favorably to certain pharmacotherapy options such as ketamine (Coyle 2015). Therefore, in order to determine the efficacy of SAGE-547 in women with less severe levels of symptoms, a separate group with moderate PPD with the same doses of the study drug used in the severe group will be investigated.

4.5.2. Route of Administration, Dosage, Dosage Regimen, and Treatment Period

SAGE-547 Injection or placebo will be administered over a 60-hour period by an IV infusion according to the dose regimens shown in Table 3 and Table 4 (see Section 10.1.1).

The specific infusion dose of SAGE-547 Injection will be calculated based on weight for each subject. Infusion bags will be changed at least every 24 hours. Details about the preparation and administration of the study drug infusions will be included in the Pharmacy Manual.

4.5.3. Dose Rationale

The infusion rate of SAGE-547 to be studied in Parts A and C of this study was chosen to achieve a mean exposure of 150 nM, roughly equivalent to the highest endogenous concentrations measured in third trimester pregnancy at approximately 157 nM (Luisi 2000). Since pregnant women tolerate this level without apparent AEs, 150 nM was selected as the target exposure for this study. This level of exposure has already been achieved in Study 547-PPD-201 as well at higher levels in a study in subjects with essential tremor (Study

547-ETD-201) and subjects with super refractory status epilepticus (Study 547-SSE-201), with no drug-related SAEs reported. Since the most common AE in 547-ETD-201 was sedation, dose adjustment rules are included in this protocol to ensure that all subjects can remain on treatment for 60 hours. A similar C_{max} was also achieved in several other studies conducted with IV allopregnanolone (Timby 2011b), with excellent tolerability (see the current SAGE-547 Investigator's Brochure for details of safety profile).

The selection of exposure in the current study is based on a cautious approach adapted to the anticipated benefit-risk in the PPD patient population, and on previous experience from the ongoing clinical studies of SAGE-547 in adult subjects with SRSE (Study 547-SSE-201) and of SAGE-547 in female subjects with PPD (Study 547-PPD-201). In the ongoing SRSE study, as determined by simulation, loading and maintenance infusions are required to achieve the target exposure. In contrast, in the current study, subjects will instead begin treatment with a 4-hour dose-titration phase. The starting dose is approximately 9- to 18-fold lower than the no observed adverse effect level (NOAEL) observed in rats and dogs, although this is not the first in human study. In Parts A and C, doses will be increased as follows: 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24-52 hours), followed by a decrease to 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours).

In Part B, a lower target dose will also be explored (ie, 60 µg/kg/hour). The use of this dose is based on observations in the open-label 547-PPD-201 study in which subjects achieved substantial improvements in their HAM-D scores within the first 12 hours of the SAGE-547 infusion. In this study, subjects received a dose of 21.5 µg/kg/h for the first 4 hours, then 43 µg/kg/h for the next 4 hours, and then 64.5 µg/kg/h for the following 4 hours before receiving the target dose of 86 µg/kg/h at 12 hours. Therefore, the 12-hour data from 547-PPD-201 suggests that SAGE-547 at target doses of 60 µg/kg/h may also be efficacious in reducing depressive symptoms associated with PPD.

Subjects will be treated in an inpatient setting and continually monitored for safety, and if any severe tolerability issues arise, the infusion may be terminated or the infusion rate reduced. The protocol includes a formal dose interruption and reduction scheme based on the occurrence of intolerable AEs.

5. ETHICS

5.1. Institutional Review Board or Independent Ethics Committee

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an Institutional Review Board (IRB) or Independent Ethics Committee (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 or IEC 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.

5.2. Ethical Conduct of the Study

This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and the most recent amendment (2008).

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol, and must also conduct the study in accordance with International Council on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP) standards as well as local regulations.

5.3. Subject Information and Informed Consent

Prior to subject participation in the study, written informed consent must be obtained from each subject according to ICH GCP and in accordance with local regulations. Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests, SAGE-547 infusion, and study evaluations. Each subject's signature must be dated by each signatory and the informed consent form (ICF) retained by the investigator as part of the study records. As an additional assessment, the ICF will contain provisions for optional consent for the collection of blood for genetic testing during screening. The ICF, as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the CFR, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject a copy of the signed and dated ICF. The ICF for subject participation must also be available as part of the subject's file for review by the site's dedicated study monitor.

All ICFs used in this study must be approved by the appropriate IRB/IEC and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB/IEC and the Sponsor.

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objective of this study is to determine if SAGE-547 Injection infused intravenously for 60 hours at up to 90 µg/kg/h reduces depressive symptoms in subjects with severe PPD compared to placebo injection as assessed by the change from baseline in HAM-D total score. This objective applies to both Parts A and B.

6.2. Secondary Objectives

The secondary objectives of the study apply to Parts A, B, and C unless otherwise stated, and are:

- To determine if SAGE-547 infusion at up to 60 µg/kg/h for 60 hours reduces depressive symptoms in subjects with severe PPD compared to placebo injection as assessed by the change from baseline in HAM-D total score (applies to Part B only).
- To determine if SAGE-547 Injection infused intravenously at up to 90 µg/kg/h for 60 hours reduces depressive symptoms in subjects with moderate PPD compared to placebo injection as assessed by the change from baseline in HAM-D total score (applies to Part C only).
- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms compared to placebo injection as assessed by HAM-D response, HAM-D remission, change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score, Clinical Global Impression – Improvement (CGI-I) response, and changes from baseline in HAM-D subscale and individual item scores
- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces other mood symptoms compared to placebo injection as assessed by changes from baseline in the Generalized Anxiety Disorder 7-Item Scale (GAD-7) total score
- To evaluate the safety and tolerability of SAGE-547 Injection compared with placebo as assessed by the incidence of AEs, vital sign measurement, clinical laboratory evaluations, electrocardiogram (ECG) parameters, and the Columbia Suicide Severity Rating Scale (C-SSRS)

6.3. Other Objectives

The other objectives of the study are:

- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces subject-reported depressive symptoms compared to placebo injection as assessed by the change from baseline in Edinburgh Postnatal Depression Scale (EPDS) total score and the change from baseline in Patient Health Questionnaire (PHQ-9) total score

- To determine if SAGE-547 Injection infused intravenously for 60 hours improves maternal behaviors compared to placebo injection as assessed by the change from baseline in Barkin Index of Maternal Functioning (BIMF) total and sub-scale scores
- To determine if SAGE-547 Injection infused intravenously for 60 hours improves the general health status compared to placebo as assessed by the change from baseline in the Short Form-36 (SF-36) total score at Day 7 and Day 30

6.4. Pharmacokinetic Objective

The PK objective of the study is:

- To assess the PK profile of SAGE-547, metabolites of SAGE-547, and betadex sulfobutyl ether sodium (SBECD)

7. INVESTIGATIONAL PLAN

7.1. Overview of Study Design

This protocol describes three multicenter, randomized, double-blind, parallel-group, placebo-controlled studies of the efficacy, safety, and PK of SAGE-547 Injection in adult female subjects diagnosed with severe or moderate PPD. Each study will be independently conducted, analyzed, and reported. In this protocol, Study 547-PPD-202A is hereafter referred to as Part A; Study 547-PPD-202B is hereafter referred to as Part B; and Study 547-PPD-202C is hereafter referred to as Part C.

The study designs for Part A, Part B, and Part C are presented in Figure 1, Figure 2, and Figure 3, respectively; Parts B and C will run concurrently. For all parts, the study will consist of a Screening Period (up to 5-days [Day -5 to -1; Part A] or up to 7-days [Day -7 to -1; Parts B and C]), a 3-day (60 hours of treatment and an additional 12 hours for completion of 72-hour assessments) Treatment Period, and a 30-day Follow-up Period. Subjects must remain as inpatients during the study Treatment Period, which is approximately 72 hours/3 days in duration. The Screening Period assessments may be conducted on an inpatient or an outpatient basis. The Follow-up Period assessments are conducted on an outpatient basis.

Figure 1: Study Design - Part A

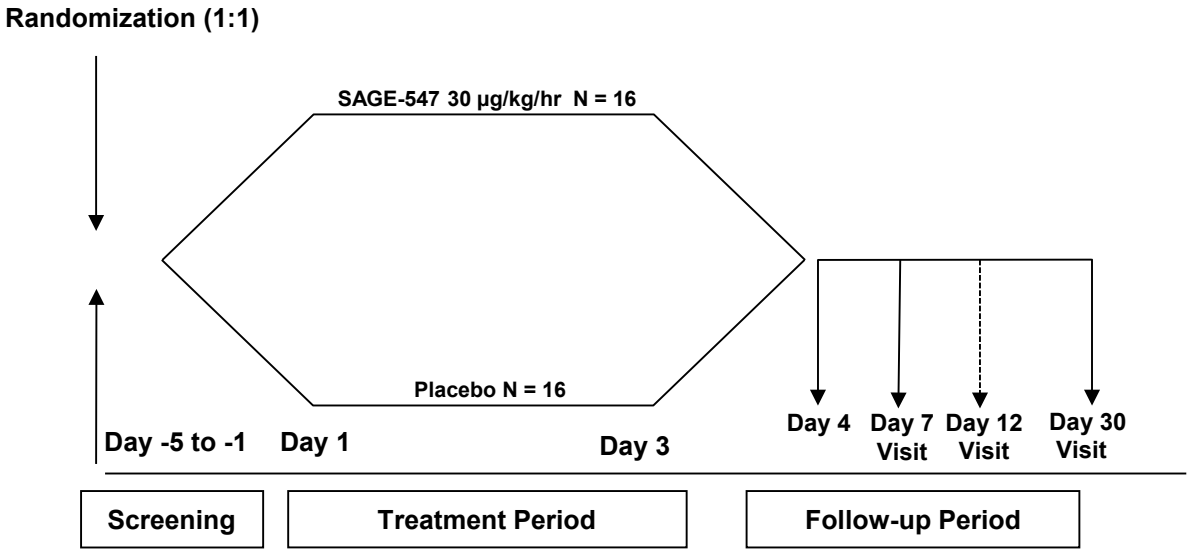


Figure 2: Study Design - Part B

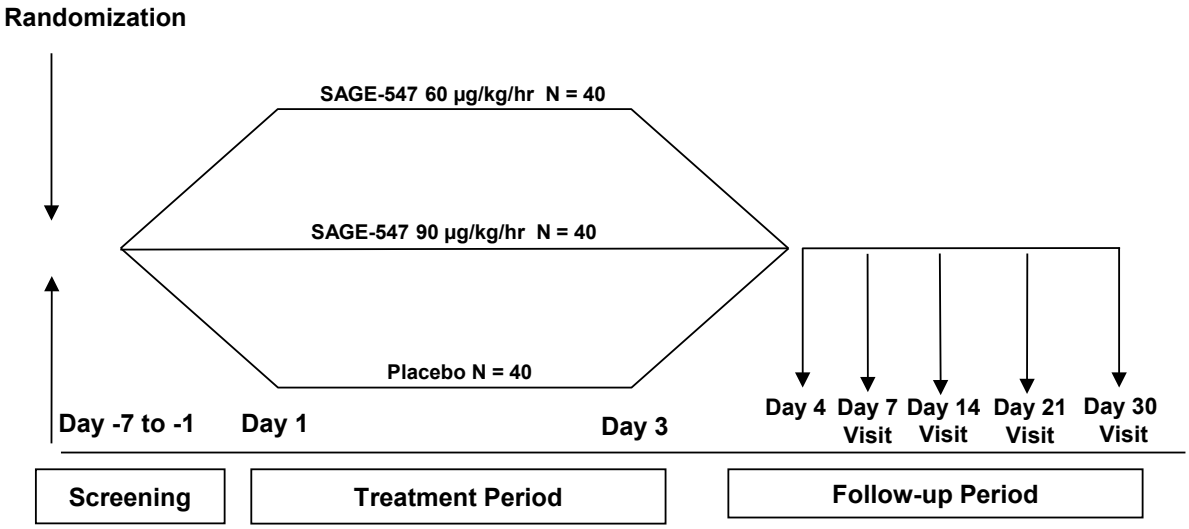
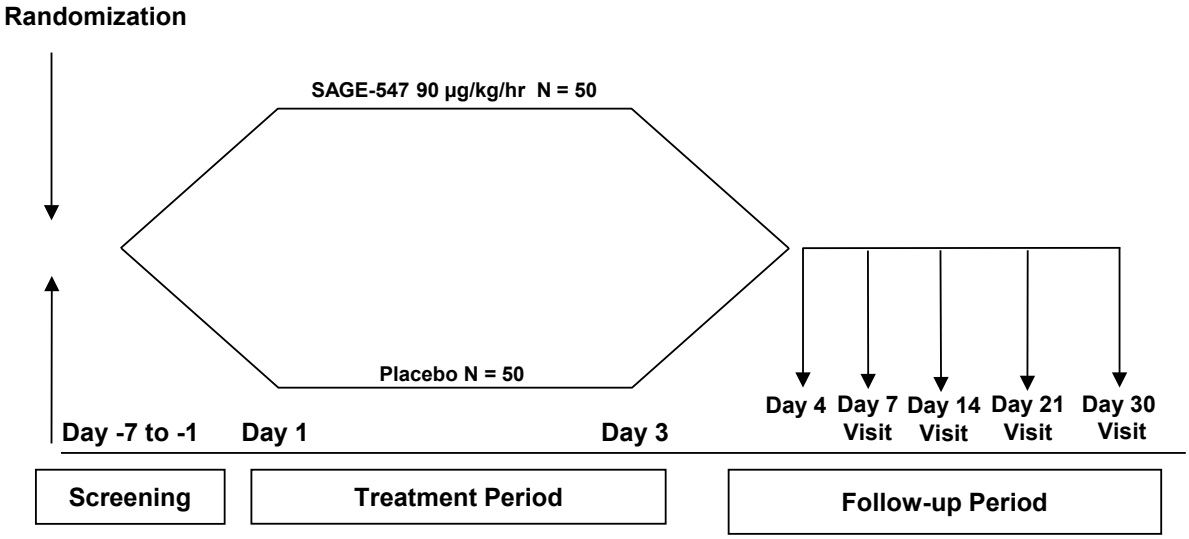


Figure 3: Study Design - Part C



SAGE-547 Injection or placebo will be administered at the study center. Subjects will be monitored for safety during the Treatment and Follow-up Periods (through Study Day 30 [±3 days]) including monitoring for AEs/SAEs, routine clinical laboratory assessments, physical examination, vital signs, and ECG.

All study-related procedures will occur after written informed consent is obtained at the screening visit, which will occur during the Screening Period window (Day -5 through Day -1 for Part A; Day -7 through Day -1 for Parts B and C). 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.

The end of the Screening Period coincides with the beginning of the Treatment Period. The Treatment Period is the period of Day 1 of study drug IV infusion through completion of the infusion on Day 2 and up to Day 3. Subjects will be confined to the study center from Day 1 until after the 72-hour assessments have been conducted on Day 3.

In Parts A and C, once subjects are confirmed as eligible for the study, they will be randomized to one of two treatment groups (SAGE-547 90 µg/kg/hour or placebo) on a 1:1 basis. On the morning of dosing (Day 1), subjects will begin a 4-hour dose titration period of 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24-52 hours); followed by a decrease to 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours). Subjects in the placebo group will receive infusion rates equivalent to the 90 µg/kg/hour group.

In Part B, once subjects are confirmed as eligible for the study, they will be randomized to one of three treatment groups (SAGE-547 60 µg/kg/hour, SAGE-547 90 µg/kg/hour, or placebo) on a 1:1:1 basis. For the 60 µg/kg/hour group, subjects will receive 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-56 hours), followed by 30 µg/kg/hour (56-60 hours). For the 90 µg/kg/hour group, subjects will begin a 4-hour dose titration period of 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24-52 hours); followed by a decrease to 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours). Subjects in the placebo group will receive infusion rates equivalent to either the 60 µg/kg/hour or 90 µg/kg/hour group. Parts B and C will run concurrently.

See dose regimen presented in Section 10.1.1. Total SAGE-547 Injection or placebo dosing will occur over 60 hours.

Study-specific assessments for safety, PK, efficacy, and other outcome measures will be completed at pre-specified times over the duration of the study:

- The safety and tolerability of SAGE-547 Injection will be assessed by AEs, clinical laboratory measures, physical examinations (including cognitive and mental health examinations), vital signs, ECG, use of concomitant medication, and the Columbia Suicide Severity Rating Scale (C-SSRS) during the Screening, Treatment, and Follow-up Periods (through Study Day 30 [±3 days])
- Plasma will be collected to formally assay for SAGE-547, metabolite, and SBECD levels prior to dosing through the Treatment Period and up to 12 hours post infusion on Day 3 and on Day 7
- Primary efficacy assessment of the HAM-D will be completed as scheduled during the Screening, Treatment, and Follow-up Periods (through Study Day 30 [±3 days])
- Secondary efficacy assessments of MADRS, CGI-I, EPDS, Generalized Anxiety Disorder 7-Item Scale (GAD-7), PHQ-9 will be completed as scheduled during the Screening, Treatment, and Follow-up Periods (through Study Day 30 [±3 days])

The end of the Treatment Period coincides with the beginning of the Follow-up Period.

Subjects will attend the clinic for safety follow-up assessment at 1 week (7±1d), 12 days (Part A), 2 weeks (14±2d [Part B and C]), 3 weeks (21±1d [Part B and C]), and 1 month (30±3d) after the initiation of the study drug infusion.

Scheduled assessments for all safety, PK, efficacy, and other outcome measures planned for the study are summarized in Table 1. All subjects who receive treatment with SAGE-547 are to complete all study assessments through Study Day 30 (±3 days).

The Medical Monitor will review AEs on an ongoing basis.

7.2. Blinding and Randomization

This is a double-blind study. Subjects will be randomized to receive SAGE-547 or placebo; subjects, clinicians, and the clinical site study team will be blinded to treatment allocation until the study is unblinded at final database lock. The pharmacist, who will prepare the infusion bags according to the randomization schedule, and an unblinded Monitor, who will perform drug accountability during the study, will be unblinded.

Randomization will be stratified by antidepressant use at baseline (yes/no). Subjects will be randomized within stratum to receive SAGE-547 or placebo according to a computer-generated randomization schedule.

Only the clinic pharmacist, who is responsible for preparing the infusions, will be unblinded. In the event of a medical emergency, the Principal Investigator will discuss with the Medical Monitor if unblinding is warranted. If there is agreement to unblind treatment assignment, the unblinding procedure described in the Safety Management Plan for the study will be followed. 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).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. 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 aged between 18 and 45 years of age
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 breastmilk to their infant(s) from just prior to receiving study drug through 4 days (Study Day 7) after the end of the infusion.
6. Subject must have a negative pregnancy test at screening and Day 1 prior to the start of study drug infusion
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, as diagnosed by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)
8. For Part A and B, subject has a HAM-D total score of ≥26 at screening and Day 1 (prior to dosing). For Part C, subject has a HAM-D total score of ≥20 and ≤25 at screening and Day 1 (prior to dosing)
9. Subject is ≤6 months postpartum at screening
10. Subject is willing at screening to delay the start of any new pharmacotherapy regimens, including antidepressant or anti-anxiety medication, until the study drug infusion and 72-hour assessments have been completed; if the subject is taking psychotropic medications, these must be at a stable dose from 14 days prior to screening until the 72-hour assessments have been completed.
11. (Removed)
12. Subject must use one of the following methods of birth control during participation in the study and for 30 days following the end of the study drug infusion:
    - Total abstinence (no sexual intercourse)
    - Hormonal contraceptives (birth control) including birth control pills, implantable or injectable contraceptives (Norplant® or Depo-Provera®)
    - A barrier form of contraception such as a condom or occlusive cap with a spermicide
    - An intrauterine device

8.2. Exclusion Criteria

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

1. Subject has renal failure requiring dialysis or fulminant hepatic failure or is anemic (hemoglobin ≤10 g/dL)
2. Known allergy to progesterone or allopregnanolone
3. Active psychosis per Investigator assessment
4. Attempted suicide associated with index case of postpartum depression
5. (Removed)
6. Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
7. History of active alcoholism or drug abuse (including benzodiazepines) in the 12 months prior to screening. A positive urine drug screen (except benzodiazepines under certain circumstances [see Section 10.3.3 and Section 11.1.2.6]) is exclusionary.
8. Exposure to another investigational medication or device within 30 days prior to screening
9. (Removed)
10. Subject has previously participated in this study or any other study employing SAGE-547
11. Administration of electroconvulsive therapy (ECT) within 14 days prior to screening and/or plans to administer ECT before the Study Day 7 Visit

8.3. Subject Withdrawal/Study Termination

8.3.1. Withdrawal/Discontinuation of Individual Subjects

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's eCRF. The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn for any reason, including withdrawal due to an AE.

8.3.2. Subject Withdrawal from the Study

Subjects may withdraw from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

8.3.3. Discontinuation of Study Drug by the Investigator

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

The Investigator may withdraw the subject from the study drug for any of the following reasons:

- The subject is unwilling or unable to adhere to the protocol

- The subject experiences an intolerable AE that does not respond to a dose reduction
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

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

8.3.4. Study Termination

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

9. INVESTIGATIONAL PRODUCT

9.1. Identity of Investigational Product

SAGE-547 Injection (allopregnanolone)

9.2. Clinical Supplies

9.2.1. SAGE-547

SAGE-547 Injection and ancillary supply kits containing IV administration bags, solution sets, and IV bag labels will be provided to the sites.

SAGE-547 Injection is a preservative-free, sterile, clear, colorless 5 mg/mL solution of SAGE-547 (allopregnanolone) and 250 mg/mL betadex sulfobutyl ether sodium buffered with 10 mM citrate at a pH of 6.0, intended for IV injection. All inactive excipients used in the formulation are compendial grade and conform to current United States Pharmacopeia (USP) and European Pharmacopeia (Ph. Eur.) standards. The product is aseptically processed, sterile filtered, and filled into 20 mL Type 1 parenteral glass vials with West FluroTec® coated stopper container closure systems, under current Good Manufacturing Practice (cGMP) conditions. SAGE-547 Injection is intended to be used as a single-use vial. An appropriate number of single-use vials to support the dosing duration of the study are packaged and delivered to the site. SAGE-547 Injection vials should be stored under refrigerated conditions (2–8°C). Ancillary supply kits should be stored at controlled room temperature (20–25°C).

All study drug labels will contain information to meet the applicable regulatory requirements.

9.2.2. Placebo

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and consisting of the same formulation without allopregnanolone. Placebo vials should be stored under refrigerated conditions (2–8°C).

9.3. Preparation of SAGE-547 Injection or Placebo for Dosing

The pharmacy will be responsible for preparing SAGE-547 Injection or placebo for subject dosing. The prepared admixture will be administered at room temperature. The prepared admixture will be assigned a room temperature (20–25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547 Injection or placebo is not intended to be administered to subjects undiluted. Each single-use vial of SAGE-547 Injection, which is hypertonic, will require dilution with an appropriate volume of SWFI to render it isotonic. Refer to the Pharmacy Manual for specific instructions regarding infusion preparation and administration instructions.

9.4. Administration and Accountability

The pharmacy will maintain accurate records of all investigational drug product supplies received, stored, dispensed, and discarded. Accurate records will be kept regarding the

volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate (or rates), and the date and time of preparation. Reasons for departure from the expected dosing regimen must be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication needs to be reconciled in full.

Refer to the Pharmacy Manual for complete details on preparation and administration.

10. TREATMENT OF SUBJECTS

10.1. Dosing Schedule

This is a double-blind study. Subjects will be randomized to receive 60 hours of IV treatment with either SAGE-547 Injection or placebo, according to a computer-generated randomization schedule. In Parts A and C, subjects randomized to SAGE-547 will receive the target dose of 90 µg/kg/hour; in Part B, SAGE-547 subjects will receive target doses of either 60 or 90 µg/kg/hour.

The timing of infusion is shown in Figure 4, Figure 5, and Figure 6.

Figure 4: Study Design and Timeline for Dosing – Part A

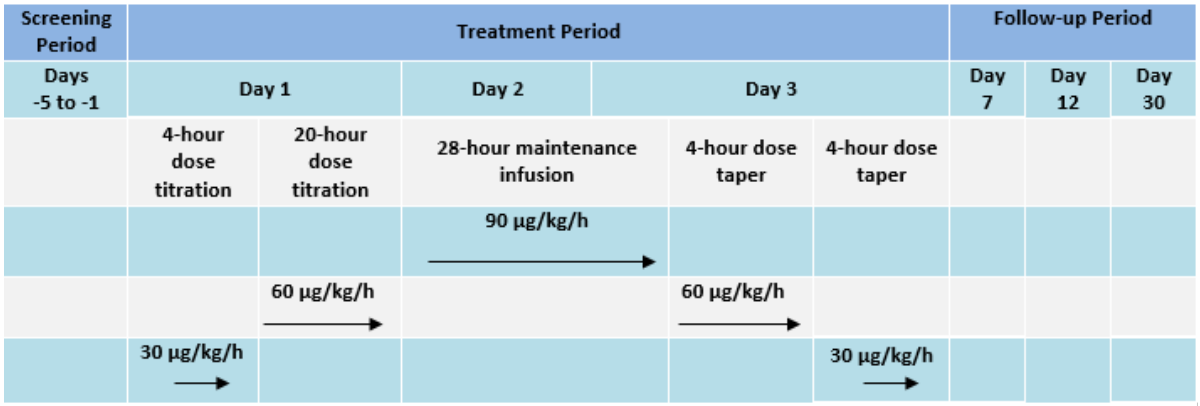
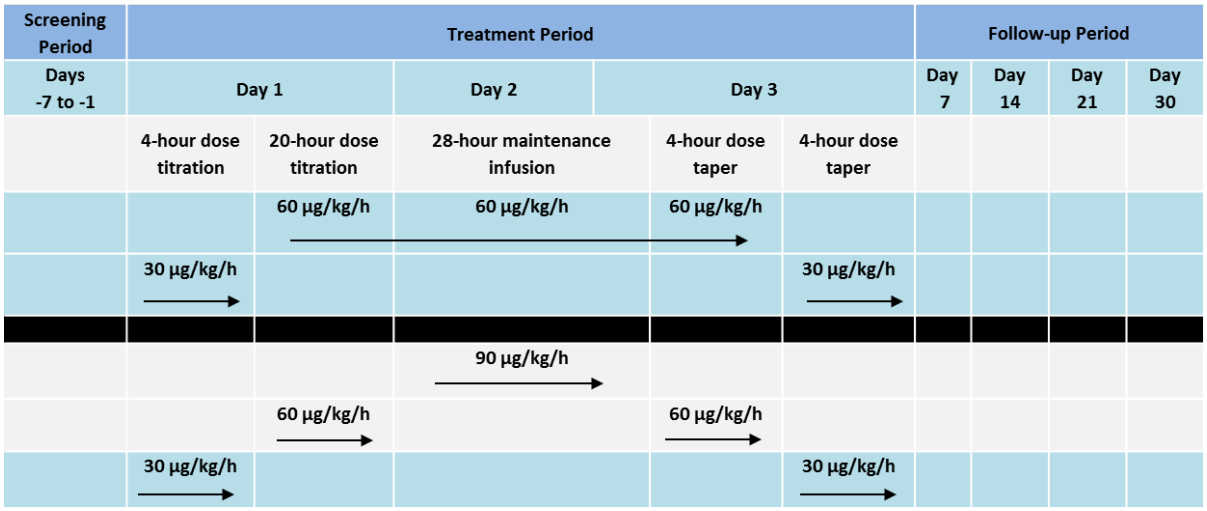
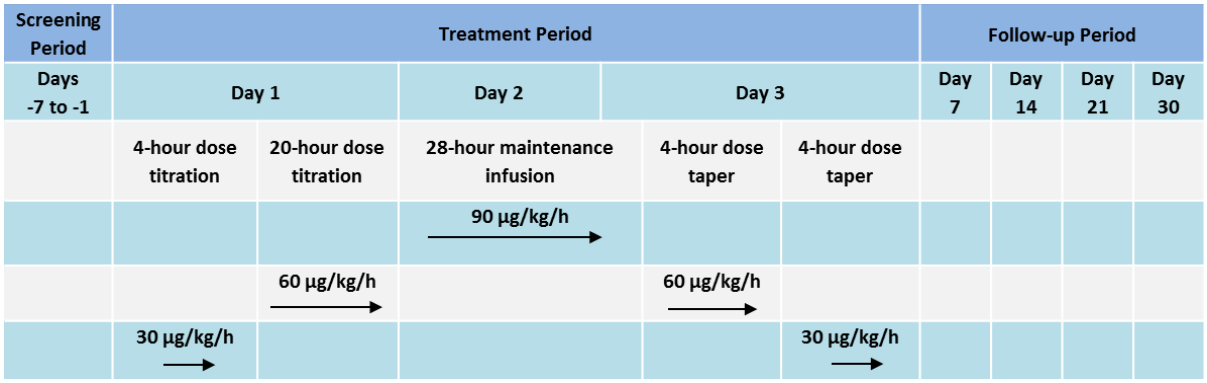


Figure 5: Study Design and Timeline for Dosing – Part B



Note: Day 3, 4-hour taper applies only to the 90 µg/kg/h dose group.

Figure 6: Study Design and Timeline for Dosing – Part C



Clinical supply and preparation of SAGE-547 Injection for dosing is described Section 9.2 and Section 9.3, respectively.

10.1.1. Dose Regimen

The specific infusion dose of SAGE-547 Injection will be calculated based on weight (obtained at screening) for each subject and administered according to dose regimen shown in Table 3 and Table 4). The infusion rates are the same for all subjects within a particular dosing period (0-4 hours, 4-24 hours, etc.).

Table 3: Infusion Rates for Part A and C

	Infusion Rate (µg/kg/hour)				
SAGE-547 Dose	**Day 1 0-4 hours**	**Day 1 4-24 hours**	**Day 2-3 24-52 hours**	**Day 3 52-56 hours**	**Day 3 56-60 hours**
90 µg	30	60	90	60	30

Table 4: Infusion Rates for Part B

	Infusion Rate (µg/kg/hour)				
SAGE-547 Dose	**Day 1 0-4 hours**	**Day 1 4-24 hours**	**Day 2-3 24-52 hours**	**Day 3 52-56 hours**	**Day 3 56-60 hours**
60 µg	30	60	60	60	30
90 µg	30	60	90	60	30

Dosing is to begin in the morning (on Day 1) to avoid awakening subjects during the night for completion of study assessments.

If any subject has an intolerable AE, such as profound sleepiness or sedation outside of normal sleeping hours, the infusion rate for this subject will be decreased to the next lowest infusion dose level (or turned off if this occurs on the 30 µg/kg/hour dose level).

10.1.2. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line with the study-approved IV administration bags and lines.

10.1.3. Treatment Period

Total dosing with SAGE-547 or placebo will occur over 60 hours.

10.1.4. Dosing of Intravenous SAGE-547 in the Case of AEs

Since allopregnanolone levels in the proposed clinical study are similar to physiological levels seen in the third trimester of pregnancy, and all the AEs reported with SAGE-547 or allopregnanolone to date in healthy volunteers and subjects with postpartum depression were mild and non-serious, it is anticipated that the AEs associated with SAGE-547 in this study will be mild and manageable without dose interruption or reduction. Based on the safety data in subjects with PPD collected to date, no subjects reported events that were serious or severe or led to discontinuation of study drug (two subjects reported sedation that led to a dose reduction, one of these subjects also reported dizziness; one subject reported rash that led to a dose reduction; refer to the current Investigator's Brochure for more information).

However, in the case of intolerable AEs occurring, the investigator is advised to reduce the infusion to the next lowest dose (or stop the infusion if this event occurs on the 30 µg/kg/hour dose level) until the AE has resolved, at which time re-escalation to the maintenance rate may be considered. If the AE recurs, the study drug infusion may be reduced again or permanently discontinued.

10.2. Dosing Compliance

Investigational product will be prepared in the site pharmacy, administered as a continuous IV infusion by the study staff, and will be documented in the study record. There should be no adjustments in dosing except those described in Section 10.1.4.

10.3. Prior Medications, Concomitant Medications, and Restrictions

10.3.1. Prior Medications

The start and end dates, route, dose/units, and frequency of all medications taken within 60 days prior to signing the informed consent will be recorded, as well as all medications given to treat the current PPD episode that are recorded on the SCID-I during the screening visit.

10.3.2. Concomitant Medications

All medications taken from signing the informed consent through the Day 30 (±3 days) visit will be recorded on the eCRF. Subjects will receive standard of care for adult female patients diagnosed with PPD. 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 10.3.

10.3.3. Prohibited Medications

Restrictions on specific classes of medications include the following:

- Subjects may not start new pharmacotherapy regimens, including antidepressant or anti-anxiety medications, from the time of informed consent until the study drug infusion and 72-hour assessments have been completed. If clinically indicated, new antidepressant medications may be started or existing antidepressant medication regimens may be changed once the 72-hour assessments have been completed. Consideration should also be given to deferring, starting, or changing antidepressant medication regimens until the Day 7, Day 12 (Part A only) or Day 14 (Parts B and C only), Day 21 (Parts B and C only), or Day 30 visits if the HAM-D score has improved.
- If the subject is taking psychotropic medications, these must be at a stable dose from 14 days prior to screening to completion of the 72-hour assessments.
- Benzodiazepines are to be avoided as much as possible owing to the potential for a synergistic sedative effect. Eligible subjects taking a benzodiazepine at the time of study entry will 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.

10.3.4. Restrictions

- Electroconvulsive therapy (ECT) is prohibited from 14 days prior to screening until after the Day 7 visit.

11. STUDY ASSESSMENTS

11.1. Safety Assessments

The safety and tolerability of SAGE-547 Injection will be evaluated by summarization of AEs by frequency, severity and seriousness, mean changes from baseline in clinical laboratory measures, physical examination, vital signs, ECGs, and concomitant medication usage. Suicidality will be monitored using the C-SSRS. All safety assessments should be performed per the study center's standard of care and will be collected according to the Schedule of Events (Table 1). All safety assessments are to be completed within ±30 minutes of the scheduled time point.

In addition to the schedule outlined in Table 1, completion of safety assessments including physical examination, vital signs, and clinical laboratory tests should occur in the event of an emergency or SAE, when possible.

11.1.1. Adverse Events

Adverse events will be collected after the ICF has been signed through the end of the study (see Section 14.2.1 for additional details). Medical conditions or AEs that occur after the ICF has been signed and *prior to* completion of screening will be captured on the Medical History eCRF.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) coding system (version 18.0 or higher).

11.1.2. Clinical Laboratory Tests

Blood samples will be collected for hematology, serum chemistry, coagulation, specific hormone parameters, and exploratory biochemistry; pregnancy testing; and genetic analysis. Urine samples for urinalysis and selected drugs of abuse will also be collected. All samples will be analyzed at the central laboratory. Patients 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 (Table 1).

These assessments will be performed in accordance with the Schedule of Events (Table 1) and as outlined individually below.

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 will be recorded as medical history. Clinical laboratory results that are Abnormal; CS during the study and indicate a worsening from baseline will be considered AEs, assessed according to Section 14, and recorded in the eCRF.

11.1.2.1. Hematology, Serum Chemistry, Coagulation

Blood samples will be collected for analysis of the following:

- **Hematology:** complete blood count (CBC) including white blood cell (WBC) count with differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils) platelet count, red blood cell (RBC) count, hemoglobin (Hgb) and hematocrit (Hct), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH)
- **Serum chemistry:** albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatinine, gamma glutamyl transferase (GGT), glucose phosphate, potassium, sodium, total protein, and triglycerides (screening only)
- **Coagulation:** activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR)

11.1.2.2. Hormones and Exploratory Biochemistry

Blood samples will be collected and may be analyzed for thyroid stimulating hormone (TSH), estrogen, progesterone, progesterone metabolites, oxytocin, tryptophan, kynurenine, and markers of inflammation.

11.1.2.3. Pregnancy Tests

All subjects will be tested for pregnancy by serum human chorionic gonadotropin (hCG) at screening and urine hCG on Day 1 prior to administration of study drug and on Day 30. Subjects with a positive pregnancy test at screening or Day 1 will be ineligible for study participation.

11.1.2.4. Genetic Testing

A blood sample for genetic testing will be collected at screening, where consent is given.

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-547. 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 allopregnanolone (eg, AKR1C4 (3a-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-547 but also susceptibility to disorders for which SAGE-547 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.

11.1.2.5. Urinalysis

Urinalysis will include assessment of bilirubin, glucose, ketones, leukocytes, nitrite, pH, protein, and specific gravity.

11.1.2.6. Drugs of Abuse and Alcohol

Urine assessment for selected drugs of abuse will be performed at screening (including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, and propoxyphene). Use of benzodiazepines at screening is not necessarily exclusionary, as subjects will be allowed to take psychotropics that have been initiated at least 14 days prior to admission to the study center at a stable dose (see Section 10.3.3). A positive urine drug screen for any of the tested drugs of abuse (except benzodiazepines) is exclusionary. Alcohol will be assessed in plasma at screening and via breathalyzer or urine dipstick on Day 1.

11.1.3. Physical Examination

Body weight and height will be measured at screening. Body mass index (BMI) will be programmatically calculated in the eCRF.

Any condition present at the post-treatment physical examination that was not present at or worsened since the baseline examination is to be documented as an AE. Whenever possible, the same individual is to perform all physical examinations. Physical examinations will include assessment of body systems (eg, HEENT, heart, lungs, abdomen, and extremities) as well as cognitive and neurological examination and mental status examination.

11.1.4. Vital Signs

Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). A full set of vital signs will be obtained at all specified time points (±30 minutes), unless the subject is asleep between the hours of 23.00h and 06.00h each day.

11.1.5. ECG

A baseline 12-lead ECG will be performed during screening. The following ECG parameters will be recorded: heart rate, PR, QRS, QT, and QTc. All ECG results will be interpreted by the Investigator as *Normal, Abnormal; not clinically significant (NCS),* or *Abnormal; clinically significant (CS)*. If Abnormal, details will be provided.

11.1.6. 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 pre-dose evaluation that assesses the lifetime and recent 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 on Day 1 prior to dosing. The "Since Last Visit" C-SSRS form will be completed for all subsequent assessments.

Copies of the C-SSRS are provided in Appendix 1.

11.2. Efficacy Assessments

For all efficacy assessments, the baseline values will be calculated as the last recorded value prior to the start of infusion of randomized treatment. 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.

11.2.1. Primary Efficacy Outcome Measure

The primary outcome measure is the HAM-D. The HAM-D will be administered before, during, and after the infusion of blinded study drug.

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

The 17-item HAM-D will be used to rate the severity of depression in subjects who are already diagnosed as depressed (Hamilton 1960). The 17-item HAM-D is comprised of 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 within ±30 minutes of the scheduled time point, but prior to starting dosing on D1 H0. Every effort should be made for the same rater to perform all HAM-D assessments for a single subject.

The HAM-D total score will be calculated as the sum of the 17 individual item scores. Item 16 can be rated according to history (item 16A) or actual weight change (item 16B). The item 16 score is calculated as the item 16 response that is not equal to 3 (ie, "Not assessed").

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. HAM-D subscale scores will be calculated as the sum of the items comprising each subscale. HAM-D response will be defined as having a 50% or greater reduction from baseline in HAM-D total score. HAM-D remission will be defined as having a HAM-D total score of $\leq$7.

A copy of the HAM-D is provided in Appendix 2.

11.2.2. Secondary Efficacy Outcome Measures

Secondary efficacy assessments include evaluation of depressive symptom severity by the HAM-D total score at the Day 30 time point, MADRS (Section 11.2.2.1), and CGI (Section 11.2.2.2). Additional assessments of depressive symptom severity and reproductive mood disorders will be measured by the following clinician- and subject-rated outcome measures: EPDS (Section 11.2.3.1), GAD-7 (Section 11.2.2.3), and PHQ-9 (Section 11.2.3.2).

11.2.2.1. Montgomery Asberg Depression Rating Scale (MADRS)

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

Higher MADRS scores indicate more severe depression, and each item yields a score of 0 to 6. The overall score ranges from 0 to 60 (McDowell 2006, Müller-Thomsen 2005).

The questionnaire includes questions on the following symptoms

1. Apparent sadness
2. Reported sadness
3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

The MADRS total score will be calculated as the sum of the 10 individual item scores.

A copy of the MADRS is provided in Appendix 3.

11.2.2.2. Clinical Global Impression (CGI) Scale

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 patient's condition. The CGI scale is comprised of three items. Only the first two items are being used in this study.

The CGI-Severity (CGI-S) item uses a 7-point Likert scale to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating 1=normal, not at all ill, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, and 7=extremely ill. The CGI-S will be rated by the clinician at screening and on Day 1 (prior to dosing).

The CGI-Improvement (CGI-I) item employs a 7-point Likert scale to measure the overall improvement in the patient's condition post-treatment. The investigator will rate the patient's total improvement whether or not it is due entirely to drug treatment. Response choices include: 0=not assessed, 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse. The CGI-I is only rated at post-treatment assessments. By definition, all CGI-I assessments are

evaluated against baseline conditions. CGI-I response will be defined as having a CGI-I score of "very much improved" or "much improved."

A copy of the CGI is provided in Appendix 4.

11.2.2.3. Generalized Anxiety Disorder 7-Item Scale (GAD-7)

The GAD-7 is a patient-rated generalized anxiety symptom severity scale (Spitzer 2006). Scoring for GAD-7 generalized anxiety is calculated by assigning scores of 0, 1, 2, and 3 to the response categories, respectively, of "not at all sure," "several days," "over half the days," and "nearly every day." GAD-7 total score for the seven items ranges from 0 to 21, where a score of 0 to 4=minimal anxiety, 5 to 9=mild anxiety, 10 to 14=moderate anxiety, and 15 to 21=severe anxiety. All assessments are to be completed within ±30 minutes of the scheduled time point.

The GAD-7 total score will be calculated as the sum of the 7 individual item scores.

A copy of the GAD-7 is provided in Appendix 6.

11.2.3. Patient Reported Outcome Measures

Other efficacy assessments include evaluation of depressive symptom severity and reproductive mood disorders. These will be measured by the following clinician- and subject-rated outcome measures: EPDS, PHQ-9, BIMF, and SF-36.

11.2.3.1. Edinburgh Postnatal Depression Scale (EPDS)

The EPDS is a patient-rated depressive symptom severity scale specific to the perinatal period (Cox 1987). The EPDS total score will be calculated as the sum of the 10 individual item scores.

A copy of the EPDS is provided in Appendix 5.

11.2.3.2. Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a patient-rated depressive symptom severity scale. To monitor severity over time for newly diagnosed patients or patients in current treatment for depression, patients may complete questionnaires at baseline and at regular intervals thereafter. Scoring is total based on responses to specific questions, as follows: not at all=0; several days=1; more than half the days=2; and nearly every day=3. All assessments are to be completed within ±30 minutes of the scheduled time point.

The PHQ-9 total score will be calculated as the sum of the 9 individual item scores. The PHQ-9 total score will be categorized as follows: 1-4=minimal depression, 5-9=mild depression, 10-14=moderate depression, 15-19=moderately severe depression; and 20-27=severe depression.

A copy of the PHQ-9 is provided in Appendix 7.

11.2.3.3. Barkin Index of Maternal Functioning (BIMF)

The BIMF is a patient reported outcome scale BIMF covers a broad range of functional areas (self-care, infant care, mother-child interaction, psychological well-being of mother, social

support, management, adjustment). This new application of maternal functional status is a robust construct where the physical and mental health of the mother is essential to optimal functioning. Each item is rated on a scale of 0 (strongly disagree) to 6 (strongly agree).

A copy of the BIMF is provided in Appendix 8.

11.2.3.4. Short Form-36 (SF-36)

The Medical Outcomes Study Short Form-36 (SF-36v2) is a 36-item measure of health status that has undergone validation in many different disease states (Ware 2007). The SF-36 covers eight health dimensions including four physical health status domains (physical functioning, role participation with physical health problems [role-physical], bodily pain, and general health) and four mental health status domains (vitality, social functioning, role participation with emotional health problems [role-emotional], and mental health). In addition, two summary scores, physical component summary (PCS) and mental component summary (MCS), are produced by taking a weighted linear combination of the eight individual domains. The SF-36v2 is available with two recall periods: the standard recall period is 4 weeks and the acute recall period is 1 week. This study will use the acute version, which asks patients to respond to questions as they pertain to the past week. Higher SF-36 scores indicate a better state of health. The SF-36 requires approximately 10 minutes to complete and can be self-administered or completed by interview in person or by telephone.

A copy of the SF-36 is provided in **Appendix 9**.

11.2.3.5. Healthcare Resource Utilization (HCRU)

Subject-reported healthcare resource utilization data, including baseline diagnosis history, baseline antidepressant treatment history, and healthcare visits, inpatient visits, and medication use, will be collected at screening and on Day 30 of follow-up (or at early termination). A copy of the health resource utilization questionnaire is provided in Appendix 10.

11.3. Pharmacokinetics

Blood samples for PK analysis will be collected in accordance with the Schedule of Events (Table 1). Scheduled time points for PK blood draws after the start of infusion will have a window of ±10 minutes. Samples will be processed according to the PK Manual, and may be analyzed for concentrations of SAGE-547, metabolites of SAGE-547, and SBECD. Additionally, PK samples may be obtained outside the planned collection times if issues administering study drug are encountered, such as incorrect infusion rate, interrupted infusion, or other administration deviations where PK level assessment may be important in understanding subject state. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.

The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve (AUC) from time zero to 60 hours ($AUC_{0\text{-}60}$), AUC from time zero to infinity (AUC_{∞}), maximum (peak) plasma concentration (C_{max}), time at maximum (peak) plasma concentration (t_{max}), steady-state drug concentration in the plasma during constant-rate infusion (C_{ss}), and average drug concentration in the

plasma at steady state during a dosing interval (C_{avg}). Each PK parameter will be derived separately for each part of the study.

The plasma samples will be drawn from the arm contralateral to that used for study drug administration. Instructions on sample collection, processing methods, storage, and shipping conditions for subject-specific plasma PK kits will be provided in the study laboratory manual.

12. STUDY PROCEDURES

The study procedures listed below by study day reflect the data collection times for this protocol.

Scheduled assessments for all safety, efficacy, PK, and other outcome measures planned for the study are summarized in Table 1 (Schedule of Events). All subjects who receive treatment with SAGE-547 should complete all study assessments through Study Day 30 (±3 days).

Subjects who complete the assessments at Hour 60 and Day 30 (±3 days) will be defined as study completers.

12.1. Screening Period

The Screening Period consists of a window from Day -7 through Day -1 prior to starting SAGE-547 treatment (up to 5-days [Day -5 to -1; Part A] or up to 7-days [Day -7 to -1; Parts B and C]). The Screening Period begins with the signature of the ICF. Eligibility is determined by applying the inclusion/exclusion criteria. The diagnosis of PPD must be by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). A full medical and family history will be taken from the subject using a SCID-I interview, including recording of all depression (major depressive disorders, premenstrual dysphoric disorder, menstrual migraine, and other psychiatric disorders per DSM), other Axis I and Axis II disorders, and pregnancy history including birth complications, and postpartum depression episodes. Family history will be collected from the subject for primary probands, including all depression (major depressive disorders, premenstrual dysphoric disorder, menstrual migraine, and other psychiatric disorders per DSM), other Axis I disorders, and postpartum depression episodes.

The following assessments/procedures will be conducted at the screening visit, which will occur during the Screening Period window. 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 examinations, 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, and all screening assessments are completed, reviewed and approved by the Investigator prior to administration of study drug.

Subjects will be confined to the study center from Day 1 until after the 72-hour assessments have been conducted on Day 3.

- Written informed consent will be obtained
- Inclusion/exclusion criteria will be reviewed to determine subject eligibility
- Demographic information and medical/family history will be collected
- Lactation status (ie, subject is breastfeeding, subject is lactating but not breastfeeding, or subject is not lactating) will be recorded
- Blood will be collected for a pregnancy test

- Completion of physical examination, including body weight. Height should be recorded. BMI will be calculated.
- Vital signs will be recorded
- Blood and urine samples will be collected for clinical laboratory testing, including drug and alcohol screening
- Blood sample will be taken for genetic analysis with subject consent
- An ECG reading will be taken
- The HAM-D, CGI-S, and MADRS will be completed
- Concomitant medications will be recorded
- AEs will be monitored

12.2. Study Drug Treatment Period (Day 1 to Day 3, Hours 0-72)

All safety, efficacy, PK, and other outcome assessments described in this section are to be completed within ±30 minutes of the scheduled time points, unless otherwise stated. Windows for PK collection time points are specified by respective time point for Study Days 1 to 3 in Section 12.2.1 to Section 12.2.3, respectively (see Section 11.3 for additional details). Subjects will be confined to the study center from Day 1 until after the 72-hour assessments have been conducted on Day 3.

Psychiatric follow-up outside the study visits will be arranged and documented, as appropriate.

12.2.1. Day 1

- Inclusion/exclusion criteria will be reviewed to determine subject eligibility
- Randomization
- Urine will be collected for a pregnancy test
- Study drug administration will begin for dose titration in the morning followed by maintenance infusion
- Vital signs will be recorded prior to infusion and at 2, 4, 8, 12, 18, and 24 hours on Day 1 (±30 minutes), unless the subject is asleep between the hours of 23.00h and 06.00h each day
- Blood and urine samples will be collected for drug and alcohol screening
- A blood sample for PK analysis will be collected prior to infusion (ie, morning of Day 1 prior to dosing), and at Hours 4 (before change in infusion rate, if applicable), 8, 12, and 24 (before change in infusion rate, if applicable) after the start of the infusion. PK blood draws after the start of infusion will have a window of ±10 minutes. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.

- The HAM-D will be completed prior to dosing and at Hours 2, 4, 8, 12, and 24 on Day 1 (±30 minutes)
- The MADRS will be completed prior to dosing and at Hour 24 on Day 1 (±30 minutes)
- The CGI-S will be completed prior to dosing and the CGI-I at Hours 2, 4, 12, and 24 on Day 1 (±30 minutes)
- The following questionnaires will be completed prior to dosing: BIMF, EPDS, GAD-7, SF-36, and PHQ-9 (±30 minutes)
- AEs will be monitored
- Concomitant medications will be recorded
- The "Baseline/Screening" C-SSRS form will be completed prior to dosing. The "Since Last Visit" C-SSRS form will be completed at Hour 24 (± 30 minutes)
- Breast milk will be pumped and discarded by subjects who are lactating

12.2.2. Day 2

- Ongoing study drug maintenance infusion administration
- Vital signs will be recorded at Hours 30, 36, 42, and 48 (±30 minutes), unless the subject is asleep between the hours of 23.00h and 06.00h each day
- A blood sample for PK analysis will be collected at Hours 30, 36, and 48. PK blood draws will have a window of ±10 minutes. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change
- The HAM-D will be completed at Hour 36 and Hour 48 (±30 minutes)
- The CGI-I will be completed at Hour 36 and Hour 48 (±30 minutes)
- The MADRS will be completed at Hour 48 (±30 minutes)
- An ECG reading will be taken at Hour 48
- AEs will be monitored
- Concomitant medications will be recorded
- Breast milk will be pumped and discarded by subjects who are lactating

12.2.3. Day 3

- Ongoing study drug maintenance infusion administration until Hour 60
- A physical examination will be completed at Hour 72
- Vital signs will be recorded at Hours 54, 60, 66, and 72 (±30 minutes)

- A blood sample for PK analysis will be collected at Hours 60 and 72 (±10 minutes). In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change
- Blood sample will be collected for clinical laboratory testing at Hour 72
- The HAM-D and MADRS will be completed at Hours 60 and 72 (±30 minutes)
- The CGI-I will be completed at Hours 60 and 72 (±30 minutes)
- The following questionnaires will be completed at Hour 60: EPDS, GAD-7, and PHQ-9 (±30 minutes)
- AEs will be monitored
- Concomitant medications will be recorded
- The C-SSRS will be completed at Hours 60 and 72
- Subjects who are lactating will pump and discard breast milk and be reminded that they must continue to pump and discard breast milk through Day 7 of the study

12.3. Follow-up Period (Day 7 through Day 30)

12.3.1. Day 7 (±1 day)

The following assessments should be completed:

- A physical examination will be completed
- Vital signs will be recorded
- Blood and urine samples will be collected for clinical laboratory testing
- An ECG reading will be taken
- The C-SSRS, HAM-D, MADRS, CGI-I, EPDS, GAD-7, PHQ-9, SF-36, and BIMF will be completed
- Subjects who are lactating will be reminded to continue to pump and discard breast milk for the remainder of the day; subjects will be instructed that they may resume breastfeeding their infant in the morning of Day 8
- AEs will be monitored
- Concomitant medications will be recorded

12.3.2. Day 12 (±2 days) (Part A); Day 14 (±2 days) and Day 21 (±3 days) (Parts B and C)

The following assessments should be completed:

- The C-SSRS, HAM-D, MADRS, CGI-I, EPDS, GAD-7, PHQ-9, SF-36, and BIMF will be completed
- AEs will be monitored

- Concomitant medications will be recorded

12.3.3. Day 30 (±3 days)

The following assessments should be completed:

- Urine will be collected for a pregnancy test
- The C-SSRS, HAM-D, MADRS, CGI-I, EPDS, GAD-7, PHQ-9, SF-36, and BIMF will be completed
- AEs will be monitored
- Concomitant medications will be recorded

12.3.4. Early Termination Visit

The following assessments should be completed if the subject discontinues from the study prior to the Day 7 Visit:

- A physical examination will be completed
- Vital signs will be recorded
- Blood and urine samples will be collected for clinical laboratory testing
- An ECG reading will be taken
- The C-SSRS, HAM-D, MADRS, CGI-I, EPDS, GAD-7, PHQ-9, SF-36, and BIMF will be completed
- AEs will be monitored
- Concomitant medications will be recorded

The visit should occur within 3 days of notification of the subject discontinuing.

13. STATISTICAL METHODS AND CONSIDERATIONS

In general, summary statistics for all study endpoints will be presented as mean, standard deviation (SD), median, and ranges for continuous endpoints, and as counts and percentages for categorical endpoints. For the purpose of all safety, efficacy, and other analyses where applicable, baseline is defined as the last pre-dose measurement closest to the start of blinded study drug infusion.

A separate statistical analysis plan (SAP) will be generated for each study (Parts A, B, and C) and approved prior to the respective database lock of each study. All statistical analyses will be conducted using SAS for Windows (version 9.1.3, or higher; Cary, NC), unless otherwise specified.

Any deviations from the planned analyses will be described and justified in the final clinical study report (CSR).

13.1. Data Analysis Sets

The **All Enrolled Population** will include all subjects who have given written informed consent. This population will be used for subject disposition and demographic characteristic summaries.

The **All Randomized Population** will include the subset of subjects from the All Enrolled Population who have been randomized. Subjects will be classified according to randomized treatment. This population will be used for subject disposition, demographic characteristic, and baseline characteristic summaries.

The **Safety Population** will include all randomized subjects who start the infusion of study drug. Subjects will be classified according to actual treatment received. This analysis population will be used for all safety analyses.

The **Efficacy Population (EFF)** will include the subset of the Safety Population who have a valid baseline HAM-D assessment and at least one post-baseline HAM-D assessment. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Per Protocol Population (PP)** will include the subset of the Efficacy Population who complete the full infusion without significant protocol violations or deviations. Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary and select secondary endpoints.

The **PK Population (PKP)** will include the subset of the Safety Population who have at least one evaluable PK sample. Subjects will be classified according to actual treatment received. This analysis population will be used for all PK analyses.

The number and percentage of subjects who receive SAGE-547 Injection or placebo, prematurely discontinue, and complete the study will be summarized. The number and percentage of subjects will also be summarized for each reason for premature discontinuation. In addition, the number of subjects whose data should be used for the planned analyses will be identified for each respective analysis population (ie, Safety, EFF, PKP, and PP).

13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis populations, using all non-missing data available. A sensitivity analysis may be carried out to investigate the impact of missing data if more than 5% of subjects are missing primary endpoint assessments. Any rules/statistical methods for the imputation of missing data will be described in the SAP.

13.3. Demographics and Baseline Characteristics

Demographics such as age, race, and ethnicity will be summarized. In addition, baseline characteristics such as height, weight, and BMI will be summarized. Categorical summaries, such as race and ethnicity, will be summarized by frequency and percentage. Continuous summaries, such as age, height, weight, BMI and baseline vital signs, will be summarized using descriptive statistics such as n, mean, SD, median, minimum, and maximum.

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

Medical/family history will be collected and listed by subject.

13.4. Primary Endpoints

For efficacy analysis purposes, centers with fewer than 15 subjects per center for Part B or 10 subjects per center for Part C will be pooled within regions (eg, North America region centers will be pooled separately those in Europe). 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 (pooled), treatment, baseline HAM-D total score, visit time point, and visit time point-by-treatment terms. Center and all other explanatory variables will be treated as fixed effects. For Parts A and C, the primary comparison will be between 90 µg SAGE-547 and placebo at the 60-hour assessment. For Part B, the primary comparison will be between 90 µg SAGE-547 and placebo at the 60-hour assessment; if this comparison is significant at the 0.05 level, then the 60 µg group will be compared to placebo at the 0.04 level of significance. More details will be provided in the SAPs regarding strong control of overall level of significance for multiple testing, including testing of key secondary endpoints. Comparisons at other time points, including the Day 30 time point, will be conducted to support the findings for the primary comparison. Model-based point estimates (ie, LS means), 95% confidence intervals, and p-values will be reported for each assessment.

Summaries of HAM-D total scores and changes from baseline values will include n, mean, SD, median, minimum, and maximum.

13.5. Secondary Endpoints

13.5.1. Efficacy Analysis

MMRM methods similar to those described in Section 13.4 will be used for the analysis of the following variables: MADRS total score, EPDS total score, GAD-7 total score, PHQ-9 total score, and select individual item and subscale scores. Separate models will be fit for each part of the study. For each model, the comparison of interest will be between each

SAGE-547 dose and placebo at the 60-hour assessment. 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 response variables: HAM-D response, HAM-D remission, and CGI-I response. GEE models will include terms for center, treatment, and baseline score. Separate models will be fit for each part of the study. The comparison of interest will be the difference between each SAGE-547 dose and placebo at the 60-hour assessment. 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.

13.5.2. Safety Analysis

Safety and tolerability of SAGE-547 Injection will be evaluated by AEs, concomitant medications, changes from baseline in physical examination, vital signs, CBC, serum chemistry, urinalysis, and 12-lead ECG. Suicidality will be monitored by the C-SSRS. In Part A only, sedation will be assessed using the Stanford Sleepiness Scale (SSS) and an analysis of SSS data will be performed comparing the treatment groups in the same way as for the primary endpoint. Safety data will be listed by individual and summarized by treatment group. All safety summaries will be performed on the Safety Population.

Safety data will be examined for possible relationships between subject characteristics and plasma allopregnanolone concentrations, as appropriate.

Scheduled visits for all safety assessments are described in Section 12 and summarized in Table 1.

13.5.2.1. Adverse Events

The analysis of AEs will be based on the concept of treatment-emergent AEs (TEAEs). A TEAE is defined as an AE with onset after the start of study drug infusion, or any worsening of a pre-existing medical condition/AE with onset after the start of study drug infusion. The incidence of TEAEs will be summarized overall and by MedDRA System Organ Class (SOC) and preferred term (PT). Incidences will be presented in order of decreasing frequency. In addition, summaries will be provided by severity (mild, moderate, severe) and by causality (related, not related) to study drug (see Section 14.2.2.1).

TEAEs leading to discontinuation and SAEs (see Section 14.1.4 for definition) with onset after the start of randomized infusion will also be summarized.

All AEs and SAEs (including those with onset or worsening before the start of randomized infusion) through the Day 30 Follow-up Visit (±3 days) will be listed.

13.5.2.2. Clinical laboratory evaluations

Results will be listed by Subject ID and timing of collection. Mean changes from baseline in clinical laboratory measures will be evaluated.

13.5.2.3. Physical examinations

Physical examinations will be evaluated at screening and Day 7. Any clinically significant change in physical examination compared to those observed at screening should be noted as an AE.

13.5.2.4. Vital signs

Vital signs, including oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing) will be obtained at the scheduled time points described in Section 11.1.4. Mean changes from baseline (pre-infusion) in vital signs will be evaluated.

13.5.2.5. 12-Lead ECG

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

13.5.2.6. Concomitant medications

A summary of all concomitant medications taken during the course of the study will be presented in tabular form by therapeutic drug class and generic drug name using the WHO Collaborating Centre for Drug Statistics Methodology Norwegian Institute of Public Health (http://www.whocc.no).

13.5.2.7. C-SSRS

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

13.5.2.8. SSS (Part A only)

Changes in score over time will be represented graphically, and change from baseline will be measured.

13.5.2.9. PK Analysis

Plasma will be collected to assay for concentrations of SAGE-547, metabolites of SAGE-547, and SBECD. The following PK parameters will be derived from the plasma concentrations (where evaluable): $AUC_{0\text{-}60}$, AUC_{∞}, C_{max}, time at maximum (peak) plasma concentration (t_{max}), steady-state drug concentration in the plasma during constant-rate infusion (C_{ss}), and average drug concentration in the plasma at steady state during a dosing interval (C_{avg}).

Plasma concentrations will be listed by subject and summarized by nominal collection time point. PK parameters will be listed by subject and summarized by collection time point. Correlations between concentrations and AEs or tolerability measures may be performed as deemed necessary.

In addition to typical descriptive statistics, summaries should include geometric mean, coefficient of variation, and geometric coefficient of variation.

13.6. Determination of Sample Size

Using a two-sided test at an alpha level of 0.05, a sample size of 10 evaluable subjects per group for Part A would provide 70% power to detect an effect size of 1.2 between the SAGE-547 and placebo groups with regard to the primary outcome variable of change from baseline in HAM-D total score. An effect size of 1.2 corresponds to a placebo-adjusted difference of 12 points in the change from baseline in HAM-D total score at 60 hours with an assumed standard deviation of 10 points. By including two treatment groups and using a 1:1 randomization ratio, a total of 20 evaluable subjects are required for Part A.

Based on the results of the interim analysis (Section 13.7), the sample size for Part A could be increased to a maximum of 32 randomized subjects. This adjustment to the sample size would allow for an effect size of 1.0 to be detected.

For Part B, a sample size of 40 evaluable subjects per group (120 total) would provide 90% power to detect a treatment difference of 9.0 between the SAGE-547 and placebo groups and a common standard deviation of 12 points (for an effect size of 0.75) using a two-sided t-test at an alpha level of 0.05.

For Part C, a sample size of 50 evaluable subjects per group (100 total) would provide 90% power to detect a treatment difference of 8.0 between the SAGE-547 and placebo groups and a common standard deviation of 12 points (for an effect size of 0.667) using a two-sided t-test at an alpha level of 0.05.

13.7. Interim Analysis

In Part A, an interim analysis will be conducted by an independent statistician for sample size re-estimation purposes when at least 16 subjects have completed efficacy assessments through 60 hours in Part A. Since the Sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing of Part A of the study. A detailed description of the interim analysis for sample size re-estimation will be included in the SAP.

No interim analyses are planned for Parts B and C of the study.

13.8. Changes from Protocol Specified Analyses

Any changes from the analytical methods outlined in the protocol will be documented in the final SAP.

Upon the completion of each study (547-PPD-202A, 547-PPD-202B, and 547-PPD-202C), the data will be unblinded and analyzed separately, and a separate final CSR will report the findings of each study.

14. ADVERSE EVENTS

Section 14.1 lists important AE definitions.

Section 14.2 summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB/IEC.

Section 14.3 summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to regulatory authorities.

14.1. Adverse Event Definitions

14.1.1. Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

14.1.2. Suspected Adverse Reaction

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

14.1.3. Life-Threatening

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

14.1.4. Serious

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE (see definition in Section 14.1.3)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- Other medically important condition (as described below)

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include

allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

14.1.5. Unexpected

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents.

"Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

In the clinical trial setting, the term "expected" would not mean "anticipated" for the condition being treated or population being studied since "expected" would indicate being "listed in the Investigator's Brochure." For example, some AEs can be anticipated to occur as a result of a disease or condition or in a certain population (eg, cancer-related deaths in a cancer trial, strokes or acute myocardial infarctions in an older population). However, for reporting purposes, these anticipated events are not considered "expected" if they are not listed in the Investigator's Brochure (ie, the investigational drug is not suspected or known to cause them).

14.2. Investigator Responsibilities

14.2.1. Identification and Documentation of Adverse Events by Investigator

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected during subject preparation, study drug administration during screening, after the initiation of study drug administration through to Day 3, and at the Follow-up Visits through Day 30 (±3 days). SAEs will also be collected until the Day 30 (±3 days) follow-up visit. Medical conditions that occur prior to completion of the screening visit will be captured on the Medical History eCRF. Adverse events that occur after completion of the screening visit will be recorded on the AE page of the eCRF (AE eCRF).

All AEs revealed by observation, physical examinations, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the AE eCRF. Any clinically significant deterioration from baseline in laboratory assessments or other clinical findings is considered an AE and must be recorded on the AE eCRF, unless otherwise stated. AE information recorded on AE eCRF will be entered into the database on an ongoing basis. The database, including AE information, will be transferred to the Sponsor on a pre-defined schedule for review.

All AEs, 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.

For all SAEs, an SAE report form must be completed with as much information as possible and submitted in the time frame described in Section 14.2.3. When new significant information is obtained as well as when the outcome of an event is known, the SAE report form should be updated on a follow-up report. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (eg, admission report, laboratory test results, discharge summary) may be requested to be included as part of the subject's medical file.

All SAEs will be followed until the events are resolved or improved and a stable status has been achieved, or the subject is lost to follow-up.

Female patients who become pregnant during the study should be followed to determine the outcome of the pregnancy. The pregnancy must be reported to the sponsor within 24 hours of the site becoming aware of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the sponsor. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

14.2.2. Adverse Event Classification

Definitions for the categories of AE classification are included in this section.

14.2.2.1. Relationship to Investigational Drug

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 or 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

14.2.2.2. Severity

The severity of an adverse experience will be defined as follows and reported as indicated on the AE eCRF:

Mild:	Discomfort noticed, but no disruption to daily activity.
Moderate:	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.
Severe:	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.

14.2.2.3. Action Taken with Investigational Drug

Action taken with regard to administration of study drug for this study will be recorded using the one of following categories (the category "dose increased" does not apply to this study):

- Drug withdrawn: An indication that a medication schedule was modified through termination of a prescribed regimen of medication
- Dose not changed: An indication that a medication schedule was maintained
- Drug interrupted: An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication
- Dose reduced: An indication that a medication schedule was modified to a reduced rate/dose
- Unknown: Unknown, not known, not observed, not recorded, or refused
- Not applicable: Determination of a value is not relevant in the current context

14.2.2.4. Assessment of Outcome

Assessment of outcome of AEs will be categorized as one of the following:

- Ongoing: At the end of the study, the event has not resolved or stabilized
- Resolved: The event has resolved or the subject recovered without sequelae
- Resolved with sequelae: The event has at least 1 secondary outcome that may result in permanent disability and/or functional limitation
- Unknown: The status of the event is unknown
- Death: The subject has expired

14.2.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact

All SAEs that occur during the course of the study must be reported by the Investigator immediately, with the designated report form sent to the Medical Monitor within 24 hours from the point in time when the Investigator becomes aware of the SAE. Investigators must report any SAE, whether or not considered drug related. The initial report must be as

complete as possible, including assessment of the causal relationship (ie, assessment of whether there is a reasonable possibility that the drug caused the event). The Medical Monitor will contact the investigator via telephone for follow-up information regarding the SAE, as appropriate.

Information not available at the time of the initial report must be documented on a follow-up report. As additional information becomes available, the designated report form must be updated and supporting information, including hospital records, laboratory and diagnostic testing results, etc. All supporting documentation must be de-identified. In addition, all SAEs that occur up to and including 30 days after administration of study drug must be reported within 24 hours from when the Investigator becomes aware of the SAE. A final report to document resolution of all SAEs is required.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care and contact the Medical Monitor.

14.2.4. Medical Monitor and Emergency Contact Information

[redacted], MD
[redacted]
Office (9-5 EST): [redacted]
24/7 Hotline: [redacted]

14.2.5. SAE Reporting Contact Information

Contact information and reporting instructions are provided in the Safety Management Plan.

14.2.6. Reporting to Institutional Review Boards/Independent Ethics Committees

It is the responsibility of the Investigator to promptly notify the institution's IRB/IEC of all SAEs that occur at his or her site if applicable per the IRB's/IEC's requirements.

14.3. Sponsor/Medical Monitor Responsibilities

14.3.1. Monitoring of Adverse Event Data

The Medical Monitor or designee will review SAEs/AEs on an ongoing basis.

14.3.2. Reporting to Regulatory Authorities

The Sponsor or its designee is responsible for SUSAR notification to the relevant regulatory authorities per applicable regulations. All investigators participating in the study will also be informed as required by regulations in order to inform their IRBs/IECs.

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to regulatory authorities as required by national laws.

14.4. Emergency Identification of Study Medication

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment from the Medical Monitor. The Investigator will not unblind the Medical Monitor during that discussion. The process of unblinding will be described in the Safety Management Plan for the study.

15. STUDY ADMINISTRATION

15.1. Quality Control and Quality Assurance

The Investigators and institutions will permit study-related monitoring, audits, IRB review, and regulatory inspections as requested by regulatory authorities, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (ie, original medical records, laboratory reports, hospital documents, progress reports, signed ICFs, etc.) in addition to CRFs.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure that 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, CRFs 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 the Sponsor with the Investigator/institution and any other parties involved with the clinical study will be in writing in a separate agreement.

15.2. Data Handling and Recordkeeping

15.2.1. Data Handling

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

15.2.2. Case Report Form Completion

Electronic CRFs (eCRFs) 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, AEs, and subject status.

The Investigator will have access to the electronic data capture (EDC) 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.

15.2.3. Retention of Study Records

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least two years after the last marketing application approval and until there are no pending or contemplated marketing applications or two years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

15.3. Confidentiality

To maintain subject privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the CRFs 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 the Sponsor. It is understood that there is an obligation to provide the Sponsor 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 authority(ies), other Investigators, corporate partners, or consultants as required.

15.4. Publication Policy

All information concerning SAGE-547 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.

15.5. Protocol Amendments

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the study (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB/IEC, as appropriate.

16. 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.

Amin Z, Mason GF, Cavus I et al. The interaction of neuroactive steroids and GABA in the development of neuropsychiatric disorders in women. Pharmacol, Biochem and Behavior 2006;84:635-43.

Austin MP, Middleton P, Reilly NM, Highet NJ. Detection and management of mood disorders in the maternity setting: the Australian Clinical Practice Guidelines. Women Birth 2013;26(1):2-9. doi: 10.1016/j.wombi.2011.12.001. Epub 2012 Jan 2.

Belelli D, Lambert JJ. Neurosteroids: endogenous regulators of the GABA(A) receptor. Nat Rev Neurosci 2005; 6(7):565-75. PMID: 15959466.

Bitran D, Hilvers RJ, Kellogg CK. Anxiolytic effects of 3α-hydroxy-5α[β]-pregnan-20-one: endogenous metabolites of progesterone that are active at the GABAA receptor. Brain Res 1991;561(1):157-161. PMID: 1686744.

Bitran D, Purdy RH, Kellog CK. Anxiolytic effect of progesterone is associated with increases in cortical allopregnanolone and GABAA receptor function. Pharmacol Biochem Behav 1993;45(2):423-8. PMID: 8392205.

Bloch M, Schmidt PJ, Danaceau M, et al. Effects of gonadal steroids in women with a history of postpartum depression. Am J Psychiatry 2000;157(6):924-30. PMID: 10831472.

Chaudron L. Postpartum depression: what pediatricians need to know. Pediatr Rev 2003;24(5);154-61. PMID: 12728188.

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.

Coyle CM, Laws KR. The use of ketamine as an antidepressant: a systematic review and meta-analysis. Hum Psychopharmacol. 2015;30(3):152-163.

Djebaili M, Guo Q, Pettus EH, Hoffman SW, Stein DG. The neurosteroids progesterone and allopregnanolone reduce cell death, gliosis, and functional deficits after traumatic brain injury in rats. J Neurotrauma 2005;22(1):106-18. PMID: 15968816.

Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL. A meta-analysis of cytokines in major depression. Biol Psychiatry 2010;67(5):446-57. PMID: 20015486.

DSM V. Diagnostic and statistical manual of mental disorders (5th ed.). American Psychiatric Association 2013. Arlington, VA: American Psychiatric Publishing.

Earls MF; Committee on Psychosocial Aspects of Child and Family Health American Academy of Pediatrics. Incorporating recognition and management of perinatal and postpartum depression into pediatric practice. Pediatrics 2010;126(5):1032-9. doi: 10.1542/peds.2010-2348.

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. PMID: 17719367.

Epperson CN, Gueorguieva R, Czarkowski KA et al. Preliminary evidence of reduced occipital GABA concentrations in puerperal women: a 1H-MRS study. Psychopharmacol 2006; 186:425-433. PMID: 16724188.

Eser D, Schüle C, Baghai TC, Romeo E, Rupprecht R. Neuroactive steroids in depression and anxiety disorders: clinical studies. Neuroendocrinology 2006;84(4):244-54. PMID: 17159334.

Fihrer I, McMahon CA, Taylor AJ. The impact of postnatal and concurrent maternal depression on child behaviour during the early school years. J Affect Disord 2009;119(1-3):116-23. PMID: 19342104.

Fournier JC, DeRubeis RJ, Hollon SD et al. Antidepressant drug effects and depression severity—a patient-level meta-analysis. JAMA 2010;303:47-53. PMID: 20051569.

Frye CA, Duncan JE. Progesterone metabolites, effective at the GABAA receptor complex, attenuate pain sensitivity in rats. Brain Res 1994;643(1-2):194-203. PMID: 8032914.

Gangisetty O and Reddy DS. Neurosteroid withdrawal regulates GABA-A receptor α4-subunit expression and seizure susceptibility by activation of progesterone receptor-independent early growth response factor-3 pathway. Neuroscience 2010; 170:865-880. PMID: 20670676.

Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol 2005;106:1071-83. PMID: 16260528.

Gaynes BN, Gavin N, Meltzer-Brody S, Lohr KN, Swinson T, Gartlehner G, et al. Perinatal depression: prevalence, screening accuracy, and screening outcomes. Evid Rep Technol Assess (Summ) 2005;(119):1-8. PMID: 15760246.

Gilbert Evans SE, Ross LE, Sellers EM, et al. 3alpha-reduced neuroactive steroids and their precursors during pregnancy and the postpartum period. Gynecol Endocrinol 2005 21, 268-279. PMID: 16373246.

Genazzani AR, Petraglia F, Bernardi F, Casarosa E, Salvestroni C, Tonetti A, et al. Circulating levels of allopregnanolone in humans: gender, age, and endocrine influences. J Clin Endocrinol Metab 1998;83(6):2099-103. PubMed PMID: 9626145.

Glantz LA, Gilmore JH, Overstreet DH, Salimi K, Lieberman JA, Jarskog LF. Pro-apoptotic Par-4 and dopamine D2 receptor in temporal cortex in schizophrenia, bipolar disorder and major depression. Schizophr Res 2010;118(1-3):292-9. PMID: 20067857.

Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56-62. PMID: 14399272.

He JQ, Tang XW, Chen HX, Xiang Z. [Study on treatment of climacteric depression with bushen tiaogan qingxin recipe]. Zhongguo Zhong Xi Yi Jie He Za Zhi 2004;24(10):889-92. [Article in Chinese]. PMID: 15553820.

Holzbauer M, Birmingham MK, De Nicola AF, Oliver JT. In vivo secretion of 3 alpha-hydroxy-5 alpha-pregnan-20-one, a potent anaesthetic steroid, by the adrenal gland of the rat. J Steroid Biochem. 1985 Jan;22(1):97-102. PubMed PMID: 3974231.

Kask K, Bäckström T, Lundgren P, Sundström Poromaa I. Allopregnanolone has no effect on startle response and prepulse inhibition of startle response in patients with premenstrual dysphoric disorder or healthy controls. Pharmacol Biochem Behav 2009;92(4):608-13. PubMed PMID: 19268499.

Kask K, Bäckström T, Nilsson LG, Sundström-Poromaa I. Allopregnanolone impairs episodic memory in healthy women. Psychopharmacology (Berl) 2008;199(2):161-8. PMID: 18551282.

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. PMID: 18303940.

Klak J, Hill M, Parízek A, Havlíková H, et al. Pregnanolone isomers, pregnenolone and their polar conjugates around parturition. Physiol Res 2003;52(2):211-21. PMID: 12678664.

Licinio J, Wong ML. The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. Mol Psychiatry 1999;4(4):317-27. PMID: 10483047.

Luisi S, Petraglia F, Benedetto C, Nappi RE, Bernardi F, Fadalti M, et al. Serum allopregnanolone levels in pregnant women: changes during pregnancy, at delivery, and in hypertensive patients. J Clin Endocrinol Metab 2000;85(7):2429-33. PMID: 10902789.

Maguire J, Mody I. GABA(A)R plasticity during pregnancy: relevance to postpartum depression. Neuron 2008;59(2):207-13. PMID: 18667149.

Maguire J, Ferando I, Simonsen C, Mody I. Excitability changes related to GABAA receptor plasticity during pregnancy. J Neurosci 2009;29(30):9592-601. PMID: 19641122.

Majewska MD, Harrison NL, Schwartz RD, Barker JL, Paul SM. Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor. Science 1986;232:1004-7. PMID: 2422758.

McDowell, I. Measuring Health: A guide to rating scales and questionnaires. 2006: 3rd Ed. New York: Oxford University Press.

Morrow AL, Devaud LL, Purdy RH, Paul SM. Neuroactive steroid modulators of the stress response. Ann N Y Acad Sci 1995;771:257-72. PMID: 8597405.

Müller-Thomsen T, Arlt S, Mann U, Maß R, Ganzer S. Detecting depression in Alzheimer's disease: evaluation of four different scales. Arch Clin Neuropsych 2005;20:271-6. PMID: 15708735.

Nappi RE, Petraglia F, Luisi S et al. Serum allopregnanolone in women with postpartum "blues". Obstet Gynecol 2001;97 (1):77-80. PMID: 11152912.

Navarro PA, Kaddouz D, de Ziegler D, Silva de Sá MF, Ferriani RA. Vaginal administration of allopregnanolone to postmenopausal women undergoing estrogen replacement therapy: preliminary results. Maturitas 2003;46(2):147-52. PubMed PMID: 14559386.

Norberg L, Backstrom T and Wahlstrom G. Anaesthetic effects of pregnanolone in combination with allopregnanolone, thiopental, hexobarbital and flurazepam: an EEG study in the rat. Br J Anaesth 1999; 82(5):731-737. PMID: 10536552.

O'Hara MW, Wisner KL. Perinatal mental illness: definition, description and aetiology. Best Pract Res Clin Obstet Gynaecol 2014;28(1):3-12. doi: 10.1016/j.bpobgyn.2013.09.002.

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.

Ottander U, Poromaa IS, Bjurulf E, Skytt A, Bäckström T, Olofsson JI. Allopregnanolone and pregnanolone are produced by the human corpus luteum. Mol Cell Endocrinol 2005 Jul 15;239(1-2):37-44. PubMed PMID: 15935549.

Paoletti AM, Romagnino S, Contu R, et al. Observational study on the stability of the psychological status during normal pregnancy and increased blood levels of neuroactive steroids with GABA-A receptor agonist activity. Psychoneuroendocrinology 2006; 31(4): 485-492. PMID: 16406349.

Paul SM, Purdy RH. Neuroactive steroids. FASEB J 1992;6(6):2311-22. PMID: 1347506.

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. doi: 10.1176/appi.ajp.2011.10111704.

Romeo E, Ströhle A, Spalletta G, di Michele F, Hermann B, Holsboer F, Pasini A, Rupprecht R. Effects of antidepressant treatment on neuroactive steroids in major depression. Am J Psychiatry 1998;155(7):910-3. PMID: 9659856.

Sayeed I, Parvez S, Wali B, Siemen D, Stein DG. Direct inhibition of the mitochondrial permeability transition pore: a possible mechanism for better neuroprotective effects of allopregnanolone over progesterone. Brain Res 2009;1263:165-73. PMID: 19368823.

Schüle C, Romeo E, Uzunov DP, Eser D, di Michele F, Baghai TC, et al. Influence of mirtazapine on plasma concentrations of neuroactive steroids in major depression and on 3α-hydroxysteroid dehydrogenase activity. Mol Psychiatry 2006;11(3):261-72. PMID: 16344854.

Schüle C, Baghai TC, di Michele F, Eser D, Pasini A, Schwarz M. Effects of combination treatment with mood stabilizers and mirtazapine on plasma concentrations of neuroactive steroids in depressed patients. Psychoneuroendocrinology 2007;32(6):669-80. PMID: 17560730.

Shelton RC, Trivedi MH. Moderators of antidepressant response in major depression. J Clin Psychiatry 2011;72(10):e32. PMID: 22075105.

Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. Arch Intern Med 2006; 166(10):1092-1097. doi: 10.1001/archinte.166.10.1092.

Ströhle A, Romeo E, Hermann B, Pasini A, Spalletta G, di Michele F, et al. Concentrations of 3α-reduced neuroactive steroids and their precursors in plasma of patients with major depression and after clinical recovery. Biol Psychiatry 1999;45(3):274-77. PMID: 10023501.

Timby E, Balgård M, Nyberg S, Spigset O, Andersson A, Porankiewicz-Asplund J, et al. Pharmacokinetic and behavioral effects of allopregnanolone in healthy women. Psychopharmacology (Berl) 2006;186(3):414-24. PMID: 16177884.

Timby E, Hedström H, Bäckström T, Sundström-Poromaa I, Nyberg S, Bixo M. Allopregnanolone, a GABAA receptor agonist, decreases gonadotropin levels in women A preliminary study. Gynecol Endocrinol 2011;27(12):1087-93. PMID: 21190418. (Timby 2011a)

Timby E. Allopregnanolone effects in women. Clinical studies in relation to the menstrual cycle, premenstrual dysphoric disorder and oral contraceptive use. Umea University Medical Dissertation 2011; New Series No. 1459. (Timby 2011b)

Uzunova V, Sheline Y, Davis JM, Rasmusson A, Uzunov DP, Costa E, et al. Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine. Proc Natl Acad Sci 1998;95(6):3239-44. PMID: 9501247.

van Broekhoven F, Bäckström T, van Luijtelaar G, Buitelaar JK, Smits P, Verkes RJ. Effects of allopregnanolone on sedation in men, and in women on oral contraceptives. Psychoneuroendocrinology. 2007;32(5):555-64. PMID: 17470385.

Verbeek T, Bockting CL, van Pampus MG et al. Postpartum depression predicts offspring mental health problems in adolescence independently of parental lifetime psychopathology. J Affect Disord 2012;136(3):948-54. doi: 10.1016/j.jad.2011.08.035.

Ware JE, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. User's Manual for the SF-36v2® Health Survey (2nd ed). 2007. Lincoln, RI: QualityMetric Incorporated.

Wieland S, Lan NC, Mirasedeghi S, Gee KW. Anxiolytic activity of the progesterone metabolite 5α-pregnan-3α-ol-20-one. Brain Res 1991;565(2):263-8. PMID: 1688192.

APPENDICES

Copies of the rating scales and questionnaires included in Appendix 1 through Appendix 10 are for reference only.

APPENDIX 1. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)

The "Baseline/Screening" and "Since Last Visit" versions of the C-SSRS begin on the next full page (Posner 2011).

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103-130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***) Past X Months - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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APPENDIX 2. HAMILTON RATING SCALE FOR DEPRESSION, 17-ITEM (HAM-D)

The HAM-D presents on the next full page (Hamilton 1960).

The HAM-D total score will be calculated as the sum of the 17 individual item scores. Item 16 can be rated according to history (item 16A) or actual weight change (item 16B). The item 16 score is calculated as the item 16 response that is not equal to 3 (ie, "Not assessed).

HAMILTON RATING SCALE FOR DEPRESSION: 17-ITEM VERSION (HAM-D-17)

Author: M. Hamilton

Instructions: For each item select one "cue" which best characterizes the patient.

1 – Depressed Mood		
	☐	0 Absent
	☐	1 Indicated only on questioning
	☐	2 Spontaneously reported verbally
	☐	3 Communicated non-verbally, i.e., facial expression, posture, voice, tendency to weep
	☐	4 VIRTUALLY ONLY those feeling states reported in spontaneous verbal and non-verbal communication
2 – Feelings of Guilt		
	☐	0 Absent
	☐	1 Self-reproach, feels he has let people down
	☐	2 Ideas of guilt or rumination over past errors or sinful deeds
	☐	3 Present illness is a punishment. Delusions of guilt
	☐	4 Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
3 – Suicide		
	☐	0 Absent
	☐	1 Feels life is not worth living
	☐	2 Wishes he were dead or any thoughts of possible death to self
	☐	3 Suicidal ideas or gesture
	☐	4 Attempts at suicide
4 – Insomnia Early		
	☐	0 No difficulty falling asleep
	☐	1 Complains of occasional difficulty falling asleep
	☐	2 Complains of nightly difficulty falling asleep

Reference: Hamilton, M. J Neurol Neurosurg Psychiatry. 1960; 22:56-62. Hamilton, M. Br J Soc Clin Psychol. 1967; 6:278-96. Copyright © public domain

HAMILTON RATING SCALE FOR DEPRESSION: 17-ITEM VERSION (HAM-D-17)

5 – Insomnia Middle		
	☐	0 No difficulty
	☐	1 Complains of being restless and disturbed during the night
	☐	2 Waking during the night - any getting out of bed (except to void)
6 – Insomnia Late		
	☐	0 No difficulty
	☐	1 Waking in early hours of morning but goes back to sleep
	☐	2 Unable to fall asleep again if gets out of bed
7 – Work and Activities		
	☐	0 No difficulty
	☐	1 Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies
	☐	2 Loss of interest in activity, hobbies or work - by direct report of the patient or indirect in listlessness, indecision and vacillation
	☐	3 Decrease in actual time spent in activities or decrease in productivity. In hosp., pt. spends less than 3 hrs. /day in activities *(hospital, job, or hobbies)* exclusive of ward chores
	☐	4 Stopped working because of present illness. In hospital, no activities except ward chores, or fails to perform ward chores unassisted
8 – Retardation		
	☐	0 Normal speech and thought
	☐	1 Slight retardation at interview
	☐	2 Obvious retardation at interview
	☐	3 Interview difficult
	☐	4 Complete stupor

Reference: Hamilton M. J Neurol Neurosurg Psychiatry. 1960; 22:56-62. Hamilton, M. Br J Soc Clin Psychol. 1967; 6:278-96. Copyright © public domain.

HAMILTON RATING SCALE FOR DEPRESSION: 17-ITEM VERSION (HAM-D-17)

9 – Agitation			
	☐	0 None	
	☐	1 Fidgetiness	
	☐	2 Playing with hands, hair, etc.	
	☐	3 Moving about, can't sit still	
	☐	4 Hand-wringing, nail biting, hair-pulling, biting of lips	
10 – Anxiety Psychic			
	☐	0 No difficulty	
	☐	1 Subjective tension and irritability	
	☐	2 Worrying about minor matters	
	☐	3 Apprehensive attitude apparent in face or speech	
	☐	4 Fears expressed without questioning	
11 – Anxiety Somatic		**Physiological concomitants of anxiety, such as:**	
	☐	0 Not present	**Gastrointestinal** - dry mouth, gas, indigestion, diarrhea, stomach cramps, belching
	☐	1 Mild	**Cardiovascular** – heart palpitations, headaches
	☐	2 Moderate	**Respiratory** - hyperventilation, sighing
	☐	3 Severe	**Urinary frequency**
	☐	4 Incapacitating	**Sweating**
12 – Somatic Symptoms Gastrointestinal			
	☐	0 None	
	☐	1 Loss of appetite but eating without encouragement	
	☐	2 Difficulty eating without urging	

Reference: Hamilton, M. J Neurol Neurosurg Psychiatry. 1960; 22:56-62. Hamilton, M. Br J Soc Clin Psychol. 1967; 6:278-96. Copyright © public domain

HAMILTON RATING SCALE FOR DEPRESSION: 17-ITEM VERSION (HAM-D-17)

13 – Somatic Symptoms General		
	☐	0 None
	☐	1 Heaviness in limbs, back, or head. Backaches, muscle aches. Loss of energy and fatigability
	☐	2 Any clear-cut symptoms
14 – Genital Symptoms		
Symptoms such as: Loss of libido Menstrual disturbances	☐	0 Absent
	☐	1 Mild
	☐	2 Severe
15 – Hypochondriasis		
	☐	0 Not present
	☐	1 Self-absorption *(bodily)*
	☐	2 Preoccupation with health
	☐	3 Frequent complaints, requests for help, etc.
	☐	4 Hypochondriacal delusions
16 – Loss of Weight		
	☐	0 No weight loss
	☐	1 Probable weight loss due to current depression
	☐	2 Definite *(according to patient)* weight loss due to depression
17 – Insight		
	☐	0 Acknowledges being depressed and ill OR not currently depressed
	☐	1 Acknowledges illness but attributes cause to bad food, overwork, virus, need for rest, etc.
	☐	2 Denies being ill at all

Reference: Hamilton M. J Neurol Neurosurg Psychiatry. 1960; 22:56-62. Hamilton, M. Br J Soc Clin Psychol. 1967; 6:278-96. Copyright © public domain.

APPENDIX 3. MONTGOMERY ASBERG DEPRESSION RATING SCALE (MADRS)

The MADRS, presented on the next full page, includes the following 10 symptoms:

1. Apparent sadness
2. Reported sadness
3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

1. ***Apparent Sadness***

Representing despondency, gloom and despair, (more than just ordinary transient low spirits)

reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

0 No sadness.
1
2 Looks dispirited but does brighten up without difficulty.
3
4 Appears sad and unhappy most of the time.
5
6 Looks miserable all the time. Extremely despondent.

---

2. *Reported sadness*

Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope.

Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

0 Occasional sadness in keeping with the circumstances.
1
2 Sad or low but brightens up without difficulty.
3
4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
5
6 Continuous or unvarying sadness, misery or despondency.

---

3. *Inner tension*

Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish.

Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 Placid. Only fleeting inner tension.
1
2 Occasional feelings of edginess and ill-defined discomfort.
3
4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
5
6 Unrelenting dread or anguish. Overwhelming panic.

---

4. *Reduced sleep*

Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

0 Sleeps as usual.
1
2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
3
4 Sleep reduced or broken by at least two hours.
5
6 Less than two or three hours sleep.

---

5. *Reduced appetite*

Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

0 Normal or increased appetite.
1
2 Slightly reduced appetite.
3
4 No appetite. Food is tasteless.
5
6 Needs persuasion to eat at all.

---

6. *Concentration difficulties*

Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

Rate according to intensity, frequency, and degree of incapacity produced.

0 No difficulties in concentrating.
1
2 Occasional difficulties in collecting one's thoughts.
3
4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
5
6 Unable to read or converse without great difficulty.

---

7. *Lassitude*

Representing a difficulty getting started or slowness initiating and performing everyday activities.

0 Hardly any difficulty in getting started. No sluggishness.
1
2 Difficulties in starting activities.
3
4 **Difficulties in starting simple routine activities which are carried out with effort.**
5
6 **Complete lassitude. Unable to do anything without help.**

---

8. *Inability to feel*

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

0 Normal interest in the surroundings and in other people.
1
2 Reduced ability to enjoy usual interests.
3
4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
5
6 The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. *Pessimistic thoughts*

Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

0 No pessimistic thoughts.
1
2 Fluctuating ideas of failure, self-reproach or self depreciation.
3
4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
5
6 Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable.

10. *Suicidal thoughts*

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide.

Suicidal attempts should not in themselves influence the rating.

0 Enjoys life or takes it as it comes.
1
2 Weary of life. Only fleeting suicidal thoughts.
3
4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5
6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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(*Received 24 April; revised 30 August 1978*)

APPENDIX 4. CLINICAL GLOBAL IMPRESSION–IMPROVEMENT SCALE (CGI-I) AND SEVERITY SCALE (CGI-S)

The CGI-I and CGI-S present on the next full page. For the purposes of Protocol 547-PPD-202, only Items 1 and 2, Severity of Illness and Global Improvement, will be assessed in subjects enrolled in the study.

1. **Severity of illness**
   Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?
   0 = Not assessed
   1 = Normal, not at all ill
   2 = Borderline mentally ill
   3 = Mildly ill
   4 = Moderately ill
   5 = Markedly ill
   6 = Severely ill
   7 = Among the most extremely ill patients

2. **Global improvement:** Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.
   Compared to his condition at admission to the project, how much has he changed?
   0 = Not assessed
   1 = Very much improved
   2 = Much improved
   3 = Minimally improved
   4 = No change
   5 = Minimally worse
   6 = Much worse
   7 = Very much worse

3. **Efficacy index:** Rate this item on the basis of **drug effect only**.
   Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.
   EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		**Side effects**			
		None	*Do not significantly interfere with patient's functioning*	*Significantly interferes with patient's functioning*	*Outweighs therapeutic effect*
Marked	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
Moderate	Decided improvement. Partial remission of symptoms	05	06	07	08
Minimal	Slight improvement which doesn't alter status of care of patient	09	10	11	12
Unchanged or worse		13	14	15	16

Not assessed = 00

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

APPENDIX 5. EDINBURGH POSTNATAL DEPRESSION SCALE (EPDS)

The EPDS presents on the next full page (Cox 1987).

Study ID:

Edinburgh Postnatal Depression Scale

As you are pregnant or have recently had a baby, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**, not just how you feel today.

Here is an example, already completed.

I have felt happy:
☐ Yes, all the time
☒ Yes, most of the time This would mean: "I have felt happy most of the time" during the past week.
☐ No, not very often
☐ No, not at all

Please complete the other questions in the same way.

In the past 7 days:

1. I have been able to laugh and see the funny side of things
☐ As much as I always could
☐ Not quite so much now
☐ Definitely not so much now
☐ Not at all

2. I have looked forward with enjoyment to things
☐ As much as I ever did
☐ Rather less than I used to
☐ Definitely less than I used to
☐ Hardly at all

***3. I have blamed myself unnecessarily when things went wrong**
☐ Yes, most of the time
☐ Yes, some of the time
☐ Not very often
☐ No, never

4. I have been anxious or worried for no good reason
☐ No, not at all
☐ Hardly ever
☐ Yes, sometimes
☐ Yes, very often

***5 I have felt scared or panicky for no very good reason**
☐ Yes, quite a lot
☐ Yes, sometimes
☐ No, not much
☐ No, not at all

***6. Things have been getting on top of me**
☐ Yes, most of the time I haven't been able to cope at all
☐ Yes, sometimes I haven't been coping as well as usual
☐ No, most of the time I have copied quite well
☐ No, I have been coping as well as ever

***7 I have been so unhappy that I have had difficulty sleeping**
☐ Yes, most of the time
☐ Yes, sometimes
☐ Not very often
☐ No, not at all

***8 I have felt sad or miserable**
☐ Yes, most of the time
☐ Yes, quite often
☐ Not very often
☐ No, not at all

***9 I have been so unhappy that I have been crying**
☐ Yes, most of the time
☐ Yes, quite often
☐ Only occasionally
☐ No, never

***10 The thought of harming myself has occurred to me**
☐ Yes, quite often
☐ Sometimes
☐ Hardly ever
☐ Never

APPENDIX 6. GENERALIZED ANXIETY DISORDER 7-ITEM SCALE (GAD-7)

The GAD-7 presents on the next full page (Spitzer 2006).

Generalized Anxiety Disorder 7-item (GAD-7) scale

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	
Total Score *(add your column scores)* =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all _____
Somewhat difficult _____
Very difficult _____
Extremely difficult _____

APPENDIX 7. PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

The PHQ-9 presents on the next full page.

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

APPENDIX 8. BARKIN INDEX OF MATERNAL FUNCTIONING (BIMF)

The BIMF is presented below.

Barkin Index of Maternal Functioning

Please **circle the number** that best represents how you have felt **over the past two weeks**. Please try to answer each question as honestly as possible as your responses will help us to better understand the postpartum experience.

	Strongly Disagree	Disagree	Somewhat Disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
1. I am a good mother.	0	1	2	3	4	5	6
2. I feel rested.	0	1	2	3	4	5	6
3. I am comfortable with the way I've chosen to feed my baby (either bottle or breast, or both).	0	1	2	3	4	5	6
4. My baby and I understand each other.	0	1	2	3	4	5	6
5. I am able to relax and enjoy time with my baby.	0	1	2	3	4	5	6
6. There are people in my life that I can trust to care for my baby when I need a break.	0	1	2	3	4	5	6
7. *I am comfortable* allowing a trusted friend or relative to care for my baby (can include baby's father or partner).	0	1	2	3	4	5	6
8. I am getting enough adult interaction.	0	1	2	3	4	5	6
9. I am getting enough encouragement from other people.	0	1	2	3	4	5	6
10. I trust my own feelings (instincts) when it comes to taking care of my baby.	0	1	2	3	4	5	6
11. I take a little time each week to do something for myself.	0	1	2	3	4	5	6
12. I am taking good care of my baby's physical needs (feedings, changing diapers, doctor's appointments).	0	1	2	3	4	5	6
13. I am taking good care of my physical needs (eating, showering, etc).	0	1	2	3	4	5	6
14. I make good decisions about my baby's health and well being.	0	1	2	3	4	5	6
15. My baby and I are getting into a routine.	0	1	2	3	4	5	6
16. I worry about how other people judge me (as a mother).	0	1	2	3	4	5	6
17. I am able to take care of my baby and my other responsibilities.	0	1	2	3	4	5	6
18. Anxiety or worry often interferes with my mothering ability.	0	1	2	3	4	5	6
19. *As time goes on*, I am getting better at taking care of my baby.	0	1	2	3	4	5	6
20. I am *satisfied* with the job I am doing as a new mother.	0	1	2	3	4	5	6

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APPENDIX 9. SHORT FORM-36 (ONE WEEK RECALL)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one week ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past week</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past week</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past week</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past week</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past week</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past week</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

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(SF-36v2® Health Survey Acute, United States (English))

APPENDIX 10. HEALTH RESOURCE UTILIZATION QUESTIONNAIRE

Health Resource Utilization Questionnaire Instructions

Purpose: The purpose of the HRU questionnaire to collect data on resource utilization in order to calculate the burden of patient care in terms of the healthcare resources required for treatment.

Administration: Survey should be completed at screening via an interview by the healthcare provider participating in the study using the questionnaire below. Additionally, the subject will be requested to provide throughout the study any updates, or new information on healthcare visits that occurred *beyond those expected per protocol*. The details of these healthcare visits will be captured in a continuous log format.

Health Resource Utilization Questionnaire (Screening)

A. Healthcare Visits

In the past 3months, did you use any of the following health care services?	Yes	No	How many visits did you have in the past 3 months?
Emergency Room Visit	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Use of an ambulance	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Outpatient Primary Care Physician Visit	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Outpatient Specialist Visit (e.g. OB/GYN, surgeon)	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Outpatient Counseling Visit (e.g. Psychiatrist, Psychologist, Therapist, mental health specialist)	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Inpatient hospital admission (beyond that required by protocol)	☐ *	☐	* Complete inpatient hospital admission detail for each admission

B. Inpatient hospital admission detail

	Length of Stay (days)	Reason for Admission
Stay 1		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other
Stay 2		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other
Stay 3		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other
Stay 4		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other
Stay 5		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other

Health Resource Utilization Questionnaire Instructions

Purpose: The purpose of the HRU questionnaire to collect data on resource utilization in order to calculate the burden of patient care in terms of the healthcare resources required for treatment.

Administration: Survey should be completed at screening via an interview by the healthcare provider participating in the study using the questionnaire below. Additionally, the subject will be requested to provide throughout the study any updates, or new information on healthcare visits that occurred ***beyond those expected per protocol***. The details of these healthcare visits will be captured in a continuous log format.

Health Resource Utilization Questionnaire (Post-screening Log)

A. Healthcare Visits

Since entering this study, did you use any of the following health care services?	Yes	No	How many visits did you have since entering this study?
Emergency Room Visit	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Use of an ambulance	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Outpatient Primary Care Physician Visit	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Outpatient Specialist Visit (e.g. OB/GYN, surgeon)	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Outpatient Counseling Visit (e.g. Psychiatrist, Psychologist, Therapist, mental health specialist)	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Inpatient hospital admission (beyond that required by protocol)	☐*	☐	* Complete inpatient hospital admission detail for each admission

B. Inpatient hospital admission detail

	Length of Stay (days)	Reason for Admission
Stay 1		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other
Stay 2		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other
Stay 3		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other
Stay 4		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other
Stay 5		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other

Summary of Changes to
Protocol 547-PPD-202, Amendment 4
Date of Amendment: 16 March 2017

The following changes were made to the attached protocol in this amendment. In addition, minor revisions to formatting, punctuation, spelling, and wording (eg, capitalization, abbreviation, word order) that are not listed below were made throughout the protocol.

Section number	**Original text:**	**Changed to:**	**Rationale:**
Title Page	Protocol 547-PPD-202 Amendment 3	Protocol 547-PPD-202 Amendment ~~3~~ **4, Version 5.0**	Administrative update
Title Page	31 January 2017	~~31 January 2017~~ **Sage Therapeutics Confidential**	Administrative update
Title Page	Confidential [page #]	~~Confidential~~ [page #]	Administrative update
Title Page		**Added Sage Logo**	Administrative update
Title Page	Sponsor: Sage Therapeutics	Sponsor: Sage Therapeutics **215 First Street** **Cambridge, MA 02142**	Administrative update
Title Page	Medical Monitor: [redacted], M.D., FAAP (with title, address, phone, and email)	**Sponsor** Medical Monitor: [redacted], M.D., FAAP (with title, ~~address,~~ phone, and email)	Administrative update and role clarification
Title Page	Medical Monitor: [redacted], M.D. (with title, address, phone, and email)	**CRO** Medical Monitor: [redacted], M.D. (with title, address, phone, and email)	Clarified role
Title Page	Date of Amendment 3: Version 4.0, 31 January 2017	Date of Amendment 3: Version 4.0, 31 January 2017 **Date of Amendment 4:** **Version 5.0, 16 March 2017**	Administrative update

Section 2, Synopsis, Inclusion Criteria; and Section 8.0 Selection and Withdrawal of Subjects, 8.1 Inclusion Criteria	5. Subject either must have ceased lactating at screening; or if still lactating or actively breast feeding at screening, must agree to temporarily cease giving breastmilk to their infant(s) from just prior to receiving study drug through 9 days (Study Day 12) after the end of infusion.	5. Subject either must have ceased lactating at screening; or if still lactating or actively breast feeding at screening, must agree to temporarily cease giving breastmilk to their infant(s) from just prior to receiving study drug through ~~9~~ **4** days (Study Day ~~12~~ **7**) after the end of infusion.	Shortened requirement for pumping and discarding breastmilk based on emerging data and advice from the FDA that 7 days is sufficient
Section 2, Synopsis, Table 1: Schedule of Events, footnote k; and Section 12, Study Procedures, 12.2 Study Drug Treatment Period (Day 1 to Day 3, Hours 0-72), 12.2.3. Day 3	Subjects who are lactating will be reminded that they must continue to pump and discard breast milk through Day 12 of the study.	Subjects who are lactating will be reminded that they must continue to pump and discard breast milk through Day ~~12~~ **7** of the study.	Shortened requirement for pumping and discarding breastmilk based on emerging data and advice from the FDA that 7 days is sufficient
Section 12 Study Procedures, 12.3 Follow-up Period (Day 7 through Day 30), 12.3.1. Day 7 (±1 Day)	• Subjects who are lactating will be reminded to continue to pump and discard breast milk through Day 12 of the study.	• Subjects who are lactating will be reminded to continue to pump and discard breast milk ~~through Day 12 of the study~~ **for the remainder of the day; subjects will be instructed that they may resume breastfeeding their infant in the morning of Study Day 8.**	Shortened requirement for pumping and discarding breastmilk based on emerging data and advice from the FDA that 7 days is sufficient

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF SAGE-547 INJECTION IN THE TREATMENT OF ADULT FEMALE SUBJECTS WITH SEVERE POSTPARTUM DEPRESSION AND ADULT FEMALE SUBJECTS WITH MODERATE POSTPARTUM DEPRESSION

NUMBER: 547-PPD-202
IND NUMBER: 122,279
EUDRA CT NUMBER: 2016-005137-68

Investigational Product:	SAGE-547 Injection (allopregnanolone)
Clinical Phase:	3
Sponsor:	Sage Therapeutics
Sponsor Contact:	Helen Colquhoun, M.D. Senior Medical Director Sage Therapeutics 215 First Street Cambridge, MA 02142 Phone: [redacted]
Medical Monitor:	[redacted], M.D., FAAP Study Medical Lead Sage Therapeutics 215 First Street Cambridge, MA 02142 Phone: [redacted] [redacted], M.D. [redacted] Phone: [redacted] 24/7 Hotline: [redacted]
Date of Original Protocol:	Version 1.0, 18 September 2015
Date of Amendment 1:	Version 2.0, 22 December 2015
Date of Amendment 2:	Version 3.0, 30 June 2016
Date of Amendment 3:	Version 4.0, 31 January 2017

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 the Sponsor.

1. SIGNATURE PAGE

Title of protocol:	A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects with Severe Postpartum Depression and Adult Female Subjects with Moderate Postpartum Depression
Protocol No:	547-PPD-202
IND No.:	122,279
Eudra CT No.:	2016-005137-68
Study Phase:	3
Sponsor:	Sage Therapeutics

Sponsor Approval

[redacted] 01 Feb 2017

Helen Colquhoun, M.D.
Senior Medical Director
Sage Therapeutics

Date (dd/mmm/yyyy)

[redacted] 01 Feb 2017

[redacted], M.P.H.
[redacted]
Sage Therapeutics

Date (dd/mmm/yyyy)

[redacted] 01 Feb2017

[redacted]
Sage Therapeutics

Date (dd/mmm/yyyy)

[redacted] 01 FEB2017

[redacted], Ph.D.
[redacted]
Sage Therapeutics

Date (dd/mmm/yyyy)

Investigator Agreement

By signing this page, I attest that I have read and understand the contents of Clinical Protocol 547-PPD-202 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: _____

Investigator's Name: _____

Institution: _____

Date (dd/mmm/yyyy): _____

2. SYNOPSIS

Name of Sponsor:

Sage Therapeutics
215 First Street
Cambridge, MA 02142

Protocol No. 547-PPD-202	**Phase:** 3

Name of Investigational Product:

SAGE-547 Injection

Name of Active Ingredient:

Allopregnanolone

Title of the Protocol:

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects With Severe Postpartum Depression and Adult Female Subjects with Moderate Postpartum Depression

Study Sites: Up to 100 global sites

Duration of Subject Participation: Up to 37 days

Primary Objective:

- To determine if SAGE-547 Injection infused intravenously for 60 hours at up to 90 μg/kg/h reduces depressive symptoms in subjects with severe postpartum depression (PPD) compared to placebo injection as assessed by the change from baseline in Hamilton Rating Scale for Depression (HAM-D) total score. This objective applies to both Parts A and B.

Secondary Objectives (unless otherwise specified, these objectives apply to Parts A, B, and C):

- To determine if SAGE-547 infusion at up to 60 μg/kg/h for 60 hours reduces depressive symptoms in subjects with severe PPD compared to placebo injection as assessed by the change from baseline in HAM-D total score. This objective applies to Part B.
- To determine if SAGE-547 Injection infused intravenously at up to 90 μg/kg/h for 60 hours reduces depressive symptoms in subjects with moderate PPD compared to placebo injection as assessed by the change from baseline in HAM-D total score. This objective applies to Part C.
- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms compared to placebo injection as assessed by HAM-D response, HAM-D remission, change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score, Clinical Global Impression – Improvement (CGI-I) response, and changes from baseline in HAM-D subscale and individual item scores.

- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces other mood symptoms compared to placebo injection as assessed by changes from baseline in the Generalized Anxiety Disorder 7-Item Scale (GAD-7) total score.
- To evaluate the safety and tolerability of SAGE-547 Injection compared with placebo as assessed by the incidence of adverse events (AEs), vital sign measurement, clinical laboratory evaluations, electrocardiogram (ECG) parameters, and the Columbia Suicide Severity Rating Scale (C-SSRS).

Other Objectives:

- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces subject-reported depressive symptoms compared to placebo injection as assessed by the change from baseline in Edinburgh Postnatal Depression Scale (EPDS) total score and the change from baseline in Patient Health Questionnaire (PHQ-9) total score.
- To determine if SAGE-547 Injection infused intravenously for 60 hours improves maternal behaviors compared to placebo injection as assessed by the change from baseline in Barkin Index of Maternal Functioning (BIMF) total and sub-scale scores.
- To determine if SAGE-547 Injection infused intravenously for 60 hours improves the general health status compared to placebo as assessed by the change from baseline in the Short Form-36 (SF-36) total score at Day 7 and Day 30.

Pharmacokinetic Objective:

To assess the pharmacokinetic (PK) profile of SAGE-547, metabolites of SAGE-547, and betadex sulfobutyl ether sodium (SBECD).

Study Design and Methodology:

This protocol comprises three multicenter, randomized, double-blind, parallel-group, placebo-controlled studies of the efficacy, safety, and PK of SAGE-547 Injection in adult female subjects diagnosed with severe or moderate PPD. Each study will be independently conducted, analyzed, and reported. In this protocol, Study 547-PPD-202A is hereafter referred to as Part A; Study 547-PPD-202B is hereafter referred to as Part B; and Study 547-PPD-202C is hereafter referred to as Part C. In Parts A and C, subjects will be randomized to one of two treatment groups (SAGE-547 90 µg/kg/hour or placebo) on a 1:1 basis. In Part B, subjects will be randomized to one of three treatment groups (SAGE-547 60 µg/kg/hour, SAGE-547 90 µg/kg/hour, or placebo) on a 1:1:1 basis. In each part, the continuous IV infusions of blinded study drug will increase and then taper. Subjects must remain as inpatients during the study Treatment Period, which is approximately 72 hours/3 days in duration (60 hours of treatment and an additional 12 hours for completion of 72-hour assessments). The Screening Period assessments may be conducted on an inpatient or an outpatient basis. The Follow-up Period assessments are conducted on an outpatient basis.

Screening Period: The Screening Period begins with the signature of the informed consent form (ICF). Eligibility is determined by applying the inclusion/exclusion criteria. The diagnosis of PPD must be by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). A full medical and family history will be taken from the subject, including recording of all depression, other Axis I and Axis II disorders, and postpartum depression episodes in primary probands.

Treatment Period: In Parts A and C, once subjects are confirmed as eligible for the study, they will be randomized to one of two treatment groups (SAGE-547 or placebo) on a 1:1 basis. Continuous intravenous (IV) infusions of blinded study drug will be administered, with a new bag hung at least

every 24 hours during the 60-hour infusion. Infusion rates will increase and then taper, with subjects in the SAGE-547 group receiving 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24-52 hours), followed by 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours). Placebo subjects will receive infusion rates equivalent to SAGE-547 90 µg/kg/hour. In Part B, once subjects are confirmed as eligible for the study, they will be randomized to one of three treatment groups (SAGE-547 60 µg/kg/hour, SAGE-547 90 µg/kg/hour, or placebo) on a 1:1:1 basis. For the 60 µg/kg/hour group, subjects will receive 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-56 hours), and 30 µg/kg/hour (56-60 hours). For the 90 µg/kg/hour group, subjects will receive 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24-52 hours), followed by 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours). Subjects in the placebo group will randomly receive infusion rates equivalent to either the 60 µg/kg/hour or 90 µg/kg/hour group. Parts B and C will run concurrently.

In all parts, subjects may be discharged after the 72-hour assessments have been completed (12 hours after completion of the study drug infusion). If their clinical condition does not allow discharge, normal standard of care will be employed in their ongoing management.

Initiation of benzodiazepines, narcotics, antibiotics, neuroleptics, and other anti-anxiety medications will not be allowed between screening and completion of the 72-hour assessments. Doses of psychotropics, which must have been initiated at least 14 days prior to screening, must remain at a stable dose until completion of the 72-hour assessments. If at the 72-hour assessment there has been no treatment response (HAM-D total score remains above 13), treatment with antidepressant medication may be optimized prior to discharge, and the subject may remain in the unit or be followed at an outpatient clinic, as clinically indicated.

Efficacy and safety assessments will be performed periodically during the study, and blood samples will be collected for analysis of SAGE-547, metabolites of SAGE-547, and SBECD concentrations, as outlined in the Schedule of Events (Table 1). Blood samples will be collected, and outcome measures will be obtained at pre-specified times over 72 hours during the Treatment Period.

Follow-up Period: For Part A, Follow-up Visits will be conducted one week (7±1 day), approximately two weeks (12±2 days), and one month (30±3 days) after the initiation of the study drug infusion. For Parts B and C, Follow-up Visits will be conducted one week (7±1 day), two weeks (14±2 days), three weeks (21±3 days), and one month (30±3 days) after the initiation of the study drug infusion. The blind will be maintained through the Follow-up period.

Number of Subjects:

Up to 32 subjects will be randomized in Part A, up to 120 subjects will be randomized in Part B, and up to 100 subjects will be randomized in Part C.

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 aged 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 breast feeding at screening, must agree to temporarily cease giving breastmilk to their infant(s) from just prior to receiving study drug through 9 days (Study Day 12) after the end of infusion.

6. Subject must have a negative pregnancy test at screening and Day 1 prior to the start of study drug infusion
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, as diagnosed by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)
8. For Part A and B, subject has a HAM-D total score of ≥26 at screening and Day 1 (prior to dosing). For Part C, subject has a HAM-D total score of ≥20 and ≤25 at screening and Day 1 (prior to dosing)
9. Subject is ≤6 months postpartum at screening
10. Subject is willing at screening to delay the start of any new pharmacotherapy regimens, including antidepressant or anti-anxiety medication, until the study drug infusion and 72-hour assessments have been completed; if the subject is taking psychotropic medications, these must be at a stable dose from 14 days prior to screening until the 72-hour assessments have been completed.
11. (Removed)
12. Subject must use one of the following methods of birth control during participation in the study and for 30 days following the end of the study drug infusion:
    - Total abstinence (no sexual intercourse)
    - Hormonal contraceptives (birth control) including birth control pills, implantable or injectable contraceptives (Norplant® or Depo-Provera®)
    - A barrier form of contraception such as a condom or occlusive cap with a spermicide
    - An intrauterine device

Exclusion Criteria:

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

1. Subject has renal failure requiring dialysis or fulminant hepatic failure or is anemic (hemoglobin ≤10 g/dL)
2. Known allergy to progesterone or allopregnanolone
3. Active psychosis per Investigator assessment
4. Attempted suicide associated with index case of postpartum depression
5. (Removed)
6. Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
7. History of active alcoholism or drug abuse (including benzodiazepines) in the 12 months prior to screening. A positive urine drug screen (except benzodiazepines under certain circumstances [see Section 10.3.3 and Section 11.1.2.6]) is exclusionary.
8. Exposure to another investigational medication or device within 30 days prior to screening
9. (Removed)
10. Subject has previously participated in this study or any other study employing SAGE-547
11. Administration of electroconvulsive therapy (ECT) within 14 days prior to screening and/or plans to administer ECT before the Study Day 7 Visit

Investigational Product, Dosage, and Mode of Administration:

SAGE-547 Injection, IV administration: SAGE-547 Injection is a sterile, clear, colorless 5 mg/mL solution of SAGE-547 (allopregnanolone) and 250 mg/mL SBECD buffered with 10 mM citrate at a pH of 6.0, supplied in single-use 20 mL vials for IV administration. As supplied, SAGE-547 Injection, which is hypertonic, requires further dilution with Sterile Water for Injection (SWFI) to render it isotonic for IV infusion. The specific infusion dose of SAGE-547 Injection will be calculated based on weight for each subject at screening and administered according to the randomization schedule. Infusion bags will be changed at least every 24 hours. Details about the preparation and administration of the study drug infusions will be included in the Pharmacy Manual.

Part A and Part C:

	Infusion Rate (μg/kg/hour)				
SAGE-547 Dose	**Day 1 0-4 hours**	**Day 1 4-24 hours**	**Day 2-3 24-52 hours**	**Day 3 52-56 hours**	**Day 3 56-60 hours**
90 μg	30	60	90	60	30

Part B:

	Infusion Rate (μg/kg/hour)				
SAGE-547 Dose	**Day 1 0-4 hours**	**Day 1 4-24 hours**	**Day 2-3 24-52 hours**	**Day 3 52-56 hours**	**Day 3 56-60 hours**
60 μg	30	60	60	60	30
90 μg	30	60	90	60	30

Reference Therapy, Dosage, and Mode of Administration:

An identical placebo IV infusion will be prepared for IV administration consisting of the same formulation without allopregnanolone. For each part of the study, the placebo infusion rate will match that of the SAGE-547 rate(s) used in that part.

Randomization:

Randomization will be stratified by antidepressant use at baseline and will follow the computer-generated randomization schedule. Subjects will be randomized within stratum to receive SAGE-547 Injection or placebo; subjects, clinicians, and study team will be blinded to treatment allocation. The pharmacist, who will prepare the infusion bags according to the randomization schedule, will be unblinded. In Parts A and C, the infusion rates are the same for all subjects within a particular dosing period (0-4 hours, 4-24 hours, etc.) regardless of randomized treatment. In Part B, the infusion rates will vary according to the randomized dose group.

Criteria for Evaluation:

Primary Endpoint

The primary outcome measure will be the 17-item Hamilton Rating Scale for Depression (HAM-D). The HAM-D will be administered before, during, and after the infusion of blinded study drug. The HAM-D total score will be calculated as the sum of the 17 individual item scores. The change from baseline in HAM-D total score at +60 hours will be the primary efficacy endpoint with comparison between the SAGE-547 and placebo treatment groups used to evaluate the efficacy of SAGE-547 in treating the depressive symptoms of PPD.

For Part A and Part C, the primary comparison will be between 90 µg SAGE-547 and placebo at the 60-hour assessment. For Part B, the primary comparison will be between 90 µg SAGE-547 and placebo at the 60-hour assessment; if this comparison is significant at the 0.05 level, then the 60 µg group will be compared to placebo at the 0.04 level of significance. More details will be provided in the statistical analysis plans (SAPs) regarding strong control of overall level of significance for multiple testing, including testing of key secondary endpoints.

Secondary Endpoints

The change from baseline in HAM-D total score at Day 30 will be included in the secondary endpoints. Additional measures of depressive symptom severity will be administered, including the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinical Global Impression (CGI) scale. Total scores and changes from baseline will be calculated where applicable. Changes from baseline at +60 hours and other time points will be evaluated as secondary efficacy endpoints with comparisons between the two treatment groups used to support the efficacy of SAGE-547 in treating the depressive symptoms of PPD. In addition to the above scales, the individual item scores and subscale scores from the HAM-D scale will also evaluated as secondary efficacy endpoints. GAD-7 will also be administered, and scores from these scales will be evaluated to assess the efficacy in other mood disorder and anxiety symptoms.

Safety and tolerability of SAGE-547 Injection will be evaluated by summarization of AEs by frequency, severity, and seriousness; clinical laboratory measures, vital signs, and ECGs (including changes from baseline); and concomitant medication usage. Suicidality will be monitored using the C-SSRS.

The doses of all anti-depressant medications will be recorded throughout the study. No changes and/or additions to antidepressant or anxiolytic medicine will be allowing during the dosing period. An analysis of time to starting/increasing the dose/decreasing the dose of each different anti-depressant medication will be undertaken for subjects discharged.

Plasma will be collected to assay for concentrations of SAGE-547, SAGE-547 metabolites, and SBECD. The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve (AUC) from time zero to 60 hours ($AUC_{0\text{-}60}$), AUC from time zero to infinity (AUC_{∞}), maximum (peak) plasma concentration (C_{max}), time at maximum (peak) plasma concentration (t_{max}), steady-state drug concentration in the plasma during constant-rate infusion (C_{ss}), and average drug concentration in the plasma at steady state during a dosing interval (C_{avg}).

Other Endpoints

Additional measures of symptoms and function related to the current episode of postpartum depression severity will be administered, including the EPDS, PHQ-9, BIMF, and SF-36.

Subscale and total scores and changes from baseline will be calculated where applicable. Changes from baseline at +60 hours and other time points will be evaluated as secondary efficacy endpoints with comparisons between the two treatment groups used to support the efficacy of SAGE-547 in treating the depressive symptoms of PPD. In addition to the above scales, the individual item scores will also be evaluated as other endpoints.

Statistical Methods:

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 infusion.

Interim Analysis

In Part A, an interim analysis will be conducted by an independent statistician for sample size re-estimation purposes when at least 16 subjects have completed efficacy assessments through 60 hours. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis for sample size re-estimation will be included in the statistical analysis plan.

There will be no interim analysis for Parts B or C.

Sample Size Calculation

Using a two-sided t-test at an alpha level of 0.05, a sample size of 10 evaluable subjects per group for Part A would provide 70% power to detect an effect size of 1.2 between the SAGE-547 and placebo groups with regard to the primary outcome variable of change from baseline in HAM-D total score. An effect size of 1.2 corresponds to a placebo-adjusted difference of 12 points in the change from baseline in HAM-D total score at 60 hours with an assumed standard deviation of 10 points. By including two treatment groups and using a 1:1 randomization ratio, a total of 20 evaluable subjects are required for Part A.

Based on the results of the interim analysis, the sample size in Part A could be increased to a maximum of 32 randomized subjects. This adjustment to the sample size would allow for an effect size of 1.0 to be detected.

For Part B, a sample size of 40 evaluable subjects per group (120 total) would provide 90% power to detect a treatment difference of 9.0 between the SAGE-547 and placebo groups and a common standard deviation of 12 points (for an effect size of 0.75) using a two-sided t-test at an alpha level of 0.05.

For Part C, a sample size of 50 evaluable subjects per group (100 total) would provide 90% power to detect a treatment difference of 8.0 between the SAGE-547 and placebo groups and a common standard deviation of 12 points (for an effect size of 0.667) using a two-sided t-test at an alpha level of 0.05.

Efficacy Analysis

The Efficacy Population will include all subjects who start the infusion of study drug and have a valid baseline HAM-D assessment and at least one post-baseline HAM-D assessment. Subjects will be classified and summarized by randomized treatment. Separate summaries will be produced for each part of the study.

For efficacy analysis purposes, centers with fewer than 15 subjects per center for Part B or 10 subjects per center for Part C will be pooled within regions (eg, North America region centers will be pooled separately those in Europe). For each part, the change from baseline in HAM-D total score will be analyzed using a mixed effects model for repeated measures; the model will include center (pooled), treatment, baseline score, visit time point, and visit time point-by-treatment terms as explanatory variables. Center and all other explanatory variables will be treated as fixed effects. The primary comparison between each SAGE-547 dose and placebo will be at the 60-hour time point. Comparisons at other time points, including the Day 30 time point, will be conducted to support the findings for the primary comparison. To account for multiple testing in Part B, (90 µg vs placebo and 60 µg vs placebo), the 90 µg group will be compared to placebo first. If this dose comparison is significant at the 0.05 level, then the 60 µg group will be compared to placebo at the 0.04 level. More details will be provided in the SAPs regarding strong control of overall level of significance for multiple testing, including testing of key secondary endpoints.

Changes from baseline in other rating scale scores will be analyzed with methods similar to the primary endpoint. Dichotomous response variables will be analyzed using Generalized Estimating Equation (GEE) method for repeated binary responses.

In addition to formal analysis, efficacy rating scale scores (including recorded and change from baseline values) will be summarized by descriptive statistics, including n, mean, standard deviation (SD), median, and minimum and maximum values. Categorical efficacy endpoints (including HAM-D, MADRS, and CGI-I response variables) will be summarized by frequency and percentage.

Safety Analysis

The Safety Population is defined as all randomized subjects who start the infusion of study drug. Subjects will be classified and summarized by actual treatment. Separate summaries will be produced for each part of the study.

Safety will be assessed using AEs, vital signs, ECG, clinical laboratory tests, C-SSRS, and concomitant medication data. Continuous safety data (including absolute and change from baseline values) will be summarized by descriptive statistics, including n, mean, standard deviation (SD), median, and minimum and maximum values. Categorical endpoints will be summarized by frequency and percentage.

Safety data will be examined for possible relationships between subject characteristics and plasma allopregnanolone concentrations, as appropriate.

Table 1: Schedule of Events

Visit Days / Hours	Screening Period	Treatment Period Clinic Period (Day 1 to Day 3)															Follow-up Period			
	Screening D-7[a] to -1	D1 H0*	D1 H2	D1 H4	D1 H8	D1 H12	D1 H18	D1 H24	D2 H30	D2 H36	D2 H42	D2 H48	D3 H54	D3 H60	D3 H66	D3 H72	D7/ET (±1d)	D14[a] (+2d)	D21[a] (+3d)	D30 (±3d)
Study Procedure																				
Informed Consent	X																			
Inclusion/Exclusion Criteria	X	X																		
Randomization		X																		
Demographics	X																			
Medical/Family History	X																			
Physical Examination	X															X	X			
Body Weight/Height	X																			
Clinical Lab[b] Assessments	X															X	X			
Urinalysis[b]	X																X			
Drug & Alcohol Screen[c]	X	X																		
Pregnancy Test[d]	X	X																		X
Genetic Sample[e]	O																			
Vital Signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
12-Lead ECG[g]	X											X					X			
C-SSRS[h]		X						X						X		X	X	X	X	X
Confinement		X																		
CGI-I[i]			X	X		X		X		X		X		X		X	X	X	X	X
CGI-S	X	X																		
SCID-I	X																			
HAM-D[i]	X	X	X	X	X	X		X		X		X		X		X	X	X	X	X
MADRS[i]	X	X						X				X		X		X	X	X	X	X
BIMF[i]		X															X	X	X	X

Visit Days / Hours	Screening Period	Treatment Period Clinic Period (Day 1 to Day 3)															Follow-up Period			
	Screening D-7[a] to -1	D1 H0*	D1 H2	D1 H4	D1 H8	D1 H12	D1 H18	D1 H24	D2 H30	D2 H36	D2 H42	D2 H48	D3 H54	D3 H60	D3 H66	D3 H72	D7/ET (±1d)	D14[a] (+2d)	D21[a] (+3d)	D30 (±3d)
Study Procedure																				
EPDS[i]		X												X			X	X	X	X
GAD-7[i]		X												X			X	X	X	X
PHQ-9[i]		X												X			X	X	X	X
SF-36 (acute version)		X															X	X	X	X
HCRU	X	X																		
Plasma PK[j]		X		X	X	X		X	X	X		X		X		X				
Instructions for Lactating Subjects[k]		X							X				X							
Study Drug Infusion		X																		
Adverse Events	X																			
Prior/Concomitant Medications[l]	X																			

BIMF = Barkin Index of Maternal Functioning; CGI-I = Clinical Global Impression of Improvement; C-SSRS = Columbia Suicide Severity Rating Scale; D = Day; ECG = electrocardiogram; EPDS = Edinburgh Postnatal Depression Scale; GAD-7 = Generalized Anxiety Disorder 7-Item Scale; HAM-D = Hamilton Rating Scale for Depression, 17-item; HCRU = Health Care Resource Utilization; MADRS = Montgomery-Asberg Depression Rating Scale; PHQ-9 = Patient Health Questionnaire; PK = pharmacokinetic; SF-36 = Short Form-36; SCID-I = Structured Clinical Interview for DSM-IV Axis I Disorders.
O = optional; * = All H0 procedures to be completed prior to dosing

[a] The screening period for Part A is from Day -5 to Day -1. Follow-up Visits for Part A are on Days 7, 12, and 30.
[b] Safety laboratory tests will include hematology, serum chemistry, coagulation, and select hormone parameters. The urine test will include a urinalysis. Lab assessments are to be completed within ±30 minutes of the scheduled time point.
[c] Urine for selected drugs of abuse and alcohol (serum or breath)
[d] Serum at screening and urine for all other time points; lactation status (ie, subject is breastfeeding, subject is lactating but not breastfeeding, or subject is not lactating) will be recorded at screening
[e] A blood sample for genetic testing, where consent is given
[f] Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). Vital signs will be obtained within ±30 minutes of the scheduled time point, unless the subject is asleep between the hours of 23.00h and 06.00h.
[g] Performed within ±30 minutes of the scheduled time point on Day 2.
[h] The "Baseline/Screening" C-SSRS form will be completed on Day 1. The "Since Last Visit" C-SSRS form will be completed at all subsequent time points.
[i] To be completed within ±30 minutes of the scheduled time point during the Treatment Period.

[j] Blood samples for PK analysis will be collected at pre-infusion and at 4 (before change in infusion rate, if applicable), 8, 12, 24 (before change in infusion rate, if applicable), 30, 36, 48, 60 (before end of infusion), and 72 hours after the start of the infusion. PK blood draws after the start of infusion will have a window of ±10 minutes. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.

[k] Breast milk will be pumped and discarded by subjects who are lactating. On Day 3, subjects who are lactating will be reminded that they must continue to pump and discard breast milk through Day 12 of the study.

[l] To include those taken within 60 days prior to signing the informed consent through the Day 30 visit.

Note: In Part A only, SSS is completed within ±15 minutes of each time point through the 72-hour assessments, unless the subject is asleep between 23.00h and 06.00h.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALLO	allopregnanolone
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{∞}	area under the concentration-time curve from time zero to infinity
AUC_{0-60}	area under the concentration-time curve from time zero to 60 hours
BIMF	Barkin Index of Maternal Functioning
BMI	body mass index
BUN	blood urea nitrogen
C_{avg}	average drug concentration in the plasma at steady-state during a dosing interval
CBC	complete blood count
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression–Improvement
CGI-S	Clinical Global Impression–Severity
cGMP	Current Good Manufacturing Practice
C_{max}	maximum (peak) plasma concentration of the drug
CNS	central nervous system
CRF	case report form
CS	clinically significant
CSF	cerebrospinal fluid
CSR	clinical study report
C_{ss}	steady-state drug concentration in the plasma during constant-rate infusion
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EEG	electroencephalography
EFF	Efficacy Population
Ph. Eur.	European Pharmacopeia
EPDS	Edinburgh Postnatal Depression Scale
ERα	estrogen receptor alfa

Abbreviation	Definition
ERß	estrogen receptor beta
ET	early termination
GABA	gamma-aminobutyric acid
$GABA_A$	gamma-aminobutyric acid–gated chloride channel
GAD-7	Generalized Anxiety Disorder 7-Item Scale
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
GGT	gamma glutamyl transferase
h	hour
HAM-D	Hamilton Rating Scale for Depression, 17-item
hCG	human chorionic gonadotropin
HCRU	Healthcare Resource Utilization
Hct	hematocrit
HEENT	head, eyes, ears, nose, and throat
Hgb	hemoglobin
ICF	informed consent form
ICH	International Council on Harmonisation
ID	identification
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	intravenous
MADRS	Montgomery-Asberg Depression Rating Scale
MCH	mean corpuscular hemoglobin
MCS	mental component summary
MCV	mean corpuscular volume
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
NCS	not clinically significant
PCS	physical component summary
PHQ-9	Patient Health Questionnaire
PK	pharmacokinetic(s)
PKP	Pharmacokinetic Population
PMID	PubMed identification
PP	Per-Protocol Population
PPD	postpartum depression

Abbreviation	Definition
PR	progesterone receptor
PT/INR	prothrombin time/international normalized ratio
RBC	red blood cell
RSE	refractory status epilepticus
SAE	serious adverse event
SAP	statistical analysis plan
SBECD	betadex sulfobutyl ether sodium
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SD	standard deviation
SF-36	Short Form-36
SOC	system organ class
SOP	standard operating procedure
SRSE	super refractory status epilepticus
SSRI	selective serotonin reuptake inhibitors
SSS	Stanford Sedation Scale
SWFI	sterile water for injection
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximum (peak) plasma concentration
TSH	thyroid stimulating hormone
US	United States
USP	United States Pharmacopeia
VAS	visual analogue scale
V_d	volume of distribution
WBC	white blood cell

4. INTRODUCTION AND RATIONALE

This study is designed to evaluate the efficacy, safety, and pharmacokinetics (PK) of SAGE-547 (allopregnanolone) as a treatment for women with severe or moderate postpartum depression (PPD), an area of high unmet medical need.

PPD is considered to be moderate to severe depression in women who have recently given birth, otherwise defined as the occurrence of major depressive disorder (MDD) within 4 weeks of delivery (DSM-V 2013) or up to a year after giving birth (Okun 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-V 2013), although this diagnosis may be confounded by the relative frequency of symptoms such as sleep disturbance or appetite problems in pregnant and postpartum women. 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).

During pregnancy, estradiol and progesterone levels increase dramatically but then rapidly decline in the acute postpartum period (Gavin 2005). The onset of PPD symptoms coincides with the rapid decrease of the gonadal steroids postpartum. The duration of a PPD episode has been estimated as shorter than depressive episodes in the general population (approximately 5 months), while other studies indicate time to remission is approximately the same (Chaudron 2003).

PPD is common and has devastating consequences for the woman and for her family (Fihrer 2009, Verbeek 2012). Perinatal depression is reported to be the most underdiagnosed obstetric complication in America (Earls 2010). Furthermore, it is the most common psychiatric illness to occur in the puerperium (O'Hara 2014). A meta-analysis of 30 studies (Gaynes 2005) found that the point prevalence of major and minor depression ranged between 6.5% and 12.9% at different times during the first postpartum year. Overall incidence is estimated at around 15% to 20% with up to 10% being considered severe (Edge 2007, O'Hara 2014).

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 non-pharmacological 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.

4.1. Role of Allopregnanolone in Affective Disturbances

The neurosteroid metabolite of progesterone, allopregnanolone, acutely regulates neuronal function (Gangisetty 2010) and appears to play a significant role in affective disturbances that occur with changes in reproductive endocrine function, such as during the postpartum period (Amin 2006, Nappi 2001, Epperson 2006).

Neurosteroids are metabolites of cholesterol-derived steroid hormones that are synthesized in the brain and nervous system; they modulate the major inhibitory and excitatory central nervous system (CNS) neurotransmitter systems: γ-aminobutyric acid (GABA) and glutamate, respectively. Neurosteroids are among the most potent and effective modulators of $GABA_A$ receptors and augment GABAergic inhibition (Belelli 2005). The powerful anxiolysis that accompanies this potentiation of $GABA_A$ receptors has led to the speculation that neurosteroid dysregulation plays a central role in the etiology of affective disorders, including reproductive mood disorders, such as PPD (Amin 2006).

There is increasing evidence supporting the role of neurosteroids in affective dysregulation. Allopregnanolone and pregnanolone have been shown to modulate the GABA receptor positively (Majewska 1986). Several groups have demonstrated decreased allopregnanolone levels in MDD, with an increase seen in both plasma and cerebrospinal fluid (CSF) following successful antidepressant treatment (Uzunova 1998, Romeo 1998, Ströhle 1999, Schüle 2006, Eser 2006, Schüle 2007). In addition, allopregnanolone has demonstrated anxiolytic effects in several animal anxiety models (Bitran 1991; Wieland 1991; Bitran 1993).

Allopregnanolone may also exert antidepressant effects by reducing the physiological impact of stress, promoting neuroprotection, and protecting against the pro-inflammatory immune activation and cytokine hypersecretion associated with MDD. In animals, allopregnanolone increases in response to stress, reduces pain sensitivity, and is thought to restore physiologic homeostasis following stress (Frye 1994, Morrow 1995). Allopregnanolone also exerts neuroprotective effects by reducing the expression of pro-apoptotic proteins and apoptotic DNA fragmentation (Djebaili 2005, Sayeed 2009), thereby reducing the cell death and gliosis associated with depression (Glantz 2010, Shelton 2011). Neuroprotection is mediated by immune regulation in depression (Licinio 1999), and allopregnanolone reduces the expression of the pro-inflammatory cytokine TNF-α (He 2004), which is elevated in depressed individuals (Dowlati 2010). Thus, allopregnanolone modulates biological processes dysregulated in MDD.

4.1.1. Rationale for Allopregnanolone Treatment of PPD

Genetic susceptibility to affective dysregulation may be unmasked during periods of reproductive hormone change such as during pregnancy and postpartum (Maguire 2008). Maguire and Mody demonstrated that a GABA receptor subunit mutation was behaviorally silent until the animal was exposed to pregnancy and the postpartum state, at which time the dams showed depressive-like behaviors and cannibalized their offspring (Maguire 2008). During pregnancy, the expression of the $GABA_A$ receptor δ-subunit is down-regulated as

allopregnanolone levels increase, and at parturition, the expression of the $GABA_A$ receptor δ-subunit is recovered in response to rapidly declining neurosteroid levels (Maguire 2009). In contrast, the $GABA_A$ receptor δ-subunit-deficient mice fail to adapt to the dramatic changes in allopregnanolone and experience depression-like and anxiety-like behavior and abnormal maternal behaviors, which are reversed by administration of allopregnanolone (Maguire 2008). This model provides compelling support for the hypothesis that changes in neurosteroid concentrations during pregnancy and postpartum are capable of provoking affective dysregulation, particularly in those with a genetically-determined susceptibility. The capacity of changes in neurosteroids, such as allopregnanolone, to function as behavioral switches suggests a potentially important treatment role of this hormone metabolite in reproductive endocrine-related mood disorders such as PPD.

The onset of PPD symptoms coincides with the rapid decrease of the gonadal steroids postpartum and has been reproduced in a pivotal clinical study (Bloch 2000). The authors investigated the possible role of changes in gonadal steroid levels in PPD by simulating 2 hormonal conditions related to pregnancy and parturition in euthymic women, 8 with and 8 without a history of PPD. They induced hypogonadism with leuprolide, adding back supra-physiologic doses of estradiol and progesterone for 8 weeks to simulate pregnancy. They then withdrew both steroids under double-blind conditions to mimic the rapid decrease of sex steroids upon delivery. Five of the 8 women with a history of postpartum depression (62.5%) and 0% of the comparison group developed significant mood symptoms typical of PPD during the withdrawal period.

Although progesterone levels were measured in this study, allopregnanolone was not. However, since allopregnanolone is the major active metabolite of progesterone, it can be assumed that the decrease in progesterone would cause a similar precipitate drop in allopregnanolone levels, as observed in the postpartum period (Gilbert Evans 2005, Paoletti 2006, Nappi 2001). These data provide direct evidence in support of the involvement of progesterone and its metabolites in the development of postpartum depression in a subgroup of women. Further, they suggest that women with a history of postpartum depression are differentially sensitive to mood-destabilizing effects of gonadal steroids (Bloch 2000).

Additional details regarding the role of allopregnanolone in the etiology of affective disorders and its nonclinical pharmacology and PK are presented in the Investigator's Brochure.

4.2. SAGE-547 Injection (Allopregnanolone)

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex, and CNS (Holzbauer 1985, Ottander 2005, Paul 1992). Allopregnanolone is a metabolite of progesterone created by the actions of 5-α reductase and 3-α hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic $GABA_A$ receptors.

SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), United States Pharmacopeia (USP), and 250 mg/mL betadex sulfobutyl ether sodium buffered with 10 mM citrate at a pH of 6.0, and will be administered intravenously. SAGE-547 Injection is also being developed for the treatment of adult patients with

refractory status epilepticus (RSE), inclusive of super refractory status epilepticus (SRSE), who have not responded to standard treatment regimens, and investigated for the treatment of adults with essential tremor.

4.3. Summary of Nonclinical and Clinical Experience with SAGE-547

4.3.1. Nonclinical Pharmacology

The primary pharmacological effects of allopregnanolone or SAGE-547 are described earlier in the rationale (Section 4.1 and Section 4.1.1). Secondary pharmacologic effects comprise mainly the binding and consequent increased activity of steroid hormone receptors (androgen receptor [(AR], progesterone receptor [PR], and estrogen receptor beta [ERß]), with some evidence of inhibition at the highest doses (AR and estrogen receptor alfa [ERα]). These non-target effects may yield some adverse events (AEs) in the clinic.

Nonclinical toxicology studies largely illustrate the sedative and anesthetic effects of allopregnanolone and/or SAGE-547 at higher equivalent doses than the proposed dose for the current study. PK data in animals indicate a short half-life ($t_{½}$) and rapid clearance with a moderate volume of distribution and cerebral levels higher than plasma. Refer to the SAGE-547 Investigator's Brochure for more details.

4.3.2. Clinical Experience

The clinical PK data with intravenous (IV) administration of allopregnanolone in healthy women, men, and women on oral contraceptives confirmed the PK observations in animals of C_{max} achievable at approximately third trimester levels (150 nM), rapid clearance and moderate volume of distribution (V_d). Refer to the SAGE-547 Investigator's Brochure for more details.

An open-label, proof-of-concept study (547-PPD-201) evaluating the safety, tolerability, PK, and efficacy of SAGE-547 Injection in the treatment of adult female subjects with severe postpartum depression was started in 2014. This was the first study in this indication. Four women experienced significant improvement in depressive symptoms within 24 hours after administration of open-label IV SAGE-547. During the SAGE-547 Treatment Period, all four subjects rapidly achieved remission, as measured by the HAM-D total score. All four subjects also demonstrated consistent improvement as measured by the CGI-I score. SAGE-547 was well-tolerated in all subjects treated with no serious adverse events (SAEs) observed during therapy or during the 30-day Follow-up Period. A total of 14 AEs were reported in four subjects. The only AE reported in more than one subject was sedation, observed in two subjects. This study was initially planned to enroll ten women; however, due to the observed clinical activity, Study 547-PPD-201 was stopped early with the plan to initiate a placebo-controlled clinical study as rapidly as possible.

There are six reported studies of allopregnanolone, mainly in healthy individuals and none in PPD (Timby 2006, Timby 2011a and 2011b, van Broekhoven 2007, Kask 2008, Kask 2009, Navarro 2003). Data indicate that normal physiological allopregnanolone levels in women vary during the menstrual cycle up to a maximum of 6 to 10 nM, with lower levels present post-menopause (Genazzani 1998). The highest physiological levels observed are in the

third trimester of pregnancy, up to around 160 nM at time of delivery (Luisi 2000). Levels drop precipitously to baseline (<10 nM) with removal of the placenta (Klak 2003).

One study demonstrated subjective improvements in contentedness in women (van Broekhoven 2007). The clinical safety data are presented below in the Risks and Benefits section (Section 4.4).

4.4. Potential Risks and Benefits

In the open-label clinical study of SAGE-547 in PPD (547-PPD-201), a total of 14 AEs were reported in four subjects. The only AE reported in more than one subject was sedation, observed in two subjects.

In the recently completed 547-PPD-202A, there were no SAEs or discontinuations due to AEs. Out of 10 subjects who received SAGE-547, four reported AEs, and of 11 subjects who received placebo, eight reported AEs (Table 2). Three subjects in each treatment group reported dizziness, sedation or somnolence. Psychiatric disorder AEs, including abnormal dreams, insomnia and anxiety, were all reported in the group that received placebo. Three subjects in the placebo group and one in the SAGE-547 group reported nausea. Other AEs reported by more than one subject were infusion site pain and headache, all reported on placebo. One subject did not tolerate 60 µg/kg/hour due to sedation, thought to be associated with concomitant administration of a high dose of benzodiazepine, so the dose was reduced to 30 µg/kg/hour from 12 to 24 hours. The subject received 60 µg/kg/hour from 24 to 30 hours and 30 µg/kg/hour from 30 to 60 hours and completed the study.

Table 2: Adverse Events That Occurred in More than One Subject

	Placebo (n=11)		SAGE-547 (n=10)	
	No. of Subjects[a] n (%)	No of Events	No. of Subjects[a] n (%)	No of Events
Subjects with at least 1 TEAE	8 (72.7)	23	4 (40.0)	17
Dizziness	3 (27.3)	3	2 (20.0)	3
Somnolence	--	--	2 (20.0)	3
Nausea	3 (27.3)	3	1 (10.0)	1
Infusion Site Pain	2 (18.2)	3	--	--
Headache	2 (18.2)	2	--	--
Abnormal Dreams	2 (18.2)	2	--	--
Insomnia	2 (18.2)	2	--	--

Source: 547-PPD-202A, Table 14.3.2.2

[a] Subjects who have more than 1 AE per preferred term are counted only once

Consistent with these observations, published reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, vertigo, mild nausea, impaired episodic memory, and mild headache (Timby 2006, 2011a, and 2001b; van Broekhoven 2007). One subject experienced what was potentially a withdrawal effect, an anxiety attack (Timby 2011b). No

SAEs were reported in the six clinical studies conducted to date (Timby 2006, Timby 2011a and 2011b, van Broekhoven 2007, Kask 2008, Kask 2009, Navarro 2003).

There is also a potential risk of synergistic sedative effects with other drugs interacting with the $GABA_A$ receptor, such as benzodiazepines and anti-epileptic medications (Norberg 1999); therefore, the Investigator is advised to avoid co-medication if possible and to exercise caution with these drug classes.

In 547-PPD-202A, the primary endpoint of the mean change from baseline in HAM-D total score at 60 hours compared with placebo [LS mean treatment difference of 12.2] was highly significant (p=0.008). In addition, the significant separation between the active and placebo groups was evident at 24 hours, and remained so at subsequent time points through 72 hours, 7 days, and 30 days after initiation of treatment.

In view of the limited nature of the demonstrated risks of exogenous allopregnanolone infusion and the potential for benefit in PPD, there is a favorable benefit-risk evaluation for the continued conduct of the present study.

4.5. Study No. 547-PPD-202

4.5.1. Study Population

This study will evaluate the efficacy, safety, and PK of SAGE-547 Injection in the treatment of adult female subjects diagnosed with severe or moderate postpartum depression.

Parts A and B of this study will study women with severe PPD, and Part C will study women with moderate PPD (Parts B and C will run concurrently). Moderate severity level will be studied because the pathogenesis of severe postpartum depression may not be generalized to those patients with a less severe form of illness. For example, outside of postpartum depression, findings suggest that patient's treatment-resistant depression may respond more favorably to certain pharmacotherapy options such as ketamine (Coyle 2015). Therefore, in order to determine the efficacy of SAGE-547 in women with less severe levels of symptoms, a separate group with moderate PPD with the same doses of the study drug used in the severe group will be investigated.

4.5.2. Route of Administration, Dosage, Dosage Regimen, and Treatment Period

SAGE-547 Injection or placebo will be administered over a 60-hour period by an IV infusion according to the dose regimens shown in Table 3 and Table 4 (see Section 10.1.1).

The specific infusion dose of SAGE-547 Injection will be calculated based on weight for each subject. Infusion bags will be changed at least every 24 hours. Details about the preparation and administration of the study drug infusions will be included in the Pharmacy Manual.

4.5.3. Dose Rationale

The infusion rate of SAGE-547 to be studied in Parts A and C of this study was chosen to achieve a mean exposure of 150 nM, roughly equivalent to the highest endogenous concentrations measured in third trimester pregnancy at approximately 157 nM (Luisi 2000). Since pregnant women tolerate this level without apparent AEs, 150 nM was selected as the

target exposure for this study. This level of exposure has already been achieved in Study 547-PPD-201 as well at higher levels in a study in subjects with essential tremor (Study 547-ETD-201) and subjects with super refractory status epilepticus (Study 547-SSE-201), with no drug-related SAEs reported. Since the most common AE in 547-ETD-201 was sedation, dose adjustment rules are included in this protocol to ensure that all subjects can remain on treatment for 60 hours. A similar C_{max} was also achieved in several other studies conducted with IV allopregnanolone (Timby 2011b), with excellent tolerability (see the current SAGE-547 Investigator's Brochure for details of safety profile).

The selection of exposure in the current study is based on a cautious approach adapted to the anticipated benefit-risk in the PPD patient population, and on previous experience from the ongoing clinical studies of SAGE-547 in adult subjects with SRSE (Study 547-SSE-201) and of SAGE-547 in female subjects with PPD (Study 547-PPD-201). In the ongoing SRSE study, as determined by simulation, loading and maintenance infusions are required to achieve the target exposure. In contrast, in the current study, subjects will instead begin treatment with a 4-hour dose-titration phase. The starting dose is approximately 9- to 18-fold lower than the no observed adverse effect level (NOAEL) observed in rats and dogs, although this is not the first in human study. In Parts A and C, doses will be increased as follows: 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24-52 hours), followed by a decrease to 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours).

In Part B, a lower target dose will also be explored (ie, 60 µg/kg/hour). The use of this dose is based on observations in the open-label 547-PPD-201 study in which subjects achieved substantial improvements in their HAM-D scores within the first 12 hours of the SAGE-547 infusion. In this study, subjects received a dose of 21.5 µg/kg/h for the first 4 hours, then 43 µg/kg/h for the next 4 hours, and then 64.5 µg/kg/h for the following 4 hours before receiving the target dose of 86 µg/kg/h at 12 hours. Therefore, the 12-hour data from 547-PPD-201 suggests that SAGE-547 at target doses of 60 µg/kg/h may also be efficacious in reducing depressive symptoms associated with PPD.

Subjects will be treated in an inpatient setting and continually monitored for safety, and if any severe tolerability issues arise, the infusion may be terminated or the infusion rate reduced. The protocol includes a formal dose interruption and reduction scheme based on the occurrence of intolerable AEs.

5. ETHICS

5.1. Institutional Review Board or Independent Ethics Committee

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an Institutional Review Board (IRB) or Independent Ethics Committee (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 or IEC 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.

5.2. Ethical Conduct of the Study

This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and the most recent amendment (2008).

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol, and must also conduct the study in accordance with International Council on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP) standards as well as local regulations.

5.3. Subject Information and Informed Consent

Prior to subject participation in the study, written informed consent must be obtained from each subject according to ICH GCP and in accordance with local regulations. Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests, SAGE-547 infusion, and study evaluations. Each subject's signature must be dated by each signatory and the informed consent form (ICF) retained by the investigator as part of the study records. As an additional assessment, the ICF will contain provisions for optional consent for the collection of blood for genetic testing during screening. The ICF, as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the CFR, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject a copy of the signed and dated ICF. The ICF for subject participation must also be available as part of the subject's file for review by the site's dedicated study monitor.

All ICFs used in this study must be approved by the appropriate IRB/IEC and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB/IEC and the Sponsor.

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objective of this study is to determine if SAGE-547 Injection infused intravenously for 60 hours at up to 90 µg/kg/h reduces depressive symptoms in subjects with severe PPD compared to placebo injection as assessed by the change from baseline in HAM-D total score. This objective applies to both Parts A and B.

6.2. Secondary Objectives

The secondary objectives of the study apply to Parts A, B, and C unless otherwise stated, and are:

- To determine if SAGE-547 infusion at up to 60 µg/kg/h for 60 hours reduces depressive symptoms in subjects with severe PPD compared to placebo injection as assessed by the change from baseline in HAM-D total score (applies to Part B only).
- To determine if SAGE-547 Injection infused intravenously at up to 90 µg/kg/h for 60 hours reduces depressive symptoms in subjects with moderate PPD compared to placebo injection as assessed by the change from baseline in HAM-D total score (applies to Part C only).
- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms compared to placebo injection as assessed by HAM-D response, HAM-D remission, change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score, Clinical Global Impression – Improvement (CGI-I) response, and changes from baseline in HAM-D subscale and individual item scores
- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces other mood symptoms compared to placebo injection as assessed by changes from baseline in the Generalized Anxiety Disorder 7-Item Scale (GAD-7) total score
- To evaluate the safety and tolerability of SAGE-547 Injection compared with placebo as assessed by the incidence of AEs, vital sign measurement, clinical laboratory evaluations, electrocardiogram (ECG) parameters, and the Columbia Suicide Severity Rating Scale (C-SSRS)

6.3. Other Objectives

The other objectives of the study are:

- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces subject-reported depressive symptoms compared to placebo injection as assessed by the change from baseline in Edinburgh Postnatal Depression Scale (EPDS) total score and the change from baseline in Patient Health Questionnaire (PHQ-9) total score

- To determine if SAGE-547 Injection infused intravenously for 60 hours improves maternal behaviors compared to placebo injection as assessed by the change from baseline in Barkin Index of Maternal Functioning (BIMF) total and sub-scale scores
- To determine if SAGE-547 Injection infused intravenously for 60 hours improves the general health status compared to placebo as assessed by the change from baseline in the Short Form-36 (SF-36) total score at Day 7 and Day 30

6.4. Pharmacokinetic Objective

The PK objective of the study is:

- To assess the PK profile of SAGE-547, metabolites of SAGE-547, and betadex sulfobutyl ether sodium (SBECD)

7. INVESTIGATIONAL PLAN

7.1. Overview of Study Design

This protocol describes three multicenter, randomized, double-blind, parallel-group, placebo-controlled studies of the efficacy, safety, and PK of SAGE-547 Injection in adult female subjects diagnosed with severe or moderate PPD. Each study will be independently conducted, analyzed, and reported. In this protocol, Study 547-PPD-202A is hereafter referred to as Part A; Study 547-PPD-202B is hereafter referred to as Part B; and Study 547-PPD-202C is hereafter referred to as Part C.

The study designs for Part A, Part B, and Part C are presented in Figure 1, Figure 2, and Figure 3, respectively; Parts B and C will run concurrently. For all parts, the study will consist of a Screening Period (up to 5-days [Day -5 to -1; Part A] or up to 7-days [Day -7 to -1; Parts B and C]), a 3-day (60 hours of treatment and an additional 12 hours for completion of 72-hour assessments) Treatment Period, and a 30-day Follow-up Period. Subjects must remain as inpatients during the study Treatment Period, which is approximately 72 hours/3 days in duration. The Screening Period assessments may be conducted on an inpatient or an outpatient basis. The Follow-up Period assessments are conducted on an outpatient basis.

Figure 1: Study Design - Part A

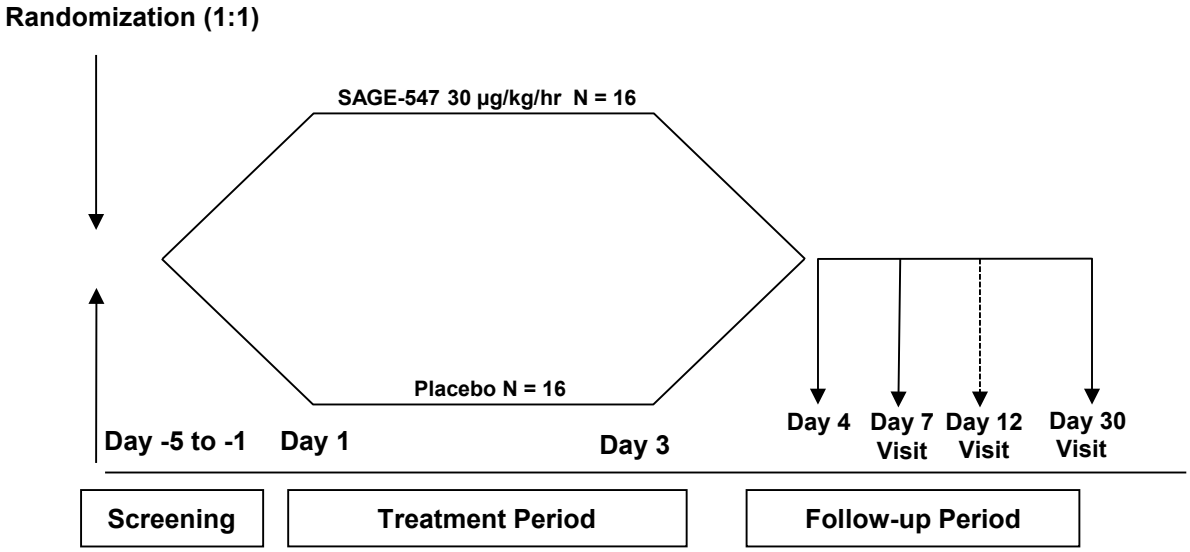


Figure 2: Study Design - Part B

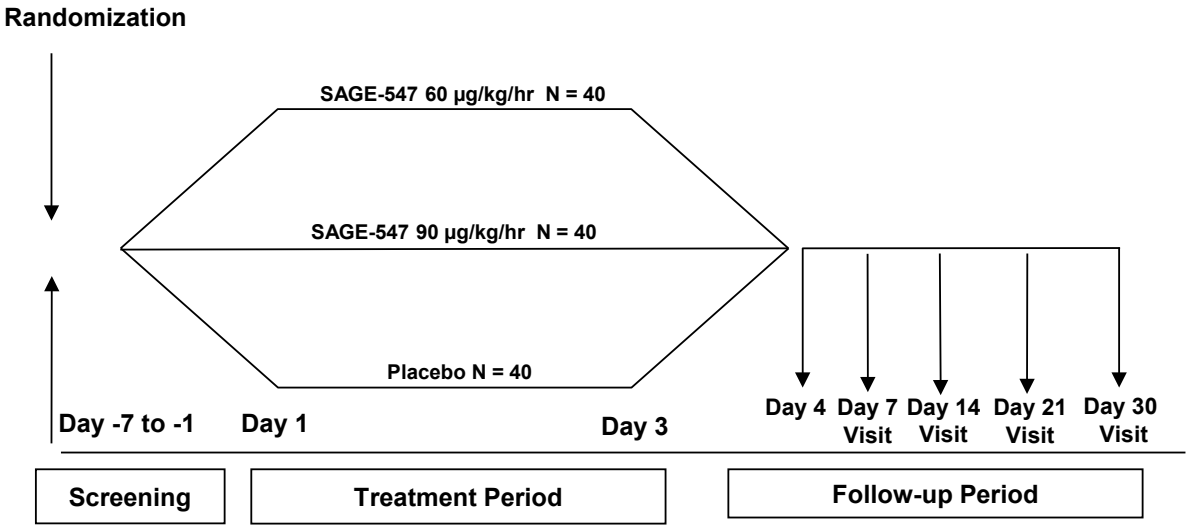
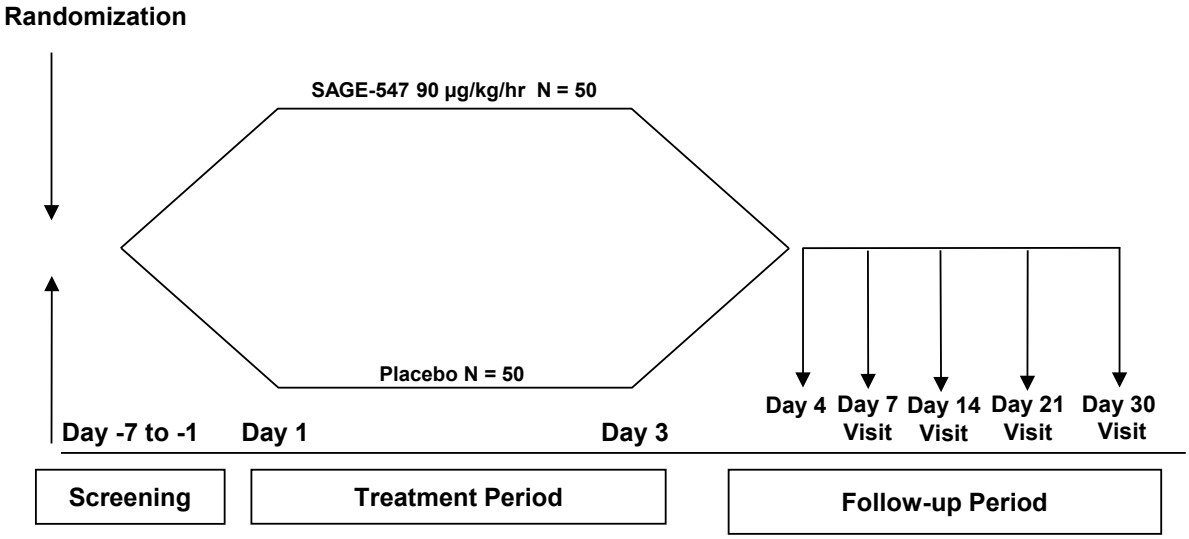


Figure 3: Study Design - Part C



SAGE-547 Injection or placebo will be administered at the study center. Subjects will be monitored for safety during the Treatment and Follow-up Periods (through Study Day 30 [±3 days]) including monitoring for AEs/SAEs, routine clinical laboratory assessments, physical examination, vital signs, and ECG.

All study-related procedures will occur after written informed consent is obtained at the screening visit, which will occur during the Screening Period window (Day -5 through Day -1 for Part A; Day -7 through Day -1 for Parts B and C). 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.

The end of the Screening Period coincides with the beginning of the Treatment Period. The Treatment Period is the period of Day 1 of study drug IV infusion through completion of the infusion on Day 2 and up to Day 3. Subjects will be confined to the study center from Day 1 until after the 72-hour assessments have been conducted on Day 3.

In Parts A and C, once subjects are confirmed as eligible for the study, they will be randomized to one of two treatment groups (SAGE-547 90 µg/kg/hour or placebo) on a 1:1 basis. On the morning of dosing (Day 1), subjects will begin a 4-hour dose titration period of 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24-52 hours); followed by a decrease to 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours). Subjects in the placebo group will receive infusion rates equivalent to the 90 µg/kg/hour group.

In Part B, once subjects are confirmed as eligible for the study, they will be randomized to one of three treatment groups (SAGE-547 60 µg/kg/hour, SAGE-547 90 µg/kg/hour, or placebo) on a 1:1:1 basis. For the 60 µg/kg/hour group, subjects will receive 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-56 hours), followed by 30 µg/kg/hour (56-60 hours). For the 90 µg/kg/hour group, subjects will begin a 4-hour dose titration period of 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24-52 hours); followed by a decrease to 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours). Subjects in the placebo group will receive infusion rates equivalent to either the 60 µg/kg/hour or 90 µg/kg/hour group. Parts B and C will run concurrently.

See dose regimen presented in Section 10.1.1. Total SAGE-547 Injection or placebo dosing will occur over 60 hours.

Study-specific assessments for safety, PK, efficacy, and other outcome measures will be completed at pre-specified times over the duration of the study:

- The safety and tolerability of SAGE-547 Injection will be assessed by AEs, clinical laboratory measures, physical examinations (including cognitive and mental health examinations), vital signs, ECG, use of concomitant medication, and the Columbia Suicide Severity Rating Scale (C-SSRS) during the Screening, Treatment, and Follow-up Periods (through Study Day 30 [±3 days])
- Plasma will be collected to formally assay for SAGE-547, metabolite, and SBECD levels prior to dosing through the Treatment Period and up to 12 hours post infusion on Day 3 and on Day 7
- Primary efficacy assessment of the HAM-D will be completed as scheduled during the Screening, Treatment, and Follow-up Periods (through Study Day 30 [±3 days])
- Secondary efficacy assessments of MADRS, CGI-I, EPDS, Generalized Anxiety Disorder 7-Item Scale (GAD-7), PHQ-9 will be completed as scheduled during the Screening, Treatment, and Follow-up Periods (through Study Day 30 [±3 days])

The end of the Treatment Period coincides with the beginning of the Follow-up Period.

Subjects will attend the clinic for safety follow-up assessment at 1 week (7±1d), 12 days (Part A), 2 weeks (14±2d [Part B and C]), 3 weeks (21±1d [Part B and C]), and 1 month (30±3d) after the initiation of the study drug infusion.

Scheduled assessments for all safety, PK, efficacy, and other outcome measures planned for the study are summarized in Table 1. All subjects who receive treatment with SAGE-547 are to complete all study assessments through Study Day 30 (±3 days).

The Medical Monitor will review AEs on an ongoing basis.

7.2. Blinding and Randomization

This is a double-blind study. Subjects will be randomized to receive SAGE-547 or placebo; subjects, clinicians, and the clinical site study team will be blinded to treatment allocation until the study is unblinded at final database lock. The pharmacist, who will prepare the infusion bags according to the randomization schedule, and an unblinded Monitor, who will perform drug accountability during the study, will be unblinded.

Randomization will be stratified by antidepressant use at baseline (yes/no). Subjects will be randomized within stratum to receive SAGE-547 or placebo according to a computer-generated randomization schedule.

Only the clinic pharmacist, who is responsible for preparing the infusions, will be unblinded. In the event of a medical emergency, the Principal Investigator will discuss with the Medical Monitor if unblinding is warranted. If there is agreement to unblind treatment assignment, the unblinding procedure described in the Safety Management Plan for the study will be followed. 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).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. 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 aged between 18 and 45 years of age
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 breastmilk to their infant(s) from just prior to receiving study drug through 9 days (Study Day 12) after the end of the infusion.
6. Subject must have a negative pregnancy test at screening and Day 1 prior to the start of study drug infusion
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, as diagnosed by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)
8. For Part A and B, subject has a HAM-D total score of ≥26 at screening and Day 1 (prior to dosing). For Part C, subject has a HAM-D total score of ≥20 and ≤25 at screening and Day 1 (prior to dosing)
9. Subject is ≤6 months postpartum at screening
10. Subject is willing at screening to delay the start of any new pharmacotherapy regimens, including antidepressant or anti-anxiety medication, until the study drug infusion and 72-hour assessments have been completed; if the subject is taking psychotropic medications, these must be at a stable dose from 14 days prior to screening until the 72-hour assessments have been completed.
11. (Removed)
12. Subject must use one of the following methods of birth control during participation in the study and for 30 days following the end of the study drug infusion:
    - Total abstinence (no sexual intercourse)
    - Hormonal contraceptives (birth control) including birth control pills, implantable or injectable contraceptives (Norplant® or Depo-Provera®)
    - A barrier form of contraception such as a condom or occlusive cap with a spermicide
    - An intrauterine device

8.2. Exclusion Criteria

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

1. Subject has renal failure requiring dialysis or fulminant hepatic failure or is anemic (hemoglobin ≤10 g/dL)
2. Known allergy to progesterone or allopregnanolone
3. Active psychosis per Investigator assessment
4. Attempted suicide associated with index case of postpartum depression
5. (Removed)
6. Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
7. History of active alcoholism or drug abuse (including benzodiazepines) in the 12 months prior to screening. A positive urine drug screen (except benzodiazepines under certain circumstances [see Section 10.3.3 and Section 11.1.2.6]) is exclusionary.
8. Exposure to another investigational medication or device within 30 days prior to screening
9. (Removed)
10. Subject has previously participated in this study or any other study employing SAGE-547
11. Administration of electroconvulsive therapy (ECT) within 14 days prior to screening and/or plans to administer ECT before the Study Day 7 Visit

8.3. Subject Withdrawal/Study Termination

8.3.1. Withdrawal/Discontinuation of Individual Subjects

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's eCRF. The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn for any reason, including withdrawal due to an AE.

8.3.2. Subject Withdrawal from the Study

Subjects may withdraw from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

8.3.3. Discontinuation of Study Drug by the Investigator

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

The Investigator may withdraw the subject from the study drug for any of the following reasons:

- The subject is unwilling or unable to adhere to the protocol

- The subject experiences an intolerable AE that does not respond to a dose reduction
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

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

8.3.4. Study Termination

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

9. INVESTIGATIONAL PRODUCT

9.1. Identity of Investigational Product

SAGE-547 Injection (allopregnanolone)

9.2. Clinical Supplies

9.2.1. SAGE-547

SAGE-547 Injection and ancillary supply kits containing IV administration bags, solution sets, and IV bag labels will be provided to the sites.

SAGE-547 Injection is a preservative-free, sterile, clear, colorless 5 mg/mL solution of SAGE-547 (allopregnanolone) and 250 mg/mL betadex sulfobutyl ether sodium buffered with 10 mM citrate at a pH of 6.0, intended for IV injection. All inactive excipients used in the formulation are compendial grade and conform to current United States Pharmacopeia (USP) and European Pharmacopeia (Ph. Eur.) standards. The product is aseptically processed, sterile filtered, and filled into 20 mL Type 1 parenteral glass vials with West FluroTec® coated stopper container closure systems, under current Good Manufacturing Practice (cGMP) conditions. SAGE-547 Injection is intended to be used as a single-use vial. An appropriate number of single-use vials to support the dosing duration of the study are packaged and delivered to the site. SAGE-547 Injection vials should be stored under refrigerated conditions (2–8°C). Ancillary supply kits should be stored at controlled room temperature (20–25°C).

All study drug labels will contain information to meet the applicable regulatory requirements.

9.2.2. Placebo

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and consisting of the same formulation without allopregnanolone. Placebo vials should be stored under refrigerated conditions (2–8°C).

9.3. Preparation of SAGE-547 Injection or Placebo for Dosing

The pharmacy will be responsible for preparing SAGE-547 Injection or placebo for subject dosing. The prepared admixture will be administered at room temperature. The prepared admixture will be assigned a room temperature (20–25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547 Injection or placebo is not intended to be administered to subjects undiluted. Each single-use vial of SAGE-547 Injection, which is hypertonic, will require dilution with an appropriate volume of SWFI to render it isotonic. Refer to the Pharmacy Manual for specific instructions regarding infusion preparation and administration instructions.

9.4. Administration and Accountability

The pharmacy will maintain accurate records of all investigational drug product supplies received, stored, dispensed, and discarded. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate (or rates), and the date and time of preparation. Reasons for departure from the expected dosing regimen must be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication needs to be reconciled in full.

Refer to the Pharmacy Manual for complete details on preparation and administration.

10. TREATMENT OF SUBJECTS

10.1. Dosing Schedule

This is a double-blind study. Subjects will be randomized to receive 60 hours of IV treatment with either SAGE-547 Injection or placebo, according to a computer-generated randomization schedule. In Parts A and C, subjects randomized to SAGE-547 will receive the target dose of 90 µg/kg/hour; in Part B, SAGE-547 subjects will receive target doses of either 60 or 90 µg/kg/hour.

The timing of infusion is shown in Figure 4, Figure 5, and Figure 6.

Figure 4: Study Design and Timeline for Dosing – Part A

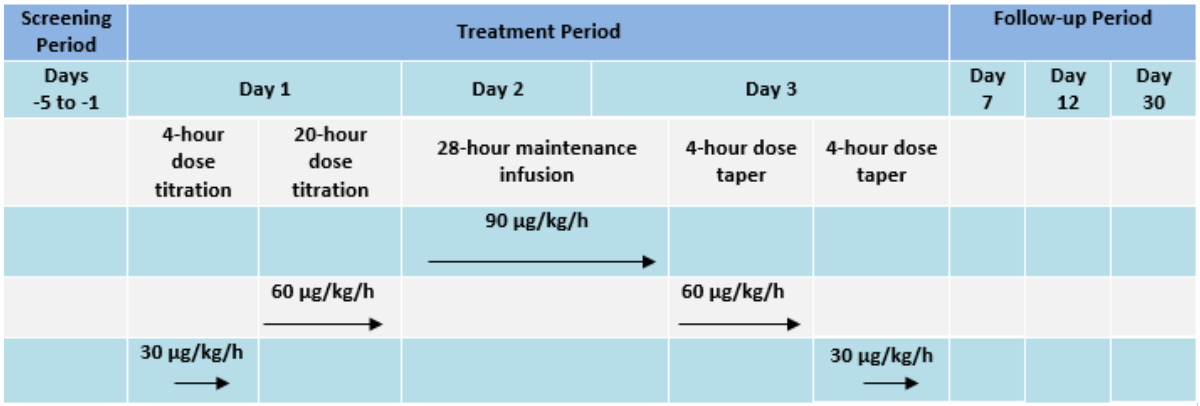
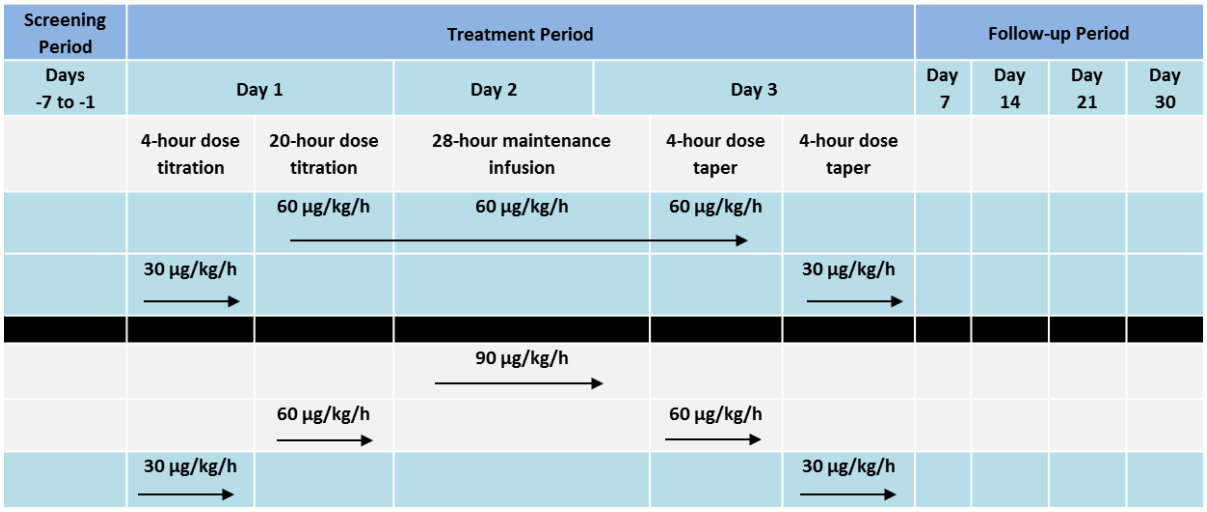
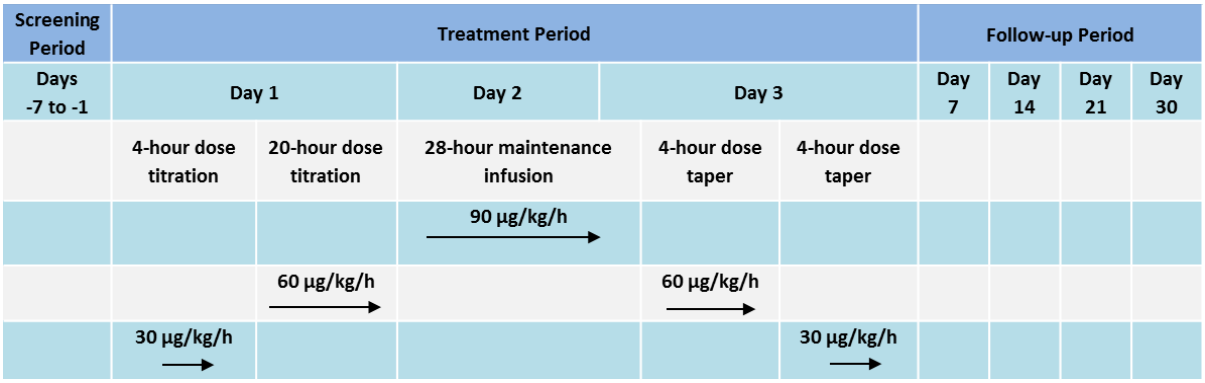


Figure 5: Study Design and Timeline for Dosing – Part B



Note: Day 3, 4-hour taper applies only to the 90 µg/kg/h dose group.

Figure 6: Study Design and Timeline for Dosing – Part C



Clinical supply and preparation of SAGE-547 Injection for dosing is described Section 9.2 and Section 9.3, respectively.

10.1.1. Dose Regimen

The specific infusion dose of SAGE-547 Injection will be calculated based on weight (obtained at screening) for each subject and administered according to dose regimen shown in Table 3 and Table 4). The infusion rates are the same for all subjects within a particular dosing period (0-4 hours, 4-24 hours, etc.).

Table 3: Infusion Rates for Part A and C

	Infusion Rate (µg/kg/hour)				
SAGE-547 Dose	**Day 1 0-4 hours**	**Day 1 4-24 hours**	**Day 2-3 24-52 hours**	**Day 3 52-56 hours**	**Day 3 56-60 hours**
90 µg	30	60	90	60	30

Table 4: Infusion Rates for Part B

	Infusion Rate (µg/kg/hour)				
SAGE-547 Dose	**Day 1 0-4 hours**	**Day 1 4-24 hours**	**Day 2-3 24-52 hours**	**Day 3 52-56 hours**	**Day 3 56-60 hours**
60 µg	30	60	60	60	30
90 µg	30	60	90	60	30

Dosing is to begin in the morning (on Day 1) to avoid awakening subjects during the night for completion of study assessments.

If any subject has an intolerable AE, such as profound sleepiness or sedation outside of normal sleeping hours, the infusion rate for this subject will be decreased to the next lowest infusion dose level (or turned off if this occurs on the 30 µg/kg/hour dose level).

10.1.2. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line with the study-approved IV administration bags and lines.

10.1.3. Treatment Period

Total dosing with SAGE-547 or placebo will occur over 60 hours.

10.1.4. Dosing of Intravenous SAGE-547 in the Case of AEs

Since allopregnanolone levels in the proposed clinical study are similar to physiological levels seen in the third trimester of pregnancy, and all the AEs reported with SAGE-547 or allopregnanolone to date in healthy volunteers and subjects with postpartum depression were mild and non-serious, it is anticipated that the AEs associated with SAGE-547 in this study will be mild and manageable without dose interruption or reduction. Based on the safety data in subjects with PPD collected to date, no subjects reported events that were serious or severe or led to discontinuation of study drug (two subjects reported sedation that led to a dose reduction, one of these subjects also reported dizziness; one subject reported rash that led to a dose reduction; refer to the current Investigator's Brochure for more information).

However, in the case of intolerable AEs occurring, the investigator is advised to reduce the infusion to the next lowest dose (or stop the infusion if this event occurs on the 30 µg/kg/hour dose level) until the AE has resolved, at which time re-escalation to the maintenance rate may be considered. If the AE recurs, the study drug infusion may be reduced again or permanently discontinued.

10.2. Dosing Compliance

Investigational product will be prepared in the site pharmacy, administered as a continuous IV infusion by the study staff, and will be documented in the study record. There should be no adjustments in dosing except those described in Section 10.1.4.

10.3. Prior Medications, Concomitant Medications, and Restrictions

10.3.1. Prior Medications

The start and end dates, route, dose/units, and frequency of all medications taken within 60 days prior to signing the informed consent will be recorded, as well as all medications given to treat the current PPD episode that are recorded on the SCID-I during the screening visit.

10.3.2. Concomitant Medications

All medications taken from signing the informed consent through the Day 30 (±3 days) visit will be recorded on the eCRF. Subjects will receive standard of care for adult female patients diagnosed with PPD. 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 10.3.

10.3.3. Prohibited Medications

Restrictions on specific classes of medications include the following:

- Subjects may not start new pharmacotherapy regimens, including antidepressant or anti-anxiety medications, from the time of informed consent until the study drug infusion and 72-hour assessments have been completed. If clinically indicated, new antidepressant medications may be started or existing antidepressant medication regimens may be changed once the 72-hour assessments have been completed. Consideration should also be given to deferring, starting, or changing antidepressant medication regimens until the Day 7, Day 12 (Part A only) or Day 14 (Parts B and C only), Day 21 (Parts B and C only), or Day 30 visits if the HAM-D score has improved.
- If the subject is taking psychotropic medications, these must be at a stable dose from 14 days prior to screening to completion of the 72-hour assessments.
- Benzodiazepines are to be avoided as much as possible owing to the potential for a synergistic sedative effect. Eligible subjects taking a benzodiazepine at the time of study entry will 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.

10.3.4. Restrictions

- Electroconvulsive therapy (ECT) is prohibited from 14 days prior to screening until after the Day 7 visit.

11. STUDY ASSESSMENTS

11.1. Safety Assessments

The safety and tolerability of SAGE-547 Injection will be evaluated by summarization of AEs by frequency, severity and seriousness, mean changes from baseline in clinical laboratory measures, physical examination, vital signs, ECGs, and concomitant medication usage. Suicidality will be monitored using the C-SSRS. All safety assessments should be performed per the study center's standard of care and will be collected according to the Schedule of Events (Table 1). All safety assessments are to be completed within ±30 minutes of the scheduled time point.

In addition to the schedule outlined in Table 1, completion of safety assessments including physical examination, vital signs, and clinical laboratory tests should occur in the event of an emergency or SAE, when possible.

11.1.1. Adverse Events

Adverse events will be collected after the ICF has been signed through the end of the study (see Section 14.2.1 for additional details). Medical conditions or AEs that occur after the ICF has been signed and *prior to* completion of screening will be captured on the Medical History eCRF.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) coding system (version 18.0 or higher).

11.1.2. Clinical Laboratory Tests

Blood samples will be collected for hematology, serum chemistry, coagulation, specific hormone parameters, and exploratory biochemistry; pregnancy testing; and genetic analysis. Urine samples for urinalysis and selected drugs of abuse will also be collected. All samples will be analyzed at the central laboratory. Patients 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 (Table 1).

These assessments will be performed in accordance with the Schedule of Events (Table 1) and as outlined individually below.

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 will be recorded as medical history. Clinical laboratory results that are Abnormal; CS during the study and indicate a worsening from baseline will be considered AEs, assessed according to Section 14, and recorded in the eCRF.

11.1.2.1. Hematology, Serum Chemistry, Coagulation

Blood samples will be collected for analysis of the following:

- **Hematology:** complete blood count (CBC) including white blood cell (WBC) count with differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils) platelet count, red blood cell (RBC) count, hemoglobin (Hgb) and hematocrit (Hct), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH)
- **Serum chemistry:** albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatinine, gamma glutamyl transferase (GGT), glucose phosphate, potassium, sodium, total protein, and triglycerides (screening only)
- **Coagulation:** activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR)

11.1.2.2. Hormones and Exploratory Biochemistry

Blood samples will be collected and may be analyzed for thyroid stimulating hormone (TSH), estrogen, progesterone, progesterone metabolites, oxytocin, tryptophan, kynurenine, and markers of inflammation.

11.1.2.3. Pregnancy Tests

All subjects will be tested for pregnancy by serum human chorionic gonadotropin (hCG) at screening and urine hCG on Day 1 prior to administration of study drug and on Day 30. Subjects with a positive pregnancy test at screening or Day 1 will be ineligible for study participation.

11.1.2.4. Genetic Testing

A blood sample for genetic testing will be collected at screening, where consent is given.

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-547. 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 allopregnanolone (eg, AKR1C4 (3a-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-547 but also susceptibility to disorders for which SAGE-547 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.

11.1.2.5. Urinalysis

Urinalysis will include assessment of bilirubin, glucose, ketones, leukocytes, nitrite, pH, protein, and specific gravity.

11.1.2.6. Drugs of Abuse and Alcohol

Urine assessment for selected drugs of abuse will be performed at screening (including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, and propoxyphene). Use of benzodiazepines at screening is not necessarily exclusionary, as subjects will be allowed to take psychotropics that have been initiated at least 14 days prior to admission to the study center at a stable dose (see Section 10.3.3). A positive urine drug screen for any of the tested drugs of abuse (except benzodiazepines) is exclusionary. Alcohol will be assessed in plasma at screening and via breathalyzer or urine dipstick on Day 1.

11.1.3. Physical Examination

Body weight and height will be measured at screening. Body mass index (BMI) will be programmatically calculated in the eCRF.

Any condition present at the post-treatment physical examination that was not present at or worsened since the baseline examination is to be documented as an AE. Whenever possible, the same individual is to perform all physical examinations. Physical examinations will include assessment of body systems (eg, HEENT, heart, lungs, abdomen, and extremities) as well as cognitive and neurological examination and mental status examination.

11.1.4. Vital Signs

Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). A full set of vital signs will be obtained at all specified time points (±30 minutes), unless the subject is asleep between the hours of 23.00h and 06.00h each day.

11.1.5. ECG

A baseline 12-lead ECG will be performed during screening. The following ECG parameters will be recorded: heart rate, PR, QRS, QT, and QTc. All ECG results will be interpreted by the Investigator as *Normal, Abnormal; not clinically significant (NCS),* or *Abnormal; clinically significant (CS)*. If Abnormal, details will be provided.

11.1.6. 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 pre-dose evaluation that assesses the lifetime and recent 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 on Day 1 prior to dosing. The "Since Last Visit" C-SSRS form will be completed for all subsequent assessments.

Copies of the C-SSRS are provided in Appendix 1.

11.2. Efficacy Assessments

For all efficacy assessments, the baseline values will be calculated as the last recorded value prior to the start of infusion of randomized treatment. 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.

11.2.1. Primary Efficacy Outcome Measure

The primary outcome measure is the HAM-D. The HAM-D will be administered before, during, and after the infusion of blinded study drug.

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

The 17-item HAM-D will be used to rate the severity of depression in subjects who are already diagnosed as depressed (Hamilton 1960). The 17-item HAM-D is comprised of 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 within ±30 minutes of the scheduled time point, but prior to starting dosing on D1 H0. Every effort should be made for the same rater to perform all HAM-D assessments for a single subject.

The HAM-D total score will be calculated as the sum of the 17 individual item scores. Item 16 can be rated according to history (item 16A) or actual weight change (item 16B). The item 16 score is calculated as the item 16 response that is not equal to 3 (ie, "Not assessed").

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. HAM-D subscale scores will be calculated as the sum of the items comprising each subscale. HAM-D response will be defined as having a 50% or greater reduction from baseline in HAM-D total score. HAM-D remission will be defined as having a HAM-D total score of ≤ 7.

A copy of the HAM-D is provided in Appendix 2.

11.2.2. Secondary Efficacy Outcome Measures

Secondary efficacy assessments include evaluation of depressive symptom severity by the HAM-D total score at the Day 30 time point, MADRS (Section 11.2.2.1), and CGI (Section 11.2.2.2). Additional assessments of depressive symptom severity and reproductive mood disorders will be measured by the following clinician- and subject-rated outcome measures: EPDS (Section 11.2.3.1), GAD-7 (Section 11.2.2.3), and PHQ-9 (Section 11.2.3.2).

11.2.2.1. Montgomery Asberg Depression Rating Scale (MADRS)

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

Higher MADRS scores indicate more severe depression, and each item yields a score of 0 to 6. The overall score ranges from 0 to 60 (McDowell 2006, Müller-Thomsen 2005).

The questionnaire includes questions on the following symptoms

1. Apparent sadness
2. Reported sadness
3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

The MADRS total score will be calculated as the sum of the 10 individual item scores.

A copy of the MADRS is provided in Appendix 3.

11.2.2.2. Clinical Global Impression (CGI) Scale

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 patient's condition. The CGI scale is comprised of three items. Only the first two items are being used in this study.

The CGI-Severity (CGI-S) item uses a 7-point Likert scale to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating 1=normal, not at all ill, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, and 7=extremely ill. The CGI-S will be rated by the clinician at screening and on Day 1 (prior to dosing).

The CGI-Improvement (CGI-I) item employs a 7-point Likert scale to measure the overall improvement in the patient's condition post-treatment. The investigator will rate the patient's total improvement whether or not it is due entirely to drug treatment. Response choices include: 0=not assessed, 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse. The CGI-I is only rated at post-treatment assessments. By definition, all CGI-I assessments are

evaluated against baseline conditions. CGI-I response will be defined as having a CGI-I score of "very much improved" or "much improved."

A copy of the CGI is provided in Appendix 4.

11.2.2.3. Generalized Anxiety Disorder 7-Item Scale (GAD-7)

The GAD-7 is a patient-rated generalized anxiety symptom severity scale (Spitzer 2006). Scoring for GAD-7 generalized anxiety is calculated by assigning scores of 0, 1, 2, and 3 to the response categories, respectively, of "not at all sure," "several days," "over half the days," and "nearly every day." GAD-7 total score for the seven items ranges from 0 to 21, where a score of 0 to 4=minimal anxiety, 5 to 9=mild anxiety, 10 to 14=moderate anxiety, and 15 to 21=severe anxiety. All assessments are to be completed within ±30 minutes of the scheduled time point.

The GAD-7 total score will be calculated as the sum of the 7 individual item scores.

A copy of the GAD-7 is provided in Appendix 6.

11.2.3. Patient Reported Outcome Measures

Other efficacy assessments include evaluation of depressive symptom severity and reproductive mood disorders. These will be measured by the following clinician- and subject-rated outcome measures: EPDS, PHQ-9, BIMF, and SF-36.

11.2.3.1. Edinburgh Postnatal Depression Scale (EPDS)

The EPDS is a patient-rated depressive symptom severity scale specific to the perinatal period (Cox 1987). The EPDS total score will be calculated as the sum of the 10 individual item scores.

A copy of the EPDS is provided in Appendix 5.

11.2.3.2. Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a patient-rated depressive symptom severity scale. To monitor severity over time for newly diagnosed patients or patients in current treatment for depression, patients may complete questionnaires at baseline and at regular intervals thereafter. Scoring is total based on responses to specific questions, as follows: not at all=0; several days=1; more than half the days=2; and nearly every day=3. All assessments are to be completed within ±30 minutes of the scheduled time point.

The PHQ-9 total score will be calculated as the sum of the 9 individual item scores. The PHQ-9 total score will be categorized as follows: 1-4=minimal depression, 5-9=mild depression, 10-14=moderate depression, 15-19=moderately severe depression; and 20-27=severe depression.

A copy of the PHQ-9 is provided in Appendix 7.

11.2.3.3. Barkin Index of Maternal Functioning (BIMF)

The BIMF is a patient reported outcome scale BIMF covers a broad range of functional areas (self-care, infant care, mother-child interaction, psychological well-being of mother, social

support, management, adjustment). This new application of maternal functional status is a robust construct where the physical and mental health of the mother is essential to optimal functioning. Each item is rated on a scale of 0 (strongly disagree) to 6 (strongly agree).

A copy of the BIMF is provided in Appendix 8.

11.2.3.4. Short Form-36 (SF-36)

The Medical Outcomes Study Short Form-36 (SF-36v2) is a 36-item measure of health status that has undergone validation in many different disease states (Ware 2007). The SF-36 covers eight health dimensions including four physical health status domains (physical functioning, role participation with physical health problems [role-physical], bodily pain, and general health) and four mental health status domains (vitality, social functioning, role participation with emotional health problems [role-emotional], and mental health). In addition, two summary scores, physical component summary (PCS) and mental component summary (MCS), are produced by taking a weighted linear combination of the eight individual domains. The SF-36v2 is available with two recall periods: the standard recall period is 4 weeks and the acute recall period is 1 week. This study will use the acute version, which asks patients to respond to questions as they pertain to the past week. Higher SF-36 scores indicate a better state of health. The SF-36 requires approximately 10 minutes to complete and can be self-administered or completed by interview in person or by telephone.

A copy of the SF-36 is provided in Appendix 9.

11.2.3.5. Healthcare Resource Utilization (HCRU)

Subject-reported healthcare resource utilization data, including baseline diagnosis history, baseline antidepressant treatment history, and healthcare visits, inpatient visits, and medication use, will be collected at screening and on Day 30 of follow-up (or at early termination). A copy of the health resource utilization questionnaire is provided in Appendix 10.

11.3. Pharmacokinetics

Blood samples for PK analysis will be collected in accordance with the Schedule of Events (Table 1). Scheduled time points for PK blood draws after the start of infusion will have a window of ±10 minutes. Samples will be processed according to the PK Manual, and may be analyzed for concentrations of SAGE-547, metabolites of SAGE-547, and SBECD. Additionally, PK samples may be obtained outside the planned collection times if issues administering study drug are encountered, such as incorrect infusion rate, interrupted infusion, or other administration deviations where PK level assessment may be important in understanding subject state. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.

The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve (AUC) from time zero to 60 hours ($AUC_{0\text{-}60}$), AUC from time zero to infinity (AUC_{∞}), maximum (peak) plasma concentration (C_{max}), time at maximum (peak) plasma concentration (t_{max}), steady-state drug concentration in the plasma during constant-rate infusion (C_{ss}), and average drug concentration in the

plasma at steady state during a dosing interval (C_{avg}). Each PK parameter will be derived separately for each part of the study.

The plasma samples will be drawn from the arm contralateral to that used for study drug administration. Instructions on sample collection, processing methods, storage, and shipping conditions for subject-specific plasma PK kits will be provided in the study laboratory manual.

12. STUDY PROCEDURES

The study procedures listed below by study day reflect the data collection times for this protocol.

Scheduled assessments for all safety, efficacy, PK, and other outcome measures planned for the study are summarized in Table 1 (Schedule of Events). All subjects who receive treatment with SAGE-547 should complete all study assessments through Study Day 30 (±3 days).

Subjects who complete the assessments at Hour 60 and Day 30 (±3 days) will be defined as study completers.

12.1. Screening Period

The Screening Period consists of a window from Day -7 through Day -1 prior to starting SAGE-547 treatment (up to 5-days [Day -5 to -1; Part A] or up to 7-days [Day -7 to -1; Parts B and C]). The Screening Period begins with the signature of the ICF. Eligibility is determined by applying the inclusion/exclusion criteria. The diagnosis of PPD must be by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). A full medical and family history will be taken from the subject using a SCID-I interview, including recording of all depression (major depressive disorders, premenstrual dysphoric disorder, menstrual migraine, and other psychiatric disorders per DSM), other Axis I and Axis II disorders, and pregnancy history including birth complications, and postpartum depression episodes. Family history will be collected from the subject for primary probands, including all depression (major depressive disorders, premenstrual dysphoric disorder, menstrual migraine, and other psychiatric disorders per DSM), other Axis I disorders, and postpartum depression episodes.

The following assessments/procedures will be conducted at the screening visit, which will occur during the Screening Period window. 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 examinations, 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, and all screening assessments are completed, reviewed and approved by the Investigator prior to administration of study drug.

Subjects will be confined to the study center from Day 1 until after the 72-hour assessments have been conducted on Day 3.

- Written informed consent will be obtained
- Inclusion/exclusion criteria will be reviewed to determine subject eligibility
- Demographic information and medical/family history will be collected
- Lactation status (ie, subject is breastfeeding, subject is lactating but not breastfeeding, or subject is not lactating) will be recorded
- Blood will be collected for a pregnancy test

- Completion of physical examination, including body weight. Height should be recorded. BMI will be calculated.
- Vital signs will be recorded
- Blood and urine samples will be collected for clinical laboratory testing, including drug and alcohol screening
- Blood sample will be taken for genetic analysis with subject consent
- An ECG reading will be taken
- The HAM-D, CGI-S, and MADRS will be completed
- Concomitant medications will be recorded
- AEs will be monitored

12.2. Study Drug Treatment Period (Day 1 to Day 3, Hours 0-72)

All safety, efficacy, PK, and other outcome assessments described in this section are to be completed within ±30 minutes of the scheduled time points, unless otherwise stated. Windows for PK collection time points are specified by respective time point for Study Days 1 to 3 in Section 12.2.1 to Section 12.2.3, respectively (see Section 11.3 for additional details). Subjects will be confined to the study center from Day 1 until after the 72-hour assessments have been conducted on Day 3.

Psychiatric follow-up outside the study visits will be arranged and documented, as appropriate.

12.2.1. Day 1

- Inclusion/exclusion criteria will be reviewed to determine subject eligibility
- Randomization
- Urine will be collected for a pregnancy test
- Study drug administration will begin for dose titration in the morning followed by maintenance infusion
- Vital signs will be recorded prior to infusion and at 2, 4, 8, 12, 18, and 24 hours on Day 1 (±30 minutes), unless the subject is asleep between the hours of 23.00h and 06.00h each day
- Blood and urine samples will be collected for drug and alcohol screening
- A blood sample for PK analysis will be collected prior to infusion (ie, morning of Day 1 prior to dosing), and at Hours 4 (before change in infusion rate, if applicable), 8, 12, and 24 (before change in infusion rate, if applicable) after the start of the infusion. PK blood draws after the start of infusion will have a window of ±10 minutes. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.

- The HAM-D will be completed prior to dosing and at Hours 2, 4, 8, 12, and 24 on Day 1 (±30 minutes)
- The MADRS will be completed prior to dosing and at Hour 24 on Day 1 (±30 minutes)
- The CGI-S will be completed prior to dosing and the CGI-I at Hours 2, 4, 12, and 24 on Day 1 (±30 minutes)
- The following questionnaires will be completed prior to dosing: BIMF, EPDS, GAD-7, SF-36, and PHQ-9 (±30 minutes)
- AEs will be monitored
- Concomitant medications will be recorded
- The "Baseline/Screening" C-SSRS form will be completed prior to dosing. The "Since Last Visit" C-SSRS form will be completed at Hour 24 (± 30 minutes)
- Breast milk will be pumped and discarded by subjects who are lactating

12.2.2. Day 2

- Ongoing study drug maintenance infusion administration
- Vital signs will be recorded at Hours 30, 36, 42, and 48 (±30 minutes), unless the subject is asleep between the hours of 23.00h and 06.00h each day
- A blood sample for PK analysis will be collected at Hours 30, 36, and 48. PK blood draws will have a window of ±10 minutes. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change
- The HAM-D will be completed at Hour 36 and Hour 48 (±30 minutes)
- The CGI-I will be completed at Hour 36 and Hour 48 (±30 minutes)
- The MADRS will be completed at Hour 48 (±30 minutes)
- An ECG reading will be taken at Hour 48
- AEs will be monitored
- Concomitant medications will be recorded
- Breast milk will be pumped and discarded by subjects who are lactating

12.2.3. Day 3

- Ongoing study drug maintenance infusion administration until Hour 60
- A physical examination will be completed at Hour 72
- Vital signs will be recorded at Hours 54, 60, 66, and 72 (±30 minutes)

- A blood sample for PK analysis will be collected at Hours 60 and 72 (±10 minutes). In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change
- Blood sample will be collected for clinical laboratory testing at Hour 72
- The HAM-D and MADRS will be completed at Hours 60 and 72 (±30 minutes)
- The CGI-I will be completed at Hours 60 and 72 (±30 minutes)
- The following questionnaires will be completed at Hour 60: EPDS, GAD-7, and PHQ-9 (±30 minutes)
- AEs will be monitored
- Concomitant medications will be recorded
- The C-SSRS will be completed at Hours 60 and 72
- Subjects who are lactating will pump and discard breast milk and be reminded that they must continue to pump and discard breast milk through Day 12 of the study

12.3. Follow-up Period (Day 7 through Day 30)

12.3.1. Day 7 (±1 day)

The following assessments should be completed:

- A physical examination will be completed
- Vital signs will be recorded
- Blood and urine samples will be collected for clinical laboratory testing
- An ECG reading will be taken
- The C-SSRS, HAM-D, MADRS, CGI-I, EPDS, GAD-7, PHQ-9, SF-36, and BIMF will be completed
- Subjects who are lactating will be reminded to continue to pump and discard breast milk through Day 12 of the study
- AEs will be monitored
- Concomitant medications will be recorded

12.3.2. Day 12 (±2 days) (Part A); Day 14 (±2 days) and Day 21 (±3 days) (Parts B and C)

The following assessments should be completed:

- The C-SSRS, HAM-D, MADRS, CGI-I, EPDS, GAD-7, PHQ-9, SF-36, and BIMF will be completed
- AEs will be monitored

- Concomitant medications will be recorded

12.3.3. Day 30 (±3 days)

The following assessments should be completed:

- Urine will be collected for a pregnancy test
- The C-SSRS, HAM-D, MADRS, CGI-I, EPDS, GAD-7, PHQ-9, SF-36, and BIMF will be completed
- AEs will be monitored
- Concomitant medications will be recorded

12.3.4. Early Termination Visit

The following assessments should be completed if the subject discontinues from the study prior to the Day 7 Visit:

- A physical examination will be completed
- Vital signs will be recorded
- Blood and urine samples will be collected for clinical laboratory testing
- An ECG reading will be taken
- The C-SSRS, HAM-D, MADRS, CGI-I, EPDS, GAD-7, PHQ-9, SF-36, and BIMF will be completed
- AEs will be monitored
- Concomitant medications will be recorded

The visit should occur within 3 days of notification of the subject discontinuing.

13. STATISTICAL METHODS AND CONSIDERATIONS

In general, summary statistics for all study endpoints will be presented as mean, standard deviation (SD), median, and ranges for continuous endpoints, and as counts and percentages for categorical endpoints. For the purpose of all safety, efficacy, and other analyses where applicable, baseline is defined as the last pre-dose measurement closest to the start of blinded study drug infusion.

A separate statistical analysis plan (SAP) will be generated for each study (Parts A, B, and C) and approved prior to the respective database lock of each study. All statistical analyses will be conducted using SAS for Windows (version 9.1.3, or higher; Cary, NC), unless otherwise specified.

Any deviations from the planned analyses will be described and justified in the final clinical study report (CSR).

13.1. Data Analysis Sets

The **All Enrolled Population** will include all subjects who have given written informed consent. This population will be used for subject disposition and demographic characteristic summaries.

The **All Randomized Population** will include the subset of subjects from the All Enrolled Population who have been randomized. Subjects will be classified according to randomized treatment. This population will be used for subject disposition, demographic characteristic, and baseline characteristic summaries.

The **Safety Population** will include all randomized subjects who start the infusion of study drug. Subjects will be classified according to actual treatment received. This analysis population will be used for all safety analyses.

The **Efficacy Population (EFF)** will include the subset of the Safety Population who have a valid baseline HAM-D assessment and at least one post-baseline HAM-D assessment. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Per Protocol Population (PP)** will include the subset of the Efficacy Population who complete the full infusion without significant protocol violations or deviations. Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary and select secondary endpoints.

The **PK Population (PKP)** will include the subset of the Safety Population who have at least one evaluable PK sample. Subjects will be classified according to actual treatment received. This analysis population will be used for all PK analyses.

The number and percentage of subjects who receive SAGE-547 Injection or placebo, prematurely discontinue, and complete the study will be summarized. The number and percentage of subjects will also be summarized for each reason for premature discontinuation. In addition, the number of subjects whose data should be used for the

planned analyses will be identified for each respective analysis population (ie, Safety, EFF, PKP, and PP).

13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis populations, using all non-missing data available. A sensitivity analysis may be carried out to investigate the impact of missing data if more than 5% of subjects are missing primary endpoint assessments. Any rules/statistical methods for the imputation of missing data will be described in the SAP.

13.3. Demographics and Baseline Characteristics

Demographics such as age, race, and ethnicity will be summarized. In addition, baseline characteristics such as height, weight, and BMI will be summarized. Categorical summaries, such as race and ethnicity, will be summarized by frequency and percentage. Continuous summaries, such as age, height, weight, BMI and baseline vital signs, will be summarized using descriptive statistics such as n, mean, SD, median, minimum, and maximum.

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

Medical/family history will be collected and listed by subject.

13.4. Primary Endpoints

For efficacy analysis purposes, centers with fewer than 15 subjects per center for Part B or 10 subjects per center for Part C will be pooled within regions (eg, North America region centers will be pooled separately those in Europe). 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 (pooled), treatment, baseline HAM-D total score, visit time point, and visit time point-by-treatment terms. Center and all other explanatory variables will be treated as fixed effects. For Parts A and C, the primary comparison will be between 90 µg SAGE-547 and placebo at the 60-hour assessment. For Part B, the primary comparison will be between 90 µg SAGE-547 and placebo at the 60-hour assessment; if this comparison is significant at the 0.05 level, then the 60 µg group will be compared to placebo at the 0.04 level of significance. More details will be provided in the SAPs regarding strong control of overall level of significance for multiple testing, including testing of key secondary endpoints. Comparisons at other time points, including the Day 30 time point, will be conducted to support the findings for the primary comparison. Model-based point estimates (ie, LS means), 95% confidence intervals, and p-values will be reported for each assessment.

Summaries of HAM-D total scores and changes from baseline values will include n, mean, SD, median, minimum, and maximum.

13.5. Secondary Endpoints

13.5.1. Efficacy Analysis

MMRM methods similar to those described in Section 13.4 will be used for the analysis of the following variables: MADRS total score, EPDS total score, GAD-7 total score, PHQ-9 total score, and select individual item and subscale scores. Separate models will be fit for each part of the study. For each model, the comparison of interest will be between each SAGE-547 dose and placebo at the 60-hour assessment. 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 response variables: HAM-D response, HAM-D remission, and CGI-I response. GEE models will include terms for center, treatment, and baseline score. Separate models will be fit for each part of the study. The comparison of interest will be the difference between each SAGE-547 dose and placebo at the 60-hour assessment. 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.

13.5.2. Safety Analysis

Safety and tolerability of SAGE-547 Injection will be evaluated by AEs, concomitant medications, changes from baseline in physical examination, vital signs, CBC, serum chemistry, urinalysis, and 12-lead ECG. Suicidality will be monitored by the C-SSRS. In Part A only, sedation will be assessed using the Stanford Sleepiness Scale (SSS) and an analysis of SSS data will be performed comparing the treatment groups in the same way as for the primary endpoint. Safety data will be listed by individual and summarized by treatment group. All safety summaries will be performed on the Safety Population.

Safety data will be examined for possible relationships between subject characteristics and plasma allopregnanolone concentrations, as appropriate.

Scheduled visits for all safety assessments are described in Section 12 and summarized in Table 1.

13.5.2.1. Adverse Events

The analysis of AEs will be based on the concept of treatment-emergent AEs (TEAEs). A TEAE is defined as an AE with onset after the start of study drug infusion, or any worsening of a pre-existing medical condition/AE with onset after the start of study drug infusion. The incidence of TEAEs will be summarized overall and by MedDRA System Organ Class (SOC) and preferred term (PT). Incidences will be presented in order of decreasing frequency. In addition, summaries will be provided by severity (mild, moderate, severe) and by causality (related, not related) to study drug (see Section 14.2.2.1).

TEAEs leading to discontinuation and SAEs (see Section 14.1.4 for definition) with onset after the start of randomized infusion will also be summarized.

All AEs and SAEs (including those with onset or worsening before the start of randomized infusion) through the Day 30 Follow-up Visit (±3 days) will be listed.

13.5.2.2. Clinical laboratory evaluations

Results will be listed by Subject ID and timing of collection. Mean changes from baseline in clinical laboratory measures will be evaluated.

13.5.2.3. Physical examinations

Physical examinations will be evaluated at screening and Day 7. Any clinically significant change in physical examination compared to those observed at screening should be noted as an AE.

13.5.2.4. Vital signs

Vital signs, including oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing) will be obtained at the scheduled time points described in Section 11.1.4. Mean changes from baseline (pre-infusion) in vital signs will be evaluated.

13.5.2.5. 12-Lead ECG

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

13.5.2.6. Concomitant medications

A summary of all concomitant medications taken during the course of the study will be presented in tabular form by therapeutic drug class and generic drug name using the WHO Collaborating Centre for Drug Statistics Methodology Norwegian Institute of Public Health (http://www.whocc.no).

13.5.2.7. C-SSRS

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

13.5.2.8. SSS (Part A only)

Changes in score over time will be represented graphically, and change from baseline will be measured.

13.5.2.9. PK Analysis

Plasma will be collected to assay for concentrations of SAGE-547, metabolites of SAGE-547, and SBECD. The following PK parameters will be derived from the plasma concentrations (where evaluable): $AUC_{0\text{-}60}$, AUC_{∞}, C_{max}, time at maximum (peak) plasma concentration (t_{max}), steady-state drug concentration in the plasma during constant-rate infusion (C_{ss}), and average drug concentration in the plasma at steady state during a dosing interval (C_{avg}).

Plasma concentrations will be listed by subject and summarized by nominal collection time point. PK parameters will be listed by subject and summarized by collection time point. Correlations between concentrations and AEs or tolerability measures may be performed as deemed necessary.

In addition to typical descriptive statistics, summaries should include geometric mean, coefficient of variation, and geometric coefficient of variation.

13.6. Determination of Sample Size

Using a two-sided test at an alpha level of 0.05, a sample size of 10 evaluable subjects per group for Part A would provide 70% power to detect an effect size of 1.2 between the SAGE-547 and placebo groups with regard to the primary outcome variable of change from baseline in HAM-D total score. An effect size of 1.2 corresponds to a placebo-adjusted difference of 12 points in the change from baseline in HAM-D total score at 60 hours with an assumed standard deviation of 10 points. By including two treatment groups and using a 1:1 randomization ratio, a total of 20 evaluable subjects are required for Part A.

Based on the results of the interim analysis (Section 13.7), the sample size for Part A could be increased to a maximum of 32 randomized subjects. This adjustment to the sample size would allow for an effect size of 1.0 to be detected.

For Part B, a sample size of 40 evaluable subjects per group (120 total) would provide 90% power to detect a treatment difference of 9.0 between the SAGE-547 and placebo groups and a common standard deviation of 12 points (for an effect size of 0.75) using a two-sided t-test at an alpha level of 0.05.

For Part C, a sample size of 50 evaluable subjects per group (100 total) would provide 90% power to detect a treatment difference of 8.0 between the SAGE-547 and placebo groups and a common standard deviation of 12 points (for an effect size of 0.667) using a two-sided t-test at an alpha level of 0.05.

13.7. Interim Analysis

In Part A, an interim analysis will be conducted by an independent statistician for sample size re-estimation purposes when at least 16 subjects have completed efficacy assessments through 60 hours in Part A. Since the Sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing of Part A of the study. A detailed description of the interim analysis for sample size re-estimation will be included in the SAP.

No interim analyses are planned for Parts B and C of the study.

13.8. Changes from Protocol Specified Analyses

Any changes from the analytical methods outlined in the protocol will be documented in the final SAP.

Upon the completion of each study (547-PPD-202A, 547-PPD-202B, and 547-PPD-202C), the data will be unblinded and analyzed separately, and a separate final CSR will report the findings of each study.

14. ADVERSE EVENTS

Section 14.1 lists important AE definitions.

Section 14.2 summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB/IEC.

Section 14.3 summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to regulatory authorities.

14.1. Adverse Event Definitions

14.1.1. Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

14.1.2. Suspected Adverse Reaction

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

14.1.3. Life-Threatening

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

14.1.4. Serious

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE (see definition in Section 14.1.3)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- Other medically important condition (as described below)

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent

one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

14.1.5. Unexpected

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents.

"Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

In the clinical trial setting, the term "expected" would not mean "anticipated" for the condition being treated or population being studied since "expected" would indicate being "listed in the Investigator's Brochure." For example, some AEs can be anticipated to occur as a result of a disease or condition or in a certain population (eg, cancer-related deaths in a cancer trial, strokes or acute myocardial infarctions in an older population). However, for reporting purposes, these anticipated events are not considered "expected" if they are not listed in the Investigator's Brochure (ie, the investigational drug is not suspected or known to cause them).

14.2. Investigator Responsibilities

14.2.1. Identification and Documentation of Adverse Events by Investigator

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected during subject preparation, study drug administration during screening, after the initiation of study drug administration through to Day 3, and at the Follow-up Visits through Day 30 (±3 days). SAEs will also be collected until the Day 30 (±3 days) follow-up visit. Medical conditions that occur prior to completion of the screening visit will be captured on the Medical History eCRF. Adverse events that occur after completion of the screening visit will be recorded on the AE page of the eCRF (AE eCRF).

All AEs revealed by observation, physical examinations, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the AE eCRF. Any clinically significant deterioration from baseline in laboratory assessments or other clinical findings is considered an AE and must be recorded on the AE eCRF, unless otherwise stated. AE information recorded on AE eCRF will be entered into the database on an ongoing basis. The database, including AE information, will be transferred to the Sponsor on a pre-defined schedule for review.

All AEs, 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.

For all SAEs, an SAE report form must be completed with as much information as possible and submitted in the time frame described in Section 14.2.3. When new significant information is obtained as well as when the outcome of an event is known, the SAE report form should be updated on a follow-up report. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (eg, admission report, laboratory test results, discharge summary) may be requested to be included as part of the subject's medical file.

All SAEs will be followed until the events are resolved or improved and a stable status has been achieved, or the subject is lost to follow-up.

Female patients who become pregnant during the study should be followed to determine the outcome of the pregnancy. The pregnancy must be reported to the sponsor within 24 hours of the site becoming aware of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the sponsor. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

14.2.2. Adverse Event Classification

Definitions for the categories of AE classification are included in this section.

14.2.2.1. Relationship to Investigational Drug

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 or 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

14.2.2.2. Severity

The severity of an adverse experience will be defined as follows and reported as indicated on the AE eCRF:

Mild:	Discomfort noticed, but no disruption to daily activity.
Moderate:	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.
Severe:	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.

14.2.2.3. Action Taken with Investigational Drug

Action taken with regard to administration of study drug for this study will be recorded using the one of following categories (the category "dose increased" does not apply to this study):

- Drug withdrawn: An indication that a medication schedule was modified through termination of a prescribed regimen of medication
- Dose not changed: An indication that a medication schedule was maintained
- Drug interrupted: An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication
- Dose reduced: An indication that a medication schedule was modified to a reduced rate/dose
- Unknown: Unknown, not known, not observed, not recorded, or refused
- Not applicable: Determination of a value is not relevant in the current context

14.2.2.4. Assessment of Outcome

Assessment of outcome of AEs will be categorized as one of the following:

- Ongoing: At the end of the study, the event has not resolved or stabilized
- Resolved: The event has resolved or the subject recovered without sequelae
- Resolved with sequelae: The event has at least 1 secondary outcome that may result in permanent disability and/or functional limitation
- Unknown: The status of the event is unknown
- Death: The subject has expired

14.2.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact

All SAEs that occur during the course of the study must be reported by the Investigator immediately, with the designated report form sent to the Medical Monitor within 24 hours from the point in time when the Investigator becomes aware of the SAE. Investigators must report any SAE, whether or not considered drug related. The initial report must be as

complete as possible, including assessment of the causal relationship (ie, assessment of whether there is a reasonable possibility that the drug caused the event). The Medical Monitor will contact the investigator via telephone for follow-up information regarding the SAE, as appropriate.

Information not available at the time of the initial report must be documented on a follow-up report. As additional information becomes available, the designated report form must be updated and supporting information, including hospital records, laboratory and diagnostic testing results, etc. All supporting documentation must be de-identified. In addition, all SAEs that occur up to and including 30 days after administration of study drug must be reported within 24 hours from when the Investigator becomes aware of the SAE. A final report to document resolution of all SAEs is required.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care and contact the Medical Monitor.

14.2.4. Medical Monitor and Emergency Contact Information

[redacted], MD
[redacted]
Office (9-5 EST): [redacted]
24/7 Hotline: [redacted]

14.2.5. SAE Reporting Contact Information

Contact information and reporting instructions are provided in the Safety Management Plan.

14.2.6. Reporting to Institutional Review Boards/Independent Ethics Committees

It is the responsibility of the Investigator to promptly notify the institution's IRB/IEC of all SAEs that occur at his or her site if applicable per the IRB's/IEC's requirements.

14.3. Sponsor/Medical Monitor Responsibilities

14.3.1. Monitoring of Adverse Event Data

The Medical Monitor or designee will review SAEs/AEs on an ongoing basis.

14.3.2. Reporting to Regulatory Authorities

The Sponsor or its designee is responsible for SUSAR notification to the relevant regulatory authorities per applicable regulations. All investigators participating in the study will also be informed as required by regulations in order to inform their IRBs/IECs.

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to regulatory authorities as required by national laws.

14.4. Emergency Identification of Study Medication

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment from the Medical Monitor. The Investigator will not unblind the Medical Monitor during that discussion. The process of unblinding will be described in the Safety Management Plan for the study.

15. STUDY ADMINISTRATION

15.1. Quality Control and Quality Assurance

The Investigators and institutions will permit study-related monitoring, audits, IRB review, and regulatory inspections as requested by regulatory authorities, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (ie, original medical records, laboratory reports, hospital documents, progress reports, signed ICFs, etc.) in addition to CRFs.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure that 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, CRFs 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 the Sponsor with the Investigator/institution and any other parties involved with the clinical study will be in writing in a separate agreement.

15.2. Data Handling and Recordkeeping

15.2.1. Data Handling

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

15.2.2. Case Report Form Completion

Electronic CRFs (eCRFs) 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, AEs, and subject status.

The Investigator will have access to the electronic data capture (EDC) 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.

15.2.3. Retention of Study Records

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least two years after the last marketing application approval and until there are no pending or contemplated marketing applications or two years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

15.3. Confidentiality

To maintain subject privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the CRFs 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 the Sponsor. It is understood that there is an obligation to provide the Sponsor 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 authority(ies), other Investigators, corporate partners, or consultants as required.

15.4. Publication Policy

All information concerning SAGE-547 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.

15.5. Protocol Amendments

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the study (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB/IEC, as appropriate.

16. 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.

Amin Z, Mason GF, Cavus I et al. The interaction of neuroactive steroids and GABA in the development of neuropsychiatric disorders in women. Pharmacol, Biochem and Behavior 2006;84:635-43.

Austin MP, Middleton P, Reilly NM, Highet NJ. Detection and management of mood disorders in the maternity setting: the Australian Clinical Practice Guidelines. Women Birth 2013;26(1):2-9. doi: 10.1016/j.wombi.2011.12.001. Epub 2012 Jan 2.

Belelli D, Lambert JJ. Neurosteroids: endogenous regulators of the GABA(A) receptor. Nat Rev Neurosci 2005; 6(7):565-75. PMID: 15959466.

Bitran D, Hilvers RJ, Kellogg CK. Anxiolytic effects of 3α-hydroxy-5α[β]-pregnan-20-one: endogenous metabolites of progesterone that are active at the GABAA receptor. Brain Res 1991;561(1):157-161. PMID: 1686744.

Bitran D, Purdy RH, Kellog CK. Anxiolytic effect of progesterone is associated with increases in cortical allopregnanolone and GABAA receptor function. Pharmacol Biochem Behav 1993;45(2):423-8. PMID: 8392205.

Bloch M, Schmidt PJ, Danaceau M, et al. Effects of gonadal steroids in women with a history of postpartum depression. Am J Psychiatry 2000;157(6):924-30. PMID: 10831472.

Chaudron L. Postpartum depression: what pediatricians need to know. Pediatr Rev 2003;24(5);154-61. PMID: 12728188.

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.

Coyle CM, Laws KR. The use of ketamine as an antidepressant: a systematic review and meta-analysis. Hum Psychopharmacol. 2015;30(3):152-163.

Djebaili M, Guo Q, Pettus EH, Hoffman SW, Stein DG. The neurosteroids progesterone and allopregnanolone reduce cell death, gliosis, and functional deficits after traumatic brain injury in rats. J Neurotrauma 2005;22(1):106-18. PMID: 15968816.

Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL. A meta-analysis of cytokines in major depression. Biol Psychiatry 2010;67(5):446-57. PMID: 20015486.

DSM V. Diagnostic and statistical manual of mental disorders (5th ed.). American Psychiatric Association 2013. Arlington, VA: American Psychiatric Publishing.

Earls MF; Committee on Psychosocial Aspects of Child and Family Health American Academy of Pediatrics. Incorporating recognition and management of perinatal and postpartum depression into pediatric practice. Pediatrics 2010;126(5):1032-9. doi: 10.1542/peds.2010-2348.

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. PMID: 17719367.

Epperson CN, Gueorguieva R, Czarkowski KA et al. Preliminary evidence of reduced occipital GABA concentrations in puerperal women: a 1H-MRS study. Psychopharmacol 2006; 186:425-433. PMID: 16724188.

Eser D, Schüle C, Baghai TC, Romeo E, Rupprecht R. Neuroactive steroids in depression and anxiety disorders: clinical studies. Neuroendocrinology 2006;84(4):244-54. PMID: 17159334.

Fihrer I, McMahon CA, Taylor AJ. The impact of postnatal and concurrent maternal depression on child behaviour during the early school years. J Affect Disord 2009;119(1-3):116-23. PMID: 19342104.

Fournier JC, DeRubeis RJ, Hollon SD et al. Antidepressant drug effects and depression severity—a patient-level meta-analysis. JAMA 2010;303:47-53. PMID: 20051569.

Frye CA, Duncan JE. Progesterone metabolites, effective at the GABAA receptor complex, attenuate pain sensitivity in rats. Brain Res 1994;643(1-2):194-203. PMID: 8032914.

Gangisetty O and Reddy DS. Neurosteroid withdrawal regulates GABA-A receptor α4-subunit expression and seizure susceptibility by activation of progesterone receptor-independent early growth response factor-3 pathway. Neuroscience 2010; 170:865-880. PMID: 20670676.

Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol 2005;106:1071-83. PMID: 16260528.

Gaynes BN, Gavin N, Meltzer-Brody S, Lohr KN, Swinson T, Gartlehner G, et al. Perinatal depression: prevalence, screening accuracy, and screening outcomes. Evid Rep Technol Assess (Summ) 2005;(119):1-8. PMID: 15760246.

Gilbert Evans SE, Ross LE, Sellers EM, et al. 3alpha-reduced neuroactive steroids and their precursors during pregnancy and the postpartum period. Gynecol Endocrinol 2005 21, 268-279. PMID: 16373246.

Genazzani AR, Petraglia F, Bernardi F, Casarosa E, Salvestroni C, Tonetti A, et al. Circulating levels of allopregnanolone in humans: gender, age, and endocrine influences. J Clin Endocrinol Metab 1998;83(6):2099-103. PubMed PMID: 9626145.

Glantz LA, Gilmore JH, Overstreet DH, Salimi K, Lieberman JA, Jarskog LF. Pro-apoptotic Par-4 and dopamine D2 receptor in temporal cortex in schizophrenia, bipolar disorder and major depression. Schizophr Res 2010;118(1-3):292-9. PMID: 20067857.

Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56-62. PMID: 14399272.

He JQ, Tang XW, Chen HX, Xiang Z. [Study on treatment of climacteric depression with bushen tiaogan qingxin recipe]. Zhongguo Zhong Xi Yi Jie He Za Zhi 2004;24(10):889-92. [Article in Chinese]. PMID: 15553820.

Holzbauer M, Birmingham MK, De Nicola AF, Oliver JT. In vivo secretion of 3 alpha-hydroxy-5 alpha-pregnan-20-one, a potent anaesthetic steroid, by the adrenal gland of the rat. J Steroid Biochem. 1985 Jan;22(1):97-102. PubMed PMID: 3974231.

Kask K, Bäckström T, Lundgren P, Sundström Poromaa I. Allopregnanolone has no effect on startle response and prepulse inhibition of startle response in patients with premenstrual dysphoric disorder or healthy controls. Pharmacol Biochem Behav 2009;92(4):608-13. PubMed PMID: 19268499.

Kask K, Bäckström T, Nilsson LG, Sundström-Poromaa I. Allopregnanolone impairs episodic memory in healthy women. Psychopharmacology (Berl) 2008;199(2):161-8. PMID: 18551282.

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. PMID: 18303940.

Klak J, Hill M, Parízek A, Havlíková H, et al. Pregnanolone isomers, pregnenolone and their polar conjugates around parturition. Physiol Res 2003;52(2):211-21. PMID: 12678664.

Licinio J, Wong ML. The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. Mol Psychiatry 1999;4(4):317-27. PMID: 10483047.

Luisi S, Petraglia F, Benedetto C, Nappi RE, Bernardi F, Fadalti M, et al. Serum allopregnanolone levels in pregnant women: changes during pregnancy, at delivery, and in hypertensive patients. J Clin Endocrinol Metab 2000;85(7):2429-33. PMID: 10902789.

Maguire J, Mody I. GABA(A)R plasticity during pregnancy: relevance to postpartum depression. Neuron 2008;59(2):207-13. PMID: 18667149.

Maguire J, Ferando I, Simonsen C, Mody I. Excitability changes related to GABAA receptor plasticity during pregnancy. J Neurosci 2009;29(30):9592-601. PMID: 19641122.

Majewska MD, Harrison NL, Schwartz RD, Barker JL, Paul SM. Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor. Science 1986;232:1004-7. PMID: 2422758.

McDowell, I. Measuring Health: A guide to rating scales and questionnaires. 2006: 3rd Ed. New York: Oxford University Press.

Morrow AL, Devaud LL, Purdy RH, Paul SM. Neuroactive steroid modulators of the stress response. Ann N Y Acad Sci 1995;771:257-72. PMID: 8597405.

Müller-Thomsen T, Arlt S, Mann U, Maß R, Ganzer S. Detecting depression in Alzheimer's disease: evaluation of four different scales. Arch Clin Neuropsych 2005;20:271-6. PMID: 15708735.

Nappi RE, Petraglia F, Luisi S et al. Serum allopregnanolone in women with postpartum "blues". Obstet Gynecol 2001;97 (1):77-80. PMID: 11152912.

Navarro PA, Kaddouz D, de Ziegler D, Silva de Sá MF, Ferriani RA. Vaginal administration of allopregnanolone to postmenopausal women undergoing estrogen replacement therapy: preliminary results. Maturitas 2003;46(2):147-52. PubMed PMID: 14559386.

Norberg L, Backstrom T and Wahlstrom G. Anaesthetic effects of pregnanolone in combination with allopregnanolone, thiopental, hexobarbital and flurazepam: an EEG study in the rat. Br J Anaesth 1999; 82(5):731-737. PMID: 10536552.

O'Hara MW, Wisner KL. Perinatal mental illness: definition, description and aetiology. Best Pract Res Clin Obstet Gynaecol 2014;28(1):3-12. doi: 10.1016/j.bpobgyn.2013.09.002.

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.

Ottander U, Poromaa IS, Bjurulf E, Skytt A, Bäckström T, Olofsson JI. Allopregnanolone and pregnanolone are produced by the human corpus luteum. Mol Cell Endocrinol 2005 Jul 15;239(1-2):37-44. PubMed PMID: 15935549.

Paoletti AM, Romagnino S, Contu R, et al. Observational study on the stability of the psychological status during normal pregnancy and increased blood levels of neuroactive steroids with GABA-A receptor agonist activity. Psychoneuroendocrinology 2006; 31(4): 485-492. PMID: 16406349.

Paul SM, Purdy RH. Neuroactive steroids. FASEB J 1992;6(6):2311-22. PMID: 1347506.

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. doi: 10.1176/appi.ajp.2011.10111704.

Romeo E, Ströhle A, Spalletta G, di Michele F, Hermann B, Holsboer F, Pasini A, Rupprecht R. Effects of antidepressant treatment on neuroactive steroids in major depression. Am J Psychiatry 1998;155(7):910-3. PMID: 9659856.

Sayeed I, Parvez S, Wali B, Siemen D, Stein DG. Direct inhibition of the mitochondrial permeability transition pore: a possible mechanism for better neuroprotective effects of allopregnanolone over progesterone. Brain Res 2009;1263:165-73. PMID: 19368823.

Schüle C, Romeo E, Uzunov DP, Eser D, di Michele F, Baghai TC, et al. Influence of mirtazapine on plasma concentrations of neuroactive steroids in major depression and on 3α-hydroxysteroid dehydrogenase activity. Mol Psychiatry 2006;11(3):261-72. PMID: 16344854.

Schüle C, Baghai TC, di Michele F, Eser D, Pasini A, Schwarz M. Effects of combination treatment with mood stabilizers and mirtazapine on plasma concentrations of neuroactive steroids in depressed patients. Psychoneuroendocrinology 2007;32(6):669-80. PMID: 17560730.

Shelton RC, Trivedi MH. Moderators of antidepressant response in major depression. J Clin Psychiatry 2011;72(10):e32. PMID: 22075105.

Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. Arch Intern Med 2006; 166(10):1092-1097. doi: 10.1001/archinte.166.10.1092.

Ströhle A, Romeo E, Hermann B, Pasini A, Spalletta G, di Michele F, et al. Concentrations of 3α-reduced neuroactive steroids and their precursors in plasma of patients with major depression and after clinical recovery. Biol Psychiatry 1999;45(3):274-77. PMID: 10023501.

Timby E, Balgård M, Nyberg S, Spigset O, Andersson A, Porankiewicz-Asplund J, et al. Pharmacokinetic and behavioral effects of allopregnanolone in healthy women. Psychopharmacology (Berl) 2006;186(3):414-24. PMID: 16177884.

Timby E, Hedström H, Bäckström T, Sundström-Poromaa I, Nyberg S, Bixo M. Allopregnanolone, a GABAA receptor agonist, decreases gonadotropin levels in women A preliminary study. Gynecol Endocrinol 2011;27(12):1087-93. PMID: 21190418. (Timby 2011a)

Timby E. Allopregnanolone effects in women. Clinical studies in relation to the menstrual cycle, premenstrual dysphoric disorder and oral contraceptive use. Umea University Medical Dissertation 2011; New Series No. 1459. (Timby 2011b)

Uzunova V, Sheline Y, Davis JM, Rasmusson A, Uzunov DP, Costa E, et al. Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine. Proc Natl Acad Sci 1998;95(6):3239-44. PMID: 9501247.

van Broekhoven F, Bäckström T, van Luijtelaar G, Buitelaar JK, Smits P, Verkes RJ. Effects of allopregnanolone on sedation in men, and in women on oral contraceptives. Psychoneuroendocrinology. 2007;32(5):555-64. PMID: 17470385.

Verbeek T, Bockting CL, van Pampus MG et al. Postpartum depression predicts offspring mental health problems in adolescence independently of parental lifetime psychopathology. J Affect Disord 2012;136(3):948-54. doi: 10.1016/j.jad.2011.08.035.

Ware JE, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. User's Manual for the SF-36v2® Health Survey (2nd ed). 2007. Lincoln, RI: QualityMetric Incorporated.

Wieland S, Lan NC, Mirasedeghi S, Gee KW. Anxiolytic activity of the progesterone metabolite 5α-pregnan-3α-ol-20-one. Brain Res 1991;565(2):263-8. PMID: 1688192.

APPENDICES

Copies of the rating scales and questionnaires included in Appendix 1 through Appendix 10 are for reference only.

Appendix 1. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)

The "Baseline/Screening" and "Since Last Visit" versions of the C-SSRS begin on the next full page (Posner 2011).

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103-130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***) Past X Months - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

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C-SSRS—Baseline/Screening (Version 1/14/09)

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

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SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ No ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ No ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ No ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ No ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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Appendix 2. HAMILTON RATING SCALE FOR DEPRESSION, 17-ITEM (HAM-D)

The HAM-D presents on the next full page (Hamilton 1960).

The HAM-D total score will be calculated as the sum of the 17 individual item scores. Item 16 can be rated according to history (item 16A) or actual weight change (item 16B). The item 16 score is calculated as the item 16 response that is not equal to 3 (ie, "Not assessed).

HAMILTON RATING SCALE FOR DEPRESSION: 17-ITEM VERSION (HAM-D-17)

Author: M. Hamilton

Instructions: For each item select one "cue" which best characterizes the patient.

1 – Depressed Mood		
	☐	0 Absent
	☐	1 Indicated only on questioning
	☐	2 Spontaneously reported verbally
	☐	3 Communicated non-verbally, i.e., facial expression, posture, voice, tendency to weep
	☐	4 VIRTUALLY ONLY those feeling states reported in spontaneous verbal and non-verbal communication
2 – Feelings of Guilt		
	☐	0 Absent
	☐	1 Self-reproach, feels he has let people down
	☐	2 Ideas of guilt or rumination over past errors or sinful deeds
	☐	3 Present illness is a punishment. Delusions of guilt
	☐	4 Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
3 – Suicide		
	☐	0 Absent
	☐	1 Feels life is not worth living
	☐	2 Wishes he were dead or any thoughts of possible death to self
	☐	3 Suicidal ideas or gesture
	☐	4 Attempts at suicide
4 – Insomnia Early		
	☐	0 No difficulty falling asleep
	☐	1 Complains of occasional difficulty falling asleep
	☐	2 Complains of nightly difficulty falling asleep

Reference: Hamilton, M. J Neurol Neurosurg Psychiatry. 1960; 22:56-62. Hamilton, M. Br J Soc Clin Psychol. 1967; 6:278-96. Copyright © public domain

HAMILTON RATING SCALE FOR DEPRESSION: 17-ITEM VERSION (HAM-D-17)

5 – Insomnia Middle		
	☐	0 No difficulty
	☐	1 Complains of being restless and disturbed during the night
	☐	2 Waking during the night - any getting out of bed (except to void)
6 – Insomnia Late		
	☐	0 No difficulty
	☐	1 Waking in early hours of morning but goes back to sleep
	☐	2 Unable to fall asleep again if gets out of bed
7 – Work and Activities		
	☐	0 No difficulty
	☐	1 Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies
	☐	2 Loss of interest in activity, hobbies or work - by direct report of the patient or indirect in listlessness, indecision and vacillation
	☐	3 Decrease in actual time spent in activities or decrease in productivity. In hosp., pt. spends less than 3 hrs. /day in activities *(hospital, job, or hobbies)* exclusive of ward chores
	☐	4 Stopped working because of present illness. In hospital, no activities except ward chores, or fails to perform ward chores unassisted
8 – Retardation		
	☐	0 Normal speech and thought
	☐	1 Slight retardation at interview
	☐	2 Obvious retardation at interview
	☐	3 Interview difficult
	☐	4 Complete stupor

Reference: Hamilton M. J Neurol Neurosurg Psychiatry. 1960; 22:56-62. Hamilton, M. Br J Soc Clin Psychol. 1967; 6:278-96. Copyright © public domain.

HAMILTON RATING SCALE FOR DEPRESSION: 17-ITEM VERSION (HAM-D-17)

9 – Agitation			
	☐	0 None	
	☐	1 Fidgetiness	
	☐	2 Playing with hands, hair, etc.	
	☐	3 Moving about, can't sit still	
	☐	4 Hand-wringing, nail biting, hair-pulling, biting of lips	
10 – Anxiety Psychic			
	☐	0 No difficulty	
	☐	1 Subjective tension and irritability	
	☐	2 Worrying about minor matters	
	☐	3 Apprehensive attitude apparent in face or speech	
	☐	4 Fears expressed without questioning	
11 – Anxiety Somatic		**Physiological concomitants of anxiety, such as:**	
	☐	0 Not present	**Gastrointestinal** - dry mouth, gas, indigestion, diarrhea, stomach cramps, belching
	☐	1 Mild	**Cardiovascular** – heart palpitations, headaches
	☐	2 Moderate	**Respiratory** - hyperventilation, sighing
	☐	3 Severe	**Urinary frequency**
	☐	4 Incapacitating	**Sweating**
12 – Somatic Symptoms Gastrointestinal			
	☐	0 None	
	☐	1 Loss of appetite but eating without encouragement	
	☐	2 Difficulty eating without urging	

Reference: Hamilton, M. J Neurol Neurosurg Psychiatry. 1960; 22:56-62. Hamilton, M. Br J Soc Clin Psychol. 1967; 6:278-96. Copyright © public domain

HAMILTON RATING SCALE FOR DEPRESSION: 17-ITEM VERSION (HAM-D-17)

13 – Somatic Symptoms General		
	☐	0 None
	☐	1 Heaviness in limbs, back, or head. Backaches, muscle aches. Loss of energy and fatigability
	☐	2 Any clear-cut symptoms
14 – Genital Symptoms		
Symptoms such as: Loss of libido Menstrual disturbances	☐	0 Absent
	☐	1 Mild
	☐	2 Severe
15 – Hypochondriasis		
	☐	0 Not present
	☐	1 Self-absorption *(bodily)*
	☐	2 Preoccupation with health
	☐	3 Frequent complaints, requests for help, etc.
	☐	4 Hypochondriacal delusions
16 – Loss of Weight		
	☐	0 No weight loss
	☐	1 Probable weight loss due to current depression
	☐	2 Definite *(according to patient)* weight loss due to depression
17 – Insight		
	☐	0 Acknowledges being depressed and ill OR not currently depressed
	☐	1 Acknowledges illness but attributes cause to bad food, overwork, virus, need for rest, etc.
	☐	2 Denies being ill at all

Reference: Hamilton M. J Neurol Neurosurg Psychiatry. 1960; 22:56-62. Hamilton, M. Br J Soc Clin Psychol. 1967; 6:278-96. Copyright © public domain.

Appendix 3. MONTGOMERY ASBERG DEPRESSION RATING SCALE (MADRS)

The MADRS, presented on the next full page, includes the following 10 symptoms:

1. Apparent sadness
2. Reported sadness
3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

1. *Apparent Sadness*

Representing despondency, gloom and despair, (more than just ordinary transient low spirits)

reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

0 No sadness.
1
2 Looks dispirited but does brighten up without difficulty.
3
4 Appears sad and unhappy most of the time.
5
6 Looks miserable all the time. Extremely despondent.

---

2. *Reported sadness*

Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope.

Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

0 Occasional sadness in keeping with the circumstances.
1
2 Sad or low but brightens up without difficulty.
3
4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
5
6 Continuous or unvarying sadness, misery or despondency.

---

3. *Inner tension*

Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish.

Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 Placid. Only fleeting inner tension.
1
2 Occasional feelings of edginess and ill-defined discomfort.
3
4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
5
6 Unrelenting dread or anguish. Overwhelming panic.

---

4. *Reduced sleep*

Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

0 Sleeps as usual.
1
2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
3
4 Sleep reduced or broken by at least two hours.
5
6 Less than two or three hours sleep.

---

5. *Reduced appetite*

Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

0 Normal or increased appetite.
1
2 Slightly reduced appetite.
3
4 No appetite. Food is tasteless.
5
6 Needs persuasion to eat at all.

---

6. *Concentration difficulties*

Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

Rate according to intensity, frequency, and degree of incapacity produced.

0 No difficulties in concentrating.
1
2 Occasional difficulties in collecting one's thoughts.
3
4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
5
6 Unable to read or converse without great difficulty.

---

7. *Lassitude*

Representing a difficulty getting started or slowness initiating and performing everyday activities.

0 Hardly any difficulty in getting started. No sluggishness.
1
2 Difficulties in starting activities.
3
4 Difficulties in starting simple routine activities which are carried out with effort.
5
6 Complete lassitude. Unable to do anything without help.

---

8. *Inability to feel*

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

0 Normal interest in the surroundings and in other people.
1
2 Reduced ability to enjoy usual interests.
3
4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
5
6 The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. *Pessimistic thoughts*

Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

0 No pessimistic thoughts.
1
2 Fluctuating ideas of failure, self-reproach or self depreciation.
3
4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
5
6 Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable.

10. *Suicidal thoughts*

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide.

Suicidal attempts should not in themselves influence the rating.

0 Enjoys life or takes it as it comes.
1
2 Weary of life. Only fleeting suicidal thoughts.
3
4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5
6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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Appendix 4. CLINICAL GLOBAL IMPRESSION–IMPROVEMENT SCALE (CGI-I) AND SEVERITY SCALE (CGI-S)

The CGI-I and CGI-S present on the next full page. For the purposes of Protocol 547-PPD-202, only Items 1 and 2, Severity of Illness and Global Improvement, will be assessed in subjects enrolled in the study.

1. **Severity of illness**
   Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?
   0 = Not assessed
   1 = Normal, not at all ill
   2 = Borderline mentally ill
   3 = Mildly ill
   4 = Moderately ill
   5 = Markedly ill
   6 = Severely ill
   7 = Among the most extremely ill patients

2. **Global improvement:** Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.
   Compared to his condition at admission to the project, how much has he changed?
   0 = Not assessed
   1 = Very much improved
   2 = Much improved
   3 = Minimally improved
   4 = No change
   5 = Minimally worse
   6 = Much worse
   7 = Very much worse

3. **Efficacy index:** Rate this item on the basis of **drug effect only**.
   Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.
   EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		**Side effects**			
		None	*Do not significantly interfere with patient's functioning*	*Significantly interferes with patient's functioning*	*Outweighs therapeutic effect*
Marked	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
Moderate	Decided improvement. Partial remission of symptoms	05	06	07	08
Minimal	Slight improvement which doesn't alter status of care of patient	09	10	11	12
Unchanged or worse		13	14	15	16

Not assessed = 00

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

Appendix 5. EDINBURGH POSTNATAL DEPRESSION SCALE (EPDS)

The EPDS presents on the next full page (Cox 1987).

Study ID:

Edinburgh Postnatal Depression Scale

As you are pregnant or have recently had a baby, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**, not just how you feel today.

Here is an example, already completed.

I have felt happy:
☐ Yes, all the time
☒ Yes, most of the time This would mean: "I have felt happy most of the time" during the past week.
☐ No, not very often
☐ No, not at all

Please complete the other questions in the same way.

In the past 7 days:

1. I have been able to laugh and see the funny side of things
☐ As much as I always could
☐ Not quite so much now
☐ Definitely not so much now
☐ Not at all

2. I have looked forward with enjoyment to things
☐ As much as I ever did
☐ Rather less than I used to
☐ Definitely less than I used to
☐ Hardly at all

***3. I have blamed myself unnecessarily when things went wrong**
☐ Yes, most of the time
☐ Yes, some of the time
☐ Not very often
☐ No, never

4. I have been anxious or worried for no good reason
☐ No, not at all
☐ Hardly ever
☐ Yes, sometimes
☐ Yes, very often

***5 I have felt scared or panicky for no very good reason**
☐ Yes, quite a lot
☐ Yes, sometimes
☐ No, not much
☐ No, not at all

***6. Things have been getting on top of me**
☐ Yes, most of the time I haven't been able to cope at all
☐ Yes, sometimes I haven't been coping as well as usual
☐ No, most of the time I have copied quite well
☐ No, I have been coping as well as ever

***7 I have been so unhappy that I have had difficulty sleeping**
☐ Yes, most of the time
☐ Yes, sometimes
☐ Not very often
☐ No, not at all

***8 I have felt sad or miserable**
☐ Yes, most of the time
☐ Yes, quite often
☐ Not very often
☐ No, not at all

***9 I have been so unhappy that I have been crying**
☐ Yes, most of the time
☐ Yes, quite often
☐ Only occasionally
☐ No, never

***10 The thought of harming myself has occurred to me**
☐ Yes, quite often
☐ Sometimes
☐ Hardly ever
☐ Never

Appendix 6. GENERALIZED ANXIETY DISORDER 7-ITEM SCALE (GAD-7)

The GAD-7 presents on the next full page (Spitzer 2006).

Generalized Anxiety Disorder 7-item (GAD-7) scale

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	
Total Score *(add your column scores)* =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all _____
Somewhat difficult _____
Very difficult _____
Extremely difficult _____

APPENDIX 7. PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

The PHQ-9 presents on the next full page.

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

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PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

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APPENDIX 8. BARKIN INDEX OF MATERNAL FUNCTIONING (BIMF)

The BIMF is presented on the next full page.

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Barkin Index of Maternal Functioning

Please **circle the number** that best represents how you have felt **over the past two weeks**. Please try to answer each question as honestly as possible as your responses will help us to better understand the postpartum experience.

	Strongly Disagree	Disagree	Somewhat Disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
1. I am a good mother.	0	1	2	3	4	5	6
2. I feel rested.	0	1	2	3	4	5	6
3. I am comfortable with the way I've chosen to feed my baby (either bottle or breast, or both).	0	1	2	3	4	5	6
4. My baby and I understand each other.	0	1	2	3	4	5	6
5. I am able to relax and enjoy time with my baby.	0	1	2	3	4	5	6
6. There are people in my life that I can trust to care for my baby when I need a break.	0	1	2	3	4	5	6
7. *I am comfortable* allowing a trusted friend or relative to care for my baby (can include baby's father or partner).	0	1	2	3	4	5	6
8. I am getting enough adult interaction.	0	1	2	3	4	5	6
9. I am getting enough encouragement from other people.	0	1	2	3	4	5	6
10. I trust my own feelings (instincts) when it comes to taking care of my baby.	0	1	2	3	4	5	6
11. I take a little time each week to do something for myself.	0	1	2	3	4	5	6
12. I am taking good care of my baby's physical needs (feedings, changing diapers, doctor's appointments).	0	1	2	3	4	5	6
13. I am taking good care of my physical needs (eating, showering, etc).	0	1	2	3	4	5	6
14. I make good decisions about my baby's health and well being.	0	1	2	3	4	5	6
15. My baby and I are getting into a routine.	0	1	2	3	4	5	6
16. I worry about how other people judge me (as a mother).	0	1	2	3	4	5	6
17. I am able to take care of my baby and my other responsibilities.	0	1	2	3	4	5	6
18. Anxiety or worry often interferes with my mothering ability.	0	1	2	3	4	5	6
19. *As time goes on*, I am getting better at taking care of my baby.	0	1	2	3	4	5	6
20. I am *satisfied* with the job I am doing as a new mother.	0	1	2	3	4	5	6

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APPENDIX 9. SHORT FORM-36 (ONE WEEK RECALL)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one week ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

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4. During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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6. During the <u>past week</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past week</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past week</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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9. These questions are about how you feel and how things have been with you <u>during the past week</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past week</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past week</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

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Appendix 10. HEALTH RESOURCE UTILIZATION QUESTIONNAIRE

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Health Resource Utilization Questionnaire Instructions

Purpose: The purpose of the HRU questionnaire to collect data on resource utilization in order to calculate the burden of patient care in terms of the healthcare resources required for treatment.

Administration: Survey should be completed at screening via an interview by the healthcare provider participating in the study using the questionnaire below. Additionally, the subject will be requested to provide throughout the study any updates, or new information on healthcare visits that occurred *beyond those expected per protocol*. The details of these healthcare visits will be captured in a continuous log format.

Health Resource Utilization Questionnaire (Screening)

A. Healthcare Visits

In the past 3months, did you use any of the following health care services?	Yes	No	How many visits did you have in the past 3 months?
Emergency Room Visit	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Use of an ambulance	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Outpatient Primary Care Physician Visit	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Outpatient Specialist Visit (e.g. OB/GYN, surgeon)	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Outpatient Counseling Visit (e.g. Psychiatrist, Psychologist, Therapist, mental health specialist)	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Inpatient hospital admission (beyond that required by protocol)	☐ *	☐	* Complete inpatient hospital admission detail for each admission

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B. Inpatient hospital admission detail

	Length of Stay (days)	Reason for Admission
Stay 1		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other
Stay 2		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other
Stay 3		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other
Stay 4		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other
Stay 5		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other

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Health Resource Utilization Questionnaire Instructions

Purpose: The purpose of the HRU questionnaire to collect data on resource utilization in order to calculate the burden of patient care in terms of the healthcare resources required for treatment.

Administration: Survey should be completed at screening via an interview by the healthcare provider participating in the study using the questionnaire below. Additionally, the subject will be requested to provide throughout the study any updates, or new information on healthcare visits that occurred ***beyond those expected per protocol***. The details of these healthcare visits will be captured in a continuous log format.

Health Resource Utilization Questionnaire (Post-screening Log)

A. Healthcare Visits

Since entering this study, did you use any of the following health care services?	Yes	No	How many visits did you have since entering this study?
Emergency Room Visit	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Use of an ambulance	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Outpatient Primary Care Physician Visit	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Outpatient Specialist Visit (e.g. OB/GYN, surgeon)	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Outpatient Counseling Visit (e.g. Psychiatrist, Psychologist, Therapist, mental health specialist)	☐	☐	____ Depression related ____ Pregnancy/labor/delivery related ____ Other
Inpatient hospital admission (beyond that required by protocol)	☐*	☐	* Complete inpatient hospital admission detail for each admission

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B. Inpatient hospital admission detail

	Length of Stay (days)	Reason for Admission
Stay 1		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other
Stay 2		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other
Stay 3		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other
Stay 4		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other
Stay 5		☐ Depression related ☐ Pregnancy/labor/delivery related ☐ Other

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Summary of Changes Page
Protocol 547-PPD-202
Date 02 February 2017

The following changes were made to the attached protocol in this amendment. In addition, minor revisions to formatting, punctuation, spelling, and wording (eg, capitalization, abbreviation, word order) that are not listed below were made throughout the protocol. Where relevant, the term "SAGE-547" was replaced with "study drug" and "trial" was replaced with "study."

Section number and title in Protocol (30 Jun 2016)	**Section number and title in Amendment 3 (02 Feb 2017)**	**Original text:**	**Changed to:**	**Rationale:**
Title Page	Title Page		**EUDRA CT NUMBER: 2016-5137-68**	Added the Eudra CT number
Title Page and synopsis	Title Page and synopsis	Clinical Phase: 2a	Clinical Phase: ~~2a~~**3**	Changed clinical phase from 2a to 3
Title Page	Title Page	Sponsor contact: [redacted], MD, MBA (with phone and email)	Sponsor contact: **Helen Colquhoun, M.D.** **(with phone and email)**	Changed the sponsor contact name, phone, and email address
Title Page	Title Page		**Added [redacted], M.D, FAAP as Medical Monitor (with title, address, phone, and email)**	Added [redacted] as the sponsor's Medical Monitor
Title Page	Title Page	Date of Amendment 2: 30 June 2016	Date of Amendment 2: 30 June 2016 **Date of Amendment 3:** **02 February 2017**	Added the date of Amendment 3 to the Title Page
Signature Page	Signature Page		**IND No.: 122,279** **Eudra CT No.:** **2016-005137-68**	Added the IND number, Eudra CT number, study

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			Study Phase: 3 **Sponsor: Sage Therapeutics**	phase, and sponsor
Signature Page	Signature Page	Sponsor Approval: [redacted], MD, PhD [redacted], PhD [redacted], MPH [redacted] (with titles)	Sponsor Approval: **Helen Colquhoun, M.D.** **[redacted], M.P.H.** **[redacted]** **[redacted] Ph.D.** **(with titles)**	Updated the sponsor approval signatories
Section 2, Synopsis, Study Sites	Section 2, Synopsis, Study Sites	Up to 50 sites in the United States and Canada	Up to ~~50~~**100 global** sites ~~in the United States and Canada~~	Increased the number of study sites and specified that the study would be conducted globally
Section 2, Synopsis, Duration of Subject Participation	Section 2, Synopsis, Duration of Subject Participation	Up to 35 days	Duration of Subject Participation: Up to ~~35~~37 days	Revised the total duration of subject participation from 35 days to 37 days
Section 2, Synopsis, Secondary Objectives and Section 6.2, Secondary Objectives	Section 2, Synopsis, Secondary Objectives and Section 6.2, Secondary Objectives	• To determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms in subjects with moderate PPD compared to placebo injection as assessed by the change from baseline in HAM-D total score (applies to Part C only).	• To determine if SAGE-547 Injection infused intravenously **at up to 90 µg/kg/h** for 60 hours reduces depressive symptoms in subjects with moderate PPD compared to placebo injection as assessed by the change from baseline in HAM-D total score (applies to Part C only).	Specified the dose to be used in Part C

Section number and title in Protocol (30 Jun 2016)	**Section number and title in Amendment 3 (02 Feb 2017)**	**Original text:**	**Changed to:**	**Rationale:**
Section 2, Synopsis, Secondary Objectives and Section 2, Synopsis, Schedule of Events (Table 1) and Section 6.2, Secondary Objectives and Section 12.2.1		To determine if SAGE-547 Injection infused intravenously for 60 hours increases sedation levels compared to placebo injection as assessed by the changes from baseline in Stanford Sleepiness Scale (SSS) score • Completion of the SSS prior to dosing and at Hours 2, 4, 8, 12, 18, and 24 on Day 1 (±15 minutes) unless the subject is asleep between the hours of 23.00h and 06.00h each day	~~To determine if SAGE-547 Injection infused intravenously for 60 hours increases sedation levels compared to placebo injection as assessed by the changes from baseline in Stanford Sleepiness Scale (SSS) score~~ ~~• Completion of the SSS prior to dosing and at Hours 2, 4, 8, 12, 18, and 24 on Day 1 (±15 minutes) unless the subject is asleep between the hours of 23.00h and 06.00h each day~~	Deleted evaluation of sedation using the SSS score as a secondary objective and removed it from the Schedule of Events and from study procedures to be performed (Note: the SSS will be collected and analyzed during Part A only.)
Section 2, Synopsis, Exploratory Objectives and Section 6.3, Exploratory Objectives	Section 2, Synopsis, Other Objectives and Section 6.3, Other Objectives	Section 2, Synopsis, Exploratory Objectives and Section 6.3, Exploratory Objectives	Section 2, Synopsis, **Other** Objectives and Section 6.3, **Other** Objectives	Revised Exploratory Objectives to be Other Objectives
Section 2, Synopsis, Exploratory Objectives and Section 6.3, Exploratory Objectives	Section 2, Synopsis, Other Objectives and Section 6.3, Other Objectives		Added: • **To determine if SAGE-547 Injection infused intravenously for 60 hours improves the general health status compared to placebo**	Added the SF-36 as a measure of general health status

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			as assessed by the change from baseline in the Short Form-36 (SF-36) total score at Day 7 and Day 30.	
Section 2, Synopsis, Pharmacokinetic Objective and Section 6.4, Pharmacokinetic Objective	Section 2, Synopsis, Pharmacokinetic Objective and Section 6.4, Pharmacokinetic Objective	To assess the pharmacokinetic (PK) profile of SAGE-547, metabolites of SAGE-547, and betadex sulfobutyl ether sodium (SBECD) and the concentration of SAGE-547 in breast milk when possible.	To assess the pharmacokinetic (PK) profile of SAGE-547, metabolites of SAGE-547, and betadex sulfobutyl ether sodium (SBECD)~~ and the concentration of SAGE-547 in breast milk when possible~~.	Removed the assessment of the concentration of SAGE-547 in breast milk from the PK Objective
Section 2, Synopsis, Study Design and Methodology	Section 2, Synopsis, Study Design and Methodology	This protocol comprises three multicenter, randomized, double-blind, parallel-group, placebo controlled studies of the efficacy, safety, and PK of SAGE 547 Injection in adult female subjects diagnosed with severe or moderate PPD. Subjects must remain as inpatients during the study Treatment Period,. . .	**Added**: This protocol comprises three multicenter, randomized, double-blind, parallel-group, placebo controlled studies of the efficacy, safety, and PK of SAGE 547 Injection in adult female subjects diagnosed with severe or moderate PPD. **Each study will be independently conducted, analyzed, and reported. In this protocol, Study 547-PPD-202A is hereafter referred to as Part A; Study 547-PPD-**	Added text to clarify that Parts A, B and C refer to 3 separate studies and that each study will be conducted, analyzed and reported separately.

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			202B is hereafter referred to as Part B; and Study 547 PPD-202C is hereafter referred to as Part C. In Parts A and C, subjects will be randomized to one of two treatment groups (SAGE-547 90 µg/kg/hour or placebo) on a 1:1 basis. In Part B, subjects will be randomized to one of three treatment groups (SAGE-547 60 µg/kg/hour, SAGE-547 90 µg/kg/hour, or placebo) on a 1:1:1 basis. Subjects must remain as inpatients during the study Treatment Period,. . .	
Section 2, Synopsis, Study Design and Methodology	Section 2, Synopsis, Study Design and Methodology	Subjects in the placebo group will receive infusion rates equivalent to SAGE-547 90 µg/kg/hour	Placebo subjects will receive infusion rates equivalent to SAGE-547 90 µg/kg/hour	Made a minor wording revision
Section 2, Synopsis, Study Design and Methodology and Section 7.1, Overview of Study Design and	Section 2, Synopsis, Study Design and Methodology and Section 7.1, Overview of Study Design and	. . .the study Treatment Period, which is approximately 60 hours/2.5 days in duration	. . .the study Treatment Period, which is approximately ~~60~~**72** hours/~~2.5~~3 days in duration **(60 hours of treatment and an additional 12 hours for**	Revised wording to include the 72-hour assessments in the Treatment Period and changed 2.5 days to 3 days throughout the protocol

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
relevant sections throughout the protocol	relevant sections throughout the protocol		**completion of 72-hour assessments)**	
Section 2, Synopsis, Study Design and Methodology	Section 2, Synopsis, Study Design and Methodology	A full medical and family history will be taken including recording of all depression, other Axis 1 and Axis 2 disorders and postpartum depression episodes in primary probands (who may be subject to a SCID-I interview).	A full medical and family history will be taken **from the subject** including recording of all depression, other Axis ~~1~~I and Axis ~~2~~II disorders and postpartum depression episodes in primary probands ~~(who may be subject to a SCID-I interview).~~	Removed the potential SCID-I interview of primary probands with depression, other Axis 2 disorders and PPD episodes
Section 2, Synopsis, Study Design and Methodology, Treatment Period	Section 2, Synopsis, Study Design and Methodology, Treatment Period	. . .a new bag and line hung every 24 hours	. . .a new bag ~~and line~~ hung **at least** every 24 hours	Clarified the time at which a new bag would be hung
Section 2, Synopsis, Study Design and Methodology, Treatment Period	Section 2, Synopsis, Study Design and Methodology, Treatment Period	Infusion rates will increase and then taper, with subjects receiving 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24 52 hours), followed by 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours). Subjects in the placebo group will receive infusion rates equivalent to SAGE-547 90	Infusion rates will increase and then taper, with subjects **in the SAGE-547 group** receiving 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24 52 hours), followed by 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours). ~~Subjects in the placebo group~~**Placebo subjects** will	Clarified the infusion rates for the blinded study drug.

Section number and title in Protocol (30 Jun 2016)	**Section number and title in Amendment 3 (02 Feb 2017)**	**Original text:**	**Changed to:**	**Rationale:**
		µg/kg/hour	receive infusion rates equivalent to SAGE-547 90 µg/kg/hour.	
Section 2, Synopsis, Study Design and Methodology, Follow-up Period	Section 2, Synopsis, Study Design and Methodology, Follow-up Period	For all parts, Follow-up Visits will be conducted one week (7±1 day) and one month (30±3d) after the initiation of the study drug infusion.	**For Part A, Follow-up Visits will be conducted one week (7±1 day), approximately two weeks (12±2 days), and one month (30±3 days) after the initiation of the study drug infusion. For Parts B and C, Follow-up Visits will be conducted one week (7±1 day), two weeks (14±2 days), three weeks (21±3 days), and one month (30±3 days) after the initiation of the study drug infusion. The blind will be maintained through the Follow-up period**.	Added in the specific follow-up visits for Parts A, B, and C; clarified the blind would be maintained through the Follow-up period.
Section 2, Synopsis, Number of Subjects	Section 2, Synopsis, Number of Subjects	Up to 32 subjects will be randomized in Part A, up to 60 subjects will be randomized in Part B, and up to 36 subjects in Part C.	Up to 32 subjects will be randomized in Part A, up to ~~60~~**120** subjects will be randomized in Part B, and up to ~~36~~**100** subjects **will be randomized** in Part C.	Increased the number of subjects to the randomized into Part B and Part C

Section number and title in Protocol (30 Jun 2016)	**Section number and title in Amendment 3 (02 Feb 2017)**	**Original text:**	**Changed to:**	**Rationale:**
Section 2, Synopsis, Inclusion Criteria, Number 8 and Section 8.1, Inclusion Criteria, Number 8	Section 2, Synopsis, Inclusion Criteria, Number 8 and Section 8.1, Inclusion Criteria, Number 8	8. For Part A and B, subject has a HAM-D total score of ≥26 at screening and Day 1 (prior to randomization). For Part C, subject has a HAM-D total score of ≥20 and ≤25 at screening and Day 1 (prior to randomization)	8. For Part A and B, subject has a HAM-D total score of ≥26 at screening and Day 1 (prior to **dosing**). For Part C, subject has a HAM-D total score of ≥20 and ≤25 at screening and Day 1 (prior to **dosing**)	Since sites could randomize subjects 24 hours in advance of dosing, wording was changed from prior to randomization to prior to dosing.
Section 2, Synopsis, Inclusion Criteria, Number 9 and Section 8.1, Inclusion Criteria, Number 9	Section 2, Synopsis, Inclusion Criteria, Number 9 and Section 8.1, Inclusion Criteria, Number 9	9. Subject is ≤6 months postpartum	9. Subject is ≤6 months postpartum **at screening**	Specified that the subject was ≤6 months postpartum at screening
Section 2, Synopsis, Inclusion Criteria, Number 10 and Section 8.1, Inclusion Criteria, Number 10	Section 2, Synopsis, Inclusion Criteria, Number 10 and Section 8.1, Inclusion Criteria, Number 10	10. Subject is willing to delay the start of other antidepressant or anxiety mediations and any new pharmacotherapy regimens, including prn benzodiazepine anxiolytics, until the study drug infusion and 72-hour assessments have been completed	10. Subject is willing **at screening** to delay **the** start of ~~other antidepressant or anxiety mediations and~~ any new pharmacotherapy regimens, including ~~prn benzodiazepine anxiolytics~~ **antidepressant or anti-anxiety medication**, until the study drug infusion and 72-hour assessments have been completed; **if the subject is taking psychotropic medications, these must be at a stable dose from 14**	Clarified the timing of prior use of psychotropic medications and that dose must have been stable and remain stable throughout the study.

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			days prior to screening until the 72-hour assessments have been completed	
Section 2, Synopsis, Inclusion Criteria, Number 11 and Table 1, Schedule of Events and Section 8.1, Inclusion Criteria, Number 11 and Section 12.1 Screening Period	Section 2, Synopsis, Inclusion Criteria, Number 11	Subject has no detectable hepatitis B surface antigen (HbsAg), anti-hepatitis C virus (HCV) and human immunodeficiency virus (HIV) antibody at Screening • Blood will be collected to screen for hepatitis and HIV (at screening)	**(Removed)** ~~Subject has no detectable hepatitis B surface antigen (HbsAg), anti-hepatitis C virus (HCV) and human immunodeficiency virus (HIV) antibody at Screening~~ ~~• Blood will be collected to screen for hepatitis and HIV (at screening)~~	Virology was not considered relevant at Screening; deleted Inclusion 11 and removed hepatitis and HIV screen from the schedule of events and screening visit procedures
Section 2, Synopsis, Exclusion Criteria, Number 1 and Section 8.2, Exclusion Criteria, Number 1	Section 2, Synopsis, Exclusion Criteria, Number 1 and Section 8.2, Exclusion Criteria, Number 1	Recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, or nose and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this	**Subject has renal failure requiring dialysis or fulminant hepatic failure or is anemic (hemoglobin ≤10 g/dL)**	Specified renal failure or anemia as exclusion criteria.

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
		clinical study.		
Section 2, Synopsis, Exclusion Criteria, Number 5 and Section 8.2, Exclusion Criteria, Number 5	Section 2, Synopsis, Exclusion Criteria, Number 5 and Section 8.2, Exclusion Criteria, Number 5	Medical history of seizures	**(Removed)**	Deleted history of seizures as an exclusion criterion
Section 2, Synopsis, Exclusion Criteria, Number 7 and Section 8.2, Exclusion Criteria, Number 7	Section 2, Synopsis, Exclusion Criteria, Number 7 and Section 8.2, Exclusion Criteria, Number 7	7. History of active alcoholism or drug addiction (including benzodiazepines) in the 12 months prior to screening.	**7.** History of active alcoholism or drug ~~addiction~~ **abuse** (including benzodiazepines) in the 12 months prior to screening. **A positive urine drug screen (except benzodiazepines under certain circumstances [see Section 10.3.3 and Section 11.1.2.6]) is exclusionary.**	Clarified that use of benzodiazepines wasn't necessarily exclusionary; however, positive drug screen for any other drugs of abuse was exclusionary.
Section 2, Synopsis, Exclusion Criteria, Number 9 and Section 8.2, Exclusion Criteria, Number 9	Section 2, Synopsis, Exclusion Criteria, Number 9 and Section 8.2, Exclusion Criteria, Number 9	9. Administration of psychotropics that have been initiated within 14 days prior to Screening and are not being taken at a stable dose.	**(Removed)** ~~9. Administration of psychotropics that have been initiated within 14 days prior to Screening and are not being taken at a stable dose.~~	Deleted this exclusion criterion
	Section 2, Synopsis, Exclusion Criteria, Number 10		**Added:** **10. Subject has previously participated in this study or**	Added an exclusion criterion to exclude subjects who had participated in any study of

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
	and Section 8.2, Exclusion Criteria, Number 10		**any other study employing SAGE-547**	SAGE-547
Section 2, Synopsis, Exclusion Criteria, Number 9 and Section 8.2, Exclusion Criteria, Number 9	Section 2, Synopsis, Exclusion Criteria, Number 11 and Section 8.2, Exclusion Criteria, Number 11	9. Administration of psychotropics that have been initiated within 14 days prior to Screening and are not being taken at a stable dose	~~9. Administration of psychotropics that have been initiated within 14 days prior to Screening and are not being taken at a stable dose~~ ~~9.~~**11. Administration of electroconvulsive therapy (ECT) within 14 days prior to screening and/or plans to administer ECT before the Study Day 7 Visit**	Added an exclusion criterion to exclude subjects who received ECT within 14 days of screening through the Day 7 visit
Section 2, Synopsis, Randomization and Stopping Rules and Section 7.2, Blinding and Randomization	Section 2, Synopsis, Randomization and Section 7.2, Blinding and Randomization	Subjects will be randomized to receive SAGE-547 Injection or placebo;	**Removed: Stopping Rules** **Added: Randomization will be stratified by antidepressant use at baseline and will follow the computer-generated randomization schedule.** Subjects will be randomized **within stratum** to receive SAGE-547 Injection or placebo;	Removed Stopping Rules from the heading since no stopping rules were discussed; added that randomized would be stratified by antidepressant use at baseline according to the randomization schedule
Section 2, Synopsis, Criteria	Section 2, Synopsis, Criteria	For Part B, the primary	For Part B, the primary	Removed the statement that

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
for Evaluation, Primary Endpoint	for Evaluation, Primary Endpoint	comparison will be between 90 µg SAGE-547 and placebo at the 60-hour assessment; if this comparison is significant at the 0.05 level, then the 60 µg group will be compared to placebo at the same 0.05 level of significance; otherwise, the comparison will be carried out at the 0.025 level of significance.	comparison will be between 90 µg SAGE-547 and placebo at the 60-hour assessment; if this comparison is significant at the 0.05 level, then the 60 µg group will be compared to placebo at the ~~same~~ 0.0~~5~~**4** level of significance More **details will be provided in Statistical Analysis Plans (SAPs) regarding strong control of overall level of significance for multiple testing, including testing of key secondary endpoints.**	the level of significance for the 60 µg and placebo comparison would be 0.025 if the comparison between the 90 µg and placebo group was not significant; clarified that details regarding the level of significance for multiple testing would be provided in the SAPS.
Section 2, Synopsis, Criteria for Evaluation, Secondary Endpoints	Section 2, Synopsis, Criteria for Evaluation, Secondary Endpoints	All secondary endpoints apply to Parts A, B and C unless otherwise stated. Additional measures of depressive symptom severity will be administered before, during, and after the infusion of study drug. . . GAD-7 will also be administered before, during, and after the infusion of study drug. As with other secondary efficacy endpoints,	~~All secondary endpoints apply to Parts A, B and C unless otherwise stated.~~ Additional measures of depressive symptom severity will be administered ~~before, during, and after the infusion of study drug~~. . . GAD-7 will also be administered ~~before, during, and after the infusion of study drug. As with other secondary efficacy endpoints~~	Removed statements that questionnaires would be administered before, during and after the study drug infusion

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			and	
Section 2, Synopsis, Criteria for Evaluation, Sample Size Calculation and Section 13.6, Determination of Sample Size	Section 2, Synopsis, Criteria for Evaluation, Sample Size Calculation and Section 13.6, Determination of Sample Size	Assuming a two-sided t-test at an alpha level of 0.05, a sample size of 10 evaluable subjects per group would provide 70% power. . . For Part B, a sample size of 40 evaluable subjects per group (120 total) would provide 90% power to detect an effect size of 0.9 between the SAGE-547 and placebo groups and a common standard deviation of 12 points using a two-sided t-test at an alpha level of 0.05. For Part C, a sample size of 50 evaluable subjects per group (100 total) would provide 90% power to detect an effect size of 0.8 between the SAGE-547 and placebo groups and a common standard deviation of 12 points using a two-sided t-test at an alpha level of 0.05.	~~Assuming~~ **Using** a two-sided t-test at an alpha level of 0.05, a sample size of 10 evaluable subjects per group **for Part A** would provide 70% power. . . For Part B, a sample size of 40 evaluable subjects per group (120 total) would provide 90% power to detect **a treatment difference of** ~~an effect size of 0.~~**9.0** between the SAGE-547 and placebo groups and a common standard deviation of 12 points **(for an effect size of 0.75)** using a two-sided t-test at an alpha level of 0.05. For Part C, a sample size of 50 evaluable subjects per group (100 total) would provide 90% power to detect **a treatment difference of** ~~an effect size of 0.~~**8.0** between the SAGE-547 and placebo groups and a common standard deviation of 12	Revised the treatment difference and effect size between the SAGE-547 and placebo groups for the sample size determination

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			points (**for an effect size of 0.667**) using a two-sided t-test at an alpha level of 0.05.	
Section 2, Synopsis, Efficacy Analysis and Section 13.4, Primary Endpoints	Section 2, Synopsis, Efficacy Analysis and Section 13.4, Primary Endpoints	Center will be treated as a random effect while all other explanatory variables will be treated as fixed effects**.** Comparisons at other time points will be conducted to support the findings for the primary comparison.	**Center and all other explanatory variables will be treated as fixed effects.** Comparisons at other time points, **including the Day 30 time point,** will be conducted to support the findings for the primary comparison. If this dose comparison is significant at the 0.05 level, then the 60 µg group will be compared to placebo ~~at the same 0.05 level of significance; otherwise comparison of the 60 µg dose will be carried out at the 0.025 level of significance~~. **More details will be provided in the SAPs regarding strong control of overall level of significance for multiple testing, including testing of key secondary endpoints**.	Revised center to be treated as a fixed effect (rather than a random effect); clarified the statistical analysis; stated that details of the analyses would be provided in the SAPs for the 3 studies

Section number and title in Protocol (30 Jun 2016)	**Section number and title in Amendment 3 (02 Feb 2017)**	**Original text:**	**Changed to:**	**Rationale:**
Section 2, Synopsis, Efficacy Analysis	Section 13.5.1, Efficacy Analysis	If this dose comparison is significant at the 0.05 level, then the 60 µg group will be compared to placebo. Any dichotomous response variables will be analyzed using logistic regression methods.	**For efficacy analysis purposes, centers with fewer than 15 subjects for Part B or 10 subjects for Part C per center will be pooled within regions (eg, North America region centers will be pooled separately those in Europe).** If this dose comparison is significant at the 0.05 level, then the 60 µg group will be compared to placebo **at the 0.04 level.** ~~Logistic regression~~ **GEE analysis** methods will be used for the analysis of the following response variables:	Described pooling within region for centers with fewer than 15 subjects in Part B or 10 subjects in Part C; inserted the significance level for the comparison between 60 µg and placebo; replaced logistic regression methods with GEE analysis methods
Section 2, Synopsis, Schedule of Events (Table 1)	Section 2, Synopsis, Schedule of Events (Table 1)	Screening period, Day -5 to Day -1 Follow-up Period, Day 12 (+1d)	Screening period, Day ~~-5~~**-7** to Day -1 Follow-up Period, Day ~~12~~**14** (+~~1~~**2**d) **Day 21 (+3d)** **Added footnote "a" to Day-7, Day 14, and Day 21: The screening period for Part A is from Day -5 to**	Revised timing of screening period; revised timing of follow-up visits to be weekly; added a Day 21 visit; added a footnote to indicate the different days for screening and follow-up visits for Part A

Section number and title in Protocol (30 Jun 2016)	**Section number and title in Amendment 3 (02 Feb 2017)**	**Original text:**	**Changed to:**	**Rationale:**
			Day -1. Follow-up Visits for Part A are on Days 7, 12, and 30.	
Section 2, Synopsis, Schedule of Events (Table 1) and Section 12.2.1, Day 1 and Section 12.2.2, Day 2 and Section 12.2.3, Day 3	Section 2, Synopsis, Schedule of Events (Table 1)	Pulse Oximetry • Pulse oximetry will be monitored continuously (from H0 until H60), and checked approximately every 2 hours, including during the overnight hours, or at the alarm	~~Pulse Oximetry~~ ~~• Pulse oximetry will be monitored continuously (from H0 until H60), and checked approximately every 2 hours, including during the overnight hours, or at the alarm~~	Removed pulse oximetry assessments
Section 2, Synopsis, Schedule of Events (Table 1)	Section 2, Synopsis, Schedule of Events (Table 1)		Added SCID-I at screening and collection of HCRU at screening and throughout study and defined SCID-I and HCRU in footnote to table	SCID-I was used at screening to confirm eligibility for inclusion in the study HCRU was included.
Section 2, Synopsis, Schedule of Events (Table 1) and Section 12, Study Procedures	Section 2, Synopsis, Schedule of Events (Table 1) and Section 12, Study Procedures		Added SF-36 at Day 1, Day 7, Day 14, Day 21, and Day 30 to Schedule of Events (Table 1) and defined SF-36 in footnote to table Added SF-36 to study procedures specified for Days 1, 7, 14, 21, and 30.	Added the SF-36 to the exploratory endpoints to measure general health status at Day 1, Day 7, and Day 30.
Table of Contents, 12.3	Table of Contents, 12.3	Follow-up Period (Day 7 through Day 60)	Follow-up Period (Day 7 through Day ~~60~~**30**)	Corrected the Follow-up Period to be through Day 30

Section number and title in Protocol (30 Jun 2016)	**Section number and title in Amendment 3 (02 Feb 2017)**	**Original text:**	**Changed to:**	**Rationale:**
List of Abbreviations and Definitions of Terms	List of Abbreviations and Definitions of Terms		Added SF-36 (Short Form-36), HCRU (Healthcare Resource Utilization), MCS (mental component summary), and PCS (physical component summary) Deleted abbreviations and definitions for BMP, CYP, FDA, HCV, HIV, and SSS	Added the definitions for the abbreviation, SF-36, HCRU, MCS, and PCS, and deleted abbreviations that are no longer used in the protocol
Section 4.3, Summary of Nonclinical and Clinical Experience with Allopregnanolone or SAGE-547	Section 4.3, Summary of Nonclinical and Clinical Experience with Allopregnanolone or SAGE-547	Summary of Nonclinical and Clinical Experience with Allopregnanolone or SAGE-547	Summary of Nonclinical and Clinical Experience with ~~Allopregnanolone~~ or SAGE-547	Removed mention of allopregnanolone from the title of the heading
Section 4.3.2, Clinical Experience	Section 4.3.2, Clinical Experience	The clinical PK data with intravenous (IV) administration of allopregnanolone in healthy women, men, and women on oral contraceptives confirmed the PK observations in animals of a short half-life (t½ 20-40 mins), Cmax achievable at approximately third trimester levels. . . There are currently no double-blind, placebo-	The clinical PK data with intravenous (IV) administration of allopregnanolone in healthy women, men, and women on oral contraceptives confirmed the PK observations in animals of ~~a short half-life (t½ 20-40 mins),~~ Cmax achievable at approximately third trimester levels . . . ~~There are currently no double-blind, placebo-~~	Removed statement about half-life in animals

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
		controlled clinical efficacy data for SAGE-547 in PPD.	~~controlled clinical efficacy data for SAGE-547 in PPD.~~	
Section 4.4, Potential Risks and Benefits	Section 4.4, Potential Risks and Benefits	In the recently completed open-label clinical study of SAGE-547 in PPD (547-PPD-201), a total of 14 AEs were reported in four subjects. As this is one of the first clinical trials of SAGE 547 in PPD, the potential benefits in this population are unknown, although the risks are likely to be similar to those mentioned above. Given the nonclinical rationale and the fact that endogenous allopregnanolone in humans appears to play a role in psychiatric disorders such as major depression, premenstrual dysphoric disorder, and anxiety disorders, it is possible that subjects may have a clinical benefit at the exposures selected for this trial. In view	In the ~~recently completed~~ open-label clinical study of SAGE-547 in PPD (547-PPD-201), a total of 14 AEs were reported in four subjects. **In the recently completed 547-PPD-202A, there were no SAEs or discontinuations due to AEs. Out of 10 subjects who received SAGE-547, four reported AEs, and of 11 subjects who received placebo, eight reported AEs (Table 2). Three subjects in each treatment group reported dizziness, sedation or somnolence. Psychiatric disorder AEs, including abnormal dreams, insomnia and anxiety, were all reported in the group that received placebo. Three subjects in the placebo group and one in the SAGE-547 group reported**	Revised the text on potential risks and benefits to include AE data from 547-PPD-202A

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
		of the limited nature of the demonstrated risks of exogenous allopregnanolone infusion and the potential for benefit in severe PPD, there is a favorable benefit-risk evaluation for the conduct of the present study.	**nausea. Other AEs reported by more than one subject were infusion site pain and headache, all reported on placebo. One subject did not tolerate 60 µg/kg/hour due to sedation, thought to be associated with concomitant administration of a high dose of benzodiazepine, so the dose was reduced to 30 µg/kg/hour from 12 to 24 hours. The subject received 60 µg/kg/hour from 24 to 30 hours and 30 µg/kg/hour from 30 to 60 hours and completed the study.** **[inserted an AE table]** ~~As this is one of the first clinical trials of SAGE 547 in PPD, the potential benefits in this population are unknown, although the risks are likely to be similar to those mentioned above. Given the nonclinical rationale and the fact that endogenous allopregnanolone in humans~~	

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			~~appears to play a role in psychiatric disorders such as major depression, premenstrual dysphoric disorder, and anxiety disorders, it is possible that subjects may have a clinical benefit at the exposures selected for this trial.~~ **In 547-PPD-202A, the primary endpoint of the mean change from baseline in HAM-D total score at 60 hours compared with placebo [LS mean treatment difference of 12.2] was highly significant (p=0.008). In addition, the significant separation between the active and placebo groups was evident at 24 hours, and remained so at subsequent time points through 72 hours, 7 days, and 30 days after initiation of treatment.** In view of the limited nature of the demonstrated risks of exogenous allopregnanolone	

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			infusion and the potential for benefit in ~~severe~~ PPD, there is a favorable benefit-risk evaluation for the **continued** conduct of the present study.	
Section 5.1, Institutional Review Board or Independent Ethics Committee	Section 5.1, Institutional Review Board or Independent Ethics Committee	This trial will be initiated only after the protocol has been reviewed and approved by the Institutional Review Board (IRB) where the study is to be conducted. The IRB must meet all US Food and Drug Administration (FDA) requirements governing IRBs (Code of Federal Regulations [CFR], Title 21, Part 56). The same applies for the implementation of changes introduced by an amendment.	**The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an Institutional Review Board (IRB) or Independent Ethics Committee (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**	Clarified that IRB/IEC written approval was required before a subject could be enrolled into the study, that the PI was to inform the IRB/IEC of any amendments to the protocol, which would require re-approval, and that the IRB/IEC was to approve all advertising used to recruit subjects.

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			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 or IEC 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.**	
Section 7.1, Overview of Study Design	Section 7.1, Overview of Study Design	Figure 1: Study Design – Part A and Part C Figure 2: Study Design – Part B	**Figure 1: Study Design – Part A** Figure 2: Study Design – Part B	Revised the study design diagrams to show the different follow-up time points for Part A and Parts B and C

Section number and title in Protocol (30 Jun 2016)	**Section number and title in Amendment 3 (02 Feb 2017)**	**Original text:**	**Changed to:**	**Rationale:**
			Figure 2: Study Design – Part C **[revised the study design figures for Parts B and C]**	
Section 7.1, Overview of Study Design	Section 7.1, Overview of Study Design	All study-related procedures will occur after written informed consent is obtained at the screening visit, which will occur during the Screening Period window (Day -7 through Day 1). Subjects will attend the clinic for safety follow-up assessment at 1 week (7±1d) and 1 month (30±3d) after the initiation of the study drug infusion.	All study-related procedures will occur after written informed consent is obtained at the screening visit, which will occur during the Screening Period window (**Day -5 through Day -1 for Part A**; Day -7 through Day -1 **for Parts B and C**). Subjects will attend the clinic for safety follow-up assessment at 1 week (7±1d), **12 days (Part A), 2 weeks (14±2d [Part B and C]), 3 weeks (21±1d [Part B and C]),** and 1 month (30±3d) after the initiation of the study drug infusion.	Clarified the timing of the screening period window and the follow-up visits for Part A and Parts B and C
Section 10.1, Dosing Schedule	Section 10.1, Dosing Schedule	Subjects will be randomized to receive 60 hours of IV treatment with either SAGE-547 Injection or placebo.	Subjects will be randomized to receive 60 hours of IV treatment with either SAGE-547 Injection or placebo, **according to a computer-**	Added that subjects were randomized to a treatment group according to a computer-generated randomization schedule.

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			generated randomization schedule.	
Section 10.1, Dosing Schedule, Figure 3 and Figure 4	Section 10.1, Dosing Schedule, Figure 3, Figure 4, and Figure 5	Figure 3: Trial Design and Timeline for Dosing – Parts A and C Figure 4: Trial Design and Timeline for Dosing – Part B	**Figure 3: Trial Design and Timeline for Dosing – Part A** **Figure 4: Trial Design and Timeline for Dosing – Part B** **Figure 5: Trial Design and Timeline for Dosing – Part C** **[Figures 4 and 5 were revised to indicate follow-up on Days 14 and 21; a footnote was added to Figure 5 to indicate that the 4-hour taper on Day 3 applied only to the 90 µg/kg/h dose group]**	
Section 10.3, Concomitant Medications and Restrictions	Section 10.3, **Prior Medications,** Concomitant Medications, and Restrictions	Section 10.3, Concomitant Medications and Restrictions	Section 10.3, **Prior Medications,** Concomitant Medications, and Restrictions	Added prior medications to section heading
Section 10.3.1, Concomitant Medications	Section 10.3.1, **Prior** Medications	No text was provided relating to prior medications	The start and end dates, route, **dose/units, and frequency of all medications taken within 60 days prior to signing the**	Added information regarding use of prior medications

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			informed consent will be recorded, as well as all medications given to treat the current PPD episode that are recorded on the SCID-I during the screening visit.	
Section 10.3.1, Concomitant Medications	Section 10.3.2, Concomitant Medications	Subjects will receive standard of care for adult female patients diagnosed with PPD. 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 10.3. All concomitant medications should be documented throughout the study from Screening through Day 30 (±3 days) and recorded on the eCRF. Prior medications (ie, those taken prior to signing of informed consent) that required wash-out for study entry will also be documented.	**All medications taken from signing the informed consent through the Day 30 (±3 days) visit will be recorded on the eCRF.** Subjects will receive standard of care for adult female patients diagnosed with PPD. 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 10.3. ~~All concomitant medications should be documented throughout the study from Screening through Day 30 (±3 days) and recorded on the eCRF. Prior medications (ie, those taken~~	Clarified the timeframe for collecting use of concomitant medications.

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			~~prior to signing of informed consent) that required wash-out for study entry will also be documented.~~	
Section 10.3.2, Prohibited Medications and Appendix 10, Selected Inducers, Inhibitors, and Substrates of CYP2C9	Section 10.3.3, Prohibited Medications	• 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 on this medication for at least 30 days prior to study enrollment. • Benzodiazepines are to be avoided as much as possible. Eligible subjects taking a benzodiazepine at the time of study entry will be permitted to continue to take their current dose of the benzodiazepine (to prevent acute withdrawal), but no	~~• 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 on this medication for at least 30 days prior to study enrollment.~~ • **Subjects may not** start new pharmacotherapy regimens, including antidepressant **or anti-anxiety medications, from the time of informed consent until the study drug infusion and 72-hour assessments have been**	Revised the medications that are prohibited during the study; deleted the text relating to substrates of CYP2C9; deleted the Appendix that listed the prohibited inducers, inhibitors, and substrates of CYP2C9

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
		new benzodiazepine use will be permitted during the course of the study. Particular attention should be paid to assessment of AEs and implementation of the dose interruption and reduction scheme in subjects on concomitant benzodiazepines since they have been shown to have a supra-additive effect with pregnanolone in an animal model of anesthesia (Norberg 1999). • The use of hypnotics for sleep/insomnia such as Ambien® and trazodone are to be avoided. • Anticonvulsants and atypical antipsychotics are to be avoided if possible and are not to be initiated at any time during active treatment period (60 hours). However, if a subject is taking one of these medications for at least 30 days prior to study admission, they will be permitted to	**completed. If clinically indicated, new antidepressant medications may be started or existing antidepressant medication regimens may be changed once the 72-hour assessments have been completed. Consideration should also be given to deferring, starting, or changing antidepressant medication regimens until the Day 7, Day 14, Day 21, or Day 30 visits if the HAM-D score has improved.** • **If the subject is taking psychotropic medications, these must be at a stable dose from 14 days prior to screening to completion of the 72-hour assessments.** • Benzodiazepines are to be avoided as much as possible **owing to the potential for a synergistic sedative effect**. Eligible subjects taking a benzodiazepine at the time of	

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
		remain on this medication, at their current dose (no dose adjustments are allowed). • SAGE-547 has demonstrated inhibitory effects on cytochrome P-450 (CYP) 2C9 (CYP2C9). The following medications are primarily metabolized by CYP2C9 and therefore are prohibited during SAGE-547 administration: fluconazole and miconazole (antifungal), amentoflavone (constituent of Ginkgo biloba and St. John's Wort), sulfaphenazole (antibacterial), valproic acid (anticonvulsant, mood-stabilizing), and apigenin. See Appendix 10 for a complete list.	study entry will 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. ~~Particular attention should be paid to assessment of AEs and implementation of the dose interruption and reduction scheme in subjects on concomitant benzodiazepines since they have been shown to have a supra-additive effect with pregnanolone in an animal model of anesthesia (Norberg 1999).~~ ~~• The use of hypnotics for sleep/insomnia such as Ambien® and trazodone are to be avoided.~~ ~~• Anticonvulsants and atypical antipsychotics are to be avoided if possible and are not to be initiated at any time during active treatment period~~	

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			~~(60 hours). However, if a subject is taking one of these medications for at least 30 days prior to study admission, they will be permitted to remain on this medication, at their current dose (no dose adjustments are allowed).~~ ~~• SAGE-547 has demonstrated inhibitory effects on cytochrome P-450 (CYP) 2C9 (CYP2C9). The following medications are primarily metabolized by CYP2C9 and therefore are prohibited during SAGE-547 administration: fluconazole and miconazole (antifungal), amentoflavone (constituent of Ginkgo biloba and St. John's Wort), sulfaphenazole (antibacterial), valproic acid (anticonvulsant, mood-stabilizing), and apigenin. See Appendix 10 for a complete list.~~	
	Section 10.3.4, Restrictions		Added: **Section 10.3.4, Restrictions** • **Electroconvulsive**	

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			therapy (ECT) is prohibited from 14 days prior to screening until after the Day 7 visit.	
Section 11.1.2.6, Drug of Abuse and Alcohol	Section 11.1.2.6, Drug of Abuse and Alcohol	Alcohol will be assessed in plasma at screening and via breathalyzer or urine dipstick on Day 1.	**A positive urine drug screen for any of the tested drugs of abuse (except benzodiazepines) is exclusionary.** Alcohol will be assessed in plasma at screening and via breathalyzer or urine dipstick on Day 1.	Clarified that positive drug screen for any tested drug of abuse was exclusionary except benzodiazepines under the specified circumstances.
Section 11.2.3, Exploratory Patient Reported Outcome Measures	Section 11.2.3, Patient Reported Outcome Measures	These will be measured by the following clinician- and subject-rated outcome measures: EPDS, PHQ-9, and BIMF.	These will be measured by the following clinician- and subject-rated outcome measures: EPDS, PHQ-9, BIMF**, and SF-36.**	Added the SF-36 to the other endpoints to measure general health status
(No Section 11.2.3.4)	Section 11.2.3.4, Short Form-36 (SF-36)		**11.2.3.4 Short Form-36 (SF-36)** **The Medical Outcomes Study Short Form-36 (SF-36v2) is a 36-item measure of health status that has undergone validation in many different disease states (Ware 2007). The**	Added a description of the SF-36 and included a copy in Appendix 10

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			SF-36 covers eight health dimensions including four physical health status domains (physical functioning, role participation with physical health problems [role-physical], bodily pain, and general health) and four mental health status domains (vitality, social functioning, role participation with emotional health problems [role-emotional], and mental health). In addition, two summary scores, physical component summary (PCS) and mental component summary (MCS), are produced by taking a weighted linear combination of the eight individual domains. The SF-36v2 is available with two recall periods: the standard recall period is 4 weeks and the acute recall period is one week. This study will use the acute	

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			version, which asks patients to respond to questions as they pertain to the past week. Higher SF-36 scores indicate a better state of health. The SF-36 requires approximately 10 minutes to complete, and can be self-administered or completed by interview in person or by telephone. **A copy of the SF-36 is provided in Appendix 10.**	
(No Section 11.2.3.5)	Section 11.2.3.5, Healthcare Resource Utilization (HCRU) and Appendix 10		**Subject-reported healthcare resource utilization data, including baseline diagnosis history, baseline antidepressant treatment history, and healthcare visits, inpatient visits, and medication use, will be collected at screening and on Day 30 of follow-up (or at early termination). A copy of the health resource utilization questionnaire is provided in Appendix 10.**	Added collection of HCRU data and inserted the form to be used into Appendix 10

Section number and title in Protocol (30 Jun 2016)	**Section number and title in Amendment 3 (02 Feb 2017)**	**Original text:**	**Changed to:**	**Rationale:**
Section 11.3.1, Plasma PK Samples		Section 11.3.1, Plasma PK Samples	~~Section 11.3.1, Plasma PK Samples~~	Deleted the section subheading since Section 11.3.2 was deleted
Section 11.3.2, Breastmilk PK Samples		Women who are actively lactating at Screening, and who otherwise fulfill all of the inclusion and exclusion criteria for the study, will be asked if they will consent to pumping. Breastmilk will be collected and pooled at pre-defined intervals. The times of the first and last pumping of each collection period will be recorded. Breastmilk will be pooled within each collection period and the total volume will be measured. Detailed instructions for breastmilk PK sampling, processing methods, storage and shipping will be provided in the study PK Manual. After Study Day 12, women may resume giving breastmilk to their infant, per Inclusion Criteria 5.	~~Women who are actively lactating at Screening, and who otherwise fulfill all of the inclusion and exclusion criteria for the study, will be asked if they will consent to pumping. Breastmilk will be collected and pooled at pre-defined intervals. The times of the first and last pumping of each collection period will be recorded. Breastmilk will be pooled within each collection period and the total volume will be measured. Detailed instructions for breastmilk PK sampling, processing methods, storage and shipping will be provided in the study PK Manual. After Study Day 12, women may resume giving breastmilk to their infant, per Inclusion Criteria 5.~~	

Section number and title in Protocol (30 Jun 2016)	**Section number and title in Amendment 3 (02 Feb 2017)**	**Original text:**	**Changed to:**	**Rationale:**
Section 12, Study Procedures	Subjects who are evaluated at the Day 3 visit of the Treatment Period (ie, all Hour 60 assessments are completed, post-infusion) and complete the Day 30 (±3 days) visit during the Follow-up Period will be defined as study completers.	Section 12, Study Procedures	Subjects who ~~are evaluated at the Day 3 visit of the Treatment Period (ie, all Hour 60~~ **complete the** assessments ~~are completed, post-infusion)~~ **at Hour 60** and ~~complete the~~ Day 30 (±3 days) ~~visit during the Follow-up Period~~ will be defined as study completers.	Clarified the definition of study completers
Section 12.1, Screening Period	Section 12.1, Screening Period	The Screening Period consists of a window from Day -5 through Day -1 prior to starting SAGE 547 treatment.	The Screening Period consists of a window from Day ~~-5~~**7** through Day -1 prior to starting SAGE 547 treatment **(up to 5 days [Day -5 to -1; Part A] or up to 7 days** [Day -7 to -1; Parts B and C]).	Clarified the timing of the window for the Screening Period for Parts A, B, and C.
Section 12.1, Screening Period	Section 12.1, Screening Period	A full medical and family history will be taken including recording of all depression, other Axis 1 and Axis 2 disorders and postpartum depression episodes in primary probands (who may be subject to a SCID-I interview).	A full medical and family history will be **taken from the subject using a SCID-I interview**, including recording of all depression (**major depressive disorders, premenstrual dysphoric disorder, menstrual migraine, and other psychiatric disorders per DSM**), other Axis **I** and	Removed the potential SCID-I interview of primary probands with depression, other Axis II disorders and PPD episodes and, instead, collected family history for primary probands from the subject.

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			Axis **II** disorders, and **pregnancy history including birth complications, and postpartum** depression episodes. **Family history will be collected from the subject for primary probands** ~~(who may be subject to a SCID-I interview)~~**, including all depression (major depressive disorders, premenstrual dysphoric disorder, menstrual migraine, and other psychiatric disorders per DSM), other Axis I disorders, and postpartum depression episodes.**	
Section 12.1, Screening Period	Section 12.1, Screening Period	• Written informed consent, with optional provision for breast milk collection (see Section 5.3 for more information)	• Written informed consent will **be obtained** • **Lactation status (ie, subject is breastfeeding, subject is lactating but not breastfeeding, or subject is not lactating) will be recorded**	Removed the requirement for recording informed consent for optional breast milk collection since breast milk was not to be collected. Added recording of lactation status

Section number and title in Protocol (30 Jun 2016)	**Section number and title in Amendment 3 (02 Feb 2017)**	**Original text:**	**Changed to:**	**Rationale:**
Section 12.2, Treatment Period (Day 1 to Day 3, Hours 0-60)	Section 12.2, **Study Drug** Treatment Period (Day 1 to Day 3, Hours 0-**72**)		**Psychiatric follow-up outside the study visits will be arranged and documented, as appropriate.**	Added text regarding psychiatric follow-up outside the study visits
Section 12.2.1, Day 1 and Section 12.2.2, Day 2 and Section 12.2.3, Day 3	Section 12.2.1, Day 1 and Section 12.2.2, Day 2 and Section 12.2.3, Day 3 and Section 12.3.1		• **Breast milk will be pumped and discarded by subjects who are lactating** • **Subjects who are lactating will pump and discard breast milk and be reminded that they must continue to pump and discard breast milk through Day 12 of the study**	Removed collection of breast milk as an optional study procedure; subjects who were lactating were instructed to pump and discard breast milk through Day 12 of the study
Section 12.3, Follow-up Period (Day 7 through Day 60	Section 12.3, Follow-up Period (Day 7 through Day 30	Section 12.3, Follow-up Period (Day 7 through Day 60	Section 12.3, Follow-up Period (Day 7 through Day ~~60~~**30**	Corrected the Follow-up Period to be through Day 30
Section 12.3.2, Day 12	Section 12.3.2, **Day 14 (±2 days) and Day 21 (±3 days) (Parts B and C)**	• A blood sample for PK analysis will be collected at the time of the visit • Per subject consent (optional), collection of breast milk on the day of the visit • AEs will be monitored	~~A blood sample for PK analysis will be collected at the time of the visit~~ • ~~Per subject consent (optional), collection of breast milk on the day of the visit~~ • **The C-SSRS, HAM-D,**	Removed the visit at Day 12 and added visits at Days 14 and 21 for Parts B and C of the study; removed the PK blood sample and optional breast milk sample

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
		• Concomitant medications will be recorded This visit is only applicable to those patients who have temporarily ceased breastfeeding and are participating in the optional breast milk sampling	**MADRS, CGI-I, EPDS, GAD-7, PHQ-9, SF-36, and BIMF will be completed** • AEs will be monitored • Concomitant medications will be recorded ~~This visit is only applicable to those patients who have temporarily ceased breastfeeding and are participating in the optional breast milk sampling~~	
	Section 12.3.3, Day 30	• Vital signs • Completion of the C-SSRS, HAMD, MADRS, CGI-I, EPDS, GAD-7, PHQ-9, and BIMF	• ~~Vital signs~~ • ~~Completion of the~~ The C-SSRS, HAM-D, MADRS, CGI-I, EPDS, GAD-7, PHQ-9, **SF-36**, and BIMF **will be completed**	Removed collection of vital signs and added the SF-36
Section 13, Statistical Methods and Considerations	Section 13, Statistical Methods and Considerations	A statistical analysis plan (SAP) will be generated and approved by a representative of Sage Therapeutics prior to database lock. Separate summaries will be produced for each part of the	A **separate** statistical analysis plan (SAP) will be generated **for each study (Parts A, B, and C)** and approved ~~by a representative of Sage Therapeutics~~ prior to **the respective** database lock **of each study**.	Clarified that, prior to the database lock of each study, a SAP would be prepared for each part of the study (Parts A, B, and C).

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
		study.	~~Separate summaries will be produced for each part of the study.~~	
Section 13.1, Data Analysis Sets	Section 13.1, Data Analysis Sets	The Breast Milk Population (BMP) will include the subset of the Safety Population who have at least one evaluable breast milk sample. Subjects will be classified according to actual treatment received. This analysis population will be used for all breast milk PK analyses.	~~The Breast Milk Population (BMP) will include the subset of the Safety Population who have at least one evaluable breast milk sample. Subjects will be classified according to actual treatment received. This analysis population will be used for all breast milk PK analyses.~~	Removed the Breast Milk Population since breast milk collection was removed from the study.
Section 13.2, Handling of Missing Data	Section 13.2, Handling of Missing Data	Any rules for the imputation of missing data will be described in the SAP.	~~Any rules~~**A sensitivity analysis may be carried out to investigate the impact of missing data if more than 5% of subjects are missing primary endpoint assessments. Any rules/statistical methods** for the imputation of missing data will be described in the SAP.	Clarified the procedure to be performed if more than 5% of subjects were missing the primary endpoint assessments.
Section 13.4, Primary Endpoints	Section 13.4, Primary Endpoints	For Part B, the primary comparison will be between	**For efficacy analysis purposes, centers with**	Added text to describe pooling of centers by region

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
		90 µg SAGE-547 and placebo at the 60-hour assessment; if this comparison is significant at the 0.05 level, then the 60 µg group will then be compared to placebo.	**fewer than 15 subjects for Part B or 10 subjects for Part C per center will be pooled within regions (eg, North America region centers will be pooled separately those in Europe).** For Part B, the primary comparison will be between 90 µg SAGE-547 and placebo at the 60-hour assessment; if this comparison is significant at the 0.05 level, then the 60 µg group will ~~then~~ be compared to placebo **at the 0.04 level of significance**; **otherwise the comparison will be carried out at the 0.025 level of significance.**	for centers with fewer than 15 subjects in Part B or 10 subjects in Part C; clarified the significance levels to be used when comparing the 60 µg group to placebo, based on whether or not the 90 µg dose was significant
Section 13.5.2, Safety Analysis	Section 13.5.2, Safety Analysis	Sedation will be assessed using the SSS. Safety data will be listed by individual and summarized by treatment group. In addition, an analysis of SSS data will be performed comparing the treatment groups in the same way as for the primary	**In Part A only**, sedation will be assessed using the **Stanford Sleepiness Scale** (SSS) ~~Safety data will be listed by individual and summarized by treatment group. In addition,~~ **and** an analysis of SSS data will be performed comparing the treatment groups in the same	Clarified that the SSS would be performed and analyzed in Part A only. Switched the order of the sentences for clarity.

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
		endpoint.	way as for the primary endpoint. **Safety data will be listed by individual and summarized by treatment group.**	
Section 13.5.2.8, SSS	Section 13.5.2.8, SSS (Part A only)	Section 13.5.2.8, SSS	Section 13.5.2.8, SSS **(Part A only)**	Clarified that the SSS would be analyzed in Part A only.
Section 13.6, Determination of Sample Size	Section 13.6, Determination of Sample Size	Assuming a two-sided test at an alpha level of 0.10, a sample size of 10 evaluable subjects per group would provide 80% power to detect.	Assuming a two-sided test at an alpha level of 0.~~10~~**05**, a sample size of 10 evaluable subjects per group would provide ~~80~~**70%** power to detect	Changed the alpha level and power of the sample size determination.
Section 13.6, Determination of Sample Size	Section 13.6, Determination of Sample Size	For Part B, a sample size of 18 evaluable subjects per group (120 total) would provide at least 90% power to detect an effect size of 1.2 between the SAGE-547 and placebo groups and a common standard deviation of 12 points using a two - sided test at an alpha level of 0.05. For Part C, a sample size of 16 evaluable subjects per group (100 total) would	For Part B, a sample size of ~~18~~**40** evaluable subjects per group (**120 total**) would provide ~~at least~~ 90% power to detect an effect size of ~~1.2~~**0.9** between the SAGE-547 and placebo groups **and a common standard deviation of 12 points** using a two-sided **t**-test at an alpha level of 0.5. For Part C, a sample size of ~~16~~**50** evaluable subjects per group (**100 total**) would	Increased the number of subjects to be enrolled into Parts B and C and adjusted the wording regarding standard deviation and alpha level.

Section number and title in Protocol (30 Jun 2016)	**Section number and title in Amendment 3 (02 Feb 2017)**	**Original text:**	**Changed to:**	**Rationale:**
		provide 80% power to detect an effect size of 1.0.8 between the SAGE-547 and placebo groups and a common standard deviation of 12 points using a two-sided test at an alpha level of 0.10	provide ~~80~~**90**% power to detect an effect size of ~~1.~~**0.8** between the SAGE-547 and placebo groups **and a common standard deviation of 12** points using a two-sided **t-**test at an alpha level of ~~0.10~~**0.5**.	
Section 13.6, Determination of Sample Size	Section 13.6, Determination of Sample Size	Assuming a non-evaluability rate of 10%, up to 22 subjects will be randomized in Part A Assuming a non-evaluability rate of 10%, up to 60 subjects will be randomized in Part B. Assuming a non-evaluability rate of 10%, up to 36 subjects will be randomized in Part C.	~~Assuming a non-evaluability rate of 10%, up to 22 subjects will be randomized in Part A~~ ~~Assuming a non-evaluability rate of 10%, up to 60 subjects will be randomized in Part B.~~ ~~Assuming a non-evaluability rate of 10%, up to 36 subjects will be randomized in Part C.~~	Since the number of subjects to be enrolled into Parts B and C was increased, this text was deleted.
Section 13.7, Interim Analysis	Section 13.7, Interim Analysis	A detailed description of the interim analysis will be included in the SAP.	A detailed description of the interim analysis **for sample size re-estimation** will be included in the SAP.	Clarified that interim analysis for sample size re-estimation for Part A would be described in the SAP.
Section 13.8, Changes from Protocol-Specified Analyses	Section 13.8, Changes from Protocol-Specified Analyses	Upon the completion of each part of the study, the data may be unblinded and analyzed separately. The	Upon the completion of each ~~part of the~~ study (**547-PPD-202A, 547-PPD-202B, and 547 PPD-202C**), the data	Clarified that a separate CSR would be provided for each of the 3 studies (Parts A, B, and C) included in this protocol.

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
		final CSR will report the findings of all parts of the study.	~~may~~**will** be unblinded and analyzed separately, and a separate final CSR will report the findings of ~~all parts of the~~**each** study	
Section 14.1.2, Suspected Adverse Reaction	Section 14.1.2, Suspected Adverse Reaction	For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE.	~~For the purposes of IND safety reporting,~~ "~~r~~**R**easonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE.	Removed the phrase, "for the purposes of IND safety reporting"
Section 14.1.5, Unexpected	Section 14.1.5, Unexpected	• If an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended	~~• If an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended~~	Removed this statement from the definition of unexpected; the correct definition of unexpected was an AE not listed in the Investigator's Brochure or at the specificity or severity that had been observed
Section 14.2.1, Identification and Documentation of Adverse Events by Investigator	Section 14.2.1, Identification and Documentation of Adverse Events by Investigator	AEs will be collected during subject preparation, study drug administration during Screening, after the initiation of study drug administration through to Day 3, and at the Follow-up Visits on Day 7 (±1 day) and Day 30 (±3	AEs will be collected during subject preparation, study drug administration during ~~Screening~~screening, after the initiation of study drug administration through to Day 3, and at the Follow-up Visits ~~on Day 7 (±1 day)~~	Clarified that AEs would be collected through the Day 30 visit; added text to describe procedures to be performed if a female patient became pregnant during the study.

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
		days).	~~and~~**through** Day 30 (±3 days). Added: **Female patients who become pregnant during the study should be followed to determine the outcome of the pregnancy. The pregnancy must be reported to the sponsor within 24 hours of the site becoming aware of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the sponsor. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the**	

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			procedures for reporting an SAE.	
Section 14.2.2.4, Assessment of Outcome	Section 14.2.2.4, Assessment of Outcome	• Recovered/Resolved: The event has improved or recuperated • Recovering/Resolving: The event is improving • Not Recovered/Not Resolved: The event has not improved or recuperated • Recovered/Resolved with Sequel: The subject recuperated but retained pathological conditions resulting from the prior disease or injury • Fatal: The termination of life as a result of an adverse event • Unknown: Not known, not observed, not recorded, or refused	• ~~Recovered/~~**Ongoing: At the end of the study, the event has not resolved or stabilized** • Resolved: The event has ~~improved or recuperated~~ ~~• Recovering/Resolving: The event is improving~~ ~~• Not Recovered/Not Resolved: The event has not improved~~**resolved or** ~~recuperated~~**the subject recovered without sequelae** • ~~Recovered/~~Resolved with ~~Sequel: The subject recuperated but retained pathological conditions resulting from the prior disease or injury~~ ~~• Fatal: The termination of life as~~ **sequelae: The event has at least 1 secondary outcome that may result** ~~of an adverse event~~**in permanent disability and/or functional limitation** • Unknown: ~~Not known,~~	Revised the former 6 categories of outcome to be 5 categories: Ongoing, Resolved, Resolved with Sequelae, Unknown, or Death

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			~~not observed, not recorded, or refused~~**The status of the event is unknown** • **Death: The subject has expired**	
Section 14.2.3, Investigator Reporting to Sponsor and Sponsor Emergency Contact	Section 14.2.3, Investigator Reporting to Sponsor and Sponsor Emergency Contact	All SAEs that occur during the course of the study must be reported by the Investigator on the designated report form (study-specific SAE form or CIOMS/MedWatch 3500A form) and sent by facsimile to the medical monitor within 24 hours from the point in time when the Investigator becomes aware of the SAE. In addition, all SAEs that occur up to and including 30 days after administration of study drug must be reported within 1 working day from when the Investigator becomes aware of the SAE.	All SAEs that occur during the course of the study must be reported by the Investigator **immediately, with** the designated report form ~~(study-specific SAE form or CIOMS/MedWatch 3500A form)~~ and sent ~~by facsimile~~ to the Medical Monitor within 24 hours from the point in time when the Investigator becomes aware of the SAE. In addition, all SAEs that occur up to and including 30 days after administration of study drug must be reported within ~~1 working day~~**24 hours** from when the Investigator becomes aware of the SAE.	Removed description of forms to be used to report SAEs; removed the method of sending SAE forms (ie, by facsimile); changed the SAE reporting time from "within 1 working day" to "within 24 hours"
Section 14.2.6, Reporting to Institutional Review Boards	Section 14.2.6, Reporting to Institutional Review	Section 14.2.6, Reporting to Institutional Review Boards	Section 14.2.6, Reporting to Institutional Review Boards	Added IECs to the section heading since study was to be

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
(IRBs)	Boards/Independent Ethics Committees	(IRBs) It is the responsibility of the Investigator to promptly notify the institution's IRB/IEC of all serious and unexpected suspected adverse reactions (see Section 14.3.2).	~~(IRBs)/~~**Independent Ethics Committees** It is the responsibility of the Investigator to promptly notify the institution's IRB/IEC of all ~~serious and unexpected suspected adverse reactions (see Section 14.3.2).~~**SAEs that occur at his or her site if applicable per the IRB's/IEC's requirements.**	conducted globally
Section 14.3.1, Monitoring of Adverse Event Data	Section 14.3.1, Monitoring of Adverse Event Data	The Medical Monitor or designee will review AEs on an ongoing basis.	The Medical Monitor or designee will review **SAEs**/AEs on an ongoing basis.	Added that the Medical Monitor would review SAEs on an ongoing basis
Section 14.3.2, Reporting to FDA	Section 14.3.2, Reporting to ~~FDA~~ **Regulatory Authorities**	The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32[c][1][i]). Before submitting an IND safety report, the Sponsor will ensure the event meets all 3 of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected.	~~The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32[c][1][i]). Before submitting an IND safety report, the Sponsor will ensure the event meets all 3 of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected.~~	Revised text to clarify the procedures for reporting SUSARs to IRBs/IECs; added the requirement for providing a annual safety report to the relevant parties.

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
		If the AE does not meet all 3 of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the AE and, therefore, that the event meets the definition of a suspected adverse reaction. If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence of serious suspected adverse reactions over that listed in the protocol or Investigator's Brochure.	~~If the AE does not meet all 3 of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the AE and, therefore, that the event meets the definition of a suspected adverse reaction.~~ ~~If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence of serious suspected adverse reactions over that listed in the protocol or Investigator's Brochure.~~ **The Sponsor or its designee is responsible for SUSAR notification to the relevant**	

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			regulatory authorities per applicable regulations. All investigators participating in the study will also be informed as required by regulations in order to inform their IRBs/IECs. **In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to regulatory authorities as required by national laws.**	
Section 14.4, Emergency Identification of Study Medication	Section 14.4, Emergency Identification of Study Medication	In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment from the pharmacist; this normally requires prior approval by the Medical Monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the Medical	In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment from the ~~pharmacist; this normally requires prior approval by the~~ Medical Monitor. ~~However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the Medical~~	Clarified the procedure to be used for emergency unblinding of an individual subject.

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
		Monitor may take place after unblinding. The Investigator will not unblind the Medical Monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the Medical Monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the Medical Monitor, study management team, and data management team.	~~Monitor may take place after unblinding.~~ The Investigator will not unblind the Medical Monitor during that discussion. The process of unblinding will ~~ensure that only the investigator is unblinded; the Medical Monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented~~**described** in ~~a way that does not unblind the Medical Monitor, study management team, and data management team.~~**the Safety Management Plan for the study.**	
Section 16, References	Section 16, References		**Ware JE, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. User's Manual for the SF-36v2® Health Survey (2nd ed). 2007. Lincoln, RI: QualityMetric**	Added the reference to the User's Manual for the SF-36

Section number and title in Protocol (30 Jun 2016)	Section number and title in Amendment 3 (02 Feb 2017)	Original text:	Changed to:	Rationale:
			Incorporated.	
Appendix 2, HAMILTON RATING SCALE FOR DEPRESSION	Appendix 2, HAMILTON RATING SCALE FOR DEPRESSION		Inserted the correct version of the HAM-D	Inserted the most recent, correct version of the HAM-D
Appendix 3, MONTGOMERY ASBERG DEPRESSION RATING SCALE (MADRS)	Appendix 3, MONTGOMERY ASBERG DEPRESSION RATING SCALE (MADRS)	Included entire journal article with MADRS scale	Deleted journal article; inserted correct MADRS scale	Inserted correct MADRS scale
Appendix 5, Stanford Sleepiness Scale Appendix 6, Edinburgh Postnatal Depression Scale Appendix 7 Generalized Anxiety Disorder 7-Item Scale Appendix 8, Patient Health Questionnaire Appendix 9, Barkin Index of Maternal Functioning Appendix 10, Selected Inducers, Inhibitors, and Substrates of CYP2C9	Appendix 5, Edinburgh Postnatal Depression Scale Appendix 6 Generalized Anxiety Disorder 7-Item Scale Appendix 7, Patient Health Questionnaire Appendix 8, Barkin Index of Maternal Functioning Appendix 9, Short-form-36 Appendix 10, Health Resource Utilization Questionnaire	Appendix 5, Stanford Sleepiness Scale Appendix 6, Edinburgh Postnatal Depression Scale Appendix 7 Generalized Anxiety Disorder 7-Item Scale Appendix 8, Patient Health Questionnaire Appendix 9, Barkin Index of Maternal Functioning Appendix 10, Selected Inducers, Inhibitors, and Substrates of CYP2C9	**Appendix 5, Edinburgh Postnatal Depression Scale** **Appendix 6 Generalized Anxiety Disorder 7-Item Scale** **Appendix 7, Patient Health Questionnaire** **Appendix 8, Barkin Index of Maternal Functioning** **Appendix 9, Short-form-36** **Appendix 10, Health Resource Utilization Questionnaire**	Deleted the SSS, since sedation was removed as a secondary endpoint (appendix numbers changed); added the SF-36 and HCRU questionnaires as Appendix 9 and Appendix 10, respectively

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF SAGE-547 INJECTION IN THE TREATMENT OF ADULT FEMALE SUBJECTS WITH SEVERE POSTPARTUM DEPRESSION AND ADULT FEMALE SUBJECTS WITH MODERATE POSTPARTUM DEPRESSION

PROTOCOL NUMBER: 547-PPD-202

IND NUMBER: 122279

Investigational Product:	SAGE-547 Injection (allopregnanolone)
Clinical Phase:	2a
Sponsor:	Sage Therapeutics
Sponsor Contact:	[redacted], MD, MBA [redacted] Sage Therapeutics 215 First Street Cambridge, MA 02142 Phone: [redacted]
Medical Monitor:	[redacted], MD [redacted] Office (9-5 EST): [redacted] 24/7 Hotline: [redacted]
Date of Original Protocol:	Version 1.0, 18 September 2015
Date of Amendment 1:	Version 2.0, 22 December 2015
Date of Amendment 2:	Version 3.0, 30 June 2016

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 the Sponsor.

1. SIGNATURE PAGE

Title of protocol: A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects with Severe Postpartum Depression and Adult Female Subjects with Moderate Postpartum Depression

Protocol No: 547-PPD-202

Sponsor Approval

[redacted]
[redacted] MD, PhD
[redacted]
Sage Therapeutics

30-JUN-2016
Date (dd/mmm/yyyy)

[redacted]
[redacted], PhD
[redacted]
Sage Therapeutics

01Jul2016
Date (dd/mmm/yyyy)

[redacted]
[redacted] MPH
[redacted]
Sage Therapeutics

30-June-2016
Date (dd/mmm/yyyy)

[redacted]
[redacted]
[redacted]
Sage Therapeutics

30-JUN-2016
Date (dd/mmm/yyyy)

Investigator Agreement

By signing this page, I attest that I have read and understand the contents of Clinical Protocol 547-PPD-202 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: _____

Investigator's Name: _____

Institution: _____

Date (dd/mmm/yyyy): _____

2. SYNOPSIS

Name of Sponsor:

Sage Therapeutics
215 First Street
Cambridge, MA 02142

Protocol No. 547-PPD-202	**Phase:** 2a

Name of Investigational Product:

SAGE-547 Injection

Name of Active Ingredient:

Allopregnanolone

Title of the Protocol:

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects With Severe Postpartum Depression and Adult Female Subjects with Moderate Postpartum Depression

Study Sites: Up to 50 sites in the United States and Canada

Duration of Subject Participation: Up to 35 days

Primary Objective:

- To determine if SAGE-547 Injection infused intravenously for 60 hours at up to 90 K⅄/kg/h reduces depressive symptoms in subjects with severe postpartum depression (PPD) compared to placebo injection as assessed by the change from baseline in Hamilton Rating Scale for Depression (HAMD) total score. This objective applies to both Parts A and B.

Secondary Objectives (unless otherwise specified, these objectives apply to Parts A, B, and C):

- To determine if SAGE-547 infusion at up to 60 K⅄/k⅄/h for 60 hours reduces depressive symptoms in subjects with severe PPD compared to placebo injection as assessed by the change from baseline in HAMD total score. This objective applies to Part B.
- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms in subjects with moderate PPD compared to placebo injection as assessed by the change from baseline in HAMD total score. This objective applies to Part C.
- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms compared to placebo injection as assessed by HAMD response, HAMD remission, change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score, Clinical Global Impression – Improvement (CGI-I) response, and changes from baseline in HAMD subscale and individual item scores.
- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces other mood symptoms compared to placebo injection as assessed by changes from baseline in the Generalized Anxiety Disorder 7-Item Scale (GAD-7) total score.

- To determine if SAGE-547 Injection infused intravenously for 60 hours increases sedation levels compared to placebo injection as assessed by the changes from baseline in Stanford Sleepiness Scale (SSS) score.
- To evaluate the safety and tolerability of SAGE-547 Injection compared with placebo as assessed by the incidence of adverse events, vital sign measurement, clinical laboratory evaluations, electrocardiogram (ECG) parameters, and the Columbia Suicide Severity Rating Scale (C-SSRS).

Exploratory Objective:

- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces subject-reported depressive symptoms compared to placebo injection as assessed by the change from baseline in Edinburgh Postnatal Depression Scale (EPDS) total score and the change from baseline in Patient Health Questionnaire (PHQ-9) total score.
- To determine if SAGE-547 Injection infused intravenously for 60 hours improves maternal behaviors compared to placebo injection as assessed by the change from baseline in Barkin Index of Maternal Functioning (BIMF) total and sub-scale scores.

Pharmacokinetic Objective:

- To assess the pharmacokinetic (PK) profile of SAGE-547, metabolites of SAGE-547, and betadex sulfobutyl ether sodium (SBECD) and the concentration of SAGE-547 in breast milk, when possible.

Study Design and Methodology:

This is a multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the efficacy, safety, and pharmacokinetics of SAGE-547 Injection in adult female subjects diagnosed with severe or moderate PPD. Subjects must remain as in-patients during the study Treatment Period, which is approximately 60 hours/2.5 days in duration. The Screening Period assessments may be conducted on an in-patient or an out-patient basis. The Follow-up Period assessments are conducted on an out-patient basis.

Screening Period: The Screening Period begins with the signature of the informed consent form (ICF). Eligibility is determined by applying the inclusion/exclusion criteria. The diagnosis of PPD must be by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). A full medical and family history will be taken including recording of all depression, other Axis 1 and Axis 2 disorders and postpartum depression episodes in primary probands (who may be subject to a SCID-I interview).

Treatment Period: In Parts A and C, once subjects are confirmed as eligible for the study, they will be randomized to one of 2 treatment groups (SAGE-547 or placebo) on a 1:1 basis. Continuous intravenous infusions of blinded study drug will be administered, with a new bag and line hung every 24 hours during the 60-hour infusion. Infusion rates will increase and then taper, with subjects receiving 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24-52 hours), followed by 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours). Subjects in the placebo group will receive infusion rates equivalent to SAGE-547 90 µg/kg/hour. In Part B, once subjects are confirmed as eligible for the study, they will be randomized to one of 3 treatment groups (SAGE-547 60 µg/kg/hour, SAGE-547 90 µg/kg/hour, or placebo) on a 1:1:1 basis. For the 60 µg/kg/hour group, subjects will receive 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-56 hours), and 30 µg/kg/hour (56-60 hours). For the 90 µg/kg/hour group, subjects will receive 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24-52 hours), followed by 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours). Subjects in the placebo group will

randomly receive infusion rates equivalent to either the 60 µg/kg/hour or 90 µg/kg/hour group. Parts B and C will run concurrently.

In all parts, subjects may be discharged after the 72-hour assessments have been completed (12 hours after completion of the study drug infusion). If their clinical condition does not allow discharge, normal standard of care will be employed in their ongoing management.

Initiation of benzodiazepines, narcotics, antibiotics, neuroleptics, and other anti-anxiety medications will not be allowed between Screening and completion of the 72-hour assessments. Doses of psychotropics, which must have been initiated at least 14 days prior to screening, must remain at a stable dose until completion of the 72-hour assessments. If at the 72-hour assessment there has been no treatment response (HAMD total score remains above 13), treatment with antidepressant medication may be optimized prior to discharge, and the subject may remain in the unit or be followed at an out-patient clinic, as clinically indicated.

Efficacy and safety assessments will be performed periodically during the study, and blood samples will be collected for analysis of SAGE-547, metabolites of SAGE-547, and SBECD concentrations, as outlined in the Schedule of Events (Table 1). Blood samples will be collected, and outcome measures will be obtained at pre-specified times over 60 hours during the Treatment Period.

Follow-up Period: For all parts, follow-up visits will be conducted one week (7±1 day) and one month (30±3d) after the initiation of the study drug infusion.

Number of Subjects:

Up to 32 subjects will be randomized in Part A, up to 60 subjects will be randomized in Part B, and up to 36 subjects in Part C.

Inclusion Criteria:

The following inclusion criteria must be met for individuals to be eligible for the trial:

1. Subject has signed an ICF prior to any study-specific procedures being performed
2. Subject is an ambulatory female aged 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 breast feeding at Screening, must agree to temporarily cease giving breastmilk to their infant(s) from just prior to receiving study drug through 9 days (Study Day 12) after the end of infusion.
6. Subject must have a negative pregnancy test at Screening and Day 1 prior to the start of study drug infusion
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, as diagnosed by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)
8. For Part A and B, subject has a HAMD total score of ï 2k at Screening and Day 1 (prior to randomization). For Part C, subject has a HAMD total score of ï 2ẇand G25 at Screening and Day 1 (prior to randomization)
9. Subject is Gk months postpartum

10. Subject is willing to delay start of other antidepressant or anxiety medications and any new pharmacotherapy regimens, including prn benzodiazepine anxiolytics, until the study drug infusion and 72-hour assessments have been completed
11. Subject has no detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), and human immunodeficiency virus (HIV) antibody at Screening
12. Subject must use one of the following methods of birth control during participation in the study and for 30 days following the end of the study drug infusion:
    - Total abstinence (no sexual intercourse)
    - Hormonal contraceptives (birth control) including birth control pills, implantable or injectable contraceptives (Norplant® or Depo-Provera®)
    - A barrier form of contraception such as a condom or occlusive cap with a spermicide
    - An intrauterine device (IUD)

Exclusion Criteria:

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

1. Recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, or nose and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study
2. Known allergy to progesterone or allopregnanolone
3. Active psychosis per Investigator assessment
4. Attempted suicide associated with index case of postpartum depression
5. Medical history of seizures
6. Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
7. History of active alcoholism or drug addiction (including benzodiazepines) in the 12 months prior to Screening
8. Exposure to another investigational medication or device within 30 days prior to Screening
9. Administration of psychotropics that have been initiated within 14 days prior to Screening and are not being taken at a stable dose.

Investigational Product, Dosage, and Mode of Administration:

SAGE-547 Injection, intravenous (IV) administration: SAGE-547 Injection is a sterile, clear, colorless 5 mg/mL solution of SAGE-547 (allopregnanolone) and 250 mg/mL SBECD buffered with 10 mM citrate at a pH of 6.0, supplied in single-use 20 mL vials for IV administration. As supplied, SAGE-547 Injection, which is hypertonic, requires further dilution with Sterile Water for Injection (SWFI) to render it isotonic for IV infusion. The specific infusion dose of SAGE-547 Injection will be calculated based on weight for each subject at Screening and administered according to the randomization schedule. Infusion bags will be changed every 24 hours. Details about the preparation and administration of the study drug infusions will be included in the Pharmacy Manual.

Part A and Part C:

	Infusion Rate (µg/kg/hour)				
SAGE-547 Dose	Day 1 **0-4 hours**	Day 1 **4-24 hours**	Day 2-3 **24-52 hours**	Day 3 **52-56 hours**	Day 3 **56-60 hours**
90 µg	30	60	90	60	30

Part B:

	Infusion Rate (µg/kg/hour)				
SAGE-547 Dose	**Day 1 0-4 hours**	**Day 1 4-24 hours**	**Day 2-3 24-52 hours**	**Day 3 52-56 hours**	**Day 3 56-60 hours**
60 µg	30	60	60	60	30
90 µg	30	60	90	60	30

Reference Therapy, Dosage, and Mode of Administration:

An identical placebo IV infusion will be prepared for IV administration consisting of the same formulation without allopregnanolone. For each part of the study, the placebo infusion rate will match that of the SAGE-547 rate(s) used in that part.

Randomization and Stopping Rules:

Subjects will be randomized to receive SAGE-547 Injection or placebo; subjects, clinicians, and study team will be blinded to treatment allocation. The pharmacist, who will prepare the infusion bags according to the randomization schedule, will be unblinded. In Parts A and C, the infusion rates are the same for all subjects within a particular dosing period (0-4 hours, 4-24 hours, etc.) regardless of randomized treatment. In Part B, the infusion rates will vary according to the dose group randomized to.

If any subject has an SSS score of ř 5 for 2 or more consecutive assessments or an SSS score of řķ for a single occurrence during normal waking hours, the infusion rate for this subject will be decreased to the next lowest infusion dose level (or turned off if this occurs on the 30 µg/kg/hour dose level).

Criteria for Evaluation:

Primary Endpoint

The primary outcome measure will be the 17-item Hamilton Rating Scale for Depression (HAMD). The HAMD will be administered before, during, and after the infusion of blinded study drug. The HAMD total score will be calculated as the sum of the 17 individual item scores. The change from baseline in HAMD total score at the end of the treatment period (at +60 hours) will be the primary efficacy endpoint with comparison between the SAGE-547 and placebo treatment groups from Part A used to evaluate the efficacy of SAGE-547 in treating the depressive symptoms of PPD.

For Parts A and C, the primary comparison will be between 90 µg SAGE-547 and placebo at the 60-hour assessment. For Part B, the primary comparison will be between 90 µg SAGE-547 and placebo at the 60-hour assessment; if this comparison is significant at the 0.05 level, then the 60 µg group will then be compared to placebo.

Secondary Endpoints

All secondary endpoints apply to Parts A, B and C unless otherwise stated.

Additional measures of depressive symptom severity will be administered before, during, and after the infusion of study drug, including the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinical Global Impression (CGI) scale. Total scores and changes from baseline will be calculated where applicable. Changes from baseline at the end of the treatment period (at +60 hours) and other time points will be evaluated as secondary efficacy endpoints with comparisons between the two treatment groups used to support the efficacy of SAGE-547 in treating the depressive symptoms of PPD. In addition to the above scales, the individual item scores and subscale scores from the HAMD scale will also evaluated as secondary efficacy endpoints.

GAD-7 will also be administered before, during, and after the infusion of study drug. As with other secondary efficacy endpoints, scores from these scales will be evaluated to assess the efficacy in other mood disorder and anxiety symptoms.

An important safety endpoint will be the assessment of sedation using the SSS. The SSS will be assessed periodically before, during, and after the infusion of blinded study drug with changes from baseline over time evaluated similarly to that of efficacy endpoints.

Safety and tolerability of SAGE-547 Injection will be evaluated by summarization of adverse events (AEs) by frequency, severity, and seriousness; clinical laboratory measures, vital signs, and ECGs (including changes from baseline); and concomitant medication usage. Suicidality will be monitored using the C-SSRS.

The doses of all anti-depressant medications will be recorded throughout the study. No changes and/or additions to antidepressant or anxiolytic medicine will be allowing during the dosing period. An analysis of time to starting/increasing the dose/decreasing the dose of each different anti-depressant medication will be undertaken for subjects discharged.

Plasma will be collected to assay for concentrations of SAGE-547, SAGE-547 metabolites, and SBECD. The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve (AUC) from time zero to 60 hours (AUC_{0-60}), AUC from time zero to infinity (AUC_{∞}), maximum (peak) plasma concentration (C_{max}), time at maximum (peak) plasma concentration (t_{max}), steady-state drug concentration in the plasma during constant-rate infusion (C_{ss}), and average drug concentration in the plasma at steady state during a dosing interval

(C_{avg}).

Breast milk may be collected as an optional assessment if consent is received from the subject. Samples will be analyzed for SAGE-547 concentrations.

Exploratory Endpoints

Additional measures of symptoms and function related to the current episode of postpartum depression severity will be administered before, during, and after the infusion of study drug, including the EPDS, PHQ-9 and BIMF.

Subscale and total scores and changes from baseline will be calculated where applicable. Changes from baseline at the end of the treatment period (at +60 hours) and other time points will be evaluated as secondary efficacy endpoints with comparisons between the two treatment groups used to support the efficacy of SAGE-547 in treating the depressive symptoms of PPD. In addition to the above scales, the individual item scores will also be evaluated as exploratory endpoints.

Statistical Methods:

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

Interim Analysis

In Part A, an interim analysis will be conducted by an independent statistician for sample size re-estimation purposes when at least 16 subjects have completed efficacy assessments through 60 hours. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis will be included in the statistical analysis plan.

There will be no interim analysis for Parts B or C.

Sample Size Calculation

Assuming a two-sided test at an alpha level of 0.10, a sample size of 10 evaluable subjects per group would provide 80% power to detect an effect size of 1.2 between the SAGE-547 and placebo groups with regard to the primary outcome variable of change from baseline in HAMD total score. An effect size of 1.2 corresponds to a placebo adjusted difference of 12 points in the change from baseline in HAMD total score at 60 hours with an assumed standard deviation of 10 points. By including two treatment groups and using a 1:1 randomization ratio, a total of 20 evaluable subjects are required for Part A. Assuming a non-evaluability rate of 10%, up to 22 subjects will be randomized in Part A.

Based on the results of the interim analysis, the sample size in Part A could be increased to a maximum of 32 randomized subjects. This adjustment to the sample size would allow for an effect size of 1.0 to be detected.

For Part B, a sample size of 18 evaluable subjects per group would provide at least 90% power to detect an effect size of 1.2 between the SAGE-547 and placebo groups using a two-sided test at an alpha level of 0.05. Assuming a non-evaluability rate of 10%, up to 60 subjects will be randomized in Part B.

For Part C, a sample size of 16 evaluable subjects per group would provide 80% power to detect an effect size of 1.0 between the SAGE-547 and placebo groups using a two-sided test at an alpha level of

0.10. Assuming a non-evaluability rate of 10%, up to 36 subjects will be randomized in Part C.

Efficacy Analysis

The efficacy population will include all subjects who start the infusion of study drug and have a valid baseline HAMD assessment and at least one post-baseline HAMD assessment. Subjects will be classified and summarized by randomized treatment. Separate summaries will be produced for each part of the study.

For each part, the change from baseline in HAMD total score will be analyzed using a mixed effects repeated measures model including center, treatment, baseline score, 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. The primary comparison between each SAGE-547 dose and placebo will be at the 60-hour time point. Comparisons at other time points will be conducted to support the findings for the primary comparison. To account for multiple testing in Part B, the 90 μg group will be compared to placebo first; if this dose is significant at the 0.05 level, then the 60 μg group will then be compared to placebo.

Changes from baseline in other rating scale scores will be analyzed with methods similar to the primary endpoint. Any dichotomous response variables will be analyzed using logistic regression methods.

In addition to formal analysis, efficacy rating scale scores (including recorded and change from baseline values) will be summarized by descriptive statistics, including n, mean, standard deviation (SD), median, and minimum and maximum values. Categorical efficacy endpoints (including HAMD, MADRS, and CGI-I response variables) will be summarized by frequency and percentage.

Safety Analysis

The Safety Population (SAF) is defined as all subjects who start the infusion of study drug. Subjects will be classified and summarized by actual treatment. Separate summaries will be produced for each part of the study.

Safety will be assessed using SSS, AEs, vital signs, ECG, clinical laboratory tests, C-SSRS, and concomitant medication data. Continuous safety data (including absolute and change from baseline values) will be summarized by descriptive statistics, including n, mean, standard deviation (SD), median, and minimum and maximum values. Categorical endpoints will be summarized by frequency and percentage. In addition, an analysis of the SSS score will be performed comparing the treatment groups in the same way as for the primary endpoint.

Safety data will be examined for possible relationships between subject characteristics and plasma allopregnanolone concentrations, as appropriate.

Table 1: Schedule of Events

	Screening Period	Treatment Period Clinic Period (Day 1 to Day 3)															Follow-up Period		
Visit Days	**Screening D-5 to -1**	**D1 H0***	**D1 H2**	**D1 H4**	**D1 H8**	**D1 H12**	**D1 H18**	**D1 H24**	**D2 H30**	**D2 H36**	**D2 H42**	**D2 H48**	**D3 H54**	**D3 H60**	**D3 H66**	**D3 H72**	**D7/ET** (±1d)	**D12 (+1d)[l]**	**D30** (±3d)
Study Procedure																			
Informed Consent	X																		
Inclusion/Exclusion Criteria	X	X																	
Demographics	X																		
Medical/Family History	X																		
Physical Examination	X															X	X		
Body Weight/Height	X																		
Clinical Lab Assessments [a]	X															X	X		
Urinalysis [a]	X																X		
Drug & Alcohol Screen [b]	X	X																	
Pregnancy Test [c]	X	X																	X
Hepatitis & HIV Screen	X																		
Genetic Sample [d]	O																		
Vital Signs [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Pulse Oximetry		X																	
12-Lead ECG [f]	X											X					X		
C-SSRS [g]		X						X						X		X	X		X
Confinement		X																	
CGI-I [h]			X	X		X		X		X		X		X		X	X		X
CGI-S [h]	X	X																	
HAMD [h]	X	X	X	X	X	X		X		X		X		X		X	X		X
MADRS [h]	X	X						X				X		X		X	X		X
BIMF [h]		X															X		X
EPDS [h]		X												X			X		X

GAD-7 [h]		X												X			X		X
PHQ-9 [h]		X												X			X		X
SSS [i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Plasma PK [j]		X		X	X	X		X	X	X		X		X		X	X	X[l]	
Breast Milk PK [k]		X	X				X		X		X		X		X		X[l]	X[l]	
Study Drug Infusion		X																	
Adverse Events	X																		
Concomitant Medications	X																		

O = optional * = All H0 procedures to be completed prior to dosing

a Safety laboratory tests will include hematology, serum chemistry, coagulation, and select hormone parameters. The urine test will include a urinalysis. Lab assessments are to be completed within ±30 minutes of the scheduled time point.

b Urine for selected drugs of abuse and alcohol (serum or breath)

c Serum at Screening and urine for all other time points

d A blood sample for genetic testing, where consent is given

e Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). Vital signs will be obtained within ±30 minutes of the scheduled time point, unless the subject is asleep between the hours of 23.00h and 06.00h.

f Performed within ±30 minutes of the scheduled time point on Day 2.

g The "Baseline/Screening" C-SSRS form will be completed on Day 1. The "Since Last Visit" C-SSRS form will be completed at all subsequent time points.

h To be completed within ±30 minutes of the scheduled time point.

i To be completed within ±15 minutes of the scheduled time point, unless the subject is asleep between the hours of 23.00h and 06.00h

j Blood samples for PK analysis will be collected at pre-infusion and at 4 (before change in infusion rate), 8, 12, 24 (before change in infusion rate), 30, 36, 48, 60 (before end of infusion), and 72 hours after the start of the infusion. PK blood draws after the start of infusion will have a window of ±10 minutes. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.

k Optional assessment per subject consent, breast milk will be collected and pooled over the following time periods of interest: 0, 1-12, 12-24, 24-36, 36-48, 48-60, and 60-72 hours after the start of the infusion.

l Day 7 Breast Milk Samples/Day 12 Visit is only applicable to those patients who have temporarily ceased breastfeeding and are participating in the optional breast milk sampling.

BIMF = Barkin Index of Maternal Functioning; CGI-I = Clinical Global Impression of Improvement; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EPDS = Edinburgh Postnatal Depression Scale; GAD-7 = Generalized Anxiety Disorder 7-Item Scale; HAMD = Hamilton Rating Scale for Depression, 17-item; MADRS = Montgomery-Asberg Depression Rating Scale; PHQ-9 = Patient Health Questionnaire; PK = pharmacokinetic; SSS = Stanford Sleepiness Scale.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALLO	allopregnanolone
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{∞}	area under the concentration-time curve from time zero to infinity
$AUC_{0\text{-}60}$	area under the concentration-time curve from time zero to 60 hours
BIMF	Barkin Index of Maternal Functioning
BMI	body mass index
BMP	breast milk population
BUN	blood urea nitrogen
C_{avg}	average drug concentration in the plasma at steady-state during a dosing interval
CBC	complete blood count
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression–Improvement
CGI-S	Clinical Global Impression–Severity
cGMP	Current Good Manufacturing Practice
C_{max}	maximum (peak) plasma concentration of the drug
CNS	central nervous system
CRF	case report form
CS	clinically significant
CSF	cerebrospinal fluid
CSR	clinical study report
C_{ss}	steady-state drug concentration in the plasma during constant-rate infusion
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	Cytochrome P450 enzyme involved in drug metabolism
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG	electrocardiogram
eCRF	electronic case report form

EDC	electronic data capture
EEG	electroencephalography
EFF	efficacy population
Ph. Eur.	European Pharmacopeia
EPDS	Edinburgh Postnatal Depression Scale
ERα	estrogen receptor alfa
ERß	estrogen receptor beta
ET	early termination
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
$GABA_A$	gamma-aminobutyric acid–gated chloride channel
GAD-7	Generalized Anxiety Disorder 7-Item Scale
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
h	hour
HAMD	Hamilton Rating Scale for Depression, 17-item
HBsAg	hepatitis B surface antigen
Hct	hematocrit
HCV	hepatitis C virus
HEENT	head, eyes, ears, nose, and throat
Hgb	hemoglobin
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council on Harmonisation
ID	identification
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	intravenous
MADRS	Montgomery-Asberg Depression Rating Scale
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDD	major depressive disorder

MedDRA	Medical Dictionary for Regulatory Activities
NCS	not clinically significant
PHQ-9	Patient Health Questionnaire
PK	pharmacokinetic
PKP	pharmacokinetic population
PMID	PubMed identification
PP	per-protocol population
PPD	postpartum depression
PR	progesterone receptor
PT/INR	prothrombin time/international normalized ratio
RBC	red blood cell
RSE	refractory status epilepticus
SAE	serious adverse event
SAF	safety population
SAP	statistical analysis plan
SBECD	betadex sulfobutyl ether sodium
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SRSE	super refractory status epilepticus
SSRI	selective serotonin reuptake inhibitors
SSS	Stanford Sleepiness Scale
SWFI	sterile water for injection
$T_{1/2}$	half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum (peak) plasma concentration
TSH	thyroid stimulating hormone
US	United States
USP	United States Pharmacopeia
VAS	visual analogue scale
V_d	volume of distribution
WBC	white blood cell

4. INTRODUCTION AND RATIONALE

This study is designed to evaluate the efficacy, safety, and pharmacokinetics (PK) of SAGE-547 (allopregnanolone) as a treatment for women with severe or moderate postpartum depression (PPD), an area of high unmet medical need.

PPD is considered to be moderate to severe depression in women who have recently given birth, otherwise defined as the occurrence of major depressive disorder (MDD) within 4 weeks of delivery (DSM-V 2013) or up to a year after giving birth (Okun 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-V 2013), although this diagnosis may be confounded by the relative frequency of symptoms such as sleep disturbance or appetite problems in pregnant and postpartum women. 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).

During pregnancy, estradiol and progesterone levels increase dramatically but then rapidly decline in the acute postpartum period (Gavin 2005). The onset of PPD symptoms coincides with the rapid decrease of the gonadal steroids postpartum. The duration of a PPD episode has been estimated as shorter than depressive episodes in the general population (approximately 5 months), while other studies indicate time to remission is approximately the same (Chaudron 2003).

PPD is common and has devastating consequences for the woman and for her family (Fihrer 2009, Verbeek 2012). Perinatal depression is reported to be the most underdiagnosed obstetric complication in America (Earls 2010). Furthermore, it is the most common psychiatric illness to occur in the puerperium (O'Hara 2014). A meta-analysis of 30 studies (Gaynes 2005) found that the point prevalence of major and minor depression ranged between 6.5% and 12.9% at different times during the first postpartum year. Overall incidence is estimated at around 15% to 20% with up to 10% being considered severe (Edge 2007, O'Hara 2014).

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 non-pharmacological 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.

4.1. Role of Allopregnanolone in Affective Disturbances

The neurosteroid metabolite of progesterone, allopregnanolone, acutely regulates neuronal function (Gangisetty 2010) and appears to play a significant role in affective disturbances that occur with changes in reproductive endocrine function, such as during the postpartum period (Amin 2006, Nappi 2001, Epperson 2006).

Neurosteroids are metabolites of cholesterol-derived steroid hormones that are synthesized in the brain and nervous system; they modulate the major inhibitory and excitatory central nervous system (CNS) neurotransmitter systems: γ-aminobutyric acid (GABA) and glutamate, respectively. Neurosteroids are among the most potent and effective modulators of $GABA_A$ receptors and augment GABAergic inhibition (Belelli 2005). The powerful anxiolysis that accompanies this potentiation of $GABA_A$ receptors has led to the speculation that neurosteroid dysregulation plays a central role in the etiology of affective disorders, including reproductive mood disorders, such as PPD (Amin 2006).

There is increasing evidence supporting the role of neurosteroids in affective dysregulation. Allopregnanolone and pregnanolone have been shown to modulate the GABA receptor positively (Majewska 1986). Several groups have demonstrated decreased allopregnanolone levels in MDD, with an increase seen in both plasma and cerebrospinal fluid (CSF) following successful antidepressant treatment (Uzunova 1998, Romeo 1998, Ströhle 1999, Schüle 2006, Eser 2006, Schüle 2007). In addition, allopregnanolone has demonstrated anxiolytic effects in several animal anxiety models (Bitran 1991; Wieland 1991; Bitran 1993).

Allopregnanolone may also exert antidepressant effects by reducing the physiological impact of stress, promoting neuroprotection, and protecting against the pro-inflammatory immune activation and cytokine hypersecretion associated with MDD. In animals, allopregnanolone increases in response to stress, reduces pain sensitivity, and is thought to restore physiologic homeostasis following stress (Frye 1994, Morrow 1995). Allopregnanolone also exerts neuroprotective effects by reducing the expression of pro-apoptotic proteins and apoptotic DNA fragmentation (Djebaili 2005, Sayeed 2009), thereby reducing the cell death and gliosis associated with depression (Glantz 2010, Shelton 2011). Neuroprotection is mediated by immune regulation in depression (Licinio 1999), and allopregnanolone reduces the expression of the pro-inflammatory cytokine TNF-α (He 2004), which is elevated in depressed individuals (Dowlati 2010). Thus, allopregnanolone modulates biological processes dysregulated in MDD.

4.1.1. Rationale for Allopregnanolone Treatment of PPD

Genetic susceptibility to affective dysregulation may be unmasked during periods of reproductive hormone change such as during pregnancy and postpartum (Maguire 2008). Maguire and Mody demonstrated that a GABA receptor subunit mutation was behaviorally silent until the animal was exposed to pregnancy and the postpartum state, at which time the dams showed depressive-like behaviors and cannibalized their offspring (Maguire 2008). During pregnancy, the expression of the $GABA_A$ receptor δ-subunit is down-regulated as allopregnanolone levels increase, and at parturition, the expression of the $GABA_A$ receptor δ-subunit is recovered in response to rapidly declining neurosteroid levels (Maguire 2009). In contrast, the $GABA_A$ receptor δ-subunit-deficient mice fail to adapt to the dramatic

changes in allopregnanolone and experience depression-like and anxiety-like behavior and abnormal maternal behaviors, which are reversed by administration of allopregnanolone (Maguire 2008). This model provides compelling support for the hypothesis that changes in neurosteroid concentrations during pregnancy and postpartum are capable of provoking affective dysregulation, particularly in those with a genetically-determined susceptibility. The capacity of changes in neurosteroids, such as allopregnanolone, to function as behavioral switches suggests a potentially important treatment role of this hormone metabolite in reproductive endocrine-related mood disorders such as PPD.

The onset of PPD symptoms coincides with the rapid decrease of the gonadal steroids postpartum and has been reproduced in a pivotal clinical study (Bloch 2000). The authors investigated the possible role of changes in gonadal steroid levels in PPD by simulating 2 hormonal conditions related to pregnancy and parturition in euthymic women, 8 with and 8 without a history of PPD. They induced hypogonadism with leuprolide, adding back supra-physiologic doses of estradiol and progesterone for 8 weeks to simulate pregnancy. They then withdrew both steroids under double-blind conditions to mimic the rapid decrease of sex steroids upon delivery. Five of the 8 women with a history of postpartum depression (62.5%) and 0% of the comparison group developed significant mood symptoms typical of PPD during the withdrawal period.

Although progesterone levels were measured in this study, allopregnanolone was not. However, since allopregnanolone is the major active metabolite of progesterone, it can be assumed that the decrease in progesterone would cause a similar precipitate drop in allopregnanolone levels, as observed in the postpartum period (Gilbert Evans 2005, Paoletti 2006, Nappi 2001). These data provide direct evidence in support of the involvement of progesterone and its metabolites in the development of postpartum depression in a subgroup of women. Further, they suggest that women with a history of postpartum depression are differentially sensitive to mood-destabilizing effects of gonadal steroids (Bloch 2000).

Additional details regarding the role of allopregnanolone in the etiology of affective disorders and its nonclinical pharmacology and pharmacokinetics are presented in the Investigator's Brochure.

4.2. SAGE-547 Injection (Allopregnanolone)

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex, and CNS (Holzbauer 1985, Ottander 2005, Paul 1992). Allopregnanolone is a metabolite of progesterone created by the actions of 5-α reductase and 3-α hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic $GABA_A$ receptors.

SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), United States Pharmacopeia (USP), and 250 mg/mL betadex sulfobutyl ether sodium buffered with 10 mM citrate at a pH of 6.0, and will be administered intravenously. SAGE-547 Injection is also being developed for the treatment of adult patients with refractory status epilepticus (RSE), inclusive of super refractory status epilepticus (SRSE), who have not responded to standard treatment regimens, and investigated for the treatment of adults with essential tremor.

4.3. Summary of Nonclinical and Clinical Experience with Allopregnanolone or SAGE-547

4.3.1. Nonclinical Pharmacology

The primary pharmacological effects of allopregnanolone or SAGE-547 are described earlier in the rationale (Section 4.1 and Section 4.1.1). Secondary pharmacologic effects comprise mainly the binding and consequent increased activity of steroid hormone receptors (androgen receptor [(AR], progesterone receptor [PR], and estrogen receptor beta [ERß]), with some evidence of inhibition at the highest doses (AR and estrogen receptor alfa [ERα]). These non-target effects may yield some adverse events in the clinic.

Nonclinical toxicology studies largely illustrate the sedative and anesthetic effects of allopregnanolone and/or SAGE-547 at higher equivalent doses than the proposed dose for the current study. PK data in animals indicate a short half-life and rapid clearance with a moderate volume of distribution and cerebral levels higher than plasma. Refer to the SAGE-547 Investigator's Brochure for more details.

4.3.2. Clinical Experience

The clinical PK data with intravenous (IV) administration of allopregnanolone in healthy women, men, and women on oral contraceptives confirmed the PK observations in animals of a short half-life ($t_{½}$ 20-40 mins), C_{max} achievable at approximately third trimester levels (150 nM), rapid clearance and moderate volume of distribution (V_d). Refer to the SAGE-547 Investigator's Brochure for more details.

There are currently no double-blind, placebo-controlled clinical efficacy data for SAGE-547 in PPD. An open-label, proof-of-concept study (547-PPD-201) evaluating the safety, tolerability, pharmacokinetics, and efficacy of SAGE-547 Injection in the treatment of adult female subjects with severe postpartum depression was started in 2014. This was the first study in this indication. Four women experienced significant improvement in depressive symptoms within 24 hours after administration of open-label IV SAGE-547. During the SAGE-547 treatment period, all 4 subjects rapidly achieved remission, as measured by the HAMD total score. All 4 subjects also demonstrated consistent improvement as measured by the CGI-I score. SAGE-547 was well-tolerated in all subjects treated with no serious adverse events observed during therapy or during the 30-day follow-up period. A total of 14 adverse events were reported in 4 subjects. The only adverse event reported in more than one subject was sedation, observed in 2 subjects. This trial was initially planned to enroll 10 women, however, due to the observed clinical activity, Study 547-PPD-201 was stopped early with the plan to initiate a placebo-controlled clinical trial as rapidly as possible.

There are 6 reported studies of allopregnanolone, mainly in healthy individuals and none in PPD (Timby 2006, Timby 2011a and 2011b, van Broekhoven 2007, Kask 2008, Kask 2009, Navarro 2003). Data indicate that normal physiological allopregnanolone levels in women vary during the menstrual cycle up to a maximum of 6 to 10 nM, with lower levels present post-menopause (Genazzani 1998). The highest physiological levels observed are in the third trimester of pregnancy, up to around 160 nM at time of delivery (Luisi 2000). Levels drop precipitously to baseline (<10 nM) with removal of the placenta (Klak 2003).

One study demonstrated subjective improvements in contentedness in women (van Broekhoven 2007). The clinical safety data are presented below in the Risks and Benefits section (Section 4.4).

4.4. Potential Risks and Benefits

In the recently completed open-label clinical trial of SAGE-547 in PPD (547-PPD-201), a total of 14 adverse events were reported in 4 subjects. The only adverse event reported in more than one subject was sedation, observed in 2 subjects.

Consistent with these observations, published reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported adverse events (AEs) were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, vertigo, mild nausea, impaired episodic memory, and mild headache (Timby 2006, 2011a, and 2001b; van Broekhoven 2007). One subject experienced what was potentially a withdrawal effect, an anxiety attack (Timby 2011b). No serious AEs (SAEs) were reported in the 6 clinical studies conducted to date (Timby 2006, Timby 2011a and 2011b, van Broekhoven 2007, Kask 2008, Kask 2009, Navarro 2003).

There is also a potential risk of supra-additive sedative effects with other drugs interacting with the $GABA_A$ receptor, such as benzodiazepines and anti-epileptic medications (Norberg 1999); therefore, the Investigator is advised to avoid co-medication if possible and to exercise caution with these drug classes. As this is one of the first clinical trials of SAGE-547 in PPD, the potential benefits in this population are unknown, although the risks are likely to be similar to those mentioned above. Given the nonclinical rationale and the fact that endogenous allopregnanolone in humans appears to play a role in psychiatric disorders such as major depression, premenstrual dysphoric disorder, and anxiety disorders, it is possible that subjects may have a clinical benefit at the exposures selected for this trial. In view of the limited nature of the demonstrated risks of exogenous allopregnanolone infusion and the potential for benefit in severe PPD, there is a favorable benefit-risk evaluation for the conduct of the present study.

4.5. Study No. 547-PPD-202

4.5.1. Study Population

This study will evaluate the efficacy, safety, and pharmacokinetics (PK) of SAGE-547 Injection in the treatment of adult female subjects diagnosed with severe or moderate postpartum depression.

Parts A and B of this study will study women with severe PPD, and Part C will study women with moderate PPD (Parts B and C will run concurrently). Moderate severity level will be studied because the pathogenesis of severe postpartum depression may not be generalized to those patients with a less severe form of illness. For example, outside of postpartum depression, findings suggest that patient's treatment-resistant depression may respond more favorably to certain pharmacotherapy options such as ketamine (Coyle 2015). Therefore, in order to determine the efficacy of SAGE-547 in women with less severe levels of symptoms,

a separate group with moderate PPD with the same doses of the study drug used in the severe group will be investigated.

4.5.2. Route of Administration, Dosage, Dosage Regimen, and Treatment Period

SAGE-547 Injection or placebo will be administered over a 60 hour period by an IV infusion according to the dose regimens shown in Table 2 and Table 3 (see Section 10.1.1).

The specific infusion dose of SAGE-547 Injection will be calculated based on weight for each subject. Infusion bags will be changed every 24 hours. Details about the preparation and administration of the study drug infusions will be included in the Pharmacy Manual.

4.5.3. Dose Rationale

The infusion rate of SAGE-547 to be studied in Parts A and C of this study was chosen to achieve a mean exposure of 150 nM, roughly equivalent to the highest endogenous concentrations measured in third trimester pregnancy at approximately 157 nM (Luisi 2000). Since pregnant women tolerate this level without apparent AEs, 150 nM was selected as the target exposure for this study. This level of exposure has already been achieved in Study 547-PPD-201 as well at higher levels in a study in subjects with essential tremor (Study 547-ETD-201) and subjects with super refractory status epilepticus (Study 547-SSE-201), with no drug-related SAEs reported. Since the most common adverse event in 547-ETD-201 was sedation, dose adjustment rules are included in this protocol to ensure that all subjects can remain on treatment for 60 hours. A similar C_{max} was also achieved in several other studies conducted with intravenous allopregnanolone (Timby 2011b), with excellent tolerability (see the current SAGE-547 Investigator's Brochure for details of safety profile).

The selection of exposure in the current trial is based on a cautious approach adapted to the anticipated benefit-risk in the PPD patient population, and on previous experience from the ongoing clinical trials of SAGE-547 in adult subjects with SRSE (Study 547-SSE-201) and of SAGE-547 in female subjects with PPD (Study 547-PPD-201). In the ongoing SRSE trial, as determined by simulation, loading and maintenance infusions are required to achieve the target exposure. In contrast, in the current trial, subjects will instead begin treatment with a 4-hour dose-titration phase. The starting dose is approximately 9- to 18-fold lower than the NOAEL observed in rats and dogs, although this is not the first in human study. In Parts A and C, doses will be increased as follows: 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24-52 hours), followed by a decrease to 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours).

In Part B, a lower target dose will also be explored (ie, 60 µg/kg/hour). The use of this dose is based on observations in the open-label 547-PPD-201 study in which subjects achieved substantial improvements in their HAMD scores within the first 12 hours of the SAGE-547 infusion. In this study, subjects received a dose of 21.5 KV/kV/h for the first 4 hours, then 43 KV/kg/h for the next 4 hours, and then 64.5 KV/kV/h for the following 4 hours before receiving the target dose of 86 KV/ŎV/h at 12 hours. Therefore, the 12-hour data from 547-PPD-201 suggests that SAGE-547 at target doses of 60 KV/ŎV/h may also be efficacious in reducing depressive symptoms associated with PPD.

Subjects will be treated in an inpatient setting and continually monitored for safety, and if any severe tolerability issues arise, the infusion will be terminated. The Stanford Sleepiness

Scale (SSS) will be regularly administered to monitor sedation and allow dose adjustment based on tolerability, with a formal dose interruption and reduction scheme implemented for this and other AEs.

5. ETHICS

5.1. Institutional Review Board or Independent Ethics Committee

This trial will be initiated only after the protocol has been reviewed and approved by the Institutional Review Board (IRB) where the study is to be conducted. The IRB must meet all US Food and Drug Administration (FDA) requirements governing IRBs (Code of Federal Regulations [CFR], Title 21, Part 56). The same applies for the implementation of changes introduced by an amendment.

5.2. Ethical Conduct of the Study

This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and the most recent amendment (2008).

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol, and must also conduct the study in accordance with International Council on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP) standards as well as local regulations.

5.3. Subject Information and Informed Consent

Prior to subject participation in the trial, written informed consent must be obtained from each subject according to ICH GCP and in accordance with local regulations. Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests, SAGE-547 infusion, and study evaluations. Each subject's signature must be dated by each signatory and the informed consent form (ICF) retained by the investigator as part of the trial records. As an additional assessment, the ICF will contain provisions for optional consent for the collection of blood for genetic testing during Screening and the collection of breast milk for the duration of the 60-hour SAGE-547 infusion and up to Day 3 for biobanking and PK analysis purposes. The ICF, as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the CFR, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject a copy of the signed and dated ICF. The ICF for subject participation must also be available as part of the subject's file for review by the site's dedicated study monitor.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objective of this study is to determine if SAGE-547 Injection infused intravenously for 60 hours at up to 90 K[illegible]/Ŏ[illegible]h reduces depressive symptoms in subjects with severe PPD compared to placebo injection as assessed by the change from baseline in HAMD total score. This objective applies to both Parts A and B.

6.2. Secondary Objectives

The secondary objectives of the study apply to Parts A, B and C unless otherwise stated, and are:

- To determine if SAGE-547 infusion at up to 60 K[illegible]/k[illegible]/h for 60 hours reduces depressive symptoms in subjects with severe PPD compared to placebo injection as assessed by the change from baseline in HAMD total score (applies to Part B only).
- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms in subjects with moderate PPD compared to placebo injection as assessed by the change from baseline in HAMD total score (applies to Part C only).
- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms compared to placebo injection as assessed by HAMD response, HAMD remission, change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score, Clinical Global Impression – Improvement (CGI-I) response, and changes from baseline in HAMD subscale and individual item scores
- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces other mood symptoms compared to placebo injection as assessed by changes from baseline in the Generalized Anxiety Disorder 7-Item Scale (GAD-7) total score
- To determine if SAGE-547 Injection infused intravenously for 60 hours increases sedation levels compared to placebo injection as assessed by the changes from baseline in Stanford Sleepiness Scale (SSS) score
- To evaluate the safety and tolerability of SAGE-547 Injection compared with placebo as assessed by the incidence of adverse events, vital sign measurement, clinical laboratory evaluations, electrocardiogram (ECG) parameters, and the Columbia Suicide Severity Rating Scale (C-SSRS)

6.3. Exploratory Objectives

The exploratory objectives of the study are:

- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces subject-reported depressive symptoms compared to placebo injection as assessed by the change from baseline in Edinburgh Postnatal Depression Scale (EPDS)

total score and the change from baseline in Patient Health Questionnaire (PHQ-9) total score

- To determine if SAGE-547 Injection infused intravenously for 60 hours improves maternal behaviors compared to placebo injection as assessed by the change from baseline in Barkin Index of Maternal Functioning (BIMF) total and sub-scale scores

6.4. Pharmacokinetic Objective

The pharmacokinetics objectives of the study are:

- To assess the pharmacokinetic (PK) profile of SAGE-547, metabolites of SAGE-547, and betadex sulfobutyl ether sodium (SBECD) and the concentration of SAGE-547 in breast milk, when possible

7. INVESTIGATIONAL PLAN

7.1. Overview of Study Design

This is a 3-part multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the efficacy, safety, and pharmacokinetics of SAGE-547 Injection in adult female subjects diagnosed with severe and moderate PPD. The study design for Parts A and C is presented in Figure 1 and the study design for Part B is presented in Figure 2 (Parts B and C will run concurrently). For all parts, the study will consist of an up to 5-day Screening Period (Day -5 to -1), 3-day (60-hour) Treatment Period, and 30-day Follow-up Period. Subjects must remain as inpatient during the study Treatment Period, which is approximately 60 hours/2.5 days in duration. The Screening Period assessments may be conducted on an inpatient or an outpatient basis. The Follow-Up Period assessments are conducted on an outpatient basis.

Figure 1: Study Design - Part A and Part C

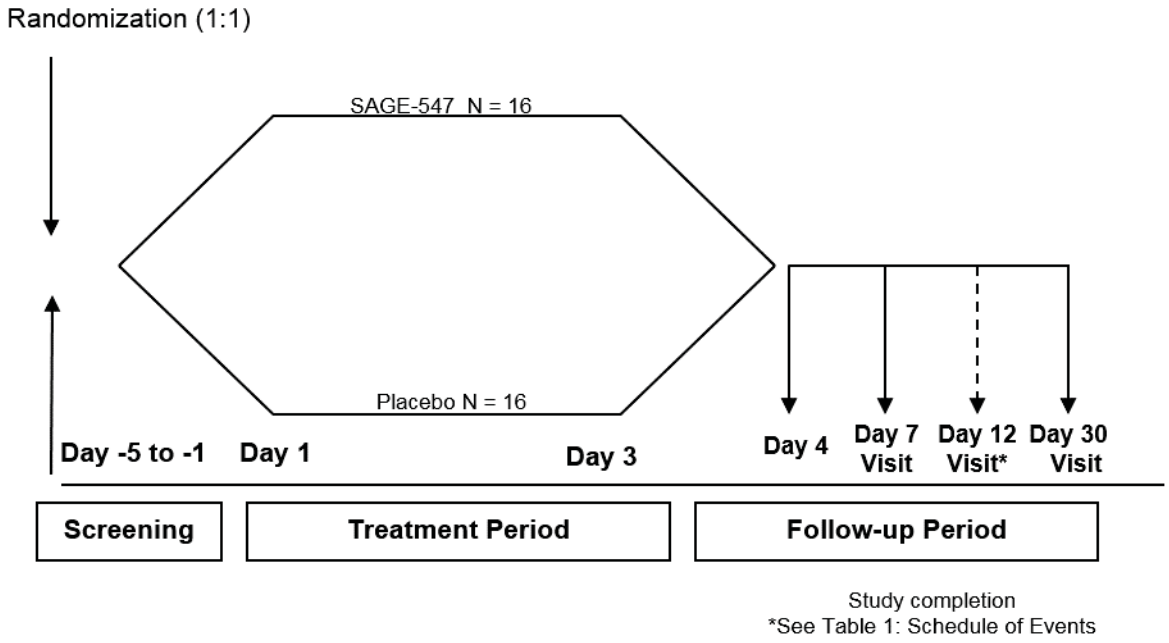
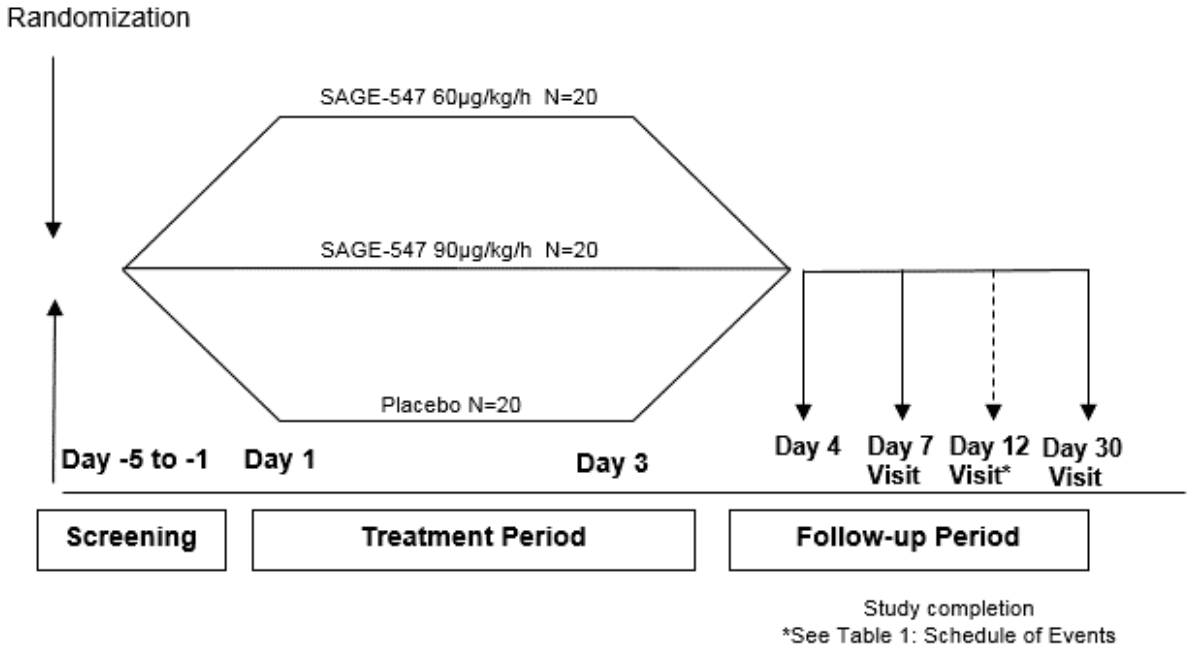


Figure 2: Study Design - Part B



SAGE-547 Injection or placebo will be administered at the study center. Subjects will be monitored for safety during the Treatment and Follow-up Periods (through Study Day 30 [±3 days]) including monitoring for AEs/SAEs, routine clinical laboratory assessments, physical examination, vital signs, and ECG.

All study-related procedures will occur after written informed consent is obtained at the Screening Visit, which will occur on any one calendar day during the Screening Period window (Day -5 through 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.

The end of the Screening Period coincides with the beginning of the Treatment Period. The Treatment Period is the period of Day 1 of SAGE-547 IV infusion through completion of the infusion on Day 2 and up to Day 3. Subjects will be confined to the study center from Day 1 until after the 60-hour assessments have been conducted on Day 3.

In Parts A and C, once subjects are confirmed as eligible for the study, they will be randomized to one of 2 treatment groups (SAGE-547 90 µg/kg/hour or placebo) on a 1:1 basis. On the morning of dosing (Day 1), subjects will begin a 4-hour dose titration period of 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24-52 hours); followed by a decrease to 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours). Subjects in the placebo group will receive infusion rates equivalent to the 90 µg/kg/hour group.

In Part B, once subjects are confirmed as eligible for the study, they will be randomized to one of 3 treatment groups (SAGE-547 60 µg/kg/hour, SAGE-547 90 µg/kg/hour, or placebo) on a 1:1:1 basis. For the 60 µg/kg/hour group, subjects will receive 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-56 hours), followed by 30 µg/kg/hour (56-60 hours). For the 90 µg/kg/hour group, subjects will begin a 4-hour dose titration period of 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24-52 hours); followed by a decrease to 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours). Subjects in the placebo group will receive infusion rates equivalent to either the 60 µg/kg/hour or 90 µg/kg/hour group. Parts B and C will run concurrently.

See dose regimen presented in Section 10.1.1. Total SAGE-547 Injection or placebo dosing will occur over 60 hours.

Trial-specific assessments for safety, PK, efficacy, and exploratory outcome measures will be completed at pre-specified times over a 72-hour period during the Treatment Period:

- The safety and tolerability of SAGE-547 Injection will be assessed by AEs, clinical laboratory measures, physical examinations (including cognitive and mental health examinations), vital signs, ECG, use of concomitant medication, and the Columbia Suicide Severity Rating Scale (C-SSRS) during the Screening, Treatment, and Follow-up Periods (through Study Day 30 [±3 days])
- Plasma will be collected to formally assay for SAGE-547, metabolite, and SBECD levels prior to dosing through the treatment period and up to 12 hours post infusion on Day 3

- Primary efficacy assessment of the HAMD will be completed as scheduled during the Screening, Treatment, and Follow-up Periods (through Study Day 30 [±3 days])
- Secondary efficacy assessments of MADRS, CGI-I, EPDS, Generalized Anxiety Disorder 7-Item Scale (GAD-7), PHQ-9 will be completed as scheduled during the Screening, Treatment, and Follow-up Periods (through Study Day 30 [±3 days])
- Concentrations of SAGE-547 in breast milk will be measured for those subjects who consent to giving breast milk samples

The end of the Treatment Period coincides with the beginning of the Follow-up Period.

Subjects will attend the clinic for safety follow-up assessment at 1 week (7±1d) and 1 month (30±3d) after the initiation of the study drug infusion.

Scheduled assessments for all safety, PK, efficacy, and exploratory outcome measures planned for the trial are summarized in Table 1. All subjects who receive treatment with SAGE-547 are to complete all study assessments through Study Day 30 (±3 days).

The Medical Monitor will review AEs on an ongoing basis.

7.2. Blinding and Randomization

This is a double-blind study. Subjects will be randomized to SAGE-547 or placebo; subjects, clinicians, and study team will be blinded to treatment allocation. The pharmacist, who will prepare the infusion bags according to the randomization schedule, and an unblinded Monitor, who will perform drug accountability during the study, will be unblinded.

Subjects will be randomly assigned to receive SAGE-547 Injection or placebo according to a computer-generated randomization schedule.

Only the clinic pharmacist, who is responsible for preparing the infusions, will be given a copy of the randomization schedule. In the event of a medical emergency, the pharmacist may reveal actual infusion contents to the primary investigator, who should also alert Sage of the emergency (see Section 14.4) 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 have been unblinded, the subject will be terminated from the study.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial:

1. Subject has signed an ICF prior to any study-specific procedures being performed
2. Subject is an ambulatory female aged between 18 and 45 years of age
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 breastmilk to their infant(s) from just prior to receiving study drug through 9 days (Study Day 12) after the end of the infusion.
6. Subject must have a negative pregnancy test at Screening and Day 1 prior to the start of study drug infusion
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, as diagnosed by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)
8. For Part A and B, subject has a HAMD total score of ř 26 at Screening and Day 1 (prior to randomization). For Part C, subject has a HAMD total score of ř 2ẇand Ġ25 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 prn benzodiazepine anxiolytics, until the study drug infusion and 72-hour assessments have been completed
11. Subject has no detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), and human immunodeficiency virus (HIV) antibody at Screening
12. Subject must use one of the following methods of birth control during participation in the study and for 30 days following the end of the study drug infusion:
    - Total abstinence (no sexual intercourse)
    - Hormonal contraceptives (birth control) including birth control pills, implantable or injectable contraceptives (Norplant® or Depo-Provera®)
    - A barrier form of contraception such as a condom or occlusive cap with a spermicide
    - An intrauterine device (IUD)

8.2. Exclusion Criteria

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

1. Recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, or nose and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study
2. Known allergy to progesterone or allopregnanolone
3. Active psychosis per Investigator assessment
4. Attempted suicide associated with index case of postpartum depression
5. Medical history of seizures
6. Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
7. History of active alcoholism or drug addiction (including benzodiazepines) in the 12 months prior to Screening
8. Exposure to another investigational medication or device within 30 days prior to Screening
9. Administration of psychotropics that have been initiated within 14 days prior to Screening and are not being taken at a stable dose.

8.3. Subject Withdrawal/Study Termination

8.3.1. Withdrawal/Discontinuation of Individual Subjects

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

Subjects who do not have at least one efficacy observation after 12 hours of SAGE-547 infusion are not considered evaluable for the efficacy assessment and may be replaced.

8.3.2. Subject Withdrawal from the Study

Subjects may withdraw from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

8.3.3. Discontinuation of Study Drug by the Investigator

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

The Investigator may withdraw the subject from the study drug for any of the following reasons:

- The subject is unwilling or unable to adhere to the protocol
- The subject experiences an intolerable AE
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

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

8.3.4. Study Termination

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

9. INVESTIGATIONAL PRODUCT

9.1. Identity of Investigational Product

SAGE-547 Injection (allopregnanolone)

9.2. Clinical Supplies

9.2.1. SAGE-547

SAGE-547 Injection and ancillary supply kits containing IV administration bags, solution sets, and IV bag labels will be provided to the sites.

SAGE-547 Injection is a preservative-free, sterile, clear, colorless 5 mg/mL solution of SAGE-547 (allopregnanolone) and 250 mg/mL betadex sulfobutyl ether sodium buffered with 10 mM citrate at a pH of 6.0, intended for IV injection. All inactive excipients used in the formulation are compendial grade and conform to current United States Pharmacopeia (USP) and European Pharmacopeia (Ph. Eur.) standards. The product is aseptically processed, sterile filtered, and filled into 20 mL Type 1 parenteral glass vials with West FluroTec® coated stopper container closure systems, under current Good Manufacturing Practice (cGMP) conditions. SAGE-547 Injection is intended to be used as a single-use vial. An appropriate number of single-use vials to support the dosing duration of the study are packaged and delivered to the site. SAGE-547 Injection vials should be stored under refrigerated conditions (2–8°C). Ancillary supply kits should be stored at controlled room temperature (20–25°C).

All study drug labels will contain information to meet the applicable regulatory requirements.

9.2.2. Placebo

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and consisting of the same formulation without allopregnanolone. Placebo vials should be stored under refrigerated conditions (2–8°C).

9.3. Preparation of SAGE-547 Injection or Placebo for Dosing

The pharmacy will be responsible for preparing SAGE-547 Injection or placebo for subject dosing. The prepared admixture will be administered at room temperature. The prepared admixture will be assigned a room temperature (20–25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547 Injection or placebo is not intended to be administered to subjects undiluted. Each single-use vial of SAGE-547 Injection, which is hypertonic, will require dilution with an appropriate volume of Sterile Water for Injection (SWFI) to render it isotonic. Refer to the Pharmacy Manual for specific instructions regarding infusion preparation and administration instructions.

9.4. Administration and Accountability

The pharmacy will maintain accurate records of all investigational drug product supplies received, stored, dispensed, and discarded. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate (or rates), and the date and time of preparation. Reasons for departure from the expected dosing regimen must be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication needs to be reconciled in full.

Refer to the Pharmacy Manual for complete details on preparation and administration.

10. TREATMENT OF SUBJECTS

10.1. Dosing Schedule

This is a double-blind study. Subjects will be randomized to receive 60 hours of intravenous treatment with either SAGE-547 Injection or placebo. In Parts A and C, subjects randomized to SAGE-547 will receive the target dose of 90 µg/kg/hour; in Part B, SAGE-547 subjects will receive target doses of either 60 or 90 µg/kg/hour.

The timing of infusion relative to the overall trial designs are shown in Figure 3 and Figure 4.

Figure 3: Trial Design and Timeline for Dosing – Parts A and C

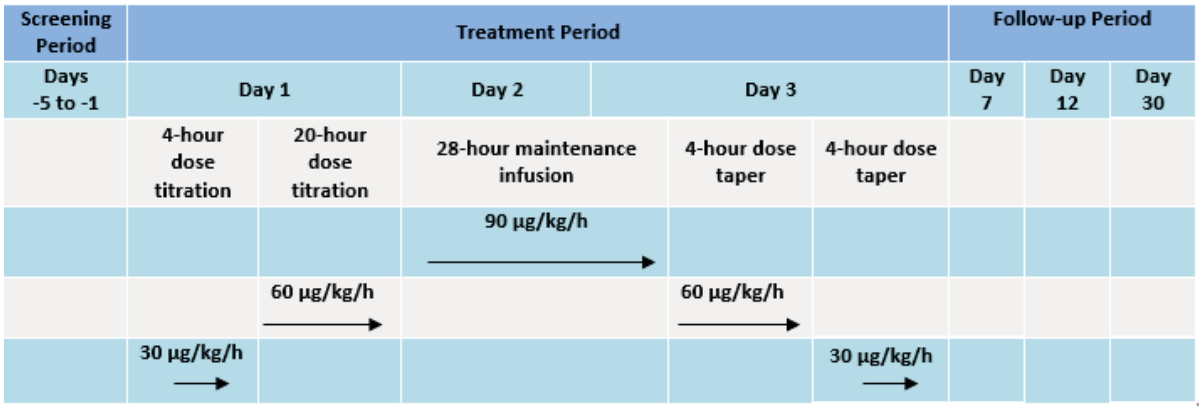
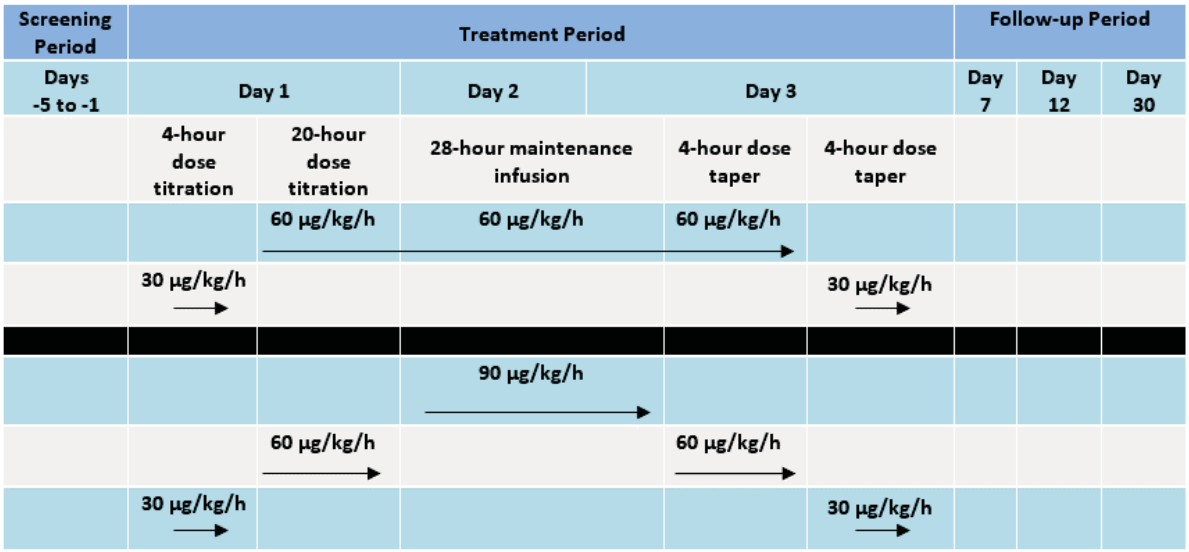


Figure 4: Trial Design and Timeline for Dosing – Part B



Clinical supply and preparation of SAGE-547 Injection for dosing is described Section 9.2 and Section 9.3, respectively.

10.1.1. Dose Regimen

The specific infusion dose of SAGE-547 Injection will be calculated based on weight (obtained at screening) for each subject and administered according to dose regimen shown in Table 2 and Table 3). The infusion rates are the same for all subjects within a particular dosing period (0-4 hours, 4-24 hours, etc.).

Table 2: Infusion rates for Part A and C

	Infusion Rate (µg/kg/hour)				
SAGE-547 Dose	**Day 1 0-4 hours**	**Day 1 4-24 hours**	**Day 2-3 24-52 hours**	**Day 3 52-56 hours**	**Day 3 56-60 hours**
90 µg	30	60	90	60	30

Table 3: Infusion Rates for Part B

	Infusion Rate (µg/kg/hour)				
SAGE-547 Dose	**Day 1 0-4 hours**	**Day 1 4-24 hours**	**Day 2-3 24-52 hours**	**Day 3 52-56 hours**	**Day 3 56-60 hours**
60 µg	30	60	60	60	30
90 µg	30	60	90	60	30

Dosing is to begin in the morning (on Day 1) to avoid awakening subjects during the night for completion of study assessments.

If any subject has an SSS score of ř 5 for 2 or more consecutive assessments or an SSS score of řk for a single occurrence during normal waking hours, the infusion rate for this subject will be decreased to the next lowest infusion dose level (or turned off if this occurs on the 30 µg/kg/hour dose level). Please refer to Section 11.1.8 for more details.

10.1.2. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line with the supplied study-specific IV administration bags and lines.

10.1.3. Treatment Period

Total dosing with SAGE-547 or placebo will occur over 60 hours, including a 24-hour dose titration, a 28-hour maintenance infusion, and an 8-hour taper.

10.1.4. Dosing of Intravenous SAGE-547 in the Case of AEs

Since allopregnanolone levels in the proposed clinical trial are similar to physiological levels seen in the third trimester of pregnancy, and all the AEs reported with SAGE-547 or allopregnanolone to date in healthy volunteers and subjects with postpartum depression were

mild and non-serious, it is anticipated that the AEs associated with SAGE-547 in this study will be mild and manageable without dose interruption or reduction. Based on the safety data in subjects with PPD collected to date, no subjects reported events that were serious or severe and none led to discontinuation of study drug (2 subjects reported sedation that lead to a dose reduction, one of these subjects also reported dizziness; one subject reported rash that lead to a dose reduction; refer to the current Investigator's Brochure for more information).

However, in the case of severe or life-threatening AEs occurring, the investigator is advised to stop study treatment until the AE resolves and only resume study treatment if it is considered to be in the best interest of the subject based on the Investigator's assessment. Resumption of infusion at the next lowest dose (or turned off if this event occurs on the 30 μg/kg/hour dose level) for one hour, followed by re-escalation to the maintenance rate, may be considered to address potential recurrence of the AE. If the AE recurs, study treatment should be permanently discontinued.

10.2. Dosing Compliance

Investigational product will be prepared in the site pharmacy, administered as a continuous IV infusion by the study staff, and will be documented in the study record. There should be no adjustments in dosing except those described in Section 10.1.4.

10.3. Concomitant Medications and Restrictions

10.3.1. Concomitant Medications

Subjects will receive standard of care for adult female patients diagnosed with PPD. 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 10.3. All concomitant medications should be documented throughout the study from Screening through Day 30 (±3 days) and recorded on the eCRF. Prior medications (ie, those taken prior to signing of informed consent) that required wash-out for study entry will also be documented.

10.3.2. Prohibited 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 on this medication for at least 30 days prior to study enrollment.

- Benzodiazepines are to be avoided as much as possible. Eligible subjects taking a benzodiazepine at the time of study entry will 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. Particular attention should be paid to assessment of AEs and implementation of the dose interruption and reduction scheme in subjects on concomitant benzodiazepines since they have been shown to have a supra-additive effect with pregnanolone in an animal model of anesthesia (Norberg 1999).
- The use of hypnotics for sleep/insomnia such as Ambien® and trazodone are to be avoided.
- Anticonvulsants and atypical antipsychotics are to be avoided if possible and are not to be initiated at any time during active treatment period (60 hours). However, if a subject is taking one of these medications for at least 30 days prior to study admission, they will be permitted to remain on this medication, at their current dose (no dose adjustments are allowed).
- SAGE-547 has demonstrated inhibitory effects on cytochrome P-450 (CYP) 2C9 (CYP2C9). The following medications are primarily metabolized by CYP2C9 and therefore are prohibited during SAGE-547 administration: fluconazole and miconazole (antifungal), amentoflavone (constituent of Ginkgo biloba and St. John's Wort), sulfaphenazole (antibacterial), valproic acid (anticonvulsant, mood-stabilizing), and apigenin. See Appendix 10 for a complete list.

11. STUDY ASSESSMENTS

11.1. Safety Assessments

The safety and tolerability of SAGE-547 Injection will be evaluated by summarization of AEs by frequency, severity and seriousness, mean changes from baseline in clinical laboratory measures, physical examination, vital signs, ECGs, and concomitant medication usage. Suicidality will be monitored using the C-SSRS. All safety assessments should be performed per the study center's standard of care and will be collected according to the Schedule of Events (Table 1). All safety assessments are to be completed within ±30 minutes of the scheduled time point.

In addition to the schedule outlined in Table 1, completion of safety assessments including physical examination, vital signs, and clinical laboratory tests should occur in the event of an emergency or SAE, when possible.

11.1.1. Adverse Events

Adverse events will be collected after the ICF has been signed through the end of the study (see Section 14.2.1 for additional details). Medical conditions or adverse events that occur after the ICF has been signed and *prior to* completion of Screening will be captured on the Medical History eCRF.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (version 17.0 or higher).

11.1.2. Clinical Laboratory Tests

Blood samples will be collected for hematology, serum chemistry, coagulation, and specific hormone parameters, hepatitis, human immunodeficiency virus (HIV), pregnancy and genetic analysis. Urine samples for urinalysis and selected drugs of abuse will also be collected. All samples will be analyzed at the central laboratory. Patients 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 (Table 1).

These assessments will be performed in accordance with the Schedule of Events (Table 1) and as outlined individually below.

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 will be recorded as medical history. Clinical laboratory results that are Abnormal; CS during the study and indicate a worsening from baseline will be considered AEs, assessed according to Section 14, and recorded in the eCRF.

11.1.2.1. Hematology, Serum Chemistry, Coagulation

Blood samples will be collected for analysis of the following:

- **Hematology:** complete blood count (CBC) including white blood cell (WBC) count with differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils) platelet count, red blood cell (RBC) count, hemoglobin (Hgb) and hematocrit (Hct), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH)
- **Serum chemistry:** albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatinine, gamma glutamyl transferase (GGT), glucose phosphate, potassium, sodium, total protein, and triglycerides (Screening only)
- **Coagulation:** activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR)

11.1.2.2. Hepatitis and HIV

Blood samples will be collected for analysis of the following:

- **Hepatitis**: hepatitis B virus surface antigen (HBsAg), antibody against hepatitis C virus (anti-HCV)
- **HIV**: antibody against human immunodeficiency virus type 1/2 (anti-HIV 1/2)

11.1.2.3. Hormones and Exploratory Biochemistry

Blood samples will be collected and may be analyzed for thyroid stimulating hormone (TSH), estrogen, progesterone, progesterone metabolites, oxytocin, tryptophan, kynurenine, and markers of inflammation.

11.1.2.4. Pregnancy Test

All subjects will be tested for pregnancy by serum hCG at Screening and urine hCG on Day 1 prior to administration of study drug. Subjects with a positive pregnancy test at Screening or Day 1will be ineligible for study participation.

11.1.2.5. Genetic Testing

A blood sample for genetic testing will be collected at screening, where consent is given.

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-547. 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 allopregnanolone (eg, AKR1C4 (3a-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-547 but also susceptibility to disorders for which SAGE-547 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.

11.1.2.6. Urinalysis

Urinalysis will include assessment of bilirubin, glucose, ketones, leukocytes, nitrite, pH, protein, and specific gravity.

11.1.2.7. Drugs of Abuse and Alcohol

Urine assessment for selected drugs of abuse (including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine and propoxyphene). Use of benzodiazepines at screening is not necessarily exclusionary, as subjects will be allowed to take psychotropics that have been initiated at least 14 days prior to admission to the study center at a stable dose (see Section 10.3.2). Alcohol will be assessed in plasma at Screening and in serum, via breathalyzer or urine dipstick on Day 1.

11.1.3. Physical Examination

Body weight and height will be measured at Screening. Body mass index (BMI) will be programmatically calculated in the eCRF.

Any condition present at the post-treatment physical examination that was not present at or worsened since the baseline examination is to be documented as an AE. Whenever possible, the same individual is to perform all physical examinations. Physical examinations will include assessment of body systems (eg, HEENT, heart, lungs, abdomen, and extremities) as well as cognitive and neurological examination and mental status examination.

11.1.4. Vital Signs

Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). A full set of vital signs will be obtained at all specified time points (±30 minutes), unless the subject is asleep between the hours of 23.00h and 06.00h each day.

11.1.5. Pulse Oximetry

Pulse oximetry will be monitored continuously from H0 until H60, and checked approximately every 2 hours, including during the overnight hours, or at the alarm. If there is an indication of oxygen desaturation, this should be recorded as an adverse event at the discretion of the Investigator. No pulse oximetry data will be recorded in the eCRF.

11.1.6. ECG

A baseline 12-lead ECG will be performed during Screening to assess the presence of any current or historical cardiovascular conditions. The following ECG parameters will be recorded: heart rate, PR, QRS, QT, and QTc. Subjects with clinically significant abnormalities should not be entered into the study.

11.1.7. 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 pre-dose evaluation that assesses the lifetime and recent 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 on Day 1 prior to dosing. The "Since Last Visit" C-SSRS form will be completed for all subsequent assessments.

Copies of the C-SSRS are provided in Appendix 1.

11.1.8. Stanford Sleepiness Scale (SSS)

The Stanford Sleepiness Scale is patient-rated scale designed to quickly assess how sedated or sleepy a patient is feeling. The degree of sleepiness is rated on a scale of 1 to 7, where the lowest score of 1 indicates that the patient is "feeling active, vital, alert, or wide awake" and the highest score of 7 indicates that the patient is "no longer fighting sleep, sleep onset soon; having dream-like thoughts." The SSS will be administered unless the subject is asleep between the hours of 23.00h and 06.00h each day. If the SSS is not scored due to a subject being asleep, a score of X will be reported in the CRF to indicate that the subject was asleep. All SSS assessments are to be completed within ±15 minutes of the scheduled time point.

A copy of the SSS is provided in Appendix 5.

11.2. Efficacy Assessments

For all efficacy assessments, the baseline values will be calculated as the last recorded value prior to the start of infusion of randomized treatment. 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.

11.2.1. Primary Efficacy Outcome Measure

The primary outcome measure is the HAMD. The HAMD will be administered before, during, and after the infusion of blinded study drug.

11.2.1.1. Hamilton Rating Scale for Depression (HAMD)

The 17-item HAMD will be used to rate the severity of depression in subjects who are already diagnosed as depressed (Hamilton 1960). The 17-item HAMD is comprised of 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 HAMD assessments are to be completed within ±30 minutes of the scheduled time point, but prior to starting dosing on D1 H0. Every effort should be made for the same rater to perform all HAMD assessments for a single patient.

The HAMD total score will be calculated as the sum of the 17 individual item scores. Item 16 can be rated according to history (item 16A) or actual weight change (item 16B). The item 16 score is calculated as the item 16 response that is not equal to 3 (ie, "Not assessed").

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

A copy of the HAMD is provided in Appendix 2.

11.2.2. Secondary Efficacy Outcome Measures

Secondary efficacy assessments include evaluation of depressive symptom severity by the MADRS (Section 11.2.2.1) and CGI (Section 11.2.2.2). Additional assessments of depressive symptom severity and reproductive mood disorders will be measured by the following clinician- and subject-rated outcome measures: EPDS (Section 11.2.3.1), GAD-7 (Section 11.2.2.3), and PHQ-9 (Section 11.2.3.2).

11.2.2.1. Montgomery Asberg Depression Rating Scale (MADRS)

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

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

1. Apparent sadness
2. Reported sadness
3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

The MADRS total score will be calculated as the sum of the 10 individual item scores.

A copy of the MADRS is provided in Appendix 3.

11.2.2.2. Clinical Global Impression (CGI) Scale

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 patient's condition. The CGI scale is comprised of 3 items. Only the first 2 items are being used in this study.

The CGI-Severity (CGI-S) item uses a 7-point Likert scale to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating 1=normal, not at all ill, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, and 7=extremely ill. The CGI-S will be rated by the clinician at screening and on Day 1 (prior to dosing).

The CGI-Improvement (CGI-I) item employs a 7-point Likert scale to measure the overall improvement in the patient's condition post-treatment. The investigator will rate the patient's total improvement whether or not it is due entirely to drug treatment. Response choices include: 0=not assessed, 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse. The CGI-I is only rated at post-treatment assessments. By definition, all CGI-I assessments are evaluated against baseline conditions. CGI-I response will be defined as having a CGI-I score of "very much improved" or "much improved."

A copy of the CGI is provided in Appendix 4.

11.2.2.3. Generalized Anxiety Disorder 7-Item Scale (GAD-7)

The GAD-7 is a patient-rated generalized anxiety symptom severity scale (Spitzer 2006). Scoring for GAD-7 generalized anxiety is calculated by assigning scores of 0, 1, 2, and 3 to the response categories, respectively, of "not at all sure," "several days," "over half the days," and "nearly every day." GAD-7 total score for the seven items ranges from 0 to 21, where a score of 0 to 4=minimal anxiety, 5 to 9=mild anxiety, 10 to 14=moderate anxiety, and 15 to 21=severe anxiety. All assessments are to be completed within ±30 minutes of the scheduled time point.

The GAD-7 total score will be calculated as the sum of the 7 individual item scores.

A copy of the GAD-7 is provided in Appendix 7.

11.2.3. Exploratory Patient Reported Outcome Measures

Exploratory efficacy assessments include evaluation of depressive symptom severity and reproductive mood disorders. These will be measured by the following clinician- and subject-rated outcome measures: EPDS, PHQ-9, and BIMF.

11.2.3.1. Edinburgh Postnatal Depression Scale (EPDS)

The EPDS is a patient-rated depressive symptom severity scale specific to the perinatal period (Cox 1987). The EPDS total score will be calculated as the sum of the 10 individual item scores.

A copy of the EPDS is provided in Appendix 6.

11.2.3.2. Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a patient-rated depressive symptom severity scale. To monitor severity over time for newly diagnosed patients or patients in current treatment for depression, patients may complete questionnaires at baseline and at regular intervals thereafter. Scoring is total based on responses to specific questions, as follows: not at all=0; several days=1; more than half the days=2; and nearly every day=3. All assessments are to be completed within ±30 minutes of the scheduled time point.

The PHQ-9 total score will be calculated as the sum of the 9 individual item scores. The PHQ-9 total score will be categorized as follows: 1-4=minimal depression, 5-9=mild depression, 10-14=moderate depression, 15-19=moderately severe depression; and 20-27=severe depression.

A copy of the PHQ-9 is provided in Appendix 8.

11.2.3.3. Barkin Index of Maternal Functioning (BIMF)

The BIMF is a patient reported outcome scale BIMF covers a broad range of functional areas (self-care, infant care, mother-child interaction, psychological well-being of mother, social support, management, adjustment). This new application of maternal functional status is a robust construct where the physical and mental health of the mother is essential to optimal functioning. Each item is rated on a scale of 0 (strongly disagree) to 6 (strongly agree).

A copy of the BIMF is provided in Appendix 9.

11.3. Pharmacokinetics

11.3.1. Plasma PK Samples

Blood samples for PK analysis will be collected in accordance with the Schedule of Events (Table 1). Scheduled time points for PK blood draws after the start of infusion will have a window of ±10 minutes. Samples will be processed according to the PK Manual, and may be analyzed for concentrations of SAGE-547, metabolites of SAGE-547, and SBECD. Additionally, PK samples may be obtained outside the planned collection times if issues administering study drug are encountered, such as incorrect infusion rate, interrupted infusion, or other administration deviations where PK level assessment may be important in understanding subject state. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.

The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve (AUC) from time zero to 60 hours ($AUC_{0\text{-}60}$), AUC from time zero to infinity (AUC_{∞}), maximum (peak) plasma concentration (C_{max}), time at maximum (peak) plasma concentration (t_{max}), steady-state drug concentration in the plasma during constant-rate infusion (C_{ss}), and average drug concentration in the plasma at steady state during a dosing interval (C_{avg}). Each PK parameter will be derived separately for each part of the study.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Subject-specific plasma PK kits for sampling including instructions on

sample collection, processing methods, storage and shipping conditions, will be provided in the study PK Manual.

11.3.2. Breastmilk PK Samples

Women who are actively lactating at Screening, and who otherwise fulfill all of the inclusion and exclusion criteria for the study, will be asked if they will consent to pumping. Breastmilk will be collected and pooled at pre-defined intervals. The times of the first and last pumping of each collection period will be recorded. Breastmilk will be pooled within each collection period and the total volume will be measured. Detailed instructions for breastmilk PK sampling, processing methods, storage and shipping will be provided in the study PK Manual. After Study Day 12, women may resume giving breastmilk to their infant, per Inclusion Criteria 5.

12. STUDY PROCEDURES

The study procedures listed below by study day reflect the data collection times for this protocol.

Scheduled assessments for all safety, efficacy, PK, and exploratory outcome measures planned for the trial are summarized in Table 1 (Schedule of Events). All subjects who receive treatment with SAGE-547 should complete all study assessments through Study Day 30 (±3 days).

Subjects who are evaluated at the Day 3 visit of the Treatment Period (ie, all Hour 60 assessments are completed, post-infusion) and complete the Day 30 (±3 days) visit during the Follow-up Period will be defined as study completers.

12.1. Screening Period

The Screening Period consists of a window from Day -5 through Day -1 prior to starting SAGE-547 treatment. The Screening Period begins with the signature of the ICF. Eligibility is determined by applying the inclusion/exclusion criteria. The diagnosis of PPD must be by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). A full medical and family history will be taken including recording of all depression, other Axis 1 and Axis 2 disorders and post-partum depression episodes in primary probands (who may be subject to a SCID-I interview).

The following assessments/procedures will be conducted at the Screening Visit, which will occur on any one calendar day of the Screening Period. 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 examinations, 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, and all screening assessments are completed, reviewed and approved by the Investigator prior to administration of SAGE-547.

Subjects will be confined to the study center from Day 1 until after the 60-hour assessments have been conducted on Day 3.

- Written informed consent, with optional provision for breast milk collection (see Section 5.3 for more information)
- Review of inclusion/exclusion criteria to determine subject eligibility
- Demographic information and medical/family history collected
- Blood will be collected for a pregnancy test
- Blood will be collected to screen for hepatitis and HIV
- Completion of physical examination, including body weight. Height should be recorded. BMI will be calculated.
- Vital signs
- Blood and urine samples collected for clinical laboratory testing, including drug and alcohol screening

- Blood sample will be taken for genetic analysis with subject consent
- An ECG reading taken
- Completion of the HAMD, CGI-S, and MADRS
- Recording of concomitant medications

12.2. SAGE-547 Treatment Period (Day 1 to Day 3, Hours 0-60)

All safety, efficacy, pharmacokinetic and other outcome assessments described in this section are to be completed within ±30 minutes of the scheduled time points, unless otherwise stated. Windows for PK collection time points are specified by respective time point for Study Days 1 to 3 in Section 12.2.1 to Section 12.2.3, respectively (see Section 11.3 for additional details). Subjects will be confined to the study center from the Screening Visit until after the 60-hour assessments have been conducted on Day 3.

12.2.1. Day 1

- Review of inclusion/exclusion criteria to determine subject eligibility
- Randomization (on a 1:1 basis: one group will receive SAGE-547 and one group will receive placebo)
- Urine will be collected for a pregnancy test
- Begin study drug administration for dose titration in the morning followed by maintenance infusion
- Vital signs will be recorded prior to infusion and at 2, 4, 8, 12, 18, and 24 hours on Day 1 (±30 minutes), unless the subject is asleep between the hours of 23.00h and 06.00h each day
- Pulse oximetry will be monitored continuously (from H0 until H60), and checked approximately every 2 hours, including during the overnight hours, or at the alarm
- Blood and urine samples collected for drug and alcohol screening
- A blood sample for PK analysis will be collected prior to infusion (ie, morning of Day 1 prior to dosing), and at Hours 4 (before change in infusion rate), 8, 12, and 24 (before change in infusion rate) after the start of the infusion. PK blood draws after the start of infusion will have a window of ±10 minutes. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.
- Completion of the HAMD prior to dosing and at Hours 2, 4, 8, 12, and 24 on Day 1 (±30 minutes)
- Completion of the MADRS prior to dosing and at Hour 24 on Day 1 (±30 minutes)
- Completion of the CGI-S prior to dosing and the CGI-I at Hours 2, 4, 12, and 24 on Day 1 (±30 minutes)

- Completion of the following questionnaires prior to dosing: BIMF, EPDS, GAD-7, and PHQ-9 (±30 minutes)
- Completion of the SSS prior to dosing and at Hours 2, 4, 8, 12, 18, and 24 on Day 1 (±15 minutes) unless the subject is asleep between the hours of 23.00h and 06.00h each day
- AEs will be monitored
- Concomitant medications will be recorded
- Completion of the "Baseline/Screening" C-SSRS form prior to dosing. Completion of the "Since Last Visit" C-SSRS form at Hour 24 (± 30 minutes)
- Per subject consent (optional), collection of breast milk at pre-infusion and at the following time periods of interest: 0, 1-12, 12-24, 24-36, 36-48, 48-60, and 60-72 hours after the start of the infusion

12.2.2. Day 2

- Ongoing SAGE-547 maintenance infusion administration
- Vital signs will be recorded at Hours 30, 36, 42, and 48 (±30 minutes), unless the subject is asleep between the hours of 23.00h and 06.00h each day
- Pulse oximetry will be monitored continuously (from H0 until H60), and checked approximately every 2 hours, including during the overnight hours, or at the alarm
- A blood sample for PK analysis will be collected at Hours 30, 36, and 48. PK blood draws will have a window of ±10 minutes. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change
- Completion of the HAMD at Hour 36 and Hour 48 (±30 minutes)
- Completion of the CGI-I at Hour 36 and Hour 48 (±30 minutes)
- Completion of the MADRS at Hour 48 (±30 minutes)
- Completion of the SSS at Hours 30, 36, 42, and 48 on Day 2 (±15 minutes) unless the subject is asleep between the hours of 23.00h and 06.00h each day
- An ECG reading taken at Hour 48
- AEs will be monitored
- Concomitant medications will be recorded
- Per subject consent (optional), ongoing collection of breast milk during the maintenance phase of infusion

12.2.3. Day 3

- Ongoing SAGE-547 maintenance infusion administration until Hour 60
- Completion of physical examination at Hour 72

- Vital signs will be recorded at Hours 54, 60, 66, and 72 (±30 minutes)
- Pulse oximetry will be monitored continuously (from H0 until H60), and checked approximately every 2 hours, including during the overnight hours, or at the alarm
- A blood sample for PK analysis will be collected at Hours 60 and 72 (±10 minutes). In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change
- Blood sample collected for clinical laboratory testing at Hour 72
- Completion of the HAMD and MADRS at Hour 60 and 72 (±30 minutes)
- Completion of the CGI-I at Hours 60 and 72 (±30 minutes)
- Completion of the following questionnaires at Hour 60: EPDS, GAD-7, and PHQ-9 (±30 minutes)
- Completion of the SSS at Hours 54, 60, 66, and 72 on Day 3 (±15 minutes) unless the subject is asleep between the hours of 23.00h and 06.00h each day
- AEs will be monitored
- Concomitant medications will be recorded
- Completion of the C-SSRS at Hours 60 and 72
- Per subject consent (optional), ongoing collection of breast milk

12.3. Follow-up Period (Day 7 through Day 60)

12.3.1. Day 7 (±1 day)

The following assessments should be completed:

- Completion of physical examination
- Vital signs
- Blood and urine samples collected for clinical laboratory testing
- An ECG reading taken
- Completion of the C-SSRS, HAMD, MADRS, CGI-I, EPDS, GAD-7, PHQ-9, and BIMF
- A blood sample for PK analysis will be collected at the time of the visit
- Per subject consent (optional), collection of breast milk on the day of the visit*
- AEs will be monitored
- Concomitant medications will be recorded

*Assessment is only applicable to those patients who have temporarily ceased breastfeeding and are participating in the optional breast milk sampling.

12.3.2. Day 12 (+1 day)

- A blood sample for PK analysis will be collected at the time of the visit
- Per subject consent (optional), collection of breast milk on the day of the visit
- AEs will be monitored
- Concomitant medications will be recorded

This visit is only applicable to those patients who have temporarily ceased breastfeeding and are participating in the optional breast milk sampling.

12.3.3. Day 30 (±3 days)

The following assessments should be completed:

- Urine will be collected for a pregnancy test
- Vital signs
- Completion of the C-SSRS, HAMD, MADRS, CGI-I, EPDS, GAD-7, PHQ-9, and BIMF
- AEs will be monitored
- Concomitant medications will be recorded

12.3.4. Early Termination Visit

The following assessments should be completed if the patient discontinues from the study prior to the Day 7 Visit:

- Completion of physical examination
- Vital signs
- Blood and urine samples collected for clinical laboratory testing
- An ECG reading taken
- Completion of the C-SSRS, HAMD, MADRS, CGI-I, EPDS, GAD-7, PHQ-9, and BIMF
- AEs will be monitored
- Concomitant medications will be recorded

The visit should occur within 3 days of notification of the patient discontinuing.

13. STATISTICAL METHODS AND CONSIDERATIONS

In general, summary statistics for all study endpoints will be presented as mean, standard deviation (SD), median, and ranges for continuous endpoints, and as counts and percentages for categorical endpoints. For the purpose of all safety, efficacy, and exploratory analyses where applicable, baseline is defined as the last pre-dose measurement closest to the start of blinded study drug infusion.

A statistical analysis plan (SAP) will be generated and approved by a representative of Sage Therapeutics prior to database lock. All statistical analyses will be conducted using SAS for Windows (version 9.1.3, or higher; Cary, NC), unless otherwise specified.

Any deviations from the planned analyses will be described and justified in the final clinical study report (CSR).

Separate summaries will be produced for each part of the study.

13.1. Data Analysis Sets

The **All Enrolled Population** will include all subjects who have given written informed consent. This population will be used for subject disposition and demographic characteristic summaries.

The **All Randomized Population** will include the subset of subjects from the All Enrolled Population who have been randomized. Subjects will be classified according to randomized treatment. This population will be used for subject disposition, demographic characteristic, and baseline characteristic summaries.

The **Safety Population** will include all randomized subjects who start the infusion of study drug. Subjects will be classified according to actual treatment received. This analysis population will be used for all safety analyses.

The **Efficacy Population (EFF)** will include the subset of the Safety Population who have a valid baseline HAMD assessment and at least one post-baseline HAMD assessment. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Per Protocol Population (PP)** will include the subset of the Efficacy Population who complete the full infusion without significant protocol violations or deviations. Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary and select secondary endpoints.

The **PK Population (PKP)** will include the subset of the Safety Population who have at least one evaluable PK sample. Subjects will be classified according to actual treatment received. This analysis population will be used for all PK analyses.

The **Breast Milk Population (BMP)** will include the subset of the Safety Population who have at least one evaluable breast milk sample. Subjects will be classified according to actual treatment received. This analysis population will be used for all breast milk PK analyses.

The number and percentage of subjects who receive SAGE-547 Injection or placebo, prematurely discontinue, and complete the study will be summarized. The number and percentage of subjects will also be summarized for each reason for premature discontinuation. In addition, the number of subjects whose data should be used for the planned analyses will be identified for each respective analysis population (ie, SAF, EFF, PKP, PP, and BMP).

13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis populations, using all non-missing data available. Any rules for the imputation of missing data will be described in the SAP.

13.3. Demographics and Baseline Characteristics

Demographics such as age, race, and ethnicity will be summarized. In addition, baseline characteristics such as height, weight, and BMI will be summarized. Categorical summaries, such as race and ethnicity, will be summarized by frequency and percentage. Continuous summaries, such as age, height, weight, BMI and baseline vital signs, will be summarized using descriptive statistics such as n, mean, SD, median, minimum, and maximum.

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

Medical/family history will be collected and listed by subject.

13.4. Primary Endpoints

Change from baseline to each assessment in HAMD total score will be analyzed using a mixed effects repeated measures model (MMRM) including center, treatment, baseline HAMD total score, assessment time point, and time point-by-treatment. Center will be treated as a random effect while all other explanatory variables will be treated as fixed effects. Separate models will be fit for each part of the study. For Parts A and C, the primary comparison will be between 90 µg SAGE-547 and placebo at the 60-hour assessment. For Part B, the primary comparison will be between 90 µg SAGE-547 and placebo at the 60-hour assessment; if this comparison is significant at the 0.05 level, then the 60 µg group will then be compared to placebo. Comparisons at other time points will be conducted to support the findings for the primary comparison. Model based point estimates (ie, LS means), 95% confidence intervals, and p-values will be reported for each assessment.

Summaries of HAMD total scores and changes from baseline values will include n, mean, SD, median, minimum, and maximum.

13.5. Secondary Endpoints

13.5.1. Efficacy Analysis

MMRM methods similar to those described in Section 13.4 will be used for the analysis of the following variables: MADRS total score, EPDS total score, GAD-7 total score, PHQ-9 total score, and select individual item and subscale scores. Separate models will be fit for

each part of the study. For each model, the comparison of interest will be between each SAGE-547 dose and placebo at the 60-hour assessment. Model based point estimates (ie, LS means), 95% confidence intervals, and p-values will be reported.

Logistic regression methods will be used for the analysis of the following response variables: HAMD response, HAMD remission, and CGI-I response. Logistic regression models will include terms for center, treatment, and baseline score. Separate models will be fit for each part of the study. The comparison of interest will be the difference between each SAGE-547 dose and placebo at the 60-hour assessment. 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.

13.5.2. Safety Analysis

Safety and tolerability of SAGE-547 Injection will be evaluated by AEs, concomitant medications, changes from baseline in physical examination, vital signs, CBC, serum chemistry, urinalysis, and 12-lead ECG. Suicidality will be monitored by the C-SSRS. Sedation will be assessed using the SSS. Safety data will be listed by individual and summarized by treatment group. In addition, an analysis of SSS data will be performed comparing the treatment groups in the same way as for the primary endpoint. All safety summaries will be performed on the SAF population.

Safety data will be examined for possible relationships between subject characteristics and plasma allopregnanolone concentrations, as appropriate.

Scheduled visits for all safety assessments are described in Section 12 and summarized in Table 1.

13.5.2.1. Adverse Events

The analysis of AEs will be based on the concept of treatment-emergent AEs (TEAEs). A TEAE is defined as an AE with onset after the start of SAGE-547 infusion, or any worsening of a pre-existing medical condition/AE with onset after the start of SAGE-547 infusion and until 7 days after the end of infusion. The incidence of TEAEs will be summarized overall and by MedDRA System Organ Class (SOC) and preferred term (PT). Incidences will be presented in order of decreasing frequency. In addition, summaries will be provided by severity (mild, moderate, severe) and by causality (related, not related) to study drug (see Section 14.2.2.1).

TEAEs leading to discontinuation and SAEs (see Section 14.1.4 for definition) with onset after the start of randomized infusion will also be summarized.

All AEs and SAEs (including those with onset or worsening before the start of randomized infusion) through the Day 30 follow-up visit (±3 days) will be listed.

13.5.2.2. Clinical laboratory evaluations

Results will be listed by Subject ID and timing of collection. Mean changes from baseline in clinical laboratory measures will be evaluated.

13.5.2.3. Physical examinations

Physical examinations will be evaluated at Screening and Day 7. Any clinically significant change in physical examination compared to those observed at Screening should be noted as an AE.

13.5.2.4. Vital signs

Vital signs, including oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing) will be obtained at the scheduled time points described in Section 11.1.4. Mean changes from baseline (pre-infusion) in vital signs will be evaluated.

13.5.2.5. 12-Lead ECG

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

13.5.2.6. Concomitant medications

A summary of all concomitant medications taken during the course of the study will be presented in tabular form by therapeutic drug class and generic drug name using the WHO Collaborating Centre for Drug Statistics Methodology Norwegian Institute of Public Health (http://www.whocc.no).

13.5.2.7. C-SSRS

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

13.5.2.8. SSS

Changes in score over time will be represented graphically, and change from baseline will be measured.

13.5.2.9. PK Analysis

Plasma will be collected to assay for concentrations of SAGE-547, metabolites of SAGE-547, and SBECD. The following PK parameters will be derived from the plasma concentrations (where evaluable): $AUC_{0\text{-}60}$, AUC_{Y}, C_{max}, time at maximum (peak) plasma concentration (t_{max}), steady-state drug concentration in the plasma during constant-rate infusion (C_{ss}), and average drug concentration in the plasma at steady state during a dosing interval (C_{avg}).

Plasma concentrations will be listed by subject and summarized by nominal collection time point. PK parameters will be listed by subject and summarized by collection time point.

Correlations between concentrations and AEs or tolerability measures may be performed as deemed necessary.

In addition to typical descriptive statistics, summaries should include geometric mean, coefficient of variation, and geometric coefficient of variation.

13.6. Determination of Sample Size

Assuming a two-sided test at an alpha level of 0.10, a sample size of 10 evaluable subjects per group would provide 80% power to detect an effect size of 1.2 between the SAGE-547 and placebo groups with regard to the primary outcome variable of change from baseline in HAMD total score. An effect size of 1.2 corresponds to a placebo adjusted difference of 12 points in the change from baseline in HAMD total score at 60 hours with an assumed standard deviation of 10 points. By including 2 treatment groups and using a 1:1 randomization ratio, a total of 20 evaluable subjects are required for Part A. Assuming a non-evaluability rate of 10%, up to 22 subjects will be randomized in Part A.

Based on the results of the interim analysis (Section 13.7), the sample size for Part A could be increased to a maximum of 32 randomized subjects. This adjustment to the sample size would allow for an effect size of 1.0 to be detected.

For Part B, a sample size of 18 evaluable subjects per group would provide at least 90% power to detect an effect size of 1.2 between the SAGE-547 and placebo groups using a two-sided test at an alpha level of 0.05. Assuming a non-evaluability rate of 10%, up to 60 subjects will be randomized in Part B.

For Part C, a sample size of 16 evaluable subjects per group would provide 80% power to detect an effect size of 1.0 between the SAGE-547 and placebo groups using a two-sided test at an alpha level of 0.10. Assuming a non-evaluability rate of 10%, up to 36 subjects will be randomized in Part C.

13.7. Interim Analysis

In Part A, an interim analysis will be conducted by an independent statistician for sample size re-estimation purposes when at least 16 subjects have completed efficacy assessments through 60 hours in Part A. Since the Sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing of Part A of the study. A detailed description of the interim analysis will be included in the SAP.

No interim analyses are planned for Parts B and C of the study.

13.8. Changes from Protocol Specified Analyses

Any changes from the analytical methods outlined in the protocol will be documented in the final SAP.

Upon the completion of each part of the study, the data may be unblinded and analyzed separately. The final CSR will report the findings of all parts of the study.

14. ADVERSE EVENTS

Section 14.1 lists important AE definitions.

Section 14.2 summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

Section 14.3 summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

14.1. Adverse Event Definitions

14.1.1. Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

14.1.2. Suspected Adverse Reaction

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

14.1.3. Life-Threatening

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

14.1.4. Serious

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE (see definition in Section 14.1.3)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- Other medically important condition (as described below)

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include

allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

14.1.5. Unexpected

An AE or suspected adverse reaction is considered "unexpected:"

- If it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents.

"Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

In the clinical trial setting, the term "expected" would not mean "anticipated" for the condition being treated or population being studied since "expected" would indicate being "listed in the Investigator's Brochure." For example, some adverse events can be anticipated to occur as a result of a disease or condition or in a certain population (eg, cancer-related deaths in a cancer trial, strokes or acute myocardial infarctions in an older population). However, for reporting purposes, these anticipated events are not considered "expected" if they are not listed in the Investigator's Brochure (ie, the investigational drug is not suspected or known to cause them).

14.2. Investigator Responsibilities

14.2.1. Identification and Documentation of Adverse Events by Investigator

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected during subject preparation, study drug administration during Screening, after the initiation of study drug administration through to Day 3, and at the Follow-up Visits on Day 7 (±1 day) and Day 30 (±3 days). SAEs will also be collected until the Day 30 (±3 days) follow-up visit. Medical conditions that occur prior to completion of the Screening Visit will be captured on the Medical History eCRF. Adverse events that occur after completion of the Screening Visit will be recorded on the AE page of the eCRF (AE eCRF).

All AEs revealed by observation, physical examinations, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the AE eCRF. Any clinically significant deterioration from

baseline in laboratory assessments or other clinical findings is considered an AE and must be recorded on the AE eCRF, unless otherwise stated. AE information recorded on AE eCRF will be entered into the database on an ongoing basis. The database, including AE information, will be transferred to the Sponsor on a pre-defined schedule for review.

All AEs, 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.

For all SAEs, an SAE report form must be completed with as much information as possible and submitted in the time frame described in Section 14.2.3. When new significant information is obtained as well as when the outcome of an event is known, the SAE report form should be updated on a follow-up report. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (eg, admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject's medical file.

All SAEs will be followed until the events are resolved or improved and a stable status has been achieved, or the subject is lost to follow-up.

14.2.2. Adverse Event Classification

Definitions for the categories of AE classification are included in this section.

14.2.2.1. Relationship to Investigational Drug

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

14.2.2.2. Severity

The severity of an adverse experience will be defined as follows and reported as indicated on the AE eCRF:

Mild:	Discomfort noticed, but no disruption to daily activity.
Moderate:	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.
Severe:	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.

14.2.2.3. Action Taken with Investigational Drug

Action taken with regard to administration of SAGE-547 Injection for this trial will be recorded using the one of following categories (the category "dose increased" does not apply to this trial):

- Drug withdrawn: An indication that a medication schedule was modified through termination of a prescribed regimen of medication
- Dose not changed: An indication that a medication schedule was maintained
- Drug interrupted: An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication
- Dose reduced: An indication that a medication schedule was modified to a reduced rate/dose
- Unknown: Unknown, not known, not observed, not recorded, or refused
- Not applicable: Determination of a value is not relevant in the current context

14.2.2.4. Assessment of Outcome

Assessment of outcome of AEs will be categorized as one of the following:

- Recovered/Resolved: The event has improved or recuperated
- Recovering/Resolving: The event is improving
- Not Recovered/Not Resolved: The event has not improved or recuperated
- Recovered/Resolved with Sequel: The subject recuperated but retained pathological conditions resulting from the prior disease or injury
- Fatal: The termination of life as a result of an adverse event
- Unknown: Not known, not observed, not recorded, or refused

14.2.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact

All SAEs that occur during the course of the study must be reported by the Investigator on the designated report form (study-specific SAE form or MedWatch 3500A form) and sent by

facsimile to the medical monitor within 24 hours from the point in time when the Investigator becomes aware of the SAE. Investigators must report any SAE, whether or not considered drug related. The initial report must be as complete as possible, including assessment of the causal relationship (ie, assessment of whether there is a reasonable possibility that the drug caused the event). The medical monitor will contact the investigator via telephone for follow-up information regarding the SAE, as appropriate.

Information not available at the time of the initial report must be documented on a follow-up report. As additional information becomes available, the designated report form must be updated and supporting information, including hospital records, laboratory and diagnostic testing results, etc. All supporting documentation must be de-identified. In addition, all SAEs that occur up to and including 30 days after administration of study drug must be reported within 1 working day from when the Investigator becomes aware of the SAE. A final report to document resolution of all SAEs is required.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care and contact the Medical Monitor.

14.2.4. Medical Monitor and Emergency Contact Information

[redacted], MD
[redacted]
Office (9-5 EST): [redacted]
24/7 Hotline: [redacted]

14.2.5. SAE Reporting Contact Information

Contact information and reporting instructions are provided in the Safety Management Plan.

14.2.6. Reporting to Institutional Review Boards (IRBs)

It is the responsibility of the Investigator to promptly notify the institution's IRB of all serious and unexpected suspected adverse reactions (see Section 14.3.2).

14.3. Sponsor/Medical Monitor Responsibilities

14.3.1. Monitoring of Adverse Event Data

The Medical Monitor or designee will review AEs on an ongoing basis.

14.3.2. Reporting to FDA

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32[c][1][i]). Before submitting an IND safety report, the Sponsor will ensure the event meets all 3 of the definitions:

(1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all 3 of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the AE and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence of serious suspected adverse reactions over that listed in the protocol or Investigator's Brochure.

14.4. Emergency Identification of Study Medication

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment from the pharmacist; this normally requires prior approval by the Medical Monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the Medical Monitor may take place after unblinding. The Investigator will not unblind the Medical Monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the Medical Monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the Medical Monitor, study management team, and data management team.

15. STUDY ADMINISTRATION

15.1. Quality Control and Quality Assurance

The Investigators and institutions will permit trial-related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (ie, original medical records, laboratory reports, hospital documents, progress reports, signed ICFs, etc.) in addition to CRFs.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure that this trial 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, CRFs 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 the Sponsor with the Investigator/institution and any other parties involved with the clinical trial will be in writing in a separate agreement.

15.2. Data Handling and Recordkeeping

15.2.1. Data Handling

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

15.2.2. Case Report Form Completion

Electronic CRFs (eCRFs) 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, AEs, and subject status.

The Investigator will have access to the electronic data capture (EDC) 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.

15.2.3. Retention of Study Records

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least two years after the last marketing application approval and until there are no pending or contemplated marketing applications or two years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

15.3. Confidentiality

To maintain subject privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the CRFs 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 the Sponsor. It is understood that there is an obligation to provide the Sponsor 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 authority(ies), other Investigators, corporate partners, or consultants as required.

15.4. Publication Policy

All information concerning SAGE-547 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.

15.5. Protocol Amendments

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

16. 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.

Amin Z, Mason GF, Cavus I et al. The interaction of neuroactive steroids and GABA in the development of neuropsychiatric disorders in women. Pharmacol, Biochem and Behavior 2006;84:635-43.

Austin MP, Middleton P, Reilly NM, Highet NJ. Detection and management of mood disorders in the maternity setting: the Australian Clinical Practice Guidelines. Women Birth 2013;26(1):2-9. doi: 10.1016/j.wombi.2011.12.001. Epub 2012 Jan 2.

Belelli D, Lambert JJ. Neurosteroids: endogenous regulators of the GABA(A) receptor. Nat Rev Neurosci 2005; 6(7):565-75. PMID: 15959466.

Bitran D, Hilvers RJ, Kellogg CK. Anxiolytic effects of 3α-hydroxy-5α[β]-pregnan-20-one: endogenous metabolites of progesterone that are active at the GABAA receptor. Brain Res 1991;561(1):157-161. PMID: 1686744.

Bitran D, Purdy RH, Kellog CK. Anxiolytic effect of progesterone is associated with increases in cortical allopregnanolone and GABAA receptor function. Pharmacol Biochem Behav 1993;45(2):423-8. PMID: 8392205.

Bloch M, Schmidt PJ, Danaceau M, et al. Effects of gonadal steroids in women with a history of postpartum depression. Am J Psychiatry 2000;157(6):924-30. PMID: 10831472.

Chaudron L. Postpartum depression: what pediatricians need to know. Pediatr Rev 2003;24(5);154-61. PMID: 12728188.

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.

Coyle CM, Laws KR. The use of ketamine as an antidepressant: a systematic review and meta-analysis. Hum Psychopharmacol. 2015;30(3):152-163.

Djebaili M, Guo Q, Pettus EH, Hoffman SW, Stein DG. The neurosteroids progesterone and allopregnanolone reduce cell death, gliosis, and functional deficits after traumatic brain injury in rats. J Neurotrauma 2005;22(1):106-18. PMID: 15968816.

Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL. A meta-analysis of cytokines in major depression. Biol Psychiatry 2010;67(5):446-57. PMID: 20015486.

DSM V. Diagnostic and statistical manual of mental disorders (5th ed.). American Psychiatric Association 2013. Arlington, VA: American Psychiatric Publishing.

Earls MF; Committee on Psychosocial Aspects of Child and Family Health American Academy of Pediatrics. Incorporating recognition and management of perinatal and postpartum depression into pediatric practice. Pediatrics 2010;126(5):1032-9. doi: 10.1542/peds.2010-2348.

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. PMID: 17719367.

Epperson CN, Gueorguieva R, Czarkowski KA et al. Preliminary evidence of reduced occipital GABA concentrations in puerperal women: a 1H-MRS study. Psychopharmacol 2006; 186:425-433. PMID: 16724188.

Eser D, Schüle C, Baghai TC, Romeo E, Rupprecht R. Neuroactive steroids in depression and anxiety disorders: clinical studies. Neuroendocrinology 2006;84(4):244-54. PMID: 17159334.

Fihrer I, McMahon CA, Taylor AJ. The impact of postnatal and concurrent maternal depression on child behaviour during the early school years. J Affect Disord 2009;119(1-3):116-23. PMID: 19342104.

Fournier JC, DeRubeis RJ, Hollon SD et al. Antidepressant drug effects and depression severity—a patient-level meta-analysis. JAMA 2010;303:47-53. PMID: 20051569.

Frye CA, Duncan JE. Progesterone metabolites, effective at the GABAA receptor complex, attenuate pain sensitivity in rats. Brain Res 1994;643(1-2):194-203. PMID: 8032914.

Gangisetty O and Reddy DS. Neurosteroid withdrawal regulates GABA-A receptor α4-subunit expression and seizure susceptibility by activation of progesterone receptor-independent early growth response factor-3 pathway. Neuroscience 2010; 170:865-880. PMID: 20670676.

Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, and Swinson T. Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol 2005;106:1071-83. PMID: 16260528.

Gaynes BN, Gavin N, Meltzer-Brody S, Lohr KN, Swinson T, Gartlehner G, et al. Perinatal depression: prevalence, screening accuracy, and screening outcomes. Evid Rep Technol Assess (Summ) 2005;(119):1-8. PMID: 15760246.

Gilbert Evans SE, Ross LE, Sellers EM et al. 3alpha-reduced neuroactive steroids and their precursors during pregnancy and the postpartum period. Gynecol Endocrinol 2005 21, 268-279. PMID: 16373246.

Genazzani AR, Petraglia F, Bernardi F, Casarosa E, Salvestroni C, Tonetti A, et al. Circulating levels of allopregnanolone in humans: gender, age, and endocrine influences. J Clin Endocrinol Metab 1998;83(6):2099-103. PubMed PMID: 9626145.

Glantz LA, Gilmore JH, Overstreet DH, Salimi K, Lieberman JA, Jarskog LF. Pro-apoptotic Par-4 and dopamine D2 receptor in temporal cortex in schizophrenia, bipolar disorder and major depression. Schizophr Res 2010;118(1-3):292-9. PMID: 20067857.

Hamilton M: A rating scale for depression. Journal Neurol Neurosurg Psychiatry 1960; 23:56-62. PMID: 14399272.

He JQ, Tang XW, Chen HX, Xiang Z. [Study on treatment of climacteric depression with bushen tiaogan qingxin recipe]. Zhongguo Zhong Xi Yi Jie He Za Zhi 2004;24(10):889-92. [Article in Chinese]. PMID: 15553820.

Holzbauer M, Birmingham MK, De Nicola AF, Oliver JT. In vivo secretion of 3 alpha-hydroxy-5 alpha-pregnan-20-one, a potent anaesthetic steroid, by the adrenal gland of the rat. J Steroid Biochem. 1985 Jan;22(1):97-102. PubMed PMID: 3974231.

Kask K, Bäckström T, Lundgren P, Sundström Poromaa I. Allopregnanolone has no effect on startle response and prepulse inhibition of startle response in patients with premenstrual dysphoric disorder or healthy controls. Pharmacol Biochem Behav 2009;92(4):608-13. PubMed PMID: 19268499.

Kask K, Bäckström T, Nilsson LG, Sundström-Poromaa I. Allopregnanolone impairs episodic memory in healthy women. Psychopharmacology (Berl) 2008;199(2):161-8. PMID: 18551282.

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. PMID: 18303940.

Klak J, Hill M, Parízek A, Havlíková H, et al. Pregnanolone isomers, pregnenolone and their polar conjugates around parturition. Physiol Res 2003;52(2):211-21. PMID: 12678664.

Licinio J, Wong ML. The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. Mol Psychiatry 1999;4(4):317-27. PMID: 10483047.

Luisi S, Petraglia F, Benedetto C, Nappi RE, Bernardi F, Fadalti M, et al. Serum allopregnanolone levels in pregnant women: changes during pregnancy, at delivery, and in hypertensive patients. J Clin Endocrinol Metab 2000;85(7):2429-33. PMID: 10902789.

Maguire J, Mody I. GABA(A)R plasticity during pregnancy: relevance to postpartum depression. Neuron 2008;59(2):207-13. PMID: 18667149.

Maguire J, Ferando I, Simonsen C, Mody I. Excitability changes related to GABAA receptor plasticity during pregnancy. J Neurosci 2009;29(30):9592-601. PMID: 19641122.

Majewska MD, Harrison NL, Schwartz RD, Barker JL, Paul SM. Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor. Science 1986;232:1004-7. PMID: 2422758.

McDowell, I. Measuring Health: A guide to rating scales and questionnaires. 2006: 3rd Ed. New York: Oxford University Press.

Morrow AL, Devaud LL, Purdy RH, Paul SM. Neuroactive steroid modulators of the stress response. Ann N Y Acad Sci 1995;771:257-72. PMID: 8597405.

Müller-Thomsen T, Arlt S, Mann U, Maß R, Ganzer S. Detecting depression in Alzheimer's disease: evaluation of four different scales. Archives of Clinical Neuropsychology 2005;20:271-6. PMID: 15708735.

Nappi RE, Petraglia F, Luisi S et al. Serum allopregnanolone in women with postpartum "blues". Obstet Gynecol 2001;97 (1):77-80. PMID: 11152912.

Navarro PA, Kaddouz D, de Ziegler D, Silva de Sá MF, Ferriani RA. Vaginal administration of allopregnanolone to postmenopausal women undergoing estrogen replacement therapy: preliminary results. Maturitas 2003;46(2):147-52. PubMed PMID: 14559386.

Norberg L, Backstrom T and Wahlstrom G. Anaesthetic effects of pregnanolone in combination with allopregnanolone, thiopental, hexobarbital and flurazepam: an EEG study in the rat. Br J Anaesth 1999; 82(5):731-737. PMID: 10536552.

O'Hara MW, Wisner KL. Perinatal mental illness: definition, description and aetiology. Best Pract Res Clin Obstet Gynaecol 2014;28(1):3-12. doi: 10.1016/j.bpobgyn.2013.09.002.

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.

Ottander U, Poromaa IS, Bjurulf E, Skytt A, Bäckström T, Olofsson JI. Allopregnanolone and pregnanolone are produced by the human corpus luteum. Mol Cell Endocrinol 2005 Jul 15;239(1-2):37-44. PubMed PMID: 15935549.

Paoletti AM, Romagnino S, Contu R, et al. Observational study on the stability of the psychological status during normal pregnancy and increased blood levels of neuroactive steroids with GABA-A receptor agonist activity. Psychoneuroendocrinology 2006; 31(4): 485-492. PMID: 16406349.

Paul SM, Purdy RH. Neuroactive steroids. FASEB J 1992;6(6):2311-22. PMID: 1347506.

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. doi: 10.1176/appi.ajp.2011.10111704.

Romeo E, Ströhle A, Spalletta G, di Michele F, Hermann B, Holsboer F, Pasini A, Rupprecht R. Effects of antidepressant treatment on neuroactive steroids in major depression. Am J Psychiatry 1998;155(7):910-3. PMID: 9659856.

Sayeed I, Parvez S, Wali B, Siemen D, Stein DG. Direct inhibition of the mitochondrial permeability transition pore: a possible mechanism for better neuroprotective effects of allopregnanolone over progesterone. Brain Res 2009;1263:165-73. PMID: 19368823.

Schüle C, Romeo E, Uzunov DP, Eser D, di Michele F, Baghai TC, et al. Influence of mirtazapine on plasma concentrations of neuroactive steroids in major depression and on 3α-hydroxysteroid dehydrogenase activity. Mol Psychiatry 2006;11(3):261-72. PMID: 16344854.

Schüle C, Baghai TC, di Michele F, Eser D, Pasini A, Schwarz M. Effects of combination treatment with mood stabilizers and mirtazapine on plasma concentrations of neuroactive steroids in depressed patients. Psychoneuroendocrinology 2007;32(6):669-80. PMID: 17560730.

Shelton RC, Trivedi MH. Moderators of antidepressant response in major depression. J Clin Psychiatry 2011;72(10):e32. PMID: 22075105.

Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. Arch Intern Med 2006; 166(10):1092-1097. doi: 10.1001/archinte.166.10.1092.

Ströhle A, Romeo E, Hermann B, Pasini A, Spalletta G, di Michele F, et al. Concentrations of 3α-reduced neuroactivesteroids and their precursors in plasma of patients with major depression and after clinical recovery. Biol Psychiatry 1999;45(3):274-77. PMID: 10023501.

Timby E, Balgård M, Nyberg S, Spigset O, Andersson A, Porankiewicz-Asplund J, et al. Pharmacokinetic and behavioral effects of allopregnanolone in healthy women. Psychopharmacology (Berl) 2006 Jun;186(3):414-24. PMID: 16177884.

Timby E, Hedström H, Bäckström T, Sundström-Poromaa I, Nyberg S, Bixo M. Allopregnanolone, a GABAA receptor agonist, decreases gonadotropin levels in women A preliminary study. Gynecol Endocrinol 2011 Dec;27(12):1087-93. PMID: 21190418. (Timby 2011a)

Timby E. Allopregnanolone effects in women. Clinical studies in relation to the menstrual cycle, premenstrual dysphoric disorder and oral contraceptive use. Umea University Medical Dissertation 2011; New Series No. 1459. (Timby 2011b)

Uzunova V, Sheline Y, Davis JM, Rasmusson A, Uzunov DP, Costa E, et al. Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine. Proc Natl Acad Sci 1998;95(6):3239-44. PMID: 9501247.

van Broekhoven F, Bäckström T, van Luijtelaar G, Buitelaar JK, Smits P, Verkes RJ. Effects of allopregnanolone on sedation in men, and in women on oral contraceptives. Psychoneuroendocrinology. 2007 Jun;32(5):555-64. PMID: 17470385.

Verbeek T, Bockting CL, van Pampus MG et al. Postpartum depression predicts offspring mental health problems in adolescence independently of parental lifetime psychopathology. J Affect Disord 2012;136(3):948-54. doi: 10.1016/j.jad.2011.08.035.

Wieland S, Lan NC, Mirasedeghi S, Gee KW. Anxiolytic activity of the progesterone metabolite 5α-pregnan-3α-ol-20-one. Brain Res 1991;565(2):263-8. PMID: 1688192.

APPENDICES

Copies of the rating scales and questionnaires included in Appendix 1 through Appendix 9 are for reference only.

Appendix 1. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)

The “Baseline/Screening” and “Since Last Visit” versions of the C-SSRS begin on the next full page (Posner 2011).

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103-130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***) Past X Months - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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Appendix 2. HAMILTON RATING SCALE FOR DEPRESSION, 17-ITEM (HAMD)

The HAMD presents on the next full page (Hamilton 1960).

The HAMD total score will be calculated as the sum of the 17 individual item scores. Item 16 can be rated according to history (item 16A) or actual weight change (item 16B). The item 16 score is calculated as the item 16 response that is not equal to 3 (ie, "Not assessed).

Patient Name:_____ Date:_____

Hamilton Rating Scale for Depression (17-items)

Instructions: For each item select the "cue" which best characterizes the patient during the past week.

1. **Depressed Mood**
(sadness, hopeless, helpless, worthless)
0 Absent
1 These feeling states indicated only on questioning
2 These feeling states spontaneously reported verbally
3 Communicates feeling states nonverbally, i.e., through facial expression, posture, voice and tendency to weep
4 Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and nonverbal communication

2. **Feelings of Guilt**
0 Absent
1 Self-reproach, feels he has let people down
2 Ideas of guilt or rumination over past errors or sinful deeds
3 Present illness is a punishment. Delusions of guilt
4 Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. **Suicide**
0 Absent
1 Feels life is not worth living
2 Wishes he were dead or any thoughts of possible death to self
3 Suicide ideas or gesture
4 Attempts at suicide (any serious attempt rates 4)

4. **Insomnia - Early**
0 No difficulty falling asleep
1 Complains of occasional difficulty falling asleep i.e., more than ½ hour
2 Complains of nightly difficulty falling asleep

5. **Insomnia - Middle**
0 No difficulty
1 Patient complains of being restless and disturbed during the night
2 Waking during the night – any getting out of bed rates 2 (except for purposes of voiding)

6. **Insomnia - Late**
0 No difficulty
1 Waking in early hours of the morning but goes back to sleep
2 Unable to fall asleep again if gets out of bed

7. **Work and Activities**
0 No difficulty
1 Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
2 Loss of interest in activity; hobbies or work – either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
3 Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores.
4 Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores, or if patient fails to perform ward chores unassisted.

8. **Retardation**
(slowness of thought and speech; impaired ability to concentrate; decreased motor activity)
0 Normal speech and thought
1 Slight retardation at interview
2 Obvious retardation at interview
3 Interview difficult
4 Complete stupor

9. **Agitation**
0 None
1 "Playing with" hand, hair, etc.
2 Hand-wringing, nail-biting, biting of lips

10. **Anxiety - Psychic**
0 No difficulty
1 Subjective tension and irritability
2 Worrying about minor matters
3 Apprehensive attitude apparent in face or speech
4 Fears expressed without questioning

11. **Anxiety - Somatic**
0 Absent
1 Mild
2 Moderate
3 Severe
4 Incapacitating
Physiological concomitants of anxiety such as:
Gastrointestinal - dry mouth, wind, indigestion, diarrhea, cramps, belching
Cardiovascular – palpitations, headaches
Respiratory - hyperventilation, sighing
Urinary frequency
Sweating

12. **Somatic Symptoms - Gastrointestinal**
0 None
1 Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
2 Difficulty eating without staff urging. Requests or requires laxatives or medications for bowels or medication for G.I. symptoms.

13. **Somatic Symptoms - General**
0 None
1 Heaviness in limbs, back or head, backaches, headache, muscle aches, loss of energy and fatigability
2 Any clear-cut symptom rates 2

14. **Genital Symptoms**
0 Absent
1 Mild
2 Severe
0 Not ascertained
Symptoms such as: loss of libido, menstrual disturbances

15. **Hypochondriasis**
0 Not present
1 Self-absorption (bodily)
2 Preoccupation with health
3 Frequent complaints, requests for help, etc.
4 Hypochondriacal delusions

16. **Loss of Weight**
A. When Rating by History:
0 No weight loss
1 Probable weight loss associated with present illness
2 Definite (according to patient) weight loss

B. On Weekly Ratings by Ward Psychiatrist, When Actual Changes are Measured:
0 Less than 1 lb. weight loss in week
1 Greater than 1 lb. weight loss in week
2 Greater than 2 lb. weight loss in week

17. **Insight**
0 Acknowledges being depressed and ill
1 Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2 Denies being ill at all

Total Score:_____

Appendix 3. MONTGOMERY ASBERG DEPRESSION RATING SCALE (MADRS)

The MADRS presents on the next full page (McDowell 2006, Müller-Thomsen 2005).

Montgomery-Åsberg Depression Rating Scale (MADRS)

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5) and then report the appropriate number. The items should be rated with regards to how the patient has done over the past week.

1. Apparent sadness

Representing despondency, gloom and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

0 = No sadness.
2 = Looks dispirited but does brighten up without difficulty.
4 = Appears sad and unhappy most of the time.
6 = Looks miserable all the time. Extremely despondent

2. Reported sadness

Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope.

0 = Occasional sadness in keeping with the circumstances.
2 = Sad or low but brightens up without difficulty.
4 = Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
6 = Continuous or unvarying sadness, misery or despondency.

3. Inner tension

Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 = Placid. Only fleeting inner tension.
2 = Occasional feelings of edginess and ill-defined discomfort.
4 = Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
6 = Unrelenting dread or anguish. Overwhelming panic.

4. Reduced sleep

Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

0 = Sleeps as normal.
2 = Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
4 = Moderate stiffness and resistance
6 = Sleep reduced or broken by at least 2 hours.

5. Reduced appetite

Representing the feeling of a loss of appetite compared with when-well. Rate by loss of desire for food or the need to force oneself to eat.

0 = Normal or increased appetite.
2 = Slightly reduced appetite.
4 = No appetite. Food is tasteless.
6 = Needs persuasion to eat at all.

6. Concentration difficulties

Representing difficulties in collecting one's thoughts mounting to an incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.
0 = No difficulties in concentrating.
2 = Occasional difficulties in collecting one's thoughts.
4 = Difficulties in concentrating and sustaining thought which reduced ability to read or hold a conversation.
6 = Unable to read or converse without great difficulty.

7. Lassitude

Representing difficulty in getting started or slowness in initiating and performing everyday activities.
0 = Hardly any difficulty in getting started. No sluggishness.
2 = Difficulties in starting activities.
4 = Difficulties in starting simple routine activities which are carried out with effort.
6 = Complete lassitude. Unable to do anything without help.

8. Inability to feel

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.
0 = Normal interest in the surroundings and in other people.
2 = Reduced ability to enjoy usual interests.
4 = Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
6 = The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. Pessimistic thoughts

Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.
0 = No pessimistic thoughts.
2 = Fluctuating ideas of failure, self-reproach or self- depreciation.
4 = Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
6 = Delusions of ruin, remorse or irredeemable sin. Self- accusations which are absurd and unshakable.

10. Suicidal thoughts

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicide attempts should not in themselves influence the rating.
0 = Enjoys life or takes it as it comes.
2 = Weary of life. Only fleeting suicidal thoughts.
4 = Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intenstion.
6 = Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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Appendix 4. CLINICAL GLOBAL IMPRESSION–IMPROVEMENT SCALE (CGI-I) AND SEVERITY SCALE (CGI-S)

The CGI-I and CGI-S presents on the next full page. For the purposes of Protocol 547-PPD-202, only Items 1 and 2, Severity of Illness and Global Improvement, will be assessed in subjects enrolled in the study.

1. **Severity of illness**
   Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?
   0 = Not assessed
   1 = Normal, not at all ill
   2 = Borderline mentally ill
   3 = Mildly ill
   4 = Moderately ill
   5 = Markedly ill
   6 = Severely ill
   7 = Among the most extremely ill patients

2. **Global improvement:** Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.
   Compared to his condition at admission to the project, how much has he changed?
   0 = Not assessed
   1 = Very much improved
   2 = Much improved
   3 = Minimally improved
   4 = No change
   5 = Minimally worse
   6 = Much worse
   7 = Very much worse

3. **Efficacy index:** Rate this item on the basis of **drug effect only**.
   Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.
   EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		**Side effects**			
		None	*Do not significantly interfere with patient's functioning*	*Significantly interferes with patient's functioning*	*Outweighs therapeutic effect*
Marked	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
Moderate	Decided improvement. Partial remission of symptoms	05	06	07	08
Minimal	Slight improvement which doesn't alter status of care of patient	09	10	11	12
Unchanged or worse		13	14	15	16

Not assessed = 00

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

Appendix 5. STANFORD SLEEPINESS SCALE (SSS)

The SSS presents on the next full page.

Stanford Sleepiness Scale

This is a quick way to assess how alert you are feeling. If it is during the day when you go about your business, ideally you would want a rating of a one. Take into account that most people have two peak times of alertness daily, at about 9 a.m. and 9 p.m. Alertness wanes to its lowest point at around 3 p.m.; after that it begins to build again. Rate your alertness at different times during the day. If you go below a three when you should be feeling alert, this is an indication that you have a serious sleep debt and you need more sleep.

An Introspective Measure of Sleepiness
The Stanford Sleepiness Scale (SSS)

Degree of Sleepiness	**Scale Rating**
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

Appendix 6. EDINBURGH POSTNATAL DEPRESSION SCALE (EPDS)

The EPDS presents on the next full page (Cox 1987).

Study ID:

Edinburgh Postnatal Depression Scale

As you are pregnant or have recently had a baby, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**, not just how you feel today.

Here is an example, already completed.

I have felt happy:
☐ Yes, all the time
☒ Yes, most of the time This would mean: "I have felt happy most of the time" during the past week.
☐ No, not very often
☐ No, not at all

Please complete the other questions in the same way.

In the past 7 days:

1. I have been able to laugh and see the funny side of things
☐ As much as I always could
☐ Not quite so much now
☐ Definitely not so much now
☐ Not at all

2. I have looked forward with enjoyment to things
☐ As much as I ever did
☐ Rather less than I used to
☐ Definitely less than I used to
☐ Hardly at all

***3. I have blamed myself unnecessarily when things went wrong**
☐ Yes, most of the time
☐ Yes, some of the time
☐ Not very often
☐ No, never

4. I have been anxious or worried for no good reason
☐ No, not at all
☐ Hardly ever
☐ Yes, sometimes
☐ Yes, very often

***5 I have felt scared or panicky for no very good reason**
☐ Yes, quite a lot
☐ Yes, sometimes
☐ No, not much
☐ No, not at all

***6. Things have been getting on top of me**
☐ Yes, most of the time I haven't been able to cope at all
☐ Yes, sometimes I haven't been coping as well as usual
☐ No, most of the time I have copied quite well
☐ No, I have been coping as well as ever

***7 I have been so unhappy that I have had difficulty sleeping**
☐ Yes, most of the time
☐ Yes, sometimes
☐ Not very often
☐ No, not at all

***8 I have felt sad or miserable**
☐ Yes, most of the time
☐ Yes, quite often
☐ Not very often
☐ No, not at all

***9 I have been so unhappy that I have been crying**
☐ Yes, most of the time
☐ Yes, quite often
☐ Only occasionally
☐ No, never

***10 The thought of harming myself has occurred to me**
☐ Yes, quite often
☐ Sometimes
☐ Hardly ever
☐ Never

Appendix 7. GENERALIZED ANXIETY DISORDER 7-ITEM SCALE (GAD-7)

The GAD-7 presents on the next full page (Spitzer 2006).

Generalized Anxiety Disorder 7-item (GAD-7) scale

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	
Total Score *(add your column scores)* =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all _____
Somewhat difficult _____
Very difficult _____
Extremely difficult _____

APPENDIX 8. PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

The PHQ-9 presents on the next full page.

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

APPENDIX 9. BARKIN INDEX OF MATERNAL FUNCTIONING (BIMF)

The BIMF is presented on the next full page.

Barkin Index of Maternal Functioning

Please **circle the number** that best represents how you have felt **over the past two weeks**. Please try to answer each question as honestly as possible as your responses will help us to better understand the postpartum experience.

	Strongly Disagree	Disagree	Somewhat Disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
1. I am a good mother.	0	1	2	3	4	5	6
2. I feel rested.	0	1	2	3	4	5	6
3. I am comfortable with the way I've chosen to feed my baby (either bottle or breast, or both).	0	1	2	3	4	5	6
4. My baby and I understand each other.	0	1	2	3	4	5	6
5. I am able to relax and enjoy time with my baby.	0	1	2	3	4	5	6
6. There are people in my life that I can trust to care for my baby when I need a break.	0	1	2	3	4	5	6
7. *I am comfortable* allowing a trusted friend or relative to care for my baby (can include baby's father or partner).	0	1	2	3	4	5	6
8. I am getting enough adult interaction.	0	1	2	3	4	5	6
9. I am getting enough encouragement from other people.	0	1	2	3	4	5	6
10. I trust my own feelings (instincts) when it comes to taking care of my baby.	0	1	2	3	4	5	6
11. I take a little time each week to do something for myself.	0	1	2	3	4	5	6
12. I am taking good care of my baby's physical needs (feedings, changing diapers, doctor's appointments).	0	1	2	3	4	5	6
13. I am taking good care of my physical needs (eating, showering, etc).	0	1	2	3	4	5	6
14. I make good decisions about my baby's health and well being.	0	1	2	3	4	5	6
15. My baby and I are getting into a routine.	0	1	2	3	4	5	6
16. I worry about how other people judge me (as a mother).	0	1	2	3	4	5	6
17. I am able to take care of my baby and my other responsibilities.	0	1	2	3	4	5	6
18. Anxiety or worry often interferes with my mothering ability.	0	1	2	3	4	5	6
19. *As time goes on*, I am getting better at taking care of my baby.	0	1	2	3	4	5	6
20. I am *satisfied* with the job I am doing as a new mother.	0	1	2	3	4	5	6

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APPENDIX 10. SELECTED INDUCERS, INHIBITORS, AND SUBSTRATES OF CYP2C9

Inhibitors of CYP2C9 can be classified by their potency, such as:

- **Strong** being one that causes at least a 5-fold increase in the plasma AUC values, or more than 80% decrease in clearance.
- **Moderate** being one that causes at least a 2-fold increase in the plasma AUC values, or 50-80% decrease in clearance.
- **Weak** being one that causes at least a 1.25-fold but less than 2-fold increase in the plasma AUC values, or 20-50% decrease in clearance.

Substrates	Inhibitors	Inducers

• NSAIDs (analgesic, antipyretic, anti-inflammatory)
  ○ celecoxib
  ○ lornoxicam
  ○ diclofenac
  ○ ibuprofen
  ○ naproxen
  ○ ketoprofen
  ○ piroxicam
  ○ meloxicam
  ○ suprofen
• phenytoin (antiepileptic)
• fluvastatin (statin)
• sulfonylureas (antidiabetic)
  ○ glipizide
  ○ glibenclamide
  ○ glimepiride
  ○ tolbutamide
  ○ glyburide
• angiotensin II receptor antagonists (in hypertension, diabetic nephropathy, CHF)
  ○ irbesartan
  ○ losartan
• S-warfarin (anticoagulant)
• sildenafil (in erectile dysfunction)
• terbinafine (antifungal)
• amitriptyline (tricyclic antidepressant)
• fluoxetine (SSRI antidepressant)
• nateglinide (antidiabetic)
• rosiglitazone (antidiabetic)
• tamoxifen (SERM)
• torasemide (loop diuretic)
• ketamine
• THC
• JWH-018
• AM-2201
	Strong
	• fluconazole (antifungal)
	• miconazole (antifungal)
	• amentoflavone (constituent of Ginkgo biloba and St. John's Wort)
	• sulfaphenazole (antibacterial)
	• valproic acid (anticonvulsant, mood-stabilizing)
	• apigenin
	
	Moderate
	• amiodarone (antiarrhythmic)
	
	Unspecified potency
	• antihistamines (H_1 receptor antagonists)
	  ○ cyclizine
	  ○ promethazine
	• chloramphenicol
	• fenofibrate (fibrate)
	• flavones
	• flavonols
	• fluvastatin (statin)
	• fluvoxamine (SSRI)
	• isoniazid (in tuberculosis)
	• lovastatin (statin)
	• phenylbutazone (NSAID)
	• probenecid (uricosuric)
	• sertraline (SSRI)
	• sulfamethoxazole (antibiotic)
	• teniposide (chemotherapeutic)
	• voriconazole (antifungal)
	• zafirlukast (leukotriene antagonist)
	• quercetin (anti-inflammatory)
		Strong
		• rifampicin (bactericidal)
		• secobarbital (barbiturate)

Summary of Changes
Protocol-547-PPD-202
Dated 30 June 2016

The following changes were made to the attached protocol in this amendment. Minor typographical/editorial errors throughout the document were also corrected. The Synopsis, Tables, Figures and Abbreviations were corrected to be consistent with the changes in the main body of the protocol.

Section number and title in Protocol Version 2.0 (22 December 2015)	**Section number and title in Version 3.0 (30 June 2016)**	**Original text:**	**Changed to:**	**Rationale**
Global	Global	N/A	Protocol amended to include Parts A, B, and C. Part A is the existing completed part. Part A and Part B will study women with severe postpartum depression (PPD). Part C will study women with moderate PPD.	*Addition of Part B to evaluate women with severe PPD at lower target doses of SAGE-547. Addition of Part C to evaluate women with moderate PPD.*
Title Page, 1. Signature Page, 2. Synopsis	Title Page, 1. Signature Page, 2. Synopsis	A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY, SAFETY, AND	A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY, SAFETY, AND	*Inclusion of subjects with moderate postpartum depression.*

Section number and title in Protocol Version 2.0 (22 December 2015)	Section number and title in Version 3.0 (30 June 2016)	Original text:	Changed to:	Rationale
		PHARMACOKINETICS OF SAGE-547 INJECTION IN THE TREATMENT OF ADULT FEMALE SUBJECTS WITH SEVERE POSTPARTUM DEPRESSION	PHARMACOKINETICS OF SAGE-547 INJECTION IN THE TREATMENT OF ADULT FEMALE SUBJECTS WITH SEVERE POSTPARTUM DEPRESSION **AND ADULT FEMALE SUBJECTS WITH MODERATE POSTPARTUM DEPRESSION**	
1. Signature Page	1. Signature Page	N/A	[redacted], PhD Sage Therapeutics [redacted], MPH Sage Therapeutics [redacted] Sage Therapeutics	*Addition of signatories for Sponsor Approval*
2. Synopsis	2. Synopsis	Approximately 15 sites in the United States	**Up to 50 sites** in the United States **and Canada**	*Additional sites and country added to support enrollment in Parts B and C.*

Section number and title in Protocol Version 2.0 (22 December 2015)	**Section number and title in Version 3.0 (30 June 2016)**	**Original text:**	**Changed to:**	**Rationale**
5. Introduction and Rationale	4. Introduction and Rationale	This study is designed to evaluate the efficacy, safety, and pharmacokinetics (PK) of SAGE-547 (allopregnanolone) as a treatment for women with severe postpartum depression (PPD), an area of high unmet medical need.	This study is designed to evaluate the efficacy, safety, and pharmacokinetics (PK) of SAGE-547 (allopregnanolone) as a treatment for women with severe **or moderate** postpartum depression (PPD), an area of high unmet medical need.	
5.5.1 Study Population	4.5.1 Study Population	This study will evaluate the efficacy, safety, and pharmacokinetics (PK) of SAGE-547 Injection in the treatment of adult female subjects diagnosed with severe postpartum depression.	This study will evaluate the efficacy, safety, and pharmacokinetics (PK) of SAGE-547 Injection in the treatment of adult female subjects diagnosed with severe **or moderate** postpartum depression.	*Inclusion of subjects with moderate postpartum depression*
5.5.1 Study Population	4.5.1 Study Population	N/A	Part A of this study will study women with severe PPD, and Part C will study women with moderate PPD (Part B and C will run concurrently). Moderate severity level will be studied because the pathogenesis of severe postpartum depression may not be generalized to those patients with a less severe form of illness. For example, outside of postpartum	*Addition of Parts A and C study population.*

Section number and title in Protocol Version 2.0 (22 December 2015)	Section number and title in Version 3.0 (30 June 2016)	Original text:	Changed to:	Rationale
			depression, findings suggest that patient's treatment-resistant depression may respond more favorably to certain pharmacotherapy options such as ketamine (Coyle 2015). Therefore, in order to determine the efficacy of SAGE-547 in women with less severe levels of symptoms, a separate group with moderate PPD with the same doses of the study drug used in the severe group will be investigated.	
5.5.3 Dose Rationale	4.5.3 Dose Rationale	The infusion rate of SAGE-547 to be studied in this trial was chosen to achieve a mean exposure of 150 nM, roughly equivalent to the highest endogenous concentrations measured in third trimester pregnancy at approximately 157 nM (Luisi 2000).	The infusion rate of SAGE-547 to be studied in **Parts A and C of** this study was chosen to achieve a mean exposure of 150 nM, roughly equivalent to the highest endogenous concentrations measured in third trimester pregnancy at approximately 157 nM (Luisi 2000).	*Addition of Parts A and C.*
5.5.3 Dose Rationale	4.5.3 Dose Rationale	Doses will be increased as follows: 30 µg /kg/hour [(0-4 hours],), then 60 µg/kg/hour [(4-24 hours],), then 90 µg/kg/hour [(24-52 hours],), followed by a decrease to 60 µg/kg/hour (52- 56	**In Parts A and C**, doses will be increased as follows: 30 µg/kg/hour [(0-4 hours],), then 60 µg/kg/hour [(4- 24 hours],), then 90 µg/kg/hour [(24-52 hours],), followed by a decrease to 60 µg/kg/hour	*Addition of Parts A and C.*

Section number and title in Protocol Version 2.0 (22 December 2015)	**Section number and title in Version 3.0 (30 June 2016)**	**Original text:**	**Changed to:**	**Rationale**
		hours), and 30 µg/kg/hour (56-60 hours).	(52-56 hours), and 30 µg/kg/hour (56-60 hours).	
5.5.3 Dose Rationale	4.5.3 Dose Rationale	N/A	In Part B, lower target doses will be explored (ie, 30 and 60 µg/kg/hour). These doses are based on observations in the open-label 547-PPD-201 study in which subjects achieved substantial improvements in their HAMD scores within the first 12 hours of the SAGE-547 infusion. In this study, subjects received a dose of 21.5 µg/kg/h for the first 4 hours, then 43 µg/kg/h for the next 4 hours, and then 64.5 µg/kg/h for the following 4 hours before receiving the target dose of 86 µg/kg/h at 12 hours. Therefore, the 12-hour data from 547-PPD-201 suggests that SAGE-547 at target doses of 60 µg/kg/h or less may also be efficacious in reducing depressive symptoms associated with PPD.	*Addition of Part B.*
5.3 Subject Information and Informed Consent	5.3 Subject Information and Informed Consent	As an additional assessment, the ICF will contain a provision for optional consent for the collection of breast milk for the duration of	As an additional assessment, the ICF will contain provisions for optional consent for **the collection of blood for genetic testing during**	*Addition of language to clarify that there will be*

Section number and title in Protocol Version 2.0 (22 December 2015)	**Section number and title in Version 3.0 (30 June 2016)**	**Original text:**	**Changed to:**	**Rationale**
		the 60-hour SAGE-547 infusion and up to Day 3 for biobanking and PK analysis purposes	**Screening and the collection of** breast milk for the duration of the 60-hour SAGE-547 infusion and up to Day 3 for biobanking and PK analysis purposes.	*an optional consent for genetic testing.*
7.1 Primary Objective	6.1 Primary Objective	The primary objective of this study is to determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms in subjects with postpartum depression (PPD) compared to placebo injection as assessed by the change from baseline in Hamilton Rating Scale for Depression (HAMD) total score.	The primary objective of this study is to determine if SAGE-547 Injection infused intravenously for 60 hours **at up to 90 µg/kg/h** reduces depressive symptoms in subjects with **severe** PPD compared to placebo injection as assessed by the change from baseline in HAMD total score. **This objective applies to both Parts A and B.**	*Addition of infusion rate associated with the timeframe. Addition of language to specify the Parts included in the objective.*
7.2 Secondary Objective	6.2 Secondary Objective	The secondary objectives of the study are:	The secondary objectives of the study **apply to Parts A, B and C unless otherwise stated**, and are:	*Additional of language to specify the Parts included in the objective.*
7.2 Secondary Objective	6.2 Secondary Objective	N/A	• To determine if SAGE-547 infusion at up to 60 µg/kg/h for 60 hours reduces depressive symptoms in subjects with severe PPD compared to placebo injection as assessed by the change from	*Addition of secondary objectives.*

Section number and title in Protocol Version 2.0 (22 December 2015)	Section number and title in Version 3.0 (30 June 2016)	Original text:	Changed to:	Rationale
			baseline in HAMD total score (applies to Part B only). • To determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms in subjects with moderate PPD compared to placebo injection as assessed by the change from baseline in HAMD total score (applies to Part C only).	
8.1 Overview of Study Design	7.1 Overview of Study Design	This is a multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the efficacy, safety, and pharmacokinetics of SAGE-547 Injection in adult female subjects diagnosed with severe PPD. The study design is presented in Figure 1. The study will consist of an up to 5 day Screening Period (Day -5 to -1), 3- day (60-hour) Treatment Period, and 30-day Follow-up Period.	This is a **3-part** multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the efficacy, safety, and pharmacokinetics of SAGE-547 Injection in adult female subjects diagnosed with severe **and moderate** PPD. The study design **for Parts A and C** is presented in **Figure 1 and the study design for Part B is presented in Figure 2 (Parts B and C will run concurrently)**. **For all parts**, **the study** will consist of an up to 5-day Screening Period (Day -5 to -1), 3-day (60-hour) Treatment Period, and 30-day Follow-up Period.	*Addition of language to specify three parts.* *Addition of Figure 2.*

Section number and title in Protocol Version 2.0 (22 December 2015)	**Section number and title in Version 3.0 (30 June 2016)**	**Original text:**	**Changed to:**	**Rationale**
8.1 Overview of Study Design	7.1 Overview of Study Design	Subjects will be confined to the study center from the Screening Visit until after the 60-hour assessments have been conducted on Day 3.	Subjects will be confined to the study center from ~~Screening Visit~~ **Day 1** until after the 60-hour assessments have been conducted on Day 3.	*Start time of subject confinement corrected to be consistent with SOE.*
8.1 Overview of Study Design	7.1 Overview of Study Design	N/A	In Parts A and C, once subjects are confirmed as eligible for the study, they will be randomized to one of 2 treatment groups (SAGE-547 90 µg/kg/hour or placebo) on a 1:1 basis.	*Addition of language for design of Parts A and C.*
8.1 Overview of Study Design	7.1 Overview of Study Design	N/A	Subjects in the placebo group will receive infusion rates equivalent to the 90 µg/kg/hour group.	*Language to clarify infusion rates for placebo group.*
8.1 Overview of Study Design	7.1 Overview of Study Design	N/A	In Part B, once subjects are confirmed as eligible for the study, they will be randomized to one of 3 treatment groups (SAGE-547 60 µg/kg/hour, SAGE-547 90 µg/kg/hour, or placebo) on a 1:1:1 basis. For the 60 µg/kg/hour group, subjects will receive 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-56 hours), followed by 30 µg/kg/hour	*Addition of language for design of Part B.*

Section number and title in Protocol Version 2.0 (22 December 2015)	Section number and title in Version 3.0 (30 June 2016)	Original text:	Changed to:	Rationale
			(56-60 hours). For the 90 µg/kg/hour group, subjects will begin a 4-hour dose titration period of 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24-52 hours); followed by a decrease to 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours). Subjects in the placebo group will receive infusion rates equivalent to either the 60 µg/kg/hour or 90 µg/kg/hour group. Parts B and C will run concurrently. See dose regimen presented in Section 10.1.1. Total SAGE-547 Injection or placebo dosing will occur over 60 hours**.**	
9.1 Inclusion Criteria, 8	8.1 Inclusion Criteria, 8	8. Subject has a HAMD total score of ≥26 at Screening and Day 1 (prior to randomization).	8. **For Part A and B**, subject has a HAMD total score of ≥26 at Screening and Day 1 (prior to randomization). **For Part C, subject has a HAMD total score of ≥20 and ≤25 at Screening and Day 1 (prior to randomization).**	*Addition of criteria language for Parts A, B, and C.*
11.1 Dosing	10.1 Dosing	N/A	In Parts A and C, subjects	*Addition of*

Section number and title in Protocol Version 2.0 (22 December 2015)	**Section number and title in Version 3.0 (30 June 2016)**	**Original text:**	**Changed to:**	**Rationale**
Schedule	Schedule		randomized to SAGE-547 will receive the target dose of 90 µg/kg/hour; in Part B, SAGE-547 subjects will receive target doses of either 60 or 90 µg/kg/hour.	*dosing schedule for Parts A, B and C.*
11.1 Dosing Schedule	10.1 Dosing Schedule	Figure 3. Trial Design and Timeline for Dosing	Figure 3. Trial Design and Timeline for Dosing - **Parts A and C** **Figure 4. Trial Design and Timeline for Dosing – Part B**	*Language added to specify Figure 3 relates to Parts A and C.* *Addition of Figure 4 for addition of Part B*
11.1.1 Dose Regimen	10.1.1. Dose Regimen	Table 2. Infusion Rates	Table 2: Infusion rates **for Part A and C** **Table 3: Infusion Rates for Part B**	*Language added to specify Figure 3 relates to Parts A and C.* *Addition of Figure 4 for addition of Part B*
11.1.4 Dosing of Intravenous SAGE-547 in	10.1.4 Dosing of Intravenous SAGE-547 in Case of AEs	Since allopregnanolone levels in the proposed clinical trial are	Since allopregnanolone levels in the proposed clinical trial are similar to physiological levels seen in the	*Addition of safety data.*

Section number and title in Protocol Version 2.0 (22 December 2015)	**Section number and title in Version 3.0 (30 June 2016)**	**Original text:**	**Changed to:**	**Rationale**
Case of AEs		similar to physiological levels seen in the third trimester of pregnancy, and all the AEs reported with SAGE-547 or allopregnanolone to date were mild and non-serious, it is anticipated that the AEs associated with SAGE-547 will be mild and manageable without dose interruption or reduction. Based on the observed adverse events to date, the adverse events most likely to result in AE are sedation with or without hypotension.	third trimester of pregnancy, and all the AEs reported with SAGE-547 or allopregnanolone to date **in healthy volunteers and subjects with postpartum depression** were mild and non-serious, it is anticipated that the AEs associated with SAGE-547 **in this study** will be mild and manageable without dose interruption or reduction. Based on the **safety data in subjects with PPD collected to date, no subjects reported events that were serious or severe and none led to discontinuation of study drug (2 subjects reported** sedation **that lead to a dose reduction, one of these subjects also reported dizziness; one subject reported rash that lead to a dose reduction; refer to the current Investigator's Brochure for more information).**	
12.1.2.3 Hormones and Exploratory Biochemistry	11.1.2.3. Hormones and Exploratory Biochemistry	Blood samples will be collected for analysis of thyroid stimulating hormone (TSH), estrogen, progesterone, progesterone	Blood samples will be collected **and may be analyzed for** thyroid stimulating hormone (TSH), estrogen, progesterone,	*Language added to clarify the potential analysis of*

Section number and title in Protocol Version 2.0 (22 December 2015)	**Section number and title in Version 3.0 (30 June 2016)**	**Original text:**	**Changed to:**	**Rationale**
		metabolites, oxytocin, tryptophan, kynurenine, and markers of inflammation.	progesterone metabolites, oxytocin, tryptophan, kynurenine, and markers of inflammation.	*samples.*
12.1.5 Pulse Oximetry	11.1.5 Pulse Oximetry	Pulse oximetry will be monitored continuously from H0 until H60 on Day 1, and checked approximately every 2 hours, including during the overnight hours, or at the alarm.	Pulse oximetry will be monitored continuously from H0 until H60 and checked approximately every 2 hours, including during the overnight hours, or at the alarm.	*"Day 1" removed for clarification.*
12.3.1 Plasma PK Samples	11.3.1. Plasma PK Samples	N/A	Each PK parameter will be derived separately for each part of the study.	*Language added to clarify how the specified parameters will be derived.*
13.1 Screening Period	12.1 Screening Period	Subjects will be confined to the study center from the Screening Visit until after the 60-hour assessments have been conducted on Day 3.	Subjects will be confined to the study center from **Day 1** until after the 60-hour assessments have been conducted on Day 3.	*Clarification of confinement to be consistent with the SOE.*
13.2.1 Day 1	12.2.1 Day 1	N/A	• Pulse oximetry will be monitored continuously from H0 until H60 on Day 1, and checked approximately every	*Language added to clarify the monitoring and collection*

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			2 hours, including during the overnight hours, or at the alarm	*of pulse oximetry on Day 1.*
13.2.2 Day 2	12.2.2 Day 2	N/A	• Pulse oximetry will be monitored continuously (from H0 until H60), and checked approximately every 2 hours, including during the overnight hours, or at the alarm	*Language added to clarify the monitoring and collection of pulse oximetry on Day 2.*
13.2.2 Day 2	12.2.2 Day 2	• Additional measures of pulse oximetry will be collected during sleeping hours	• ~~Additional~~ measures ~~of pulse oximetry will be collected during sleeping hours~~	*Language deleted as assessment clarified in Day 2 description.*
13.2.3 Day 3	12.2.3 Day 3	• Completion of physical examination	• Completion of physical examination **at Hour 72**	*Clarification of timing of assessment.*
13.2.3 Day 3	12.2.3 Day 3	N/A	• Pulse oximetry will be monitored continuously (from H0 until H60), and checked approximately every 2 hours, including during the overnight hours, or at the alarm	*Addition of assessment on Day 3.*
14. Statistical	13. Statistical	N/A	Separate summaries will be	*Addition of*

Section number and title in Protocol Version 2.0 (22 December 2015)	**Section number and title in Version 3.0 (30 June 2016)**	**Original text:**	**Changed to:**	**Rationale**
Methods and Considerations	Methods and Considerations		produced for each part of the study.	*language explaining production of separate summaries for each study part.*
14. 4. Primary Endpoints	13.4. Primary Endpoints	The primary comparison will be between SAGE-547 and placebo at the 60-hour assessment.	**Separate models will be fit for each part of the study. For Parts A and C, the** primary comparison will be between 90 µg SAGE-547 and placebo at the 60-hour assessment. **For Part B, the primary comparison will be between 90 µg SAGE-547 and placebo at the 60-hour assessment; if this comparison is significant at the 0.05 level, then the 60 µg group will then be compared to placebo. Comparisons at other time points will be conducted to support the findings for the primary comparison**.	*To redefine the primary endpoints based on the additions of Parts A, B, and C.*
14.5 Secondary Endpoints	13.5 Secondary Endpoints	For each model, the comparison of interest will be between SAGE-547 and placebo at the 48-hour assessment. Model based point	**Separate models will be fit for each part of the study.** For each model, the comparison of interest will be between **each** SAGE-547	*Language added to specify used of separate*

Section number and title in Protocol Version 2.0 (22 December 2015)	**Section number and title in Version 3.0 (30 June 2016)**	**Original text:**	**Changed to:**	**Rationale**
		estimates (ie, LS means), 95% confidence intervals, and p-values will be reported.	**dose** and placebo at the **60**-hour assessment. Model based point estimates (ie, LS means), 95% confidence intervals, and p-values will be reported.	*models for comparison and time point change from the 48 hour to the 60 hour.*
14.5 Secondary Endpoints, Efficacy Analysis	13.5.1 Efficacy Analysis	N/A	Separate models will be fit for each part of the study.	*Additional language for analysis of each study part.*
14.5 Secondary Endpoints, Efficacy Analysis	13.5.1 Efficacy Analysis	For each model, the comparison of interest will be between each SAGE-547 and placebo at the 48 - hour assessment.	For each model, the comparison of interest will be between each SAGE-547 dose and placebo at the **60-hour** assessment.	*Change of comparison time point.*
14.5 Secondary Endpoints, Efficacy Analysis	13.5.1 Efficacy Analysis	N/A	Separate models will be fit for each part of the study.	*Additional language for analysis of each study part.*
14.6 Determination of Sample Size	13.6 Determination of Sample Size	By including two treatment groups and using a 1:1 randomization ratio, a total of 20 evaluable subjects are required. Assuming a non-evaluability rate of 10%, at least 22 subjects will be randomized.	By including 2 treatment groups and using a 1:1 randomization ratio, a total of 20 evaluable subjects are required **for Part A**. Assuming a non-evaluability rate of 10%, **up to** 22 subjects will be randomized **in Part A.**	*Additional language added to specify Part A requirements.*

Section number and title in Protocol Version 2.0 (22 December 2015)	Section number and title in Version 3.0 (30 June 2016)	Original text:	Changed to:	Rationale
		Based on the results of the interim analysis (see Section 14.7), the sample size could be increased to a maximum of 32 randomized subjects.	Based on the results of the interim analysis (see Section 14.7), the sample size **for Part A** could be increased to a maximum of 32 randomized subjects.	
14.6 Determination of Sample Size	13.6 Determination of Sample Size	N/A	For Part B, a sample size of 18 evaluable subjects per group would provide at least 90% power to detect an effect size of 1.2 between the SAGE-547 and placebo groups using a two-sided test at an alpha level of 0.05. Assuming a non-evaluability rate of 10%, up to 60 subjects will be randomized in Part B. For Part C, a sample size of 16 evaluable subjects per group would provide 80% power to detect an effect size of 1.0 between the SAGE-547 and placebo groups using a two-sided test at an alpha level of 0.10. Assuming a non-evaluability rate of 10%, up to 36 subjects will be randomized in Part C.	*Addition of language for Parts B and C.*
14.7 Interim Analysis	13.7 Interim Analysis	An interim analysis will be conducted by an independent	An interim analysis will be conducted by an independent	*Addition of language to*

Section number and title in Protocol Version 2.0 (22 December 2015)	Section number and title in Version 3.0 (30 June 2016)	Original text:	Changed to:	Rationale
		statistician for sample size re-estimation purposes when at least 16 subjects have completed efficacy assessments through 60 hours. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study.	statistician for sample size re-estimation purposes when at least 16 subjects have completed efficacy assessments through 60 hours in **Part A**. Since the Sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing **Part A** of the study.	*specify analysis for Part A.*
14.8 Changes from Protocol Specified Analyses	13.8 Changes from Protocol Specified Analyses	N/A	Upon the completion of each part of the study, the data may be unblinded and analyzed separately. The final CSR will report the findings of all parts of the study.	*Addition of language for analysis of each part.*
14.1.5 Unexpected	14.1.5 Unexpected	N/A	In the clinical trial setting, the term "expected" would not mean "anticipated" for the condition being treated or population being studied since "expected" would indicate being "listed in the Investigator's Brochure." For example, some adverse events can be anticipated to occur as a result of a disease or condition or in a certain population (eg, cancer-related	*Language added to clarify the term "expected" in a clinical setting.*

Section number and title in Protocol Version 2.0 (22 December 2015)	Section number and title in Version 3.0 (30 June 2016)	Original text:	Changed to:	Rationale
			deaths in a cancer trial, strokes or acute myocardial infarctions in an older population). However, for reporting purposes, these anticipated events are not considered "expected" if they are not listed in the Investigator's Brochure (ie, the investigational drug is not suspected or known to cause them).	

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF SAGE-547 INJECTION IN THE TREATMENT OF ADULT FEMALE SUBJECTS WITH SEVERE POSTPARTUM DEPRESSION

PROTOCOL NUMBER: 547-PPD-202

IND NUMBER: 122279

Investigational Product:	SAGE-547 Injection (allopregnanolone)
Clinical Phase:	2a
Sponsor:	Sage Therapeutics
Sponsor Contact:	[redacted], MDMBA Sage Therapeutics 215 First Street Cambridge, MA 02142 Phone: [redacted]
Medical Monitor:	[redacted], MD Office (9-5 EST): [redacted] 24/7 Hotline: [redacted]
Date of Original Protocol:	Version 1.0 18 September 2015
Date of Amendment One:	Version 2.0 22 December 2015

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 the Sponsor.

1 SIGNATURE PAGE

Title of protocol: A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects With Severe Postpartum Depression

Protocol No: 547-PPD-202

Sponsor Approval

[redacted]

[redacted], MD, PhD

Sage Therapeutics

12/22/2015

Date (dd/mmm/yyyy)

Investigator Agreement

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-PPD-202 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: _____

Investigator's Name: _____

Institution: _____

Date (dd/mmm/yyyy): _____

2 SYNOPSIS

Name of Sponsor: Sage Therapeutics 215 First Street Cambridge, MA 02142	
Protocol No. 547-PPD-202	**Phase:** 2a
Name of Investigational Product: SAGE-547 Injection	
Name of Active Ingredient: Allopregnanolone	
Title of the Protocol: A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects With Severe Postpartum Depression	
Study Sites: Approximately 15 sites in the United States	
Duration of Subject Participation: Up to 35 days	
Primary Objective: • To determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms in subjects with postpartum depression (PPD) compared to placebo injection as assessed by the change from baseline in Hamilton Rating Scale for Depression (HAMD) total score **Secondary Objectives:** • To determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms compared to placebo injection as assessed by HAMD response, HAMD remission, change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score, Clinical Global Impression – Improvement (CGI-I) response, and changes from baseline in HAMD subscale and individual item scores. • To determine if SAGE-547 Injection infused intravenously for 60 hours reduces other mood symptoms compared to placebo injection as assessed by changes from baseline in the Generalized Anxiety Disorder 7-Item Scale (GAD-7) total score. • To determine if SAGE-547 Injection infused intravenously for 60 hours increases sedation levels compared to placebo injection as assessed by the changes from baseline in Stanford Sleepiness Scale (SSS) score. • To evaluate the safety and tolerability of SAGE-547 Injection compared with placebo as assessed by the incidence of adverse events, vital sign measurement, clinical laboratory	

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Protocol No. 547-PPD-202	**Phase:** 2a

evaluations, electrocardiogram (ECG) parameters, and the Columbia Suicide Severity Rating Scale (C-SSRS).

Exploratory Objective:

- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces subject-reported depressive symptoms compared to placebo injection as assessed by the change from baseline in Edinburgh Postnatal Depression Scale (EPDS) total score and the change from baseline in Patient Health Questionnaire (PHQ-9) total score.
- To determine if SAGE-547 Injection infused intravenously for 60 hours improves maternal behaviors compared to placebo injection as assessed by the change from baseline in Barkin Index of Maternal Functioning (BIMF) total and sub-scale scores.

Pharmacokinetic Objective:

- To assess the pharmacokinetic (PK) profile of SAGE-547, metabolites of SAGE-547, and betadex sulfobutyl ether sodium (SBECD) and the concentration of SAGE-547 in breast milk, when possible.

Study Design and Methodology:

This is a multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the efficacy, safety, and pharmacokinetics of SAGE-547 Injection in adult female subjects diagnosed with severe PPD. Subjects must remain as in-patients during the study Treatment Period, which is approximately 60 hours/2.5 days in duration. The Screening Period assessments may be conducted on an in-patient or an out-patient basis. The Follow-up Period assessments are conducted on an out-patient basis.

Screening Period: The Screening Period begins with the signature of the informed consent form (ICF). Eligibility is determined by applying the inclusion/exclusion criteria. The diagnosis of PPD must be by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). A full medical and family history will be taken including recording of all depression, other Axis 1 and Axis 2 disorders and postpartum depression episodes in primary probands (who may be subject to a SCID-I interview).

Treatment Period: Once subjects are confirmed as eligible for the study, they will be randomized to one of two treatment groups (SAGE-547 or placebo) on a 1:1 basis. Continuous intravenous infusions of blinded study drug will be administered, with a new bag and line hung every 24 hours during the 60-hour infusion. Infusion rates will increase and then taper, with subjects receiving 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24-52 hours), followed by 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours). Subjects may be discharged after the 72-hour assessments have been completed (12 hours after completion of the study drug infusion). If their clinical condition does not allow discharge, normal standard of care will be employed in their ongoing management.

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Initiation of benzodiazepines, narcotics, antibiotics, neuroleptics, and other anti-anxiety medications will not be allowed between Screening and completion of the 72-hour assessments. Doses of psychotropics, which must have been initiated at least 14 days prior to screening, must remain at a stable dose until completion of the 72-hour assessments. If at the 72-hour assessment there has been no treatment response (HAMD total score remains above 13), treatment with antidepressant medication may be optimized prior to discharge, and the subject may remain in the unit or be followed at an out-patient clinic, as clinically indicated. Efficacy and safety assessments will be performed periodically during the study, and blood samples will be collected for analysis of SAGE-547, metabolites of SAGE-547, and SBECD concentrations, as outlined in the Schedule of Events (Table 1). Blood samples will be collected, and outcome measures will be obtained at pre-specified times over 60 hours during the Treatment Period. **Follow-up Period:** Follow-up visits will be conducted one week (7±1 day) and one month (30±3d) after the initiation of the study drug infusion.	
Number of Subjects: Up to 32 subjects will be randomized	
Inclusion Criteria: The following inclusion criteria must be met for individuals to be eligible for the trial: 1. Subject has signed an ICF prior to any study-specific procedures being performed 2. Subject is an ambulatory female aged 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 breast feeding at Screening, must agree to temporarily cease giving breastmilk to their infant(s) from just prior to receiving study drug through 9 days (Study Day 12) after the end of infusion. 6. Subject must have a negative pregnancy test at Screening and Day 1 prior to the start of study drug infusion 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, as diagnosed by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) 8. Subject has a HAMD total score of ≥26 at Screening and Day 1 (prior to randomization) 9. Subject is ≤ six months postpartum	

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10. Subject is willing to delay start of other antidepressant or anxiety medications and any new pharmacotherapy regimens, including prn benzodiazepine anxiolytics, until the study drug infusion and 72-hour assessments have been completed
11. Subject has no detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), and human immunodeficiency virus (HIV) antibody at Screening
12. Subject must use one of the following methods of birth control during participation in the study and for 30 days following the end of the study drug infusion:
    - Total abstinence (no sexual intercourse)
    - Hormonal contraceptives (birth control) including birth control pills, implantable or injectable contraceptives (Norplant® or Depo-Provera®)
    - A barrier form of contraception such as a condom or occlusive cap with a spermicide
    - An intrauterine device (IUD)

Exclusion Criteria:

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

1. Recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, or nose and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study
2. Known allergy to progesterone or allopregnanolone
3. Active psychosis per Investigator assessment
4. Attempted suicide associated with index case of postpartum depression
5. Medical history of seizures
6. Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
7. History of active alcoholism or drug addiction (including benzodiazepines) in the 12 months prior to Screening
8. Exposure to another investigational medication or device within 30 days prior to Screening
9. Administration of psychotropics that have been initiated within 14 days prior to Screening and are not being taken at a stable dose.

Name of Sponsor:

Sage Therapeutics
215 First Street
Cambridge, MA 02142

Protocol No. 547-PPD-202	**Phase:** 2a

Investigational Product, Dosage, and Mode of Administration:

SAGE-547 Injection, intravenous (IV) administration: SAGE-547 Injection is a sterile, clear, colorless 5 mg/mL solution of SAGE-547 (allopregnanolone) and 250 mg/mL SBECD buffered with 10 mM citrate at a pH of 6.0, supplied in single-use 20 mL vials for IV administration. As supplied, SAGE-547 Injection, which is hypertonic, requires further dilution with Sterile Water for Injection (SWFI) to render it isotonic for IV infusion. The specific infusion dose of SAGE-547 Injection will be calculated based on weight for each subject at Screening and administered according to the randomization schedule. Infusion bags will be changed every 24 hours. Details about the preparation and administration of the study drug infusions will be included in the Pharmacy Manual.

Timepoint	**Day 1 0-4 hours**	**Day 1 4-24 hours**	**Day 2-3 24-52 hours**	**Day 3 52-56 hours**	**Day 3 56-60 hours**
Infusion Rate	30 µg/kg/hour	60 µg /kg/hour	90 µg /kg/hour	60 µg /kg/hour	30 µg/kg/hour

Reference Therapy, Dosage, and Mode of Administration:

An identical placebo IV infusion will be prepared for IV administration consisting of the same formulation without allopregnanolone.

Randomization and Stopping Rules:

Subjects will be randomized to receive SAGE-547 Injection or placebo; subjects, clinicians, and study team will be blinded to treatment allocation. The pharmacist, who will prepare the infusion bags according to the randomization schedule, will be unblinded. The infusion rates are the same for all subjects within a particular dosing period (0-4 hours, 4-24 hours, etc.).

If any subject has an SSS score of ≥5 for two or more consecutive assessments or an SSS score of ≥6 for a single occurrence during normal waking hours, the infusion rate for this subject will be decreased to the next lowest infusion dose level (or turned off if this occurs on the 30 µg/kg/hour dose level).

Criteria for Evaluation:

Primary Endpoint

The primary outcome measure will be the 17-item Hamilton Rating Scale for Depression (HAMD). The HAMD will be administered before, during, and after the infusion of blinded study drug. The HAMD total score will be calculated as the sum of the 17 individual item scores. The change from baseline in HAMD total score at the end of the treatment period (at +60 hours) will be the primary efficacy endpoint with comparison between the two treatment groups used to evaluate the efficacy of SAGE-547 in treating the depressive symptoms of PPD.

Secondary Endpoints

Additional measures of depressive symptom severity will be administered before, during, and after the infusion of study drug, including the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinical Global Impression (CGI) scale. Total scores and changes from baseline will be calculated where applicable. Changes from baseline at the end of the treatment period (at +60 hours) and other time points will be evaluated as secondary efficacy endpoints with comparisons between the two treatment groups used to support the efficacy of SAGE-547 in treating the depressive symptoms of PPD. In addition to the above scales, the individual item scores and subscale scores from the HAMD scale will also evaluated as secondary efficacy endpoints.

GAD-7 will also be administered before, during, and after the infusion of study drug. As with other secondary efficacy endpoints, scores from these scales will be evaluated to assess the efficacy in other mood disorder and anxiety symptoms.

An important safety endpoint will be the assessment of sedation using the SSS. The SSS will be assessed periodically before, during, and after the infusion of blinded study drug with changes from baseline over time evaluated similarly to that of efficacy endpoints.

Safety and tolerability of SAGE-547 Injection will be evaluated by summarization of adverse events (AEs) by frequency, severity, and seriousness; clinical laboratory measures, vital signs, and ECGs (including changes from baseline); and concomitant medication usage. Suicidality will be monitored using the C-SSRS.

The doses of all anti-depressant medications will be recorded throughout the study. No changes and/or additions to antidepressant or anxiolytic medicine will be allowing during the dosing period. An analysis of time to starting/increasing the dose/decreasing the dose of each different anti-depressant medication will be undertaken for subjects discharged.

Plasma will be collected to assay for concentrations of SAGE-547, SAGE-547 metabolites, and SBECD. The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve (AUC) from time zero to 60 hours (AUC_{0-60}), AUC from time zero to infinity (AUC_{inf}), maximum (peak) plasma concentration (C_{max}), time at maximum (peak) plasma concentration (T_{max}), steady-state drug concentration in the plasma during constant-rate infusion (C_{ss}), and average drug concentration in the plasma at steady state during a dosing interval (C_{avg}).

Breast milk may be collected as an optional assessment if consent is received from the subject. Samples

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will be analyzed for SAGE-547 concentrations.

Exploratory Endpoints

Additional measures of symptoms and function related to the current episode of postpartum depression severity will be administered before, during, and after the infusion of study drug, including the EPDS, PHQ-9 and BIMF.

Subscale and total scores and changes from baseline will be calculated where applicable. Changes from baseline at the end of the treatment period (at +60 hours) and other time points will be evaluated as secondary efficacy endpoints with comparisons between the two treatment groups used to support the efficacy of SAGE-547 in treating the depressive symptoms of PPD. In addition to the above scales, the individual item scores will also be evaluated as exploratory endpoints.

Statistical Methods:

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

Interim Analysis

An interim analysis will be conducted by an independent statistician for sample size re-estimation purposes when at least 16 subjects have completed efficacy assessments through 60 hours. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis will be included in the statistical analysis plan.

Sample Size Calculation

Assuming a two-sided test at an alpha level of 0.10, a sample size of 10 evaluable subjects per group would provide 80% power to detect an effect size of 1.2 between the SAGE-547 and placebo groups with regard to the primary outcome variable of change from baseline in HAMD total score. An effect size of 1.2 corresponds to a placebo adjusted difference of 12 points in the change from baseline in HAMD total score at 60 hours with an assumed standard deviation of 10 points. By including two treatment groups and using a 1:1 randomization ratio, a total of 20 evaluable subjects are required. Assuming a non-evaluability rate of 10%, at least 22 subjects will be randomized.

Based on the results of the interim analysis, the sample size could be increased to a maximum of 32 randomized subjects. This adjustment to the sample size would allow for an effect size of 1.0 to be detected.

Efficacy Analysis

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The efficacy population will include all subjects who start the infusion of study drug and have a valid baseline HAMD assessment and at least one post-baseline HAMD assessment. Subjects will be classified and summarized by randomized treatment.

The change from baseline in HAMD total score will be analyzed using a mixed effects repeated measures model including center, treatment, baseline score, timepoint, and timepoint-by-treatment as explanatory variables. Center will be treated as a random effect while all other explanatory variables will be treated as fixed effects. The primary comparison between SAGE-547 and placebo will be at the 60 hour timepoint. Comparisons at other timepoints will be conducted to support the findings for the primary comparison.

Changes from baseline in other rating scale scores will be analyzed with methods similar to the primary endpoint. Any dichotomous response variables will be analyzed using logistic regression methods.

In addition to formal analysis, efficacy rating scale scores (including recorded and change from baseline values) will be summarized by descriptive statistics, including n, mean, standard deviation (SD), median, and minimum and maximum values. Categorical efficacy endpoints (including HAMD, MADRS, and CGI-I response variables) will be summarized by frequency and percentage.

Safety Analysis

The Safety Population (SAF) is defined as all subjects who start the infusion of study drug. Subjects will be classified and summarized by actual treatment.

Safety will be assessed using SSS, AEs, vital signs, ECG, clinical laboratory tests, C-SSRS, and concomitant medication data. Continuous safety data (including absolute and change from baseline values) will be summarized by descriptive statistics, including n, mean, standard deviation (SD), median, and minimum and maximum values. Categorical endpoints will be summarized by frequency and percentage. In addition, an analysis of the SSS score will be performed comparing the treatment groups in the same way as for the primary endpoint.

Safety data will be examined for possible relationships between subject characteristics and plasma allopregnanolone concentrations, as appropriate.

TABLE 1: SCHEDULE OF EVENTS

	Screening Period	Treatment Period Clinic Period (Day 1 to Day 3)														Follow-up Period		
Visit Days	**Screening D-5 to -1**	**D1 H0***	**D1 H2**	**D1 H4**	**D1 H8**	**D1 H12**	**D1 H18**	**D1 H24**	**D2 H30**	**D2 H36**	**D2 H42**	**D2 H48**	**D3 H54**	**D3 H60**	**D3 H66**	**D3 H72**	**D7/ET** (±1d)	**D12 (+1d)[l]**	**D30** (±3d)
Study Procedure																			
Informed Consent	X																		
Inclusion/Exclusion Criteria	X	X																	
Demographics	X																		
Medical/Family History	X																		
Physical Examination	X															X	X		
Body Weight/Height	X																		
Clinical Lab Assessments [a]	X															X	X		
Urinalysis [a]	X																X		
Drug & Alcohol Screen [b]	X	X																	
Pregnancy Test [c]	X	X																	X
Hepatitis & HIV Screen	X																		
Genetic Sample [d]	O																		
Vital Signs [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Pulse Oximetry								X											
12-Lead ECG [f]	X											X					X		
C-SSRS [g]		X						X						X		X	X		X
Confinement									X										
CGI-I [h]			X	X		X		X		X		X		X		X	X		X
CGI-S [h]	X	X																	
HAMD [h]	X	X	X	X	X	X		X		X		X		X		X	X		X
MADRS [h]	X	X						X				X		X		X	X		X
BIMF [h]		X															X		X
EPDS [h]		X												X			X		X
GAD-7 [h]		X												X			X		X
PHQ-9 [h]		X												X			X		X
SSS [i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

	Screening Period	Treatment Period Clinic Period (Day 1 to Day 3)															Follow-up Period		
Visit Days	**Screening D-5 to -1**	**D1 H0***	**D1 H2**	**D1 H4**	**D1 H8**	**D1 H12**	**D1 H18**	**D1 H24**	**D2 H30**	**D2 H36**	**D2 H42**	**D2 H48**	**D3 H54**	**D3 H60**	**D3 H66**	**D3 H72**	**D7/ET** (±1d)	**D12 (+1d)[l]**	**D30** (±3d)
Study Procedure																			
Plasma PK [j]		X		X	X	X		X	X	X		X		X		X	X	X[l]	
Breast Milk PK [k]		X	X				X		X		X		X		X		X[l]	X[l]	
Study Drug Infusion		X																	
Adverse Events	X																		
Concomitant Medications	X																		

O = optional * = All H0 procedures to be completed prior to dosing

a Safety laboratory tests will include hematology, serum chemistry, coagulation, and select hormone parameters. The urine test will include a urinalysis. Lab assessments are to be completed within ± 30 minutes of the scheduled timepoint.

b Urine for selected drugs of abuse and alcohol (serum or breath)

c Serum at Screening and urine for all other timepoints

d A blood sample for genetic testing, where consent is given

e Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). Vital signs will be obtained within ± 30 minutes of the scheduled timepoint, unless the subject is asleep between the hours of 23.00h and 06.00h.

f Performed within ± 30 minutes of the scheduled time point on Day 2.

g The "Baseline/Screening" C-SSRS form will be completed on Day 1. The "Since Last Visit" C-SSRS form will be completed at all subsequent timepoints.

h To be completed within ± 30 minutes of the scheduled timepoint.

i To be completed within ± 15 minutes of the scheduled timepoint, unless the subject is asleep between the hours of 23.00h and 06.00h

j Blood samples for PK analysis will be collected at pre-infusion and at 4 (before change in infusion rate), 8, 12, 24 (before change in infusion rate), 30, 36, 48 60 (before end of infusion) and 72 hours after the start of the infusion. PK blood draws after the start of infusion will have a window of ± 10 minutes. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.

k Optional assessment per subject consent, breast milk will be collected and pooled over the following time periods of interest: 0, 1-12, 12-24, 24-36, 36-48, 48-60 and 60-72 hours after the start of the infusion.

l Day 7 Breast Milk Samples/Day 12 Visit is only applicable to those patients who have temporarily ceased breastfeeding and are participating in the optional breast milk sampling.

BIMF = Barkin Index of Maternal Functioning; CGI-I = Clinical Global Impression of Improvement; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EPDS = Edinburgh Postnatal Depression Scale; GAD-7 = Generalized Anxiety Disorder 7-Item Scale; HAMD = Hamilton Rating Scale forDepression, 17-item; MADRS = Montgomery-Asberg Depression Rating Scale; PHQ-9 = Patient Health Questionnaire; PK = pharmacokinetic; SSS = Stanford Sleepiness Scale.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Definition of Terms
AE	adverse event
ALLO	allopregnanolone
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from time zero to infinity
AUC_{0-60}	area under the concentration-time curve from time zero to 60 hours
BIMF	Barkin Index of Maternal Functioning
BMI	body mass index
BMP	breast milk population
BUN	blood urea nitrogen
C_{avg}	average drug concentration in the plasma at steady-state during a dosing interval
CBC	complete blood count
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression–Improvement
CGI-S	Clinical Global Impression–Severity
cGMP	Current Good Manufacturing Practice
C_{max}	maximum (peak) plasma concentration of the drug
CMO	Chief Medical Officer
CNS	central nervous system
CRF	case report form
CS	clinically significant
CSF	cerebrospinal fluid
CSR	clinical study report
C_{ss}	Steady-state drug concentration in the plasma during constant-rate infusion
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	Cytochrome P450 enzyme involved in drug metabolism
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EEG	electroencephalography
EFF	efficacy population
Ph. Eur.	European Pharmacopeia
EPDS	Edinburgh Postnatal Depression Scale
ERα	estrogen receptor alfa
ERß	estrogen receptor beta

Abbreviation or Specialist Term	Definition of Terms
ET	Early Termination
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
$GABA_A$	gamma-aminobutyric acid–gated chloride channel
GAD-7	Generalized Anxiety Disorder 7-Item Scale
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
h	hour
HAMD	Hamilton Rating Scale for Depression, 17-item
HBsAg	hepatitis B surface antigen
Hct	hematocrit
HCV	hepatitis C virus
HEENT	head, eyes, ears, nose, and throat
Hgb	hemoglobin
HPLC MS/MS	High-performance liquid chromatography tandem mass spectrometry
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	intention-to-treat population
IV	intravenous
LFT	liver function test
MADRS	Montgomery-Asberg Depression Rating Scale
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
NCS	not clinically significant
NF	National Formulary
NIMH	National Institute of Mental Health
PHQ-9	Patient Health Questionnaire
PK	pharmacokinetic
PKP	pharmacokinetic population
PMID	PubMed identification
PP	per-protocol population
PPD	postpartum depression
PR	progesterone receptor
PT/INR	prothrombin time/international normalized ratio
RBC	red blood cell
RSE	refractory status epilepticus
SAE	serious adverse event

Abbreviation or Specialist Term	Definition of Terms
SAF	safety population
SAP	statistical analysis plan
SBECD	betadex sulfobutyl ether sodium
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SRSE	super refractory status epilepticus
SSRI	selective serotonin reuptake inhibitors
SSS	Stanford Sleepiness Scale
SWFI	sterile water for injection
$T_{1/2}$	half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum (peak) plasma concentration
TSH	thyroid stimulating hormone
US	United States
USP	United States Pharmacopeia
VAS	Visual analogue scale
V_d	volume of distribution
WBC	white blood cell

5 INTRODUCTION AND RATIONALE

This study is designed to evaluate the efficacy, safety, and pharmacokinetics (PK) of SAGE-547 (allopregnanolone) as a treatment for women with severe postpartum depression (PPD), an area of high unmet medical need.

PPD is considered to be moderate to severe depression in women who have recently given birth, otherwise defined as the occurrence of major depressive disorder (MDD) within 4 weeks of delivery (DSM V 2013) or up to a year after giving birth (Okun 2013). There are two entry criteria for the diagnosis of depression (depressed mood and/or loss of interest) and seven 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 five symptoms of depression (DSM V 2013), although this diagnosis may be confounded by the relative frequency of symptoms such as sleep disturbance or appetite problems in pregnant and postpartum women. Most women experience onset of symptoms within the first three months following delivery, and PPD is most prevalent at 10 to 14 weeks following childbirth (Okun 2013).

During pregnancy, estradiol and progesterone levels increase dramatically but then rapidly decline in the acute postpartum period (Gavin 2005). The onset of PPD symptoms coincides with the rapid decrease of the gonadal steroids postpartum. The duration of a PPD episode has been estimated as shorter than depressive episodes in the general population (approx. 5 months), while other studies indicate time to remission is approximately the same (Chaudron 2003).

PPD is common and has devastating consequences for the woman and for her family (Fihrer 2009; Verbeek 2012). Perinatal depression is reported to be the most underdiagnosed obstetric complication in America (Earls 2010). Furthermore, it is the most common psychiatric illness to occur in the puerperium (O'Hara 2014). A meta-analysis of 30 studies (Gaynes 2005) found that the point prevalence of major and minor depression ranged between 6.5% and 12.9% at different times during the first postpartum year. Overall incidence is estimated at around 15–20% with up to 10% being considered severe (Edge 2007, O'Hara 2014).

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 non-pharmacological 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.

5.1 Role of Allopregnanolone in Affective Disturbances

The neurosteroid metabolite of progesterone, allopregnanolone, acutely regulates neuronal function (Gangisetty 2010) and appears to play a significant role in affective disturbances that occur with changes in reproductive endocrine function, such as during the postpartum period (Amin 2006, Nappi 2001, Epperson 2006).

Neurosteroids are metabolites of cholesterol-derived steroid hormones that are synthesized in the brain and nervous system; they modulate the major inhibitory and excitatory central nervous system (CNS) neurotransmitter systems: γ-aminobutyric acid (GABA) and glutamate, respectively. Neurosteroids are among the most potent and effective modulators of $GABA_A$ receptors and augment GABAergic inhibition (Belelli 2005). The powerful anxiolysis that accompanies this potentiation of $GABA_A$ receptors has led to the speculation that neurosteroid dysregulation plays a central role in the etiology of affective disorders, including reproductive mood disorders, such as PPD (Amin 2006).

There is increasing evidence supporting the role of neurosteroids in affective dysregulation. Allopregnanolone and pregnanolone have been shown to modulate the GABA receptor positively (Majewska 1986). Several groups have demonstrated decreased allopregnanolone levels in MDD, with an increase seen in both plasma and cerebrospinal fluid (CSF) following successful antidepressant treatment (Uzunova 1998; Romeo 1998; Ströhle 1999; Schüle 2006; Eser 2006; Schüle 2007). In addition, allopregnanolone has demonstrated anxiolytic effects in several animal anxiety models (Bitran 1991; Wieland 1991; Bitran 1993).

Allopregnanolone may also exert antidepressant effects by reducing the physiological impact of stress, promoting neuroprotection, and protecting against the pro-inflammatory immune activation and cytokine hypersecretion associated with MDD. In animals, allopregnanolone increases in response to stress, reduces pain sensitivity, and is thought to restore physiologic homeostasis following stress (Frye 1994; Morrow 1995). Allopregnanolone also exerts neuroprotective effects by reducing the expression of pro-apoptotic proteins and apoptotic DNA fragmentation (Djebaili 2005; Sayeed 2009), thereby reducing the cell death and gliosis associated with depression (Glantz 2010; Shelton 2011). Neuroprotection is mediated by immune regulation in depression (Licinio 1999), and allopregnanolone reduces the expression of the pro-inflammatory cytokine TNF-α (He 2004), which is elevated in depressed individuals (Dowlati 2010). Thus, allopregnanolone modulates biological processes dysregulated in major depressive disorder.

5.1.1 Rationale for Allopregnanolone Treatment of PPD

Genetic susceptibility to affective dysregulation may be unmasked during periods of reproductive hormone change such as during pregnancy and postpartum (Maguire 2008). Maguire and Mody demonstrated that a GABA receptor subunit mutation was behaviorally silent until the animal was exposed to pregnancy and the postpartum state, at which time the dams showed depressive-like behaviors and cannibalized their offspring (Maguire 2008). During pregnancy, the expression of the $GABA_A$ receptor δ-subunit is down-regulated as allopregnanolone levels increase, and at parturition, the expression of the $GABA_A$ receptor δ-subunit is recovered in response to rapidly declining neurosteroid levels (Maguire 2009). In contrast, the $GABA_A$ receptor δ-subunit-deficient mice fail to adapt to the dramatic changes in allopregnanolone and experience depression-like and anxiety-like behavior and abnormal

maternal behaviors, which are reversed by administration of allopregnanolone (Maguire 2008). This model provides compelling support for the hypothesis that changes in neurosteroid concentrations during pregnancy and postpartum are capable of provoking affective dysregulation, particularly in those with a genetically-determined susceptibility. The capacity of changes in neurosteroids, such as allopregnanolone, to function as behavioral switches suggests a potentially important treatment role of this hormone metabolite in reproductive endocrine-related mood disorders such as PPD.

The onset of PPD symptoms coincides with the rapid decrease of the gonadal steroids postpartum and has been reproduced in a pivotal clinical study (Bloch 2000). The authors investigated the possible role of changes in gonadal steroid levels in PPD by simulating two hormonal conditions related to pregnancy and parturition in euthymic women, 8 with and 8 without a history of PPD. They induced hypogonadism with leuprolide, adding back supra-physiologic doses of estradiol and progesterone for 8 weeks to simulate pregnancy. They then withdrew both steroids under double-blind conditions to mimic the rapid decrease of sex steroids upon delivery. Five of the eight women with a history of postpartum depression (62.5%) and 0% of the comparison group developed significant mood symptoms typical of PPD during the withdrawal period.

Although progesterone levels were measured in this study, allopregnanolone was not. However, since allopregnanolone is the major active metabolite of progesterone, it can be assumed that the decrease in progesterone would cause a similar precipitate drop in allopregnanolone levels, as observed in the postpartum period (Gilbert Evans 2005, Paoletti 2006, Nappi 2001).These data provide direct evidence in support of the involvement of progesterone and its metabolites in the development of postpartum depression in a subgroup of women. Further, they suggest that women with a history of postpartum depression are differentially sensitive to mood-destabilizing effects of gonadal steroids (Bloch 2000).

Additional details regarding the role of allopregnanolone in the etiology of affective disorders and its nonclinical pharmacology and pharmacokinetics are presented in the Investigational Brochure.

5.2 SAGE-547 Injection (Allopregnanolone)

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex, and CNS (Holzbauer 1985; Ottander 2005; Paul 1992). It is a metabolite of progesterone created by the actions of 5-α reductase and 3-α hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic $GABA_A$ receptors.

SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), United States Pharmacopeia (USP), and 250 mg/mL betadex sulfobutyl ether sodium buffered with 10 mM citrate at a pH of 6.0, and will be administered intravenously. SAGE-547 Injection is also being developed for the treatment of adult patients with refractory status epilepticus (RSE), inclusive of super refractory status epilepticus (SRSE), who have not responded to standard treatment regimens, and investigated for the treatment of adults with essential tremor.

5.3 Summary of Nonclinical and Clinical Experience With Allopregnanolone or SAGE-547

5.3.1 Nonclinical Pharmacology

The primary pharmacological effects of allopregnanolone or SAGE-547 are described earlier in the rationale (Sections 5.1 and 5.1.1). Secondary pharmacologic effects comprise mainly the binding and consequent increased activity of steroid hormone receptors (androgen receptor [(AR], progesterone receptor [PR], and estrogen receptor beta [ERß]), with some evidence of inhibition at the highest doses (AR and estrogen receptor alfa [ERα]). These non-target effects may yield some adverse events in the clinic.

Nonclinical toxicology studies largely illustrate the sedative and anesthetic effects of allopregnanolone and/or SAGE-547 at higher equivalent doses than the proposed dose for the current study. PK data in animals indicate a short half-life and rapid clearance with a moderate volume of distribution and cerebral levels higher than plasma. See SAGE-547 Investigational Brochure for more details.

5.3.2 Clinical Experience

The clinical PK data with intravenous (IV) administration of allopregnanolone in healthy women, men, and women on oral contraceptives confirmed the PK observations in animals of a short half-life ($T_{1/2}$ 20-40 mins), C_{max} achievable at approximately 3rd trimester levels (150 nM), rapid clearance and moderate volume of distribution (V_d). See SAGE-547 Investigational Brochure for more details.

There are currently no double-blind, placebo-controlled clinical efficacy data for SAGE-547 in PPD. An open-label, proof-of-concept study (547-PPD-201) evaluating the safety, tolerability, pharmacokinetics, and efficacy of SAGE-547 Injection in the treatment of adult female subjects with severe postpartum depression was started in 2014. This was the first-ever study in this indication. Four women experienced significant improvement in depressive symptoms within 24 hours after administration of open-label intravenous SAGE-547. During the SAGE-547 treatment period, all four subjects rapidly achieved remission, as measured by the HAMD total score. All four subjects also demonstrated consistent improvement as measured by the CGI-I score. SAGE-547 was well-tolerated in all subjects treated with no serious adverse events observed during therapy or during the 30-day follow-up period. A total of 14 adverse events were reported in four subjects. The only adverse event reported in more than one subject was sedation, observed in two subjects. This trial was initially planned to enroll 10 women, however, due to the observed clinical activity, the 547-PPD-201 trial was stopped early with the plan to initiate a placebo-controlled clinical trial as rapidly as possible.

There are six reported studies of allopregnanolone, mainly in healthy individuals and none in PPD (Timby 2006; Timby 2011a and 2011b; van Broekhoven 2007; Kask 2008; Kask 2009; Navarro 2003). Data indicate that normal physiological allopregnanolone levels in women vary during the menstrual cycle up to a maximum of 6-10 nM, with lower levels present post-menopause (Genazzani 1998). The highest physiological levels observed are in the third trimester of pregnancy, up to around 160 nM at time of delivery (Luisi 2000). Levels drop precipitously to baseline (<10 nM) with removal of the placenta (Klak 2003).

One study demonstrated subjective improvements in contentedness in women (van Broekhoven 2007). The clinical safety data are presented below in the Risks and Benefits section (Section 5.4).

5.4 Potential Risks and Benefits

In the recently completed open-label clinical trial of SAGE-547 in PPD (547-PPD-201), a total of 14 adverse events were reported in four subjects. The only adverse event reported in more than one subject was sedation, observed in two subjects.

Consistent with these observations, published reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported adverse events (AEs) were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, vertigo, mild nausea, impaired episodic memory, and mild headache (Timby 2006 and 2011a and 2001b; van Broekhoven 2007). One subject experienced what was potentially a withdrawal effect, an anxiety attack (Timby 2011b). No serious AEs (SAEs) were reported in the six clinical studies conducted to date (Timby 2006; Timby 2011a and 2011b; van Broekhoven 2007; Kask 2008; Kask 2009; Navarro 2003). There is also a potential risk of supra-additive sedative effects with other drugs interacting with the $GABA_A$ receptor, such as benzodiazepines and anti-epileptic medications (Norberg 1999); therefore, the Investigator is advised to avoid co-medication if possible and to exercise caution with these drug classes. As this is one of the first clinical trials of SAGE-547 in PPD, the potential benefits in this population are unknown, although the risks are likely to be similar to those mentioned above. Given the nonclinical rationale and the fact that endogenous allopregnanolone in humans appears to play a role in psychiatric disorders such as major depression, premenstrual dysphoric disorder, and anxiety disorders, it is possible that subjects may have a clinical benefit at the exposures selected for this trial. In view of the limited nature of the demonstrated risks of exogenous allopregnanolone infusion and the potential for benefit in severe PPD, there is a favorable benefit-risk evaluation for the conduct of the present study.

5.5 Study No. 547-PPD-202

5.5.1 Study Population

This study will evaluate the efficacy, safety, and pharmacokinetics (PK) of SAGE-547 Injection in the treatment of adult female subjects diagnosed with severe postpartum depression.

5.5.2 Route of Administration, Dosage, Dosage Regimen, and Treatment Period

SAGE-547 Injection or placebo will be administered over a 60 hour period by an IV infusion according to the dose regimen shown in Table 2 (see Section 11.1.1).

The specific infusion dose of SAGE-547 Injection will be calculated based on weight for each subject. Infusion bags will be changed every 24 hours. Details about the preparation and administration of the study drug infusions will be included in the Pharmacy Manual.

5.5.3 Dose Rationale

The infusion rate of SAGE-547 to be studied in this trial was chosen to achieve a mean exposure of 150 nM, roughly equivalent to the highest endogenous concentrations measured in third trimester pregnancy at approximately 157 nM (Luisi 2000). Since pregnant women tolerate this level without apparent AEs, 150 nM was selected as the target exposure for this study. This level of exposure has already been achieved in 547-PPD-201 as well at higher levels in a study in subjects with essential tremor (547-ETD-201) and subjects with super refractory status epilepticus (547-SSE-201), with no drug-related SAEs reported. Since the most common adverse event in 547-ETD-201 was sedation, dose adjustment rules are included in this protocol to ensure that all subjects can remain on treatment for 60 hours. A similar C_{max} was also achieved in several other studies conducted with intravenous allopregnanolone (Timby 2011b), with excellent tolerability (see SAGE-547 IB 2014 for details of safety profile).

The selection of exposure in the current trial is based on a cautious approach adapted to the anticipated benefit-risk in the PPD patient population, and on previous experience from the ongoing clinical trials of SAGE-547 in adult subjects with SRSE (Protocol 547-SSE-201) and of SAGE-547 in female subjects with PPD (Protocol 547-PPD-201). In the ongoing SRSE trial, as determined by simulation, loading and maintenance infusions are required to achieve the target exposure. In contrast, in the current trial, subjects will instead begin treatment with a four-hour dose-titration phase. The starting dose is approximately 9- to 18-fold lower than the NOAEL observed in rats and dogs, although this is not the first in human study. Doses will be increased as follows: 30 µg /kg/hour [0-4 hours], then 60 µg/kg/hour [4-24 hours], then 90 µg/kg/hour [24-52 hours], followed by a decrease to 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours).

Subjects will be treated in an inpatient setting and continually monitored for safety, and if any severe tolerability issues arise, the infusion will be terminated. The Stanford Sleepiness Scale (SSS) will be regularly administered to monitor sedation and allow dose adjustment based on tolerability, with a formal dose interruption and reduction scheme implemented for this and other adverse events.

6 ETHICS

6.1 Institutional Review Board or Independent Ethics Committee

This trial will be initiated only after the protocol has been reviewed and approved by the Institutional Review Board (IRB) where the study is to be conducted. The IRB must meet all US Food and Drug Administration (FDA) requirements governing IRBs (Code of Federal Regulations [CFR], Title 21, Part 56). The same applies for the implementation of changes introduced by an amendment.

6.2 Ethical Conduct of the Study

This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and the most recent amendment (2008).

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol, and must also conduct the study in accordance with International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP) standards as well as local regulations.

6.3 Subject Information and Informed Consent

Prior to subject participation in the trial, written informed consent must be obtained from each subject according to ICH GCP and in accordance with local regulations. Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests, SAGE-547 infusion, and study evaluations. Each subject's signature must be dated by each signatory and the informed consent form (ICF) retained by the investigator as part of the trial records. As an additional assessment, the ICF will contain a provision for optional consent for the collection of breast milk for the duration of the 60-hour SAGE-547 infusion and up to Day 3 for biobanking and PK analysis purposes. The ICF, as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the CFR, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject a copy of the signed and dated ICF. The ICF for subject participation must also be available as part of the subject's file for review by the site's dedicated study monitor.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

7 STUDY OBJECTIVES

7.1 Primary Objective

The primary objective of this study is to determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms in subjects with postpartum depression (PPD) compared to placebo injection as assessed by the change from baseline in Hamilton Rating Scale for Depression (HAMD) total score

7.2 Secondary Objectives

The secondary objectives of the study are:

- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms compared to placebo injection as assessed by HAMD response, HAMD remission, change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score, Clinical Global Impression – Improvement (CGI-I) response, and changes from baseline in HAMD subscale and individual item scores.
- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces other mood symptoms compared to placebo injection as assessed by changes from baseline in the Generalized Anxiety Disorder 7-Item Scale (GAD-7) total score.
- To determine if SAGE-547 Injection infused intravenously for 60 hours increases sedation levels compared to placebo injection as assessed by the changes from baseline in Stanford Sleepiness Scale (SSS) score.
- To evaluate the safety and tolerability of SAGE-547 Injection compared with placebo as assessed by the incidence of adverse events, vital sign measurement, clinical laboratory evaluations, electrocardiogram (ECG) parameters, and the Columbia Suicide Severity Rating Scale (C-SSRS).

7.3 Exploratory Objectives

- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces subject-reported depressive symptoms compared to placebo injection as assessed by the change from baseline in Edinburgh Postnatal Depression Scale (EPDS) total score and the change from baseline in Patient Health Questionnaire (PHQ-9) total score.
- To determine if SAGE-547 Injection infused intravenously for 60 hours improves maternal behaviors compared to placebo injection as assessed by the change from baseline in Barkin Index of Maternal Functioning (BIMF) total and sub-scale scores.

7.4 Pharmacokinetic Objective

- To assess the pharmacokinetic (PK) profile of SAGE-547, metabolites of SAGE-547, and betadex sulfobutyl ether sodium (SBECD) and the concentration of SAGE-547 in breast milk, when possible.

8 INVESTIGATIONAL PLAN

8.1 Overview of Study Design

This is a multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the efficacy, safety, and pharmacokinetics of SAGE-547 Injection in adult female subjects diagnosed with severe PPD. The study design is presented in Figure 1. The study will consist of an up to 5-day Screening Period (Day -5 to -1), 3-day (60-hour) Treatment Period, and 30-day Follow-up Period; see Figure 2. Subjects must remain as in-patient during the study Treatment Period, which is approximately 60 hours/2.5 days in duration. The Screening Period assessments may be conducted on an in-patient or an out-patient basis. The Follow-Up Period assessments are conducted on an out-patient basis.

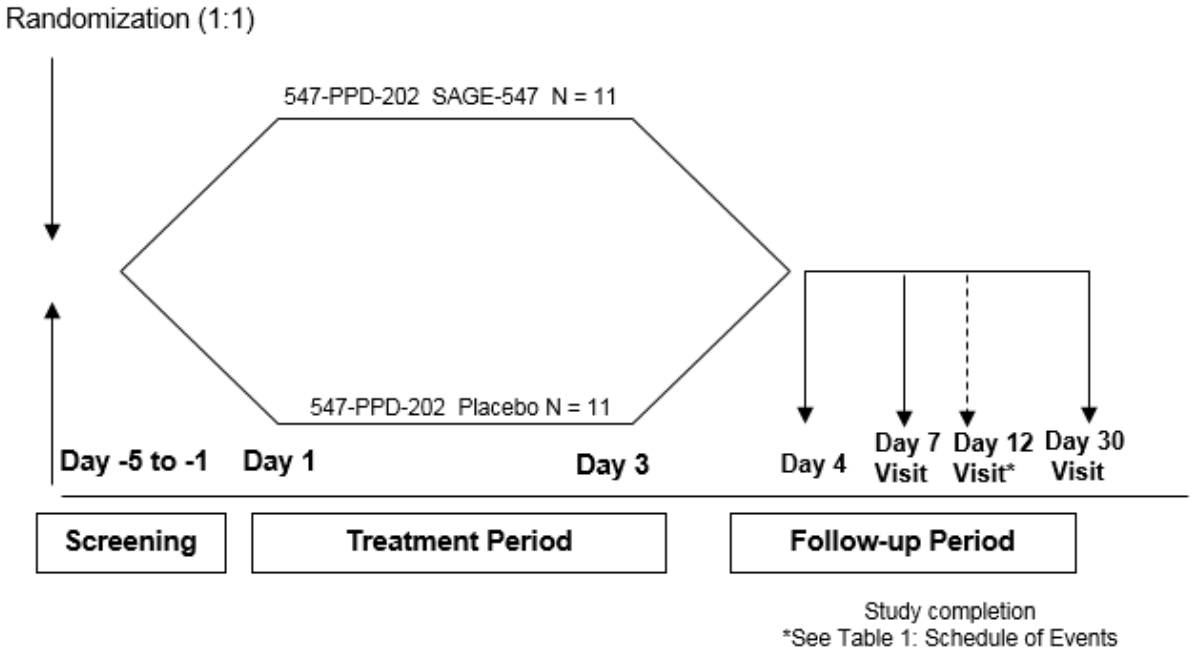

FIGURE 1: STUDY DESIGN

SAGE-547 Injection or placebo will be administered at the study center. Subjects will be monitored for safety during the Treatment and Follow-up Periods (through Study Day 30 ± 3 days) including monitoring for AEs/SAEs, routine clinical laboratory assessments, physical examination, vital signs, and ECG.

All study-related procedures will occur after written informed consent is obtained at the Screening Visit, which will occur on any one calendar day during the Screening Period window (Day -5 through 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.

The end of the Screening Period coincides with the beginning of the Treatment Period. The Treatment Period is the period of Day 1 of SAGE-547 IV infusion through completion of the infusion on Day 2 and up to Day 3. Subjects will be confined to the study center from the Screening Visit until after the 60-hour assessments have been conducted on Day 3. On the morning of dosing (Day 1), subjects will begin a 4-hour dose titration period of 30 µg/kg/hour [0-4 hours], then 60 µg/kg/hour [4-24 hours], then 90 µg/kg/hour [24-52 hours]); followed by a decrease to 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours). See dose regimen presented in Section 11.1.1. Total SAGE-547 Injection or placebo dosing will occur over 60 hours.

Trial-specific assessments for safety, PK, efficacy, and exploratory outcome measures will be completed at pre-specified times over a 72-hour period during the Treatment Period:

- The safety and tolerability of SAGE-547 Injection will be assessed by AEs, clinical laboratory measures, physical examinations (including cognitive and mental health examinations), vital signs, ECG, use of concomitant medication, and the Columbia Suicide Severity Rating Scale (C-SSRS) during the Screening, Treatment, and Follow-up Periods (through Study Day 30 ± 3 days).
- Plasma will be collected to formally assay for SAGE-547, metabolite, and SBECD levels prior to dosing through the treatment period and up to 12 hours post infusion on Day 3.
- Primary efficacy assessment of the HAMD will be completed as scheduled during the Screening, Treatment, and Follow-up Periods (through Study Day 30).
- Secondary efficacy assessments of MADRS, CGI-I, EPDS, Generalized Anxiety Disorder 7-Item Scale (GAD-7), PHQ-9 will be completed as scheduled during the Screening, Treatment, and Follow-up Periods (through Study Day 30).
- Concentrations of SAGE-547 in breast milk will be measured for those subjects who consent to giving breast milk samples.

The end of the Treatment Period coincides with the beginning of the Follow-up Period.

Subjects will attend the clinic for safety follow-up assessment at one week (7±1d) and one month (30±3d) after the initiation of the study drug infusion.

Scheduled assessments for all safety, PK, efficacy, and exploratory outcome measures planned for the trial are summarized in Table 1. All subjects who receive treatment with SAGE-547 are to complete all study assessments through Study Day 30 (±3d).

The Medical Monitor will review AEs on an ongoing basis.

8.2 Blinding and Randomization

This is a double-blind study. Subjects will be randomized to SAGE-547 or placebo; subjects, clinicians, and study team will be blinded to treatment allocation. The pharmacist, who will

prepare the infusion bags according to the randomization schedule, and an unblinded Monitor, who will perform drug accountability during the study, will be unblinded.

Subjects will be randomly assigned to receive SAGE-547 Injection or placebo according to a computer-generated randomization schedule.

Only the clinic pharmacist, who is responsible for preparing the infusions, will be given a copy of the randomization schedule. In the event of a medical emergency, the pharmacist may reveal actual infusion contents to the primary investigator, who should also alert Sage of the emergency (see Section 15.4 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 have been unblinded, the subject will be terminated from the study.

9 SELECTION AND WITHDRAWAL OF SUBJECTS

9.1 Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial:

1. Subject has signed an ICF prior to any study-specific procedures being performed
2. Subject is an ambulatory female aged between 18 and 45 years of age
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 breastmilk to their infant(s) from just prior to receiving study drug through 9 days (Study Day 12) after the end of the infusion.
6. Subject must have a negative pregnancy test at Screening and Day 1 prior to the start of study drug infusion
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, as diagnosed by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)
8. Subject has a HAMD total score of ≥26 at Screening and Day 1 (prior to randomization)
9. Subject is ≤ six months postpartum
10. Subject is willing to delay start of other antidepressant or anxiety medications and any new pharmacotherapy regimens, including prn benzodiazepine anxiolytics, until the study drug infusion and 72-hour assessments have been completed
11. Subject has no detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), and human immunodeficiency virus (HIV) antibody at Screening
12. Subject must use one of the following methods of birth control during participation in the study and for 30 days following the end of the study drug infusion:
    - Total abstinence (no sexual intercourse)
    - Hormonal contraceptives (birth control) including birth control pills, implantable or injectable contraceptives (Norplant® or Depo-Provera®)
    - A barrier form of contraception such as a condom or occlusive cap with a spermicide
    - An intrauterine device (IUD)

9.2 Exclusion Criteria

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

1. Recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal,

dermatological, urogenital, neurological, or eyes, ears, or nose and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study

2. Known allergy to progesterone or allopregnanolone
3. Active psychosis per Investigator assessment
4. Attempted suicide associated with index case of postpartum depression
5. Medical history of seizures
6. Medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
7. History of active alcoholism or drug addiction (including benzodiazepines) in the 12 months prior to Screening
8. Exposure to another investigational medication or device within 30 days prior to Screening
9. Administration of psychotropics that have been initiated within 14 days prior to Screening and are not being taken at a stable dose.

9.3 Subject Withdrawal/Study Termination

9.3.1 Withdrawal/Discontinuation of Individual Subjects

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

Subjects who do not have at least one efficacy observation after 12 hours of SAGE-547 infusion are not considered evaluable for the efficacy assessment and may be replaced.

9.3.2 Subject Withdrawal From the Study

Subjects may withdraw from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

9.3.3 Discontinuation of Study Drug by the Investigator

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

The Investigator may withdraw the subject from the study drug for any of the following reasons:

- The subject is unwilling or unable to adhere to the protocol
- The subject experiences an intolerable AE

- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

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

9.3.4 Study Termination

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

10 INVESTIGATIONAL PRODUCT

10.1 Identity of Investigational Product

SAGE-547 Injection (allopregnanolone)

10.2 Clinical Supplies

10.2.1 SAGE-547

SAGE-547 Injection and ancillary supply kits containing IV administration bags, solution sets, and IV bag labels will be provided to the sites.

SAGE-547 Injection is a preservative-free, sterile, clear, colorless 5 mg/mL solution of SAGE-547 (allopregnanolone) and 250 mg/mL betadex sulfobutyl ether sodium buffered with 10 mM citrate at a pH of 6.0, intended for IV injection. All inactive excipients used in the formulation are compendial grade and conform to current United States Pharmacopeia (USP) and European Pharmacopeia (Ph. Eur.) standards. The product is aseptically processed, sterile filtered, and filled into 20 mL Type 1 parenteral glass vials with West FluroTec® coated stopper container closure systems, under current Good Manufacturing Practice (cGMP) conditions. SAGE-547 Injection is intended to be used as a single-use vial. An appropriate number of single-use vials to support the dosing duration of the study are packaged and delivered to the site. SAGE-547 Injection vials should be stored under refrigerated conditions (2–8 °C). Ancillary supply kits should be stored at controlled room temperature (20–25 °C).

All study drug labels will contain information to meet the applicable regulatory requirements.

10.2.2 Placebo

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and consisting of the same formulation without allopregnanolone. Placebo vials should be stored under refrigerated conditions (2–8 °C).

10.3 Preparation of SAGE-547 Injection or Placebo for Dosing

The pharmacy will be responsible for preparing SAGE-547 Injection or placebo for subject dosing. The prepared admixture will be administered at room temperature. The prepared admixture will be assigned a room temperature (20–25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547 Injection or placebo is not intended to be administered to subjects undiluted. Each single-use vial of SAGE-547 Injection, which is hypertonic, will require dilution with an appropriate volume of Sterile Water for Injection (SWFI) to render it isotonic. Refer to the Pharmacy Manual for specific instructions regarding infusion preparation and administration instructions.

10.4 Administration and Accountability

The pharmacy will maintain accurate records of all investigational drug product supplies received, stored, dispensed, and discarded. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate (or rates), and the date and time of preparation. Reasons for departure from the expected dosing regimen must be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication needs to be reconciled in full.

Refer to the Pharmacy Manual for complete details on preparation and administration.

11 TREATMENT OF SUBJECTS

11.1 Dosing Schedule

This is a double-blind study. Subjects will be randomized to receive 60 hours of intravenous treatment with either SAGE-547 Injection or placebo.

The timing of infusion relative to the overall trial design is shown in Figure 2.

Screening Period	Treatment Period					Follow-up Period		
Days -5 to -1	Day 1		Day 2	Day 3		Day 7	Day 12	Day 30
	4-hour dose titration	20-hour dose titration	28-hour maintenance infusion	4-hour dose taper	4-hour dose taper			
			90 µg/kg/h →					
		60 µg/kg/h →		60 µg/kg/h →				
	30 µg/kg/h →				30 µg/kg/h →			

FIGURE 2: TRIAL DESIGN AND TIMELINE FOR DOSING

Clinical supply and preparation of SAGE-547 Injection for dosing is described Section 10.2 and Section 10.3, respectively.

11.1.1 Dose Regimen

The specific infusion dose of SAGE-547 Injection will be calculated based on weight (obtained at screening) for each subject and administered according to dose regimen shown in Table 2). The infusion rates are the same for all subjects within a particular dosing period (0-4 hours, 4-24 hours, etc.) (Table 2).

TABLE 2: INFUSION RATES

Timepoint	Day 1 0-4 hours	Day 1 4-24 hours	Day 2/3 24-52 hours	Day 3 52-56 hours	Day 3 56-60 hours
Infusion rates	30 µg/kg/hour	60 µg/kg/hour	90 µg/kg/hour	60 µg/kg/hour	30 µg/kg/hour

Dosing is to begin in the morning (on Day 1) to avoid awakening subjects during the night for completion of study assessments.

If any subject has an SSS score of ≥5 for two or more consecutive assessments or an SSS score of ≥6 for a single occurrence during normal waking hours, the infusion rate for this subject will be decreased to the next lowest infusion dose level (or turned off if this occurs on the 30 µg/kg/hour dose level). Please refer to Section 11.1.4 for more details.

11.1.2 Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line with the supplied study-specific IV administration bags and lines.

11.1.3 Treatment Period

Total dosing with SAGE-547 or placebo will occur over 60 hours, including a 24-hour dose titration, a 28-hour maintenance infusion, and an 8-hour taper.

11.1.4 Dosing of Intravenous SAGE-547 in the Case of AEs

Since allopregnanolone levels in the proposed clinical trial are similar to physiological levels seen in the third trimester of pregnancy, and all the AEs reported with SAGE-547 or allopregnanolone to date were mild and non-serious, it is anticipated that the AEs associated with SAGE-547 will be mild and manageable without dose interruption or reduction. Based on the observed adverse events to date, the adverse events most likely to result in AE are sedation with or without hypotension.

However, in the case of severe or life-threatening AEs occurring, the investigator is advised to interrupt infusion until regression of the AE to mild or resolution and only resume infusion if it is deemed in the best interest of the subject. Resumption of infusion at the next lowest dose (or turned off if this event occurs on the 30 µg/kg/hour dose level) for one hour, followed by re-escalation to the maintenance rate, may be considered to address potential recurrence of the AE. If the AE recurs infusion should be definitively discontinued.

11.2 Dosing Compliance

Investigational product will be prepared in the site pharmacy, administered as a continuous IV infusion by the study staff, and will be documented in the study record. There should be no adjustments in dosing except those described in Section 11.1.4.

11.3 Concomitant Medications and Restrictions

11.3.1 Concomitant Medications

Subjects will receive standard of care for adult female patients diagnosed with PPD. 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 11.3.2. All concomitant medications should be documented throughout the study from Screening through Day 30 (± 3 days) and recorded on the eCRF. Prior medications (i.e., those taken prior to signing of informed consent) that required wash-out for study entry will also be documented.

11.3.2 Prohibited 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 on this medication for at least 30 days prior to study enrollment.
- Benzodiazepines are to be avoided as much as possible. Eligible subjects taking a benzodiazepine at the time of study entry will 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. Particular attention should be paid to assessment of AEs and implementation of the dose interruption and reduction scheme in subjects on concomitant benzodiazepines since they have been shown to have a supra-additive effect with pregnenolone in an animal model of anesthesia (Norberg 1999).
- The use of hypnotics for sleep/insomnia such as Ambien® and trazodone are to be avoided.
- Anticonvulsants and atypical antipsychotics are to be avoided if possible and are not to be initiated at any time during active treatment period (60 hours). However, if a subject is taking one of these medications for at least 30 days prior to study admission, they will be permitted to remain on this medication, at their current dose (no dose adjustments are allowed).
- SAGE-547 has demonstrated inhibitory effects on cytochrome P-450 (CYP) 2C9 (CYP2C9). The following medications are primarily metabolized by CYP2C9 and therefore are prohibited during SAGE-547 administration: fluconazole and miconazole (antifungal), amentoflavone (constituent of Ginkgo biloba and St. John's Wort), sulfaphenazole (antibacterial), valproic acid (anticonvulsant, mood-stabilizing), and apigenin. See Appendix 10 for a more complete list.

12 STUDY ASSESSMENTS

12.1 Safety Assessments

The safety and tolerability of SAGE-547 Injection will be evaluated by summarization of AEs by frequency, severity and seriousness, mean changes from baseline in clinical laboratory measures, physical examination, vital signs, ECGs, and concomitant medication usage. Suicidality will be monitored using the C-SSRS. All safety assessments should be performed per the study center's standard of care and will be collected according to the Schedule of Events (Table 1). All safety assessments are to be completed within ± 30 minutes of the scheduled time point.

In addition to the schedule outlined in Table 1, completion of safety assessments including physical examination, vital signs, and clinical laboratory tests should occur in the event of an emergency or SAE, when possible.

12.1.1 Adverse Events

Adverse events will be collected after the ICF has been signed through the end of the study (see Section 15.2.1 for additional details). Medical conditions or adverse events that occur after the ICF has been signed and *prior to* completion of Screening will be captured on the Medical History eCRF.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (version 17.0 or higher).

12.1.2 Clinical Laboratory Tests

Blood samples will be collected for hematology, serum chemistry, coagulation, and specific hormone parameters, hepatitis, human immunodeficiency virus (HIV), pregnancy and genetic analysis. Urine samples for urinalysis and selected drugs of abuse will also be collected. All samples will be analyzed at the central laboratory. Patients 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 (Table 1).

These assessments will be performed in accordance with the Schedule of Events (Table 1) and as outlined individually below.

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 will be recorded as medical history. Clinical laboratory results that are Abnormal; CS during the study and indicate a worsening from baseline will be considered AEs, assessed according to Section 15, and recorded in the eCRF.

12.1.2.1 Hematology, Serum Chemistry, Coagulation

Blood samples will be collected for analysis of the following:

- **Hematology:** complete blood count (CBC) including white blood cell (WBC) count with differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils) platelet count, red blood cell (RBC) count, hemoglobin (Hgb) and hematocrit (Hct), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH)
- **Serum chemistry:** albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatinine, gamma glutamyl transferase (GGT), glucose phosphate, potassium, sodium, total protein and triglycerides (Screening only)
- **Coagulation:** activated partial thromboplastin time (aPTT), prothrombin time (PT), international normalized ratio (INR)

12.1.2.2 Hepatitis and HIV

Blood samples will be collected for analysis of the following:

- **Hepatitis**: hepatitis B virus surface antigen (HBsAg), antibody against hepatitis C virus (anti-HCV)
- **HIV**: antibody against human immunodeficiency virus type 1/2 (anti-HIV 1/2)

12.1.2.3 Hormones and Exploratory Biochemistry

Blood samples will be collected for analysis of thyroid stimulating hormone (TSH), estrogen, progesterone, progesterone metabolites, oxytocin, tryptophan, kynurenine, and markers of inflammation.

12.1.2.4 Pregnancy Test

All subjects will be tested for pregnancy by serum hCG at Screening and urine hGC on Day 1 prior to administration of study drug. Subjects with a positive pregnancy test at Screening or Day 1will be ineligible for study participation.

12.1.2.5 Genetic Testing

A blood sample for genetic testing will be collected at screening, where consent is given.

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 (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3a-hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. 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-547 but also susceptibility to disorders for which SAGE-547 may be

evaluated. Thus, the genetic research my involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

12.1.2.6 Urinalysis

Urinalysis will include assessment of bilirubin, glucose, ketones, leukocytes, nitrite, pH, protein and specific gravity.

12.1.2.7 Drugs of Abuse and Alcohol

Urine assessment for selected drugs of abuse (including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine and propoxyphene). Use of benzodiazepines at screening is not necessarily exclusionary, as subjects will be allowed to take psychotropics that have been initiated at least 14 days prior to admission to the study center at a stable dose (see Section 11.3). Alcohol will be assessed in plasma at Screening and in serum, via breathalyzer or urine dipstick on Day 1.

12.1.3 Physical Examination

Body weight and height will be measured at Screening. Body mass index (BMI) will be programmatically calculated in the eCRF.

Any condition present at the post-treatment physical examination that was not present at or worsened since the baseline examination is to be documented as an AE. Whenever possible, the same individual is to perform all physical examinations. Physical examinations will include assessment of body systems (e.g., HEENT, heart, lungs, abdomen, and extremities) as well as cognitive and neurological examination and mental status examination.

12.1.4 Vital Signs

Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). A full set of vital signs will be obtained at all specified timepoints (± 30 minutes), unless the subject is asleep between the hours of 23.00h and 06.00h each day.

12.1.5 Pulse Oximetry

Pulse oximetry will be monitored continuously from H0 until H60 on Day 1, and checked approximately every 2 hours, including during the overnight hours, or at the alarm. If there is an indication of oxygen desaturation, this should be recorded as an adverse event at the discretion of the Investigator. No pulse oximetry data will be recorded in the eCRF.

12.1.6 ECG

A baseline 12-lead ECG will be performed during Screening to assess the presence of any current or historical cardiovascular conditions. The following ECG parameters will be recorded: heart rate, PR, QRS, QT, and QTc. Subjects with clinically significant abnormalities should not be entered into the study.

12.1.7 Columbia Suicide Severity Rating Scale (C-SSRS)

Suicidality will be monitored during the study using the C-SSRS (Posner 2011). This scale consists of a pre-dose evaluation that assesses the lifetime and recent 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 on Day 1 prior to dosing. The "Since Last Visit" C-SSRS form will be completed for all subsequent assessments.

Copies of the C-SSRS are provided in APPENDIX 1.

12.1.8 Stanford Sleepiness Scale (SSS)

The Stanford Sleepiness Scale is patient-rated scale designed to quickly assess how sedated or sleepy a patient is feeling. The degree of sleepiness is rated on a scale of 1 to 7, where the lowest score of 1 indicates that the patient is "feeling active, vital, alert, or wide awake" and the highest score of 7 indicates that the patient is "no longer fighting sleep, sleep onset soon; having dream-like thoughts." The SSS will be administered unless the subject is asleep between the hours of 23.00h and 06.00h each day. If the SSS is not scored due to a subject being asleep, a score of X will be reported in the CRF to indicate that the subject was asleep. All SSS assessments are to be completed within ± 15 minutes of the scheduled time point.

A copy of the SSS is provided in APPENDIX 5.

12.2 Efficacy Assessments

For all efficacy assessments, the baseline values will be calculated as the last recorded value prior to the start of infusion of randomized treatment. 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.

12.2.1 Primary Efficacy Outcome Measure

The primary outcome measure is the HAMD. The HAMD will be administered before, during, and after the infusion of blinded study drug.

12.2.1.1 Hamilton Rating Scale for Depression (HAMD)

The 17-item HAMD will be used to rate the severity of depression in subjects who are already diagnosed as depressed (Hamilton 1960). The 17-item HAMD is comprised of 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 HAMD assessments are to be completed within ± 30 minutes of the scheduled time point, but prior to starting dosing on D1 H0. Every effort should be made for the same rater to perform all HAMD assessments for a single patient.

The HAMD total score will be calculated as the sum of the 17 individual item scores. Item 16 can be rated according to history (item 16A) or actual weight change (item 16B). The item 16 score is calculated as the item 16 response that is not equal to 3 (i.e., "Not assessed").

In addition to the primary efficacy endpoint of change from baseline in HAMD total score, several secondary efficacy endpoints will be derived for the HAMD. HAMD subscale scores will be calculated as the sum of the items comprising each subscale. HAMD response will be defined as having a 50% or greater reduction from baseline in HAMD total score. HAMD remission will be defined as having a HAMD total score of $\leq$7.

A copy of the HAMD is provided in APPENDIX 2.

12.2.2 Secondary Efficacy Outcome Measures

Secondary efficacy assessments include evaluation of depressive symptom severity by the MADRS and CGI, as described in Section 9. Additional assessments of depressive symptom severity and reproductive mood disorders will be measured by the following clinician- and subject-rated outcome measures: EPDS, GAD-7 and PHQ-9, as described in Sections 12.2.3.1 through 13.

12.2.2.1 Montgomery Asberg Depression Rating Scale (MADRS)

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

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 1. Apparent sadness 2. Reported sadness 3. Inner tension 4. Reduced sleep 5. Reduced appetite 6. Concentration difficulties 7. Lassitude 8. Inability to feel 9. Pessimistic thoughts 10. Suicidal thoughts.

The MADRS total score will be calculated as the sum of the 10 individual item scores.

A copy of the MADRS is provided in APPENDIX 3.

12.2.2.2 Clinical Global Impression (CGI) Scale

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 patient's condition. The CGI scale is comprised of 3 items. Only the first two items are being used in this study.

The CGI-Severity (CGI-S) item uses a 7-point Likert scale to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating 1 = normal, not at all ill, 2 = borderline mentally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, and 7 = extremely ill. The CGI-S will be rated by the clinician at screening and on Day 1 (prior to dosing).

The CGI-Improvement (CGI-I) item employs a 7-point Likert scale to measure the overall improvement in the patient's condition post-treatment. The investigator will rate the patient's total improvement whether or not it is due entirely to drug treatment. Response choices include: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. The CGI-I is only rated at post-treatment assessments. By definition, all CGI-I assessments are evaluated against baseline conditions. CGI-I response will be defined as having a CGI-I score of "very much improved" or "much improved".

A copy of the CGI is provided in APPENDIX 4.

12.2.2.3 Generalized Anxiety Disorder 7-Item Scale (GAD-7)

The GAD-7 is a patient-rated generalized anxiety symptom severity scale (Spitzer 2006). Scoring for GAD-7 generalized anxiety is calculated by assigning scores of 0, 1, 2, and 3 to the response categories, respectively, of "not at all sure," "several days," "over half the days," and "nearly every day." GAD-7 total score for the seven items ranges from 0 to 21, where a score of 0 to 4 = minimal anxiety, 5 to 9 = mild anxiety, 10 to 14 = moderate anxiety, and 15 to 21 = severe anxiety. All assessments are to be completed within ± 30 minutes of the scheduled time point.

The GAD-7 total score will be calculated as the sum of the 7 individual item scores.

A copy of the GAD-7 is provided in APPENDIX 7.

12.2.3 Exploratory Patient Reported Outcome Measures

Exploratory efficacy assessments include evaluation of depressive symptom severity and reproductive mood disorders. These will be measured by the following clinician- and subject-rated outcome measures: EPDS, PHQ-9, and BIMF.

12.2.3.1 Edinburgh Postnatal Depression Scale (EPDS)

The EPDS is a patient-rated depressive symptom severity scale specific to the perinatal period (Cox 1987). The EPDS total score will be calculated as the sum of the 10 individual item scores.

A copy of the EPDS is provided in APPENDIX 6.

12.2.3.2 Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a patient-rated depressive symptom severity scale. To monitor severity over time for newly diagnosed patients or patients in current treatment for depression, patients may complete questionnaires at baseline and at regular intervals thereafter. Scoring is total based on responses to specific questions, as follows: "not at all" = 0; "several days" = 1; "more than half the days" = 2; and "nearly every day = 3." All assessments are to be completed within ± 30 minutes of the scheduled time point.

The PHQ-9 total score will be calculated as the sum of the 9 individual item scores. The PHQ-9 total score will be categorized as follows: 1-4 = minimal depression, 5-9 = mild depression, 10-14 = moderate depression, 15-19 = moderately severe depression; and 20-27 = severe depression.

A copy of the PHQ-9 is provided in APPENDIX 8.

12.2.3.3 Barkin Index of Maternal Functioning (BIMF)

The BIMF is a patient reported outcome scale BIMF covers a broad range of functional areas (self-care, infant care, mother-child interaction, psychological well-being of mother, social support, management, adjustment). This new application of maternal functional status is a robust construct where the physical and mental health of the mother is essential to optimal functioning. Each item is rated on a scale of 0 (strongly disagree) to 6 (strongly agree).

A copy of the BIMF is provided in APPENDIX 9.

12.3 Pharmacokinetics

12.3.1 Plasma PK Samples

Blood samples for PK analysis will be collected in accordance with the Schedule of Events (Table 1). Scheduled time points for PK blood draws after the start of infusion will have a window of ± 10 minutes. Samples will be processed according to the PK Manual, and analyzed for concentrations of SAGE-547, metabolites of SAGE-547, and SBECD. Additionally, PK samples may be obtained outside the planned collection times if issues administering study drug are encountered, such as incorrect infusion rate, interrupted infusion, or other administration deviations where PK level assessment may be important in understanding subject state. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.

The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve (AUC) from time zero to 60 hours ($AUC_{0\text{-}60}$), AUC from time zero to infinity (AUC_{inf}), maximum (peak) plasma concentration (C_{max}), time at maximum (peak) plasma concentration (T_{max}), steady-state drug concentration in the plasma during constant-rate infusion (C_{ss}), and average drug concentration in the plasma at steady state during a dosing interval (C_{avg}).

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Subject-specific plasma PK kits for sampling including instructions on sample collection, processing methods, storage and shipping conditions, will be provided in the study PK Manual.

12.3.2 Breastmilk PK Samples

Women who are actively lactating at Screening, and who otherwise fulfill all of the inclusion and exclusion criteria for the study, will be asked if they will consent to pumping. Breastmilk will be collected and pooled at pre-defined intervals. The times of the first and last pumping of each collection period will be recorded. Breastmilk will be pooled within each collection period and the total volume will be measured. Detailed instructions for breastmilk PK sampling, processing methods, storage and shipping will be provided in the study PK Manual. After Study Day 12, women may resume giving breastmilk to their infant, per Inclusion Criteria 5.

13 STUDY PROCEDURES

The study procedures listed below by study day reflect the data collection times for this protocol.

Scheduled assessments for all safety, efficacy, PK and exploratory outcome measures planned for the trial are summarized in Table 1 (Schedule of Events). All subjects who receive treatment with SAGE-547 should complete all study assessments through Study Day 30 (± 3 days).

Subjects who are evaluated at the Day 3 visit of the Treatment Period (i.e., all Hour 60 assessments are completed, post-infusion) and complete the Day 30 (± 3 days) visit during the Follow-up Period will be defined as study completers.

13.1 Screening Period

The Screening Period consists of a window from Day -5 through Day -1 prior to starting SAGE-547 treatment. The Screening Period begins with the signature of the ICF. Eligibility is determined by applying the inclusion/exclusion criteria. The diagnosis of PPD must be by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). A full medical and family history will be taken including recording of all depression, other Axis 1 and Axis 2 disorders and post-partum depression episodes in primary probands (who may be subject to a SCID-I interview).

The following assessments/procedures will be conducted at the Screening Visit, which will occur on any one calendar day of the Screening Period. 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 examinations, 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, and all screening assessments are completed, reviewed and approved by the Investigator prior to administration of SAGE-547.

Subjects will be confined to the study center from the Screening Visit until after the 60-hour assessments have been conducted on Day 3.

- Written informed consent, with optional provision for breast milk collection (see Section 6.3 for more information).
- Review of inclusion/exclusion criteria to determine subject eligibility.
- Demographic information and medical/family history collected.
- Blood will be collected for a pregnancy test.
- Blood will be collected to screen for hepatitis and HIV.
- Completion of physical examination, including body weight. Height should be recorded. BMI will be calculated.
- Vital signs.
- Blood and urine samples collected for clinical laboratory testing, including drug and alcohol screening.

- Blood sample will be taken for genetic analysis with subject consent.
- An ECG reading taken.
- Completion of the HAMD, CGI-S, and MADRS.
- Recording of concomitant medications.

13.2 SAGE-547 Treatment Period (Day 1 to Day 3, Hours 0-60)

All safety, efficacy, pharmacokinetic and other outcome assessments described in this section are to be completed within ± 30 minutes of the scheduled time points, unless otherwise stated. Windows for PK collection time points are specified by respective time point for Study Days 1 to 3 in Section 13.2.1 to Section 13.2.3, respectively (see Section 12.3 for additional details). Subjects will be confined to the study center from the Screening Visit until after the 60-hour assessments have been conducted on Day 3.

13.2.1 Day 1

- Review of inclusion/exclusion criteria to determine subject eligibility.
- Randomization (on a 1:1 basis: one group will receive SAGE-547 and one group will receive placebo).
- Urine will be collected for a pregnancy test.
- Begin study drug administration for dose titration in the morning followed by maintenance infusion.
- Vital signs and pulse oximetry will be recorded prior to infusion and at 2, 4, 8, 12, 18, and 24 hours on Day 1 (± 30 minutes), unless the subject is asleep between the hours of 23.00h and 06.00h each day. Additional measures of pulse oximetry will be collected during sleeping hours.
- Blood and urine samples collected for drug and alcohol screening.
- A blood sample for PK analysis will be collected prior to infusion (i.e., morning of Day 1 prior to dosing), and at Hours 4 (before change in infusion rate), 8, 12, and 24 (before change in infusion rate) after the start of the infusion. PK blood draws after the start of infusion will have a window of ± 10 minutes. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.
- Completion of the HAMD prior to dosing and at Hours 2, 4, 8, 12, and 24 on Day 1 (± 30 minutes).
- Completion of the MADRS prior to dosing and at Hour 24 on Day 1 (± 30 minutes).
- Completion of the CGI-S prior to dosing and the CGI-I at Hours 2, 4, 12, and 24 on Day 1 (± 30 minutes).
- Completion of the following questionnaires prior to dosing: BIMF, EPDS, GAD-7, and PHQ-9 (± 30 minutes).

- Completion of the SSS prior to dosing and at Hours 2, 4, 8, 12, 18, and 24 on Day 1 (± 15 minutes) unless the subject is asleep between the hours of 23.00h and 06.00h each day.
- AEs will be monitored.
- Concomitant medications will be recorded.
- Completion of the "Baseline/Screening" C-SSRS form prior to dosing. Completion of the "Since Last Visit" C-SSRS form at Hour 24 (± 30 minutes).
- Per subject consent (optional), collection of breast milk at pre-infusion and at the following time periods of interest: 0, 1-12, 12-24, 24-36, 36-48, 48-60, and 60-72 hours after the start of the infusion.

13.2.2 Day 2

- Ongoing SAGE-547 maintenance infusion administration.
- Vital signs and pulse oximetry will be recorded at Hours 30, 36, 42, and 48 (± 30 minutes), unless the subject is asleep between the hours of 23.00h and 06.00h each day.
- Additional measures of pulse oximetry will be collected during sleeping hours.
- A blood sample for PK analysis will be collected at Hours 30, 36, and 48. PK blood draws will have a window of ± 10 minutes. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.
- Completion of the HAMD at Hour 36 and Hour 48 (± 30 minutes).
- Completion of the CGI-I at Hour 36 and Hour 48 (± 30 minutes).
- Completion of the MADRS at Hour 48 (± 30 minutes).
- Completion of the SSS at Hours 30, 36, 42, and 48 on Day 2 (± 15 minutes) unless the subject is asleep between the hours of 23.00h and 06.00h each day.
- An ECG reading taken at Hour 48.
- AEs will be monitored.
- Concomitant medications will be recorded.
- Per subject consent (optional), ongoing collection of breast milk during the maintenance phase of infusion.

13.2.3 Day 3

- Ongoing SAGE-547 maintenance infusion administration until Hour 60.
- Completion of physical examination.
- Vital signs will be recorded at Hours 54, 60, 66, and 72 (± 30 minutes).

- A blood sample for PK analysis will be collected at Hours 60 and 72 (± 10 minutes). In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.
- Blood sample collected for clinical laboratory testing at Hour 72.
- Completion of the HAMD and MADRS at Hour 60 and 72 (± 30 minutes).
- Completion of the CGI-I at Hours 60 and 72 (± 30 minutes).
- Completion of the following questionnaires at Hour 60: EPDS, GAD-7, and PHQ-9 (± 30 minutes).
- Completion of the SSS at Hours 54, 60, 66, and 72 on Day 3 (± 15 minutes) unless the subject is asleep between the hours of 23.00h and 06.00h each day.
- AEs will be monitored.
- Concomitant medications will be recorded.
- Completion of the C-SSRS at Hours 60 and 72.
- Per subject consent (optional), ongoing collection of breast milk.

13.3 Follow-up Period (Day 7 through Day 60)

13.3.1 Day 7 (± 1 day)

The following assessments should be completed:

- Completion of physical examination.
- Vital signs.
- Blood and urine samples collected for clinical laboratory testing.
- An ECG reading taken.
- Completion of the C-SSRS, HAMD, MADRS, CGI-I, EPDS, GAD-7, PHQ-9 and BIMF.
- A blood sample for PK analysis will be collected at the time of the visit
- Per subject consent (optional), collection of breast milk on the day of the visit*
- AEs will be monitored.
- Concomitant medications will be recorded.

*Assessment is only applicable to those patients who have temporarily ceased breastfeeding and are participating in the optional breast milk sampling.

13.3.2 Day12 (+1 day)

- A blood sample for PK analysis will be collected at the time of the visit
- Per subject consent (optional), collection of breast milk on the day of the visit

- AEs will be monitored.
- Concomitant medications will be recorded.

This visit is only applicable to those patients who have temporarily ceased breastfeeding and are participating in the optional breast milk sampling.

13.3.3 Day 30 (± 3 days)

The following assessments should be completed:

- Urine will be collected for a pregnancy test.
- Vital signs.
- Completion of the C-SSRS, HAMD, MADRS, CGI-I, EPDS, GAD-7, PHQ-9 and BIMF.
- AEs will be monitored.
- Concomitant medications will be recorded.

13.3.4 Early Termination Visit

The following assessments should be completed if the patient discontinues from the study prior to the Day 7 Visit:

- Completion of physical examination.
- Vital signs.
- Blood and urine samples collected for clinical laboratory testing.
- An ECG reading taken.
- Completion of the C-SSRS, HAMD, MADRS, CGI-I, EPDS, GAD-7, PHQ-9 and BIMF.
- AEs will be monitored.
- Concomitant medications will be recorded.

The visit should occur within 3 days of notification of the patient discontinuing.

14 STATISTICAL METHODS AND CONSIDERATIONS

In general, summary statistics for all study endpoints will be presented as mean, standard deviation (SD), median, and ranges for continuous endpoints, and as counts and percentages for categorical endpoints. For the purpose of all safety, efficacy, and exploratory analyses where applicable, baseline is defined as the last pre-dose measurement closest to the start of blinded study drug infusion.

A statistical analysis plan (SAP) will be generated and approved by a representative of Sage Therapeutics prior to database lock. All statistical analyses will be conducted using SAS for Windows (version 9.1.3, or higher; Cary, NC), unless otherwise specified.

Any deviations from the planned analyses will be described and justified in the final clinical study report (CSR).

14.1 Data Analysis Sets

The **All Enrolled Population** will include all subjects who have given written informed consent. This population will be used for subject disposition and demographic characteristic summaries.

The **All Randomized Population** will include the subset of subjects from the All Enrolled Population who have been randomized. Subjects will be classified according to randomized treatment. This population will be used for subject disposition, demographic characteristic, and baseline characteristic summaries.

The **Safety Population** will include all randomized subjects who start the infusion of study drug. Subjects will be classified according to actual treatment received. This analysis population will be used for all safety analyses.

The **Efficacy Population (EFF)** will include the subset of the Safety Population who have a valid baseline HAMD assessment and at least one post-baseline HAMD assessment. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Per Protocol Population (PP)** will include the subset of the Efficacy Population who complete the full infusion without significant protocol violations or deviations. Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary and select secondary endpoints.

The **PK Population (PKP)** will include the subset of the Safety Population who have at least one evaluable PK sample. Subjects will be classified according to actual treatment received. This analysis population will be used for all PK analyses.

The **Breast Milk Population (BMP)** will include the subset of the Safety Population who have at least one evaluable breast milk sample. Subjects will be classified according to actual treatment received. This analysis population will be used for all breast milk PK analyses.

The number and percentage of subjects who receive SAGE-547 Injection or placebo, prematurely discontinue, and complete the study will be summarized. The number and percentage of subjects will also be summarized for each reason for premature discontinuation. In addition, the number of subjects whose data should be used for the

planned analyses will be identified for each respective analysis population (i.e., SAF, EFF, PKP, PP, and BMP).

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 populations, using all non-missing data available. Any rules for the imputation of missing data will be described in the SAP.

14.3 Demographics and Baseline Characteristics

Demographics such as age, race, and ethnicity will be summarized. In addition, baseline characteristics such as height, weight, and BMI will be summarized. Categorical summaries, such as race and ethnicity, will be summarized by frequency and percentage. Continuous summaries, such as age, height, weight, BMI and baseline vital signs, will be summarized using descriptive statistics such as n, mean, SD, median, minimum, and maximum.

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

Medical/family history will be collected and listed by subject.

14.4 Primary Endpoints

Change from baseline to each assessment in HAMD total score will be analyzed using a mixed effects repeated measures model (MMRM) including center, treatment, baseline HAMD total score, assessment timepoint, and timepoint-by-treatment. Center will be treated as a random effect while all other explanatory variables will be treated as fixed effects. The primary comparison will be between SAGE-547 and placebo at the 60 hour assessment. Model based point estimates (i.e., LS means), 95% confidence intervals, and p-values will be reported for each assessment.

Summaries of HAMD total scores and changes from baseline values will include n, mean, SD, median, minimum, and maximum.

14.5 Secondary Endpoints

Efficacy Analysis

MMRM methods similar to those described in Section 14.4 will be used for the analysis of the following variables: MADRS total score, EPDS total score, GAD-7 total score, PHQ-9 total score, and select individual item and subscale scores. For each model, the comparison of interest will be between SAGE-547 and placebo at the 48 hour assessment. Model based point estimates (i.e., LS means), 95% confidence intervals, and p-values will be reported.

Logistic regression methods will be used for the analysis of the following response variables: HAMD response, HAMD remission, and CGI-I response. Logistic regression models will include terms for center, treatment, and baseline score. The comparison of interest will be the difference between SAGE-547 and placebo at the 60-hour assessment. Model based point estimates (i.e., 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 timepoint. Summaries will include n, mean, SD, median, minimum, and maximum.

Safety Analysis

Safety and tolerability of SAGE-547 Injection will be evaluated by AEs, concomitant medications, changes from baseline in physical examination, vital signs, CBC, serum chemistry, urinalysis, and 12-lead ECG. Suicidality will be monitored by the C-SSRS. Sedation will be assessed using the SSS. Safety data will be listed by individual and summarized by treatment group. In addition, an analysis of SSS data will be performed comparing the treatment groups in the same way as for the primary endpoint. All safety summaries will be performed on the SAF population.

Safety data will be examined for possible relationships between subject characteristics and plasma allopregnanolone concentrations, as appropriate.

Scheduled visits for all safety assessments are described in Section 12.1 and summarized in Table 1.

Adverse events: The analysis of AEs will be based on the concept of treatment-emergent AEs (TEAEs). A TEAE is defined as an AE with onset after the start of SAGE-547 infusion, or any worsening of a pre-existing medical condition/AE with onset after the start of SAGE-547 infusion and until 7 days after the end of infusion. The incidence of TEAEs will be summarized overall and by MedDRA® System Organ Class (SOC) and preferred term (PT). Incidences will be presented in order of decreasing frequency. In addition, summaries will be provided by severity (mild, moderate, severe) and by causality (related, not related) to study drug (see Section 15.2.2).

TEAEs leading to discontinuation and serious adverse events (SAEs; see Section 15.1.4 for definition) with onset after the start of randomized infusion will also be summarized.

All AEs and SAEs (including those with onset or worsening before the start of randomized infusion) through the Day 30 follow-up visit will be listed.

Clinical laboratory evaluations: Results will be listed by Subject ID and timing of collection. Mean changes from baseline in clinical laboratory measures will be evaluated.

Physical examinations: Physical examinations will be evaluated at Screening and Day 7. Any clinically significant change in physical examination compared to those observed at Screening should be noted as an AE.

Vital signs: Vital signs, including oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing) will be obtained at the scheduled time points described in Section 12.1.4. Mean changes from baseline (pre-infusion) in vital signs will be evaluated.

12-Lead ECG: The following ECG parameters will be listed for each subject: heart rate, PR, QRS, QT, and QTc. Any clinically significant abnormalities or changes in ECGs should be listed as an AE. ECG findings will be listed by subject and visit.

Concomitant medications: A summary of all concomitant medications taken during the course of the study will be presented in tabular form by therapeutic drug class and generic drug name using the WHO Collaborating Centre for Drug Statistics Methodology Norwegian Institute of Public Health (http://www.whocc.no).

C-SSRS: 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.

SSS: Changes in score over time will be represented graphically, and change from baseline will be measured.

PK Analysis: Plasma will be collected to assay for concentrations of SAGE-547, metabolites of SAGE-547, and SBECD. The following PK parameters will be derived from the plasma concentrations (where evaluable): $AUC_{0\text{-}60}$, AUC_{inf}, C_{max}, time at maximum (peak) plasma concentration (T_{max}), steady-state drug concentration in the plasma during constant-rate infusion (C_{ss}), and average drug concentration in the plasma at steady state during a dosing interval (C_{avg}).

Plasma concentrations will be listed by subject and summarized by nominal collection timepoint. PK parameters will be listed by subject and summarized by collection timepoint. Correlations between concentrations and AEs or tolerability measures may be performed as deemed necessary.

In addition to typical descriptive statistics, summaries should include geometric mean, coefficient of variation, and geometric coefficient of variation.

14.6 Determination of Sample Size

Assuming a two-sided test at an alpha level of 0.10, a sample size of 10 evaluable subjects per group would provide 80% power to detect an effect size of 1.2 between the SAGE-547 and placebo groups with regard to the primary outcome variable of change from baseline in HAMD total score. An effect size of 1.2 corresponds to a placebo adjusted difference of 12 points in the change from baseline in HAMD total score at 60 hours with an assumed standard deviation of 10 points. By including two treatment groups and using a 1:1 randomization ratio, a total of 20 evaluable subjects are required. Assuming a non-evaluability rate of 10%, at least 22 subjects will be randomized.

Based on the results of the interim analysis (see Section 14.7), the sample size could be increased to a maximum of 32 randomized subjects. This adjustment to the sample size would allow for an effect size of 1.0 to be detected.

14.7 Interim Analysis

An interim analysis will be conducted by an independent statistician for sample size re-estimation purposes when at least 16 subjects have completed efficacy assessments through 60 hours. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis will be included in the SAP.

14.8 Changes From Protocol Specified Analyses

Any changes from the analytical methods outlined in the protocol will be documented in the final SAP.

15 ADVERSE EVENTS

Section 15.1 lists important AE definitions.

Section 15.2 summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

Section 15.3 summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

15.1 Adverse Event Definitions

15.1.1 Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

15.1.2 Suspected Adverse Reaction

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

15.1.3 Life-Threatening

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

15.1.4 Serious

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE (see definition in Section 15.1.3)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- Other medically important condition (as described below)

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include

allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

15.1.5 Unexpected

An AE or suspected adverse reaction is considered "unexpected":

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

"Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

15.2 Investigator Responsibilities

15.2.1 Identification and Documentation of Adverse Events by Investigator

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected during subject preparation, study drug administration during Screening, after the initiation of study drug administration through to Day 3, and at the Follow-up Visits on Day 7 (± 1 day) and Day 30 (± 3 days). SAEs will also be collected until the Day 30 (± 3 days) follow-up visit. Medical conditions that occur prior to completion of the Screening Visit will be captured on the Medical History eCRF. Adverse events that occur after completion of the Screening Visit will be recorded on the AE page of the eCRF (AE eCRF).

All AEs revealed by observation, physical examinations, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the AE eCRF. Any clinically significant deterioration from baseline in laboratory assessments or other clinical findings is considered an AE and must be recorded on the AE eCRF, unless otherwise stated. AE information recorded on AE eCRF will be entered into the database on an ongoing basis. The database, including AE information, will be transferred to the Sponsor on a pre-defined schedule for review.

All AEs, 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.

For all SAEs, an SAE report form must be completed with as much information as possible and submitted in the time frame described in Section 15.2.3. When new significant information is obtained as well as when the outcome of an event is known, the SAE report form should be updated on a follow-up report. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject's medical file.

All SAEs will be followed until the events are resolved or improved, a stable status has been achieved, or the subject is lost to follow-up.

15.2.2 Adverse Event Classification

Definitions for the categories of AE classification are included in this section.

15.2.2.1 Relationship to Investigational Drug

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

15.2.2.2 Severity

The severity of an adverse experience will be defined as follows and reported as indicated on the AE eCRF:

Mild:	Discomfort noticed, but no disruption to daily activity.
Moderate:	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.
Severe:	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.

15.2.2.3 Action Taken With Investigational Drug

Action taken with regard to administration of SAGE-547 Injection for this trial will be recorded using the one of following categories (the category "dose increased" does not apply to this trial):

- Drug withdrawn: An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
- Dose not changed: An indication that a medication schedule was maintained.
- Drug interrupted: An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.
- Dose reduced: An indication that a medication schedule was modified to a reduced rate/dose.
- Unknown: Unknown, not known, not observed, not recorded, or refused.
- Not applicable: Determination of a value is not relevant in the current context.

15.2.2.4 Assessment of Outcome

Assessment of outcome of AEs will be categorized as one of the following:

- Recovered/Resolved: The event has improved or recuperated.
- Recovering/Resolving: The event is improving.
- Not Recovered/Not Resolved: The event has not improved or recuperated.
- Recovered/Resolved with Sequel: The subject recuperated but retained pathological conditions resulting from the prior disease or injury.
- Fatal: The termination of life as a result of an adverse event.
- Unknown: Not known, not observed, not recorded, or refused.

15.2.3 Investigator Reporting to Sponsor and Sponsor Emergency Contact

All SAEs that occur during the course of the study must be reported by the Investigator on the designated report form (study-specific SAE form or MedWatch 3500A form) and sent by facsimile to the medical monitor within 24 hours from the point in time when the Investigator becomes aware of the SAE. Investigators must report any SAE, whether or not considered drug related. The initial report must be as complete as possible, including assessment of the causal relationship (i.e., assessment of whether there is a reasonable possibility that the drug caused the event). The medical monitor will contact the investigator via telephone for follow-up information regarding the SAE, as appropriate.

Information not available at the time of the initial report must be documented on a follow-up report. As additional information becomes available, the designated report form must be updated and supporting information, including hospital records, laboratory and diagnostic testing results, etc. All supporting documentation must be de-identified. In addition, all SAEs that occur up to and including 30 days after administration of study drug must be reported within 1 working day from when the Investigator becomes aware of the SAE. A final report to document resolution of all SAEs is required.

In a medical emergency (i.e., an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care and contact the Medical Monitor.

15.2.4 Medical Monitor and Emergency Contact Information

[redacted], MD
[redacted]
Office (9-5 EST): [redacted]
24/7 Hotline: [redacted]

15.2.5 SAE Reporting Contact Information

Contact information and reporting instructions are provided in the Safety Management Plan.

15.2.6 Reporting to Institutional Review Boards (IRBs)

It is the responsibility of the Investigator to promptly notify the institution's IRB of all serious and unexpected suspected adverse reactions (see Section 15.3.2).

15.3 Sponsor/Medical Monitor Responsibilities

15.3.1 Monitoring of Adverse Event Data

The Medical Monitor or designee will review AEs on an ongoing basis.

15.3.2 Reporting to FDA

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32[c][1][i]). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the AE and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

15.4 Emergency Identification of Study Medication

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment from the pharmacist; this normally requires prior approval by the Medical Monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the Medical Monitor may take place after unblinding. The Investigator will not unblind the Medical Monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the Medical Monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the Medical Monitor, study management team, and data management team.

16 STUDY ADMINISTRATION

16.1 Quality Control and Quality Assurance

The Investigators and institutions will permit trial-related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed ICFs, etc.) in addition to CRFs.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure that this trial 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, CRFs 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 the Sponsor with the Investigator/institution and any other parties involved with the clinical trial will be in writing in a separate agreement.

16.2 Data Handling and Recordkeeping

16.2.1 Data Handling

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

16.2.2 Case Report Form Completion

Electronic CRFs (eCRFs) 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, AEs, and subject status.

The Investigator will have access to the electronic data capture (EDC) 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.

16.2.3 Retention of Study Records

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least two years after the last marketing application approval and until there are no pending or contemplated marketing applications or two years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

16.3 Confidentiality

To maintain subject privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the CRFs 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 the Sponsor. It is understood that there is an obligation to provide the Sponsor 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 authority(ies), other Investigators, corporate partners, or consultants as required.

16.4 Publication Policy

All information concerning SAGE-547 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.

16.5 Protocol Amendments

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (e.g., change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

17 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.

Amin Z, Mason GF, Cavus I et al. The interaction of neuroactive steroids and GABA in the development of neuropsychiatric disorders in women. Pharmacol, Biochem and Behavior 2006;84:635-43.

Austin MP, Middleton P, Reilly NM, Highet NJ. Detection and management of mood disorders in the maternity setting: the Australian Clinical Practice Guidelines. Women Birth 2013;26(1):2-9. doi: 10.1016/j.wombi.2011.12.001. Epub 2012 Jan 2.

Belelli D, Lambert JJ. Neurosteroids: endogenous regulators of the GABA(A) receptor. Nat Rev Neurosci 2005; 6(7):565-75. PMID: 15959466.

Bitran D, Hilvers RJ, Kellogg CK. Anxiolytic effects of 3α-hydroxy-5α[β]-pregnan-20-one: endogenous metabolites of progesterone that are active at the GABAA receptor. Brain Res 1991;561(1):157-161. PMID: 1686744.

Bitran D, Purdy RH, Kellog CK. Anxiolytic effect of progesterone is associated with increases in cortical alloprenanolone and GABAA receptor function. Pharmacol Biochem Behav 1993;45(2):423-8. PMID: 8392205.

Bloch M, Schmidt PJ, Danaceau M, et al. Effects of gonadal steroids in women with a history of postpartum depression. Am J Psychiatry 2000;157(6):924-30. PMID: 10831472.

Chaudron L. Postpartum depression: what pediatricians need to know. Pediatr Rev 2003;24(5);154-61. PMID: 12728188.

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.

Djebaili M, Guo Q, Pettus EH, Hoffman SW, Stein DG. The neurosteroids progesterone and allopregnanolone reduce cell death, gliosis, and functional deficits after traumatic brain injury in rats. J Neurotrauma 2005;22(1):106-18. PMID: 15968816.

Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL. A meta-analysis of cytokines in major depression. Biol Psychiatry 2010;67(5):446-57. PMID: 20015486.

DSM V. Diagnostic and statistical manual of mental disorders (5th ed.). American Psychiatric Association 2013. Arlington, VA: American Psychiatric Publishing.

Earls MF; Committee on Psychosocial Aspects of Child and Family Health American Academy of Pediatrics. Incorporating recognition and management of perinatal and postpartum depression into pediatric practice. Pediatrics 2010;126(5):1032-9. doi: 10.1542/peds.2010-2348.

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. PMID: 17719367.

Epperson CN, Gueorguieva R, Czarkowski KA et al. Preliminary evidence of reduced occipital GABA concentrations in puerperal women: a 1H-MRS study. Psychopharmacol 2006; 186:425-433. PMID: 16724188.

Eser D, Schüle C, Baghai TC, Romeo E, Rupprecht R. Neuroactive steroids in depression and anxiety disorders: clinical studies. Neuroendocrinology 2006;84(4):244-54. PMID: 17159334.

Fihrer I, McMahon CA, Taylor AJ. The impact of postnatal and concurrent maternal depression on child behaviour during the early school years. J Affect Disord 2009;119(1-3):116-23. PMID: 19342104.

Fournier JC, DeRubeis RJ, Hollon SD et al. Antidepressant drug effects and depression severity—a patient-level meta-analysis. JAMA 2010;303:47-53. PMID: 20051569.

Frye CA, Duncan JE. Progesterone metabolites, effective at the GABAA receptor complex, attenuate pain sensitivity in rats. Brain Res 1994;643(1-2):194-203. PMID: 8032914.

Gangisetty O and Reddy DS. Neurosteroid withdrawal regulates GABA-A receptor α4-subunit expression and seizure susceptibility by activation of progesterone receptor-independent early growth response factor-3 pathway. Neuroscience 2010; 170:865-880. PMID: 20670676.

Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, and Swinson T. Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol 2005;106:1071-83. PMID: 16260528.

Gaynes BN, Gavin N, Meltzer-Brody S, Lohr KN, Swinson T, Gartlehner G, et al. Perinatal depression: prevalence, screening accuracy, and screening outcomes. Evid Rep Technol Assess (Summ) 2005;(119):1-8. PMID: 15760246.

Gilbert Evans SE, Ross LE, Sellers EM et al. 3alpha-reduced neuroactive steroids and their precursors during pregnancy and the postpartum period. Gynecol Endocrinol 2005 21, 268-279. PMID: 16373246.

Genazzani AR, Petraglia F, Bernardi F, Casarosa E, Salvestroni C, Tonetti A, et al. Circulating levels of allopregnanolone in humans: gender, age, and endocrine influences. J Clin Endocrinol Metab 1998;83(6):2099-103. PubMed PMID: 9626145.

Glantz LA, Gilmore JH, Overstreet DH, Salimi K, Lieberman JA, Jarskog LF. Pro-apoptotic Par-4 and dopamine D2 receptor in temporal cortex in schizophrenia, bipolar disorder and major depression. Schizophr Res 2010;118(1-3):292-9. PMID: 20067857.

Hamilton M: A rating scale for depression. Journal Neurol Neurosurg Psychiatry 1960; 23:56-62. PMID: 14399272.

He JQ, Tang XW, Chen HX, Xiang Z. [Study on treatment of climacteric depression with bushen tiaogan qingxin recipe]. Zhongguo Zhong Xi Yi Jie He Za Zhi 2004;24(10):889-92. [Article in Chinese]. PMID: 15553820.

Holzbauer M, Birmingham MK, De Nicola AF, Oliver JT. In vivo secretion of 3 alpha-hydroxy-5 alpha-pregnan-20-one, a potent anaesthetic steroid, by the adrenal gland of the rat. J Steroid Biochem. 1985 Jan;22(1):97-102. PubMed PMID: 3974231.

Kask K, Bäckström T, Lundgren P, Sundström Poromaa I. Allopregnanolone has no effect on startle response and prepulse inhibition of startle response in patients with premenstrual dysphoric disorder or healthy controls. Pharmacol Biochem Behav 2009;92(4):608-13. PubMed PMID: 19268499.

Kask K, Bäckström T, Nilsson LG, Sundström-Poromaa I. Allopregnanolone impairs episodic memory in healthy women. Psychopharmacology (Berl) 2008;199(2):161-8. PMID: 18551282.

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. PMID: 18303940.

Klak J, Hill M, Parízek A, Havlíková H, et al. Pregnanolone isomers, pregnenolone and their polar conjugates around parturition. Physiol Res 2003;52(2):211-21. PMID: 12678664.

Licinio J, Wong ML. The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. Mol Psychiatry 1999;4(4):317-27. PMID: 10483047.

Luisi S, Petraglia F, Benedetto C, Nappi RE, Bernardi F, Fadalti M, et al. Serum allopregnanolone levels in pregnant women: changes during pregnancy, at delivery, and in hypertensive patients. J Clin Endocrinol Metab 2000;85(7):2429-33. PMID: 10902789.

Maguire J, Mody I. GABA(A)R plasticity during pregnancy: relevance to postpartum depression. Neuron 2008;59(2):207-13. PMID: 18667149.

Maguire J, Ferando I, Simonsen C, Mody I. Excitability changes related to GABAA receptor plasticity during pregnancy. J Neurosci 2009;29(30):9592-601. PMID: 19641122.

Majewska MD, Harrison NL, Schwartz RD, Barker JL, Paul SM. Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor. Science 1986;232:1004-7. PMID: 2422758.

McDowell, I. Measuring Health: A guide to rating scales and questionnaires. 2006: 3rd Ed. New York: Oxford University Press.

Morrow AL, Devaud LL, Purdy RH, Paul SM. Neuroactive steroid modulators of the stress response. Ann N Y Acad Sci 1995;771:257-72. PMID: 8597405.

Müller-Thomsen T, Arlt S, Mann U, Maß R, Ganzer S. Detecting depression in Alzheimer's disease: evaluation of four different scales. Archives of Clinical Neuropsychology 2005;20:271-6. PMID: 15708735.

Nappi RE, Petraglia F, Luisi S et al. Serum allopregnanolone in women with postpartum "blues". Obstet Gynecol 2001;97 (1):77-80. PMID: 11152912.

Navarro PA, Kaddouz D, de Ziegler D, Silva de Sá MF, Ferriani RA. Vaginal administration of allopregnanolone to postmenopausal women undergoing estrogen replacement therapy: preliminary results. Maturitas 2003;46(2):147-52. PubMed PMID: 14559386.

Norberg L, Backstrom T and Wahlstrom G. Anaesthetic effects of pregnanolone in combination with allopregnanolone, thiopental, hexobarbital and flurazepam: an EEG study in the rat. Br J Anaesth 1999; 82(5):731-737. PMID: 10536552.

O'Hara MW, Wisner KL. Perinatal mental illness: definition, description and aetiology. Best Pract Res Clin Obstet Gynaecol 2014;28(1):3-12. doi: 10.1016/j.bpobgyn.2013.09.002.

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.

Ottander U, Poromaa IS, Bjurulf E, Skytt A, Bäckström T, Olofsson JI. Allopregnanolone and pregnanolone are produced by the human corpus luteum. Mol Cell Endocrinol 2005 Jul 15;239(1-2):37-44. PubMed PMID: 15935549.

Paoletti AM, Romagnino S, Contu R, et al. Observational study on the stability of the psychological status during normal pregnancy and increased blood levels of neuroactive steroids with GABA-A receptor agonist activity. Psychoneuroendocrinology 2006; 31(4): 485-492. PMID: 16406349.

Paul SM, Purdy RH. Neuroactive steroids. FASEB J 1992;6(6):2311-22. PMID: 1347506.

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. doi: 10.1176/appi.ajp.2011.10111704.

Romeo E, Ströhle A, Spalletta G, di Michele F, Hermann B, Holsboer F, Pasini A, Rupprecht R. Effects of antidepressant treatment on neuroactive steroids in major depression. Am J Psychiatry 1998;155(7):910-3. PMID: 9659856.

Sayeed I, Parvez S, Wali B, Siemen D, Stein DG. Direct inhibition of the mitochondrial permeability transition pore: a possible mechanism for better neuroprotective effects of allopregnanolone over progesterone. Brain Res 2009;1263:165-73. PMID: 19368823.

Schüle C, Romeo E, Uzunov DP, Eser D, di Michele F, Baghai TC, et al. Influence of mirtazapine on plasma concentrations of neuroactive steroids in major depression and on 3α-hydroxysteroid dehydrogenase activity. Mol Psychiatry 2006;11(3):261-72. PMID: 16344854.

Schüle C, Baghai TC, di Michele F, Eser D, Pasini A, Schwarz M. Effects of combination treatment with mood stabilizers and mirtazapine on plasma concentrations of neuroactive steroids in depressed patients. Psychoneuroendocrinology 2007;32(6):669-80. PMID: 17560730.

Shelton RC, Trivedi MH. Moderators of antidepressant response in major depression. J Clin Psychiatry 2011;72(10):e32. PMID: 22075105.

Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. Arch Intern Med 2006; 166(10):1092-1097. doi: 10.1001/archinte.166.10.1092.

Ströhle A, Romeo E, Hermann B, Pasini A, Spalletta G, di Michele F, et al. Concentrations of 3α-reduced neuroactivesteroids and their precursors in plasma of patients with major depression and after clinical recovery. Biol Psychiatry 1999;45(3):274-77. PMID: 10023501.

Timby E, Balgård M, Nyberg S, Spigset O, Andersson A, Porankiewicz-Asplund J, et al. Pharmacokinetic and behavioral effects of allopregnanolone in healthy women. Psychopharmacology (Berl) 2006 Jun;186(3):414-24. PMID: 16177884.

Timby E, Hedström H, Bäckström T, Sundström-Poromaa I, Nyberg S, Bixo M. Allopregnanolone, a GABAA receptor agonist, decreases gonadotropin levels in women A preliminary study. Gynecol Endocrinol 2011 Dec;27(12):1087-93. PMID: 21190418. (Timby 2011a)

Timby E. Allopregnanolone effects in women. Clinical studies in relation to the menstrual cycle, premenstrual dysphoric disorder and oral contraceptive use. Umea University Medical Dissertation 2011; New Series No. 1459. (Timby 2011b)

Uzunova V, Sheline Y, Davis JM, Rasmusson A, Uzunov DP, Costa E, et al. Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine. Proc Natl Acad Sci 1998;95(6):3239-44. PMID: 9501247.

van Broekhoven F, Bäckström T, van Luijtelaar G, Buitelaar JK, Smits P, Verkes RJ. Effects of allopregnanolone on sedation in men, and in women on oral contraceptives. Psychoneuroendocrinology. 2007 Jun;32(5):555-64. PMID: 17470385.

Verbeek T, Bockting CL, van Pampus MG et al. Postpartum depression predicts offspring mental health problems in adolescence independently of parental lifetime psychopathology. J Affect Disord 2012;136(3):948-54. doi: 10.1016/j.jad.2011.08.035.

Wieland S, Lan NC, Mirasedeghi S, Gee KW. Anxiolytic activity of the progesterone metabolite 5α-pregnan-3α-ol-20-one. Brain Res 1991;565(2):263-8. PMID: 1688192.

18 APPENDICES

Copies of the rating scales and questionnaires included in APPENDIX 1 through APPENDIX 9 are for reference only.

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APPENDIX 1. Columbia Suicide Severity Rating Scale (C-SSRS)

The “Baseline/Screening” and “Since Last Visit” versions of the C-SSRS begin on the next full page (Posner et al. 2011).

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation*** Past X Months - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe

Most Severe Ideation: ____ _____

Type # (1-5) *Description of Ideation*

Frequency ____
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

Duration ____
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

Controllability ____
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

Deterrents ____
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

Reasons for Ideation ____
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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APPENDIX 2. Hamilton Rating Scale for Depression, 17-Item (HAMD)

The HAMD presents on the next full page (Hamilton 1960).

The HAMD total score will be calculated as the sum of the 17 individual item scores. Item 16 can be rated according to history (item 16A) or actual weight change (item 16B). The item 16 score is calculated as the item 16 response that is not equal to 3 (i.e., “Not assessed).

Patient Name:_____ Date:_____

Hamilton Rating Scale for Depression (17-items)

Instructions: For each item select the "cue" which best characterizes the patient during the past week.

1. **Depressed Mood**
   (sadness, hopeless, helpless, worthless)
   0 Absent
   1 These feeling states indicated only on questioning
   2 These feeling states spontaneously reported verbally
   3 Communicates feeling states nonverbally, i.e., through facial expression, posture, voice and tendency to weep
   4 Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and nonverbal communication

2. **Feelings of Guilt**
   0 Absent
   1 Self-reproach, feels he has let people down
   2 Ideas of guilt or rumination over past errors or sinful deeds
   3 Present illness is a punishment. Delusions of guilt
   4 Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. **Suicide**
   0 Absent
   1 Feels life is not worth living
   2 Wishes he were dead or any thoughts of possible death to self
   3 Suicide ideas or gesture
   4 Attempts at suicide (any serious attempt rates 4)

4. **Insomnia - Early**
   0 No difficulty falling asleep
   1 Complains of occasional difficulty falling asleep i.e., more than ½ hour
   2 Complains of nightly difficulty falling asleep

5. **Insomnia - Middle**
   0 No difficulty
   1 Patient complains of being restless and disturbed during the night
   2 Waking during the night – any getting out of bed rates 2 (except for purposes of voiding)

6. **Insomnia - Late**
   0 No difficulty
   1 Waking in early hours of the morning but goes back to sleep
   2 Unable to fall asleep again if gets out of bed

7. **Work and Activities**
   0 No difficulty
   1 Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
   2 Loss of interest in activity; hobbies or work – either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
   3 Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores.
   4 Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores, or if patient fails to perform ward chores unassisted.

8. **Retardation**
   (slowness of thought and speech; impaired ability to concentrate; decreased motor activity)
   0 Normal speech and thought
   1 Slight retardation at interview
   2 Obvious retardation at interview
   3 Interview difficult
   4 Complete stupor

9. **Agitation**
   0 None
   1 "Playing with" hand, hair, etc.
   2 Hand-wringing, nail-biting, biting of lips

10. **Anxiety - Psychic**
    0 No difficulty
    1 Subjective tension and irritability
    2 Worrying about minor matters
    3 Apprehensive attitude apparent in face or speech
    4 Fears expressed without questioning

11. **Anxiety - Somatic**
    0 Absent
    1 Mild
    2 Moderate
    3 Severe
    4 Incapacitating
    Physiological concomitants of anxiety such as: Gastrointestinal - dry mouth, wind, indigestion, diarrhea, cramps, belching Cardiovascular – palpitations, headaches Respiratory - hyperventilation, sighing Urinary frequency Sweating

12. **Somatic Symptoms - Gastrointestinal**
    0 None
    1 Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
    2 Difficulty eating without staff urging. Requests or requires laxatives or medications for bowels or medication for G.I. symptoms.

13. **Somatic Symptoms - General**
    0 None
    1 Heaviness in limbs, back or head, backaches, headache, muscle aches, loss of energy and fatigability
    2 Any clear-cut symptom rates 2

14. **Genital Symptoms**
    0 Absent
    1 Mild
    2 Severe
    0 Not ascertained
    Symptoms such as: loss of libido, menstrual disturbances

15. **Hypochondriasis**
    0 Not present
    1 Self-absorption (bodily)
    2 Preoccupation with health
    3 Frequent complaints, requests for help, etc.
    4 Hypochondriacal delusions

16. **Loss of Weight**
    A. When Rating by History:
    0 No weight loss
    1 Probable weight loss associated with present illness
    2 Definite (according to patient) weight loss

    B. On Weekly Ratings by Ward Psychiatrist, When Actual Changes are Measured:
    0 Less than 1 lb. weight loss in week
    1 Greater than 1 lb. weight loss in week
    2 Greater than 2 lb. weight loss in week

17. **Insight**
    0 Acknowledges being depressed and ill
    1 Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
    2 Denies being ill at all

Total Score:_____

APPENDIX 3. Montgomery Asberg Depression Rating Scale (MADRS)

The MADRS presents on the next full page. (McDowell 2006, Müller-Thomsen 2005).

Montgomery-Åsberg Depression Rating Scale (MADRS)

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5) and then report the appropriate number. The items should be rated with regards to how the patient has done over the past week.

1. Apparent sadness

Representing despondency, gloom and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

0 = No sadness.
2 = Looks dispirited but does brighten up without difficulty.
4 = Appears sad and unhappy most of the time.
6 = Looks miserable all the time. Extremely despondent

2. Reported sadness

Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope.

0 = Occasional sadness in keeping with the circumstances.
2 = Sad or low but brightens up without difficulty.
4 = Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
6 = Continuous or unvarying sadness, misery or despondency.

3. Inner tension

Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 = Placid. Only fleeting inner tension.
2 = Occasional feelings of edginess and ill-defined discomfort.
4 = Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
6 = Unrelenting dread or anguish. Overwhelming panic.

4. Reduced sleep

Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

0 = Sleeps as normal.
2 = Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
4 = Moderate stiffness and resistance
6 = Sleep reduced or broken by at least 2 hours.

5. Reduced appetite

Representing the feeling of a loss of appetite compared with when-well. Rate by loss of desire for food or the need to force oneself to eat.

0 = Normal or increased appetite.
2 = Slightly reduced appetite.
4 = No appetite. Food is tasteless.
6 = Needs persuasion to eat at all.

6. Concentration difficulties

Representing difficulties in collecting one's thoughts mounting to an incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.
0 = No difficulties in concentrating.
2 = Occasional difficulties in collecting one's thoughts.
4 = Difficulties in concentrating and sustaining thought which reduced ability to read or hold a conversation.
6 = Unable to read or converse without great difficulty.

7. Lassitude

Representing difficulty in getting started or slowness in initiating and performing everyday activities.
0 = Hardly any difficulty in getting started. No sluggishness.
2 = Difficulties in starting activities.
4 = Difficulties in starting simple routine activities which are carried out with effort.
6 = Complete lassitude. Unable to do anything without help.

8. Inability to feel

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.
0 = Normal interest in the surroundings and in other people.
2 = Reduced ability to enjoy usual interests.
4 = Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
6 = The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. Pessimistic thoughts

Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.
0 = No pessimistic thoughts.
2 = Fluctuating ideas of failure, self-reproach or self- depreciation.
4 = Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
6 = Delusions of ruin, remorse or irredeemable sin. Self- accusations which are absurd and unshakable.

10. Suicidal thoughts

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicide attempts should not in themselves influence the rating.
0 = Enjoys life or takes it as it comes.
2 = Weary of life. Only fleeting suicidal thoughts.
4 = Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intenstion.
6 = Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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APPENDIX 4. Clinical Global Impression–Improvement Scale (CGI-I) and Severity Scale (CGI-S)

The CGI-I and CGI-S presents on the next full page. For the purposes of Protocol 547-PPD-202, only Items 1 and 2, Severity of Illness and Global Improvement, will be assessed in subjects enrolled in the study.

1. **Severity of illness**
   Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?
   0 = Not assessed
   1 = Normal, not at all ill
   2 = Borderline mentally ill
   3 = Mildly ill
   4 = Moderately ill
   5 = Markedly ill
   6 = Severely ill
   7 = Among the most extremely ill patients

2. **Global improvement:** Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.
   Compared to his condition at admission to the project, how much has he changed?
   0 = Not assessed
   1 = Very much improved
   2 = Much improved
   3 = Minimally improved
   4 = No change
   5 = Minimally worse
   6 = Much worse
   7 = Very much worse

3. **Efficacy index:** Rate this item on the basis of **drug effect only**.
   Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.
   EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		**Side effects**			
		None	*Do not significantly interfere with patient's functioning*	*Significantly interferes with patient's functioning*	*Outweighs therapeutic effect*
Marked	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
Moderate	Decided improvement. Partial remission of symptoms	05	06	07	08
Minimal	Slight improvement which doesn't alter status of care of patient	09	10	11	12
Unchanged or worse		13	14	15	16

Not assessed = 00

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

APPENDIX 5. Stanford Sleepiness Scale (SSS)

The SSS presents on the next full page.

Stanford Sleepiness Scale

This is a quick way to assess how alert you are feeling. If it is during the day when you go about your business, ideally you would want a rating of a one. Take into account that most people have two peak times of alertness daily, at about 9 a.m. and 9 p.m. Alertness wanes to its lowest point at around 3 p.m.; after that it begins to build again. Rate your alertness at different times during the day. If you go below a three when you should be feeling alert, this is an indication that you have a serious sleep debt and you need more sleep.

An Introspective Measure of Sleepiness
The Stanford Sleepiness Scale (SSS)

Degree of Sleepiness	**Scale Rating**
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

APPENDIX 6. Edinburgh Postnatal Depression Scale (EPDS)

The EPDS presents on the next full page (Cox et al. 1987).

Study ID:

Edinburgh Postnatal Depression Scale

As you are pregnant or have recently had a baby, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**, not just how you feel today.

Here is an example, already completed.

I have felt happy:
☐ Yes, all the time
☒ Yes, most of the time This would mean: "I have felt happy most of the time" during the past week.
☐ No, not very often
☐ No, not at all

Please complete the other questions in the same way.

In the past 7 days:

1. I have been able to laugh and see the funny side of things
☐ As much as I always could
☐ Not quite so much now
☐ Definitely not so much now
☐ Not at all

2. I have looked forward with enjoyment to things
☐ As much as I ever did
☐ Rather less than I used to
☐ Definitely less than I used to
☐ Hardly at all

***3. I have blamed myself unnecessarily when things went wrong**
☐ Yes, most of the time
☐ Yes, some of the time
☐ Not very often
☐ No, never

4. I have been anxious or worried for no good reason
☐ No, not at all
☐ Hardly ever
☐ Yes, sometimes
☐ Yes, very often

***5 I have felt scared or panicky for no very good reason**
☐ Yes, quite a lot
☐ Yes, sometimes
☐ No, not much
☐ No, not at all

***6. Things have been getting on top of me**
☐ Yes, most of the time I haven't been able to cope at all
☐ Yes, sometimes I haven't been coping as well as usual
☐ No, most of the time I have copied quite well
☐ No, I have been coping as well as ever

***7 I have been so unhappy that I have had difficulty sleeping**
☐ Yes, most of the time
☐ Yes, sometimes
☐ Not very often
☐ No, not at all

***8 I have felt sad or miserable**
☐ Yes, most of the time
☐ Yes, quite often
☐ Not very often
☐ No, not at all

***9 I have been so unhappy that I have been crying**
☐ Yes, most of the time
☐ Yes, quite often
☐ Only occasionally
☐ No, never

***10 The thought of harming myself has occurred to me**
☐ Yes, quite often
☐ Sometimes
☐ Hardly ever
☐ Never

APPENDIX 7. Generalized Anxiety Disorder 7-Item Scale (GAD-7)

The GAD-7 presents on the next full page (Spitzer 2006).

Generalized Anxiety Disorder 7-item (GAD-7) scale

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	
Total Score *(add your column scores)* =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all _____
Somewhat difficult _____
Very difficult _____
Extremely difficult _____

APPENDIX 8. Patient Health Questionnaire (PHQ-9)

The PHQ-9 presents on the next full page.

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

APPENDIX 9. Barkin Index of Maternal Functioning (BIMF)

The BIMF is presented on the next full page.

Barkin Index of Maternal Functioning

Please **circle the number** that best represents how you have felt **over the past two weeks**. Please try to answer each question as honestly as possible as your responses will help us to better understand the postpartum experience.

	Strongly Disagree	Disagree	Somewhat Disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
1. I am a good mother.	0	1	2	3	4	5	6
2. I feel rested.	0	1	2	3	4	5	6
3. I am comfortable with the way I've chosen to feed my baby (either bottle or breast, or both).	0	1	2	3	4	5	6
4. My baby and I understand each other.	0	1	2	3	4	5	6
5. I am able to relax and enjoy time with my baby.	0	1	2	3	4	5	6
6. There are people in my life that I can trust to care for my baby when I need a break.	0	1	2	3	4	5	6
7. *I am comfortable* allowing a trusted friend or relative to care for my baby (can include baby's father or partner).	0	1	2	3	4	5	6
8. I am getting enough adult interaction.	0	1	2	3	4	5	6
9. I am getting enough encouragement from other people.	0	1	2	3	4	5	6
10. I trust my own feelings (instincts) when it comes to taking care of my baby.	0	1	2	3	4	5	6
11. I take a little time each week to do something for myself.	0	1	2	3	4	5	6
12. I am taking good care of my baby's physical needs (feedings, changing diapers, doctor's appointments).	0	1	2	3	4	5	6
13. I am taking good care of my physical needs (eating, showering, etc).	0	1	2	3	4	5	6
14. I make good decisions about my baby's health and well being.	0	1	2	3	4	5	6
15. My baby and I are getting into a routine.	0	1	2	3	4	5	6
16. I worry about how other people judge me (as a mother).	0	1	2	3	4	5	6
17. I am able to take care of my baby and my other responsibilities.	0	1	2	3	4	5	6
18. Anxiety or worry often interferes with my mothering ability.	0	1	2	3	4	5	6
19. *As time goes on*, I am getting better at taking care of my baby.	0	1	2	3	4	5	6
20. I am *satisfied* with the job I am doing as a new mother.	0	1	2	3	4	5	6

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APPENDIX 10. Selected Inducers, Inhibitors, and Substrates of CYP2C9

Inhibitors of CYP2C9 can be classified by their potency, such as:

- **Strong** being one that causes at least a 5-fold increase in the plasma AUC values, or more than 80% decrease in clearance.
- **Moderate** being one that causes at least a 2-fold increase in the plasma AUC values, or 50-80% decrease in clearance.
- **Weak** being one that causes at least a 1.25-fold but less than 2-fold increase in the plasma AUC values, or 20-50% decrease in clearance.

Substrates	Inhibitors	Inducers

• NSAIDs (analgesic, antipyretic, anti-inflammatory)
  ○ celecoxib
  ○ lornoxicam
  ○ diclofenac
  ○ ibuprofen
  ○ naproxen
  ○ ketoprofen
  ○ piroxicam
  ○ meloxicam
  ○ suprofen
• phenytoin (antiepileptic)
• fluvastatin (statin)
• sulfonylureas (antidiabetic)
  ○ glipizide
  ○ glibenclamide
  ○ glimepiride
  ○ tolbutamide
  ○ glyburide
• angiotensin II receptor antagonists (in hypertension, diabetic nephropathy, CHF)
  ○ irbesartan
  ○ losartan
• S-warfarin (anticoagulant)
• sildenafil (in erectile dysfunction)
• terbinafine (antifungal)
• amitriptyline (tricyclic antidepressant)
• fluoxetine (SSRI antidepressant)
• nateglinide (antidiabetic)
• rosiglitazone (antidiabetic)
• tamoxifen (SERM)
• torasemide (loop diuretic)
• ketamine
• THC
• JWH-018
• AM-2201
	Strong
	• fluconazole (antifungal)
	• miconazole (antifungal)
	• amentoflavone (constituent of Ginkgo biloba and St. John's Wort)
	• sulfaphenazole (antibacterial)
	• valproic acid (anticonvulsant, mood-stabilizing)
	• apigenin
	
	Moderate
	• amiodarone (antiarrhythmic)
	
	Unspecified potency
	• antihistamines (H_1 receptor antagonists)
	  ○ cyclizine
	  ○ promethazine
	• chloramphenicol
	• fenofibrate (fibrate)
	• flavones
	• flavonols
	• fluvastatin (statin)
	• fluvoxamine (SSRI)
	• isoniazid (in tuberculosis)
	• lovastatin (statin)
	• phenylbutazone (NSAID)
	• probenecid (uricosuric)
	• sertraline (SSRI)
	• sulfamethoxazole (antibiotic)
	• teniposide (chemotherapeutic)
	• voriconazole (antifungal)
	• zafirlukast (leukotriene antagonist)
	• quercetin (anti-inflammatory)
		Strong
		• rifampicin (bactericidal)
		• secobarbital (barbiturate)

Summary of Changes
Protocol-547-PPD-202
Dated 22 Dec 2015

The following changes were made to the attached protocol in this amendment. Minor typographical/editorial errors throughout the document were also corrected. The Synopsis, Tables, and Figures were corrected to be consistent with the changes in the main body of the protocol.

Section number and title in Protocol Version 1.0 (18 September 2015)	**Section number and title in Version 2.0 (22 December 2015)**	**Original text:**	**Changed to:**	**Rationale**
Title Page	Title page	[redacted], MD PhD [redacted]	[redacted], MD, MBA [redacted]	*Change in Medical Monitor*
12.2.3 Exploratory Patient Reported Outcome Measures /15 Interactive Voice Response (IVR) HAMD/13 Study Procedures	Global/12.2.3 Exploratory Patient Reported Outcome Measures/13 Study Procedures	The IVR HAMD is a validated patient reported version of the clinician rated HAMD. Similar total and subscale scores as described in Section 12.2.1.1 will be calculated for the IVR HAMD.	Removed all references throughout the document, including references in endpoints, and 12.2.3 Exploratory Patient Reported Outcome Measures	*IVR HAMD will not be implemented in this study.*
Table 1: Schedule of Events	Table 1: Schedule of Events	D7(±1d)	D7/ **ET** (±1d)	*Additional requirement for an Early Termination Visit*
Table 1: Schedule of Events/ 13.3.1 Day 7 (±1day)	Table 1: Schedule of Events/ 13.3.1 Day 7 (±1day)	N/A	A blood sample for PK analysis will be collected at the time of the visit	*Addition of Day 7 plasma sample to evaluate*

Section number and title in Protocol Version 1.0 (18 September 2015)	**Section number and title in Version 2.0 (22 December 2015)**	**Original text:**	**Changed to:**	**Rationale**
				pharmacokinetics of SAGE-547
Table 1: Schedule of Events/ 13.3.1 Day 7 (±1day)	Table 1: Schedule of Events/ 13.3.1 Day 7 (±1day)	N/A	Per subject consent (optional), collection of breast milk on the day of the visit* *Assessment is only applicable to those patients who have temporarily ceased breastfeeding and are participating in the optional breast milk sampling. *Table 1:Schedule of Events updated*	*Addition of optional Day 7 breastmilk sample to evaluate breastmilk*
Table 1: Schedule of Events	Table 1: Schedule of Events/Section 13.3.2 Day 12 (+1day)	N/A	• A blood sample for PK analysis will be collected at the time of the visit • Per subject consent (optional), collection of breast milk on the day of the visit • AEs will be monitored. • Concomitant medications will be recorded. This visit is only applicable to those patients who have temporarily	*Addition of optional Day 12 visit for purposes of collecting PK Samples at the end of the temporary ceasing of breastfeeding timepoint*

Section number and title in Protocol Version 1.0 (18 September 2015)	**Section number and title in Version 2.0 (22 December 2015)**	**Original text:**	**Changed to:**	**Rationale**
			ceased breastfeeding and are participating in the optional breast milk sampling. *Table 1:* *Day 12 (+1d)* *Footnote:* l Day 7 PK plasma and Breast Milk Samples/Day 12 Visit is only applicable to those patients who have temporarily ceased breastfeeding and are participating in the optional breast milk sampling.	
Table 1: Schedule of Events/Global Change	Table 1: Schedule of Events/Global Change	g The "Baseline" C-SSRS form will be completed on Day 1. The "Since Last Visit" C-SSRS form will be completed at all subsequent timepoints.	g The "Baseline/**Screening**" C-SSRS form will be completed on Day 1. The "Since Last Visit" C-SSRS form will be completed at all subsequent timepoints.	*Clarification of the version of the C-SSRS throughout the document*

Section number and title in Protocol Version 1.0 (18 September 2015)	**Section number and title in Version 2.0 (22 December 2015)**	**Original text:**	**Changed to:**	**Rationale**
5.5.3 Dose Rationale	5.5.3 Dose Rationale	Doses will be increased as follows: 30 µg /kg/hour [0-4 hours], then 60 µg/kg/hour [4-24 hours], then 90 µg/kg/hour [24-60 hours].	Doses will be increased as follows: 30 µg /kg/hour [0-4 hours], then 60 µg/kg/hour [4-24 hours], then 90 µg/kg/hour [24-5**2** hours], **followed by a decrease to 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours**).	*The addition of a taper the last 8 hours of the infusion to minimize the possibility of any withdrawal at the end of the infusion.*
7.2 Secondary Objectives	7.2 Secondary Objectives	• To determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms compared to placebo injection as assessed by HAMD response, HAMD remission, change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score, change from baseline in Clinical Global Impression – Severity (CGI-S) score, Clinical Global Impression –	• To determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms compared to placebo injection as assessed by HAMD response, HAMD remission, change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score, Clinical Global Impression – Improvement (CGI-I) response, and changes from baseline in HAMD subscale	*Removal of the change from baseline objective for CGI-S*

Section number and title in Protocol Version 1.0 (18 September 2015)	Section number and title in Version 2.0 (22 December 2015)	Original text:	Changed to:	Rationale
		Improvement (CGI-I) response, and changes from baseline in HAMD subscale and individual item scores.	and individual item scores.	
7.3 Exploratory Objectives	7.3 Exploratory Objectives	• To determine if SAGE-547 Injection infused intravenously for 60 hours reduces subject-reported depressive symptoms compared to placebo injection as assessed by the change from baseline in Edinburgh Postnatal Depression Scale (EPDS) total score, change from baseline in Patient Health Questionnaire (PHQ-9) total score, and change from baseline in Interactive Voice Response (IVR) HAMD total score.	• To determine if SAGE-547 Injection infused intravenously for 60 hours reduces subject-reported depressive symptoms compared to placebo injection as assessed by the change from baseline in Edinburgh Postnatal Depression Scale (EPDS) total score, and the change from baseline in Patient Health Questionnaire (PHQ-9) total score.	*IVR HAMD will not be implemented in this study.*

Section number and title in Protocol Version 1.0 (18 September 2015)	**Section number and title in Version 2.0 (22 December 2015)**	**Original text:**	**Changed to:**	**Rationale**
8.1 Overview of Study Design	8.1 Overview of Study Design	On the morning of dosing (Day 1), subjects will begin a 4-hour dose titration period 30µg/kg/hour [0-4 hours], then 60 µg/kg/hour [4-24 hours], then 90 µg/kg/hour [24-60 hours]); see dose regimen presented in Section 11.1.1.	On the morning of dosing (Day 1), subjects will begin a 4-hour dose titration period 30µg/kg/hour [0-4 hours], then 60 µg/kg/hour [4-24 hours], then 90 µg/kg/hour [24-5**2** hours]); **followed by a decrease to 60 µg/kg/hour (52-56 hours), and 30 µg/kg/hour (56-60 hours).** See dose regimen presented in Section 11.1.1. *Table 2 and Figure 2 also revised to reflect addition of taper.*	*The addition of a taper the last 8 hours of the infusion to minimize the possibility of any withdrawal symptoms at the end of the infusion.*
8.2 Blinding and Randomization	8.2 Blinding and Randomization	Subjects will be randomly assigned to receive SAGE-547 Injection followed by placebo according to a computer-generated randomization schedule.	Subjects will be randomly assigned to receive SAGE-547 Injection **or** placebo according to a computer-generated randomization schedule.	*Correction of inaccurate description of design.*
9.1 Inclusion Criteria	9.1 Inclusion Criteria	5. Subject either must have ceased lactating at Screening; or if still lactating at Screening, must have already fully and permanently weaned their infant(s) from	5. Subject either must have ceased lactating at Screening; or if still lactating or actively breastfeeding at Screening, must agree to **temporarily**	*Allowance to resume breastfeeding after a period of cessation based*

Section number and title in Protocol Version 1.0 (18 September 2015)	Section number and title in Version 2.0 (22 December 2015)	Original text:	Changed to:	Rationale
		breastmilk; or if still actively breastfeeding at Screening, must agree to cease giving breastmilk to their infant(s) prior to receiving study drug. For the avoidance of doubt, subjects who are breastfeeding and do not agree to permanently wean their infant(s) from breastmilk at Screening are not eligible for the study.	**cease giving breastmilk to their infant(s) from just prior to receiving study drug through 9 days (Study Day 12) after the end of the infusion.**	*on PK modeling*
9.1 Inclusion Criteria	9.1 Inclusion Criteria	N/A	12. Subject must use one of the following methods of birth control during participation in the study and for 30 days following the end of the study drug infusion: • Total abstinence (no sexual intercourse) • Hormonal contraceptives (birth control) including birth control pills, implantable or injectable contraceptives (Norplant®	*Contraception requirements were inadvertently omitted out of the original protocol.*

Section number and title in Protocol Version 1.0 (18 September 2015)	**Section number and title in Version 2.0 (22 December 2015)**	**Original text:**	**Changed to:**	**Rationale**
			or Depo-Provera®) • A barrier form of contraception such as a condom or occlusive cap with a spermicide • An intrauterine device (IUD)	
9.2 Exclusion Criteria	9.2 Exclusion Criteria	6. Medical history of bipolar disorder	6. Medical history of bipolar disorder, **schizophrenia, and/or schizoaffective disorder**.	*To further clarify what disorders are excluded from the patient population*
10.3 Preparation of SAGE-547 Injection or Placebo for Dosing	10.3 Preparation of SAGE-547 Injection or Placebo for Dosing	The prepared admixture will be assigned a room temperature (20–25 °C) storage shelf life of 24 hours from time of compounding.	The prepared admixture will be assigned a room temperature (20–25 °C) storage shelf life of 30 hours from time of compounding.	*To update shelf life of admixture to current data.*

Section number and title in Protocol Version 1.0 (18 September 2015)	**Section number and title in Version 2.0 (22 December 2015)**	**Original text:**	**Changed to:**	**Rationale**
11.1.1 Dose Regimen	11.1.1 Dose Regimen	If any subject has an SSS score of ≥5 for two or more consecutive assessments or an SSS score of ≥6 for a single occurrence during normal waking hours, the infusion rate will be decreased to the next lowest infusion dose (or turned off if this occurs on the 30 µg/kg/hour dose level) for the remainder of the study.	If any subject has an SSS score of ≥5 for two or more consecutive assessments or an SSS score of ≥6 for a single occurrence during normal waking hours, the infusion rate **for this subject** will be decreased to the next lowest infusion dose level (or turned off if this occurs on the 30 µg/kg/hour dose level).	*Clarification of infusion rate decreases for subjects taking into consideration of the addition of the taper.*
12.1.2 Clinical Laboratory Tests	12.1.2 Clinical Laboratory Tests	Blood samples will be collected for hematology, serum chemistry, coagulation, and specific hormone parameters, hepatitis, human immunodeficiency virus (HIV), pregnancy and genetic analysis. Urine samples for urinalysis and selected drugs of abuse will also be collected.	Blood samples will be collected for hematology, serum chemistry, coagulation, and specific hormone parameters, hepatitis, human immunodeficiency virus (HIV), pregnancy and genetic analysis. Urine samples for urinalysis and selected drugs of abuse will also be collected. **All samples will be analyzed at the central laboratory. Patients 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**	*To clarify operational activities during the Screening window.*

Section number and title in Protocol Version 1.0 (18 September 2015)	**Section number and title in Version 2.0 (22 December 2015)**	**Original text:**	**Changed to:**	**Rationale**
			Screening labs must adhere to the visit window provided in the Schedule of Events (Table 1).	
3. Hormones	12.1.2.3 Hormones **and Exploratory Biochemistry**	Blood samples will be collected for analysis of thyroid stimulating hormone (TSH), estrogen, progesterone, progesterone metabolites and oxytocin.	Blood samples will be collected for analysis of thyroid stimulating hormone (TSH), estrogen, progesterone, progesterone metabolites, oxytocin, **tryptophan, kynurenine, and markers of inflammation.**	*Addition and clarification of testing for exploratory purposes*
5. Genetic Testing	12.1.2.5 Genetic Testing	This sample will be used to test for the $GABA_A$ receptor δ-subunit. Genetic susceptibility to affective dysregulation may be unmasked during periods of reproductive hormone change such as during pregnancy and postpartum (Maguire 2008). Maguire and Mody demonstrated that a GABA receptor subunit mutation was behaviorally silent until the	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 (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g.	*Clarification and more detail of the genetic testing that will be performed.*

Section number and title in Protocol Version 1.0 (18 September 2015)	Section number and title in Version 2.0 (22 December 2015)	Original text:	Changed to:	Rationale
		animal was exposed to pregnancy and the postpartum state, at which time the dams showed depressive-like behaviors and cannibalized their offspring (Maguire 2008).	Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3a-hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. 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-547 but also susceptibility to disorders for which SAGE-547 may be evaluated. Thus, the genetic research my involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.	

Section number and title in Protocol Version 1.0 (18 September 2015)	**Section number and title in Version 2.0 (22 December 2015)**	**Original text:**	**Changed to:**	**Rationale**
12.1.4 Vital Signs	12.1.4 Vital Signs	Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing) and pulse oximetry A full set of vital signs will be obtained at all specified timepoints (± 30 minutes), unless the subject is asleep between the hours of 23.00h and 06.00h each day. Additional measures of pulse oximetry will be collected during sleeping hours.	Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing).A full set of vital signs will be obtained at all specified timepoints (± 30 minutes), unless the subject is asleep between the hours of 23.00h and 06.00h each day.	*Removal of Pulse Oximetry from Vital sign assessment description*
N/A	12.1.5 Pulse Oximetry	N/A	Pulse oximetry will be monitored continuously from H0 until H60 on Day 1, and checked approximately every 2 hours, including during the overnight hours, or at the alarm. If there is an indication of oxygen desaturation, this should be recorded as an adverse event at the discretion of the Investigator. No pulse oximetry data will be recorded in the eCRF.	*Further clarification and description of the Pulse oximetry monitoring and data collection.*

Section number and title in Protocol Version 1.0 (18 September 2015)	**Section number and title in Version 2.0 (22 December 2015)**	**Original text:**	**Changed to:**	**Rationale**
12.2.1 Primary Efficacy Outcome Measure /8. Hamilton Rating Scale for Depression (HAMD)	12.2.1 Primary Efficacy Outcome Measure /12.2.1.1 Hamilton Rating Scale for Depression (HAMD)	N/A	*Addition of:* Every effort should be made for the same rater to perform all HAMD assessments for a single patient.	*Provide guidance on raters for consistency within a patient*
12.2.2 Secondary Efficacy Outcome Measures/11. Generalized Anxiety Disorder 7-Item Scale (GAD-7)	12.2.2 Secondary Efficacy Outcome Measures/12.2.2.3 Generalized Anxiety Disorder 7-Item Scale (GAD-7)	The GAD-7 is a patient-rated depressive symptom severity scale (Spitzer 2006).	The GAD-7 is a patient-rated **generalized anxiety** symptom severity scale (Spitzer 2006).	*Correction of the description of the scale*
12.3.2 Breastmilk PK Samples	12.3.2 Breastmilk PK Samples	After collection of the last breastmilk sample, women will reduce pumping to comfortably curtail breast milk production.	After Study Day 12, women may resume giving breastmilk to their infant, per Inclusion Criteria 5.	*Description of resuming breastfeeding per new Inclusion Criteria*
14. Barkin Index of Maternal Functioning (BIMF)	12.2.3.3 Barkin Index of Maternal Functioning (BIMF)	Each item is rated on a scale of 0 (strongly disagree) to 6 (strongly agree), and subscales are drawn from these items.	Each item is rated on a scale of 0 (strongly disagree) to 6 (strongly agree).	*Removal of description of subscales. Further details will be in the SAP.*

Section number and title in Protocol Version 1.0 (18 September 2015)	**Section number and title in Version 2.0 (22 December 2015)**	**Original text:**	**Changed to:**	**Rationale**
N/A	13.3.4 Early Termination Visit	N/A	The following assessments should be completed if the patient discontinues from the study prior to the Day 7 Visit: • Completion of physical examination. • Vital signs. • Blood and urine samples collected for clinical laboratory testing. • An ECG reading taken. • Completion of the C-SSRS, HAMD, MADRS, CGI-I, EPDS, GAD-7, PHQ-9 and BIMF. • AEs will be monitored. • Concomitant medications will be recorded. The visit should occur within 3 days of notification of the patient discontinuing.	*Addition of the Early Termination Visit*

Section number and title in Protocol Version 1.0 (18 September 2015)	**Section number and title in Version 2.0 (22 December 2015)**	**Original text:**	**Changed to:**	**Rationale**
14.1 Data Analysis Sets	14.1 Data Analysis Sets		The All Enrolled Population will include all subjects who have given written informed consent. This population will be used for subject disposition and demographic characteristic summaries. The All Randomized Population will include the subset of subjects from the All Enrolled Population who have been randomized. Subjects will be classified according to randomized treatment. This population will be used for subject disposition, demographic characteristic, and baseline characteristic summaries.	*Addition of New Populations to the protocol*
14.1 Data Analysis Sets	14.1 Data Analysis Sets	The intent-to-treat (ITT) subject population in this study is adult female subjects who meet all eligibility criteria and who sign an		*To redefine the populations based on the additions of the all enrolled and all randomized*

Section number and title in Protocol Version 1.0 (18 September 2015)	**Section number and title in Version 2.0 (22 December 2015)**	**Original text:**	**Changed to:**	**Rationale**
		informed consent to participate in this trial regardless whether or not study drug is administered. **Safety Population (SAF):** All ITT subjects who begin receiving a study drug infusion will be included in the safety population. Subjects will be classified according to actual treatment received. This analysis population will be used for all safety analyses.	The **Safety Population** will include all randomized subjects who start the infusion of study drug infusion. Subjects will be classified according to actual treatment received. This analysis population will be used for all safety analyses.	*population.*
14.1 Data Analysis Sets	14.1 Data Analysis Sets	**Efficacy Population (EFF):** All SAF subjects who complete at least 12 hours of infusion and have efficacy evaluations through the 12-hour timepoint on Day 1. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.	The **Efficacy Population (EFF)** will include the subset of the Safety Population who have a valid baseline HAMD assessment and at least one post-baseline HAMD assessment. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.	*To redefine the populations based on the additions of the all enrolled and all randomized population.*

Section number and title in Protocol Version 1.0 (18 September 2015)	**Section number and title in Version 2.0 (22 December 2015)**	**Original text:**	**Changed to:**	**Rationale**
14.1 Data Analysis Sets	14.1 Data Analysis Sets	**Per Protocol Population (PP):** All EFF subjects who complete the full infusion with all efficacy assessments through hour 60, and without significant protocol violations or deviations. Subjects will be classified according to randomized treatment. This analysis population will be used for select sensitivity analyses of the primary and key secondary endpoints.	The **Per Protocol Population (PP)** will include the subset of the Efficacy Population who complete the full infusion without significant protocol violations or deviations. Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary and select secondary endpoints.	*To redefine the populations based on the additions of the all enrolled and all randomized population.*
14.1 Data Analysis Sets	14.1 Data Analysis Sets	**PK Population (PKP):** All SAF subjects treated with SAGE-547 for whom at least one evaluable PK sample is available.	The **PK Population (PKP)** will include the subset of the Safety Population who have at least one evaluable PK sample. Subjects will be classified according to actual treatment received. This analysis population will be used for all PK analyses.	*To redefine the populations based on the additions of the all enrolled and all randomized population.*

Section number and title in Protocol Version 1.0 (18 September 2015)	Section number and title in Version 2.0 (22 December 2015)	Original text:	Changed to:	Rationale
		Breast Milk Population (BMP): All SAF subjects who begin receiving a study drug infusion and have at least one breast milk sample taken.	The **Breast Milk Population (BMP)** will include the subset of the Safety Population who have at least one evaluable breast milk sample. Subjects will be classified according to actual treatment received. This analysis population will be used for all breast milk PK analyses.	*To redefine the populations based on the additions of the all enrolled and all randomized population.*
14.5 Secondary Endpoints	14.5 Secondary Endpoints	Adverse events: The analysis of AEs will be based on the concept of treatment-emergent AEs (TEAEs). A TEAE is defined as an AE with onset after the start of SAGE-547 infusion, or any worsening of a pre-existing medical condition/AE with onset after the start of SAGE-547 infusion and until 7 days after the end of infusion (i.e., Day 10). A treatment-emergent serious AE (TESAE) is defined as an AE with onset after the start of SAGE-547 infusion, or any worsening of a	Adverse events: The analysis of AEs will be based on the concept of treatment-emergent AEs (TEAEs). A TEAE is defined as an AE with onset after the start of SAGE-547 infusion, or any worsening of a pre-existing medical condition/AE with onset after the start of SAGE-547 infusion and until 7 days after the end of infusion The incidence of TEAEs will be summarized overall and by MedDRA® System Organ Class (SOC) and preferred term (PT). Incidences will be presented in order of decreasing frequency. In	*Revision of the analysis and presentation of AEs and SAEs.*

Section number and title in Protocol Version 1.0 (18 September 2015)	Section number and title in Version 2.0 (22 December 2015)	Original text:	Changed to:	Rationale
		pre-existing medical condition/AE with onset after the start of SAGE-547 infusion and until 30 days after the end of infusion (i.e., Day 33). All TEAEs will be summarized and grouped by MedDRA® System Organ Class (SOC) and specific AE preferred term (PT). Results will be displayed in order of decreasing frequency by SOC and PT. For presentation, AE verbatim text will be coded into a MedDRA term and classified by SOC and PT using MedDRA® version 17.0 or higher. In addition, summaries will be provided by severity (mild, moderate, severe) and by causality (related, not related) to study drug (see Section 15.2.2). TEAEs and TESAEs leading to discontinuation will be summarized and listed.	addition, summaries will be provided by severity (mild, moderate, severe) and by causality (related, not related) to study drug (see Section 15.2.2). TEAEs leading to discontinuation and serious adverse events (SAEs; see 15.1.4 for definition) with onset after the start of randomized infusion will also be summarized All AEs and SAEs (including those with onset or worsening before the start of randomized infusion) through the Day 30 follow-up visit will be listed.	

Section number and title in Protocol Version 1.0 (18 September 2015)	**Section number and title in Version 2.0 (22 December 2015)**	**Original text:**	**Changed to:**	**Rationale**
14.7 Interim Analysis	14.7 Interim Analysis	An interim analysis will be conducted by an independent DSMB for sample size re-estimation purposes when at least 16 subjects have completed efficacy assessments through 60 hours. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in an interim analysis plan.	An interim analysis will be conducted by an **independent statistician** for sample size re-estimation purposes when at least 16 subjects have completed efficacy assessments through 60 hours. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis will be included in the **SAP**.	*Clarify the conduct of the interim analysis. The original protocol referred to a DSMB in error.*
15.2.2 Adverse Event Classification/16 Relationship to Investigational Drug	15.2.2 Adverse Event Classification/ 15.2.2.1 Relationship to Investigational Drug	Not Related: The temporal relationship of the clinical event to study drug administration makes causal	Related: No relationship between the experience and the administration of study drug; related to other etiologies such	*Revision of definition of relationship of the AE to drug, to be consistent with other studies evaluating Sage-547; previously*

Section number and title in Protocol Version 1.0 (18 September 2015)	Section number and title in Version 2.0 (22 December 2015)	Original text:		Changed to:		Rationale
			relationship unlikely AND other drugs, therapeutic interventions, or underlying conditions provide a plausible explanation for the observed event.		as concomitant medications or subject's clinical state.	*described in an Administrative Letter*
		Related:	Reasonable temporal relationship of the clinical event to study drug administration AND cannot be reasonably explained by other factors	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	

Section number and title in Protocol Version 1.0 (18 September 2015)	Section number and title in Version 2.0 (22 December 2015)	Original text:	Changed to:	Rationale
		(such as the subject's clinical state, concomitant therapy, and/or other interventions). Possibly Related: The temporal relationship of the clinical event to study drug administration makes causal relationship possible but not unlikely AND other drugs, therapeutic interventions, or underlying conditions do not provide a	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	

Section number and title in Protocol Version 1.0 (18 September 2015)	Section number and title in Version 2.0 (22 December 2015)	Original text:	Changed to:	Rationale
		sufficient explanation for the observed event.	characteristics of the subject's clinical state or other modes of therapy administered to the subject	

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF SAGE-547 INJECTION IN THE TREATMENT OF ADULT FEMALE SUBJECTS WITH SEVERE POSTPARTUM DEPRESSION

PROTOCOL NUMBER: 547-PPD-202

IND NUMBER: 122279

Investigational Product:	SAGE-547 Injection (allopregnanolone)
Clinical Phase:	2a
Sponsor:	Sage Therapeutics
Sponsor Contact:	[redacted], MD, PhD [redacted] Sage Therapeutics 215 First Street Cambridge, MA 02142 Phone: [redacted]
Medical Monitor:	[redacted], MD [redacted] Office (9-5 EST): [redacted] 24/7 Hotline: [redacted]
Date of Original Protocol:	18 September 2015

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 the Sponsor.

1 SIGNATURE PAGE

Title of protocol: A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects With Severe Postpartum Depression

Protocol No: 547-PPD-202

Sponsor Approval

[redacted]

[redacted], MD, PhD

Sage Therapeutics

24-SEP-2015

Date (dd/mmm/yyyy)

Investigator Agreement

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-PPD-202 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: _____

Investigator's Name: _____

Institution: _____

Date (dd/mmm/yyyy): _____

2 SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor:
Sage Therapeutics
215 First Street
Cambridge, MA 02142</td></tr>
<tr><td>Protocol No. 547-PPD-202</td><td>Phase: 2a</td></tr>
<tr><td colspan="2">Name of Investigational Product:
SAGE-547 Injection</td></tr>
<tr><td colspan="2">Name of Active Ingredient:
Allopregnanolone</td></tr>
<tr><td colspan="2">Title of the Protocol:
A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects With Severe Postpartum Depression</td></tr>
<tr><td colspan="2">Study Sites: Approximately 15 sites in the United States</td></tr>
<tr><td colspan="2">Duration of Subject Participation: Up to 35 days</td></tr>
<tr><td colspan="2">Primary Objective:
• To determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms in subjects with postpartum depression (PPD) compared to placebo injection as assessed by the change from baseline in Hamilton Rating Scale for Depression (HAMD) total score

Secondary Objectives:
• To determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms compared to placebo injection as assessed by HAMD response, HAMD remission, change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score, change from baseline in Clinical Global Impression – Severity (CGI-S) score, Clinical Global Impression – Improvement (CGI-I) response, and changes from baseline in HAMD subscale and individual item scores.
• To determine if SAGE-547 Injection infused intravenously for 60 hours reduces other mood symptoms compared to placebo injection as assessed by changes from baseline in the Generalized Anxiety Disorder 7-Item Scale (GAD-7) total score.
• To determine if SAGE-547 Injection infused intravenously for 60 hours increases sedation levels compared to placebo injection as assessed by the changes from baseline in Stanford Sleepiness Scale (SSS) score.</td></tr>
</table>

Name of Sponsor: Sage Therapeutics 215 First Street Cambridge, MA 02142	
Protocol No. 547-PPD-202	**Phase:** 2a

- To evaluate the safety and tolerability of SAGE-547 Injection compared with placebo as assessed by the incidence of adverse events, vital sign measurement, clinical laboratory evaluations, electrocardiogram (ECG) parameters, and the Columbia Suicide Severity Rating Scale (C-SSRS).

Exploratory Objective:

- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces subject-reported depressive symptoms compared to placebo injection as assessed by the change from baseline in Edinburgh Postnatal Depression Scale (EPDS) total score, change from baseline in Patient Health Questionnaire (PHQ-9) total score, and change from baseline in Interactive Voice Response (IVR) HAMD total score.
- To determine if SAGE-547 Injection infused intravenously for 60 hours improves maternal behaviors compared to placebo injection as assessed by the change from baseline in Barkin Index of Maternal Functioning (BIMF) total and sub-scale scores.

Pharmacokinetic Objective:

- To assess the pharmacokinetic (PK) profile of SAGE-547, metabolites of SAGE-547, and betadex sulfobutyl ether sodium (SBECD) and the concentration of SAGE-547 in breast milk, when possible.

Study Design and Methodology:

This is a multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the efficacy, safety, and pharmacokinetics of SAGE-547 Injection in adult female subjects diagnosed with severe PPD. Subjects must remain as in-patients during the study Treatment Period, which is approximately 60 hours/2.5 days in duration. The Screening Period assessments may be conducted on an in-patient or an out-patient basis. The Follow-up Period assessments are conducted on an out-patient basis.

Screening Period: The Screening Period begins with the signature of the informed consent form (ICF). Eligibility is determined by applying the inclusion/exclusion criteria. The diagnosis of PPD must be by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). A full medical and family history will be taken including recording of all depression, other Axis 1 and Axis 2 disorders and postpartum depression episodes in primary probands (who may be subject to a SCID-I interview).

Treatment Period: Once subjects are confirmed as eligible for the study, they will be randomized to one of two treatment groups (SAGE-547 or placebo) on a 1:1 basis. Continuous intravenous infusions of blinded study drug will be administered, with a new bag and line hung every 24 hours during the 60-hour infusion. Infusion rates will increase, with subjects receiving 30 µg/kg/hour (0-4 hours), then 60 µg/kg/hour (4-24 hours), then 90 µg/kg/hour (24-60 hours). Subjects may be discharged after the 72-hour assessments have been completed (12 hours after completion of the study drug infusion). If

Name of Sponsor:	
Sage Therapeutics 215 First Street Cambridge, MA 02142	
Protocol No. 547-PPD-202	**Phase:** 2a

their clinical condition does not allow discharge, normal standard of care will be employed in their ongoing management.

Initiation of benzodiazepines, narcotics, antibiotics, neuroleptics, and other anti-anxiety medications will not be allowed between Screening and completion of the 72-hour assessments. Doses of psychotropics, which must have been initiated at least 14 days prior to screening, must remain at a stable dose until completion of the 72-hour assessments. If at the 72-hour assessment there has been no treatment response (HAMD total score remains above 13), treatment with antidepressant medication may be optimized prior to discharge, and the subject may remain in the unit or be followed at an out-patient clinic, as clinically indicated.

Efficacy and safety assessments will be performed periodically during the study, and blood samples will be collected for analysis of SAGE-547, metabolites of SAGE-547, and SBECD concentrations, as outlined in the Schedule of Events (Table 1). Blood samples will be collected, and outcome measures will be obtained at pre-specified times over 60 hours during the Treatment Period.

Follow-up Period: Follow-up visits will be conducted one week (7±1 day) and one month (30±3d) after the initiation of the study drug infusion.

Number of Subjects:

Up to 32 subjects will be randomized

Inclusion Criteria:

The following inclusion criteria must be met for individuals to be eligible for the trial:

1. Subject has signed an ICF prior to any study-specific procedures being performed
2. Subject is an ambulatory female aged 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 at Screening, must have already fully and permanently weaned their infant(s) from breastmilk; or if still actively breastfeeding at Screening, must agree to cease giving breastmilk to their infant(s) prior to receiving study drug. For the avoidance of doubt, subjects who are breastfeeding and do not agree to permanently wean their infant(s) from breastmilk at Screening are not eligible for the study.
6. Subject must have a negative pregnancy test at Screening and Day 1 prior to the start of study drug infusion

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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, as diagnosed by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)
8. Subject has a HAMD total score of ≥26 at Screening and Day 1 (prior to randomization)
9. Subject is ≤ six months postpartum
10. Subject is willing to delay start of other antidepressant or anxiety medications and any new pharmacotherapy regimens, including prn benzodiazepine anxiolytics, until the study drug infusion and 72-hour assessments have been completed
11. Subject has no detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), and human immunodeficiency virus (HIV) antibody at Screening

Exclusion Criteria:

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

1. Recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, or nose and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study
2. Known allergy to progesterone or allopregnanolone
3. Active psychosis per Investigator assessment
4. Attempted suicide associated with index case of postpartum depression
5. Medical history of seizures
6. Medical history of bipolar disorder
7. History of active alcoholism or drug addiction (including benzodiazepines) in the 12 months prior to Screening
8. Exposure to another investigational medication or device within 30 days prior to Screening
9. Administration of psychotropics that have been initiated within 14 days prior to Screening and are not being taken at a stable dose.

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Investigational Product, Dosage, and Mode of Administration:

SAGE-547 Injection, intravenous (IV) administration: SAGE-547 Injection is a sterile, clear, colorless 5 mg/mL solution of SAGE-547 (allopregnanolone) and 250 mg/mL SBECD buffered with 10 mM citrate at a pH of 6.0, supplied in single-use 20 mL vials for IV administration. As supplied, SAGE-547 Injection, which is hypertonic, requires further dilution with Sterile Water for Injection (SWFI) to render it isotonic for IV infusion. The specific infusion dose of SAGE-547 Injection will be calculated based on weight for each subject at Screening and administered according to the randomization schedule. Infusion bags will be changed every 24 hours. Details about the preparation and administration of the study drug infusions will be included in the Pharmacy Manual.

Timepoint	**Day 1** **0-4 hours**	**Day 1** **4-24 hours**	**Day 2/3** **24-60 hours**
Infusion Rate	30 µg/kg/hour	60 µg /kg/hour	90 µg /kg/hour

Reference Therapy, Dosage, and Mode of Administration:

An identical placebo IV infusion will be prepared for IV administration consisting of the same formulation without allopregnanolone.

Randomization and Stopping Rules:

Subjects will be randomized to receive SAGE-547 Injection or placebo; subjects, clinicians, and study team will be blinded to treatment allocation. Only the pharmacist, who will prepare the infusion bags according to the randomization schedule, will be unblinded. The infusion rates are the same for all subjects within a particular dosing period (0-4 hours, 4-24 hours, etc.).

If any subject has an SSS score of ≥5 for two or more consecutive assessments or an SSS score of ≥6 for a single occurrence during normal waking hours, the infusion rate will be decreased to the next lowest infusion dose (or turned off if this occurs on the 30 µg/kg/hour dose level) for the remainder of the study.

Criteria for Evaluation:

Primary Endpoint

The primary outcome measure will be the 17-item Hamilton Rating Scale for Depression (HAMD). The HAMD will be administered before, during, and after the infusion of blinded study drug. The HAMD total score will be calculated as the sum of the 17 individual item scores. The change from baseline in HAMD total score at the end of the treatment period (at +60 hours) will be the primary efficacy endpoint with comparison between the two treatment groups used to evaluate the efficacy of SAGE-547 in treating the depressive symptoms of PPD.

Secondary Endpoints

Additional measures of depressive symptom severity will be administered before, during, and after the infusion of study drug, including the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinical Global Impression (CGI) scale. Total scores and changes from baseline will be calculated where applicable. Changes from baseline at the end of the treatment period (at +60 hours) and other time points will be evaluated as secondary efficacy endpoints with comparisons between the two treatment groups used to support the efficacy of SAGE-547 in treating the depressive symptoms of PPD. In addition to the above scales, the individual item scores and subscale scores from the HAMD scale will also evaluated as secondary efficacy endpoints.

GAD-7 will also be administered before, during, and after the infusion of study drug. As with other secondary efficacy endpoints, scores from these scales will be evaluated to assess the efficacy in other mood disorder and anxiety symptoms.

An important safety endpoint will be the assessment of sedation using the SSS. The SSS will be assessed periodically before, during, and after the infusion of blinded study drug with changes from baseline over time evaluated similarly to that of efficacy endpoints.

Safety and tolerability of SAGE-547 Injection will be evaluated by summarization of adverse events (AEs) by frequency, severity, and seriousness; clinical laboratory measures, vital signs, and ECGs (including changes from baseline); and concomitant medication usage. Suicidality will be monitored using the C-SSRS.

The doses of all anti-depressant medications will be recorded throughout the study. No changes and/or additions to antidepressant or anxiolytic medicine will be allowing during the dosing period. An analysis of time to starting/increasing the dose/decreasing the dose of each different anti-depressant medication will be undertaken for subjects discharged.

Plasma will be collected to assay for concentrations of SAGE-547, SAGE-547 metabolites, and SBECD. The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve (AUC) from time zero to 60 hours (AUC_{0-60}), AUC from time zero to infinity (AUC_{inf}), maximum (peak) plasma concentration (C_{max}), time at maximum (peak) plasma concentration (T_{max}), steady-state drug concentration in the plasma during constant-rate infusion (C_{ss}), and average drug concentration in the plasma at steady state during a dosing interval (C_{avg}).

Breast milk may be collected as an optional assessment if consent is received from the subject. Samples

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will be analyzed for SAGE-547 concentrations.

Exploratory Endpoints

Additional measures of symptoms and function related to the current episode of postpartum depression severity will be administered before, during, and after the infusion of study drug, including the EPDS, PHQ-9 and BIMF.

Subscale and total scores and changes from baseline will be calculated where applicable. Changes from baseline at the end of the treatment period (at +60 hours) and other time points will be evaluated as secondary efficacy endpoints with comparisons between the two treatment groups used to support the efficacy of SAGE-547 in treating the depressive symptoms of PPD. In addition to the above scales, the individual item scores will also be evaluated as exploratory endpoints.

Statistical Methods:

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

Interim Analysis

An interim analysis will be conducted by an independent DSMB for sample size re-estimation purposes when at least 16 subjects have completed efficacy assessments through 60 hours. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis will be included in an interim analysis plan.

Sample Size Calculation

Assuming a two-sided test at an alpha level of 0.10, a sample size of 10 evaluable subjects per group would provide 80% power to detect an effect size of 1.2 between the SAGE-547 and placebo groups with regard to the primary outcome variable of change from baseline in HAMD total score. An effect size of 1.2 corresponds to a placebo adjusted difference of 12 points in the change from baseline in HAMD total score at 60 hours with an assumed standard deviation of 10 points. By including two treatment groups and using a 1:1 randomization ratio, a total of 20 evaluable subjects are required. Assuming a non-evaluability rate of 10%, at least 22 subjects will be randomized.

Based on the results of the interim analysis, the sample size could be increased to a maximum of 32 randomized subjects. This adjustment to the sample size would allow for an effect size of 1.0 to be detected.

Efficacy Analysis

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The efficacy population will include all subjects who complete at least 12 hours of infusion and have efficacy evaluations through the 12-hour time point on Day 1. Subjects will be classified and summarized by randomized treatment.

The change from baseline in HAMD total score will be analyzed using a mixed effects repeated measures model including center, treatment, baseline score, timepoint, and timepoint-by-treatment as explanatory variables. Center will be treated as a random effect while all other explanatory variables will be treated as fixed effects. The primary comparison between SAGE-547 and placebo will be at the 60 hour timepoint. Comparisons at other timepoints will be conducted to support the findings for the primary comparison.

Changes from baseline in other rating scale scores will be analyzed with methods similar to the primary endpoint. Any dichotomous response variables will be analyzed using logistic regression methods.

In addition to formal analysis, efficacy rating scale scores (including recorded and change from baseline values) will be summarized by descriptive statistics, including n, mean, standard deviation (SD), median, and minimum and maximum values. Categorical efficacy endpoints (including HAMD, MADRS, and CGI-I response variables) will be summarized by frequency and percentage.

Safety Analysis

The Safety Population (SAF) is defined as all subjects who begin an infusion of study drug. Subjects will be classified and summarized by actual treatment.

Safety will be assessed using SSS, AEs, vital signs, ECG, clinical laboratory tests, C-SSRS, and concomitant medication data. Continuous safety data (including absolute and change from baseline values) will be summarized by descriptive statistics, including n, mean, standard deviation (SD), median, and minimum and maximum values. Categorical endpoints will be summarized by frequency and percentage. In addition, an analysis of the SSS score will be performed comparing the treatment groups in the same way as for the primary endpoint.

Safety data will be examined for possible relationships between subject characteristics and plasma allopregnanolone concentrations, as appropriate.

TABLE 1: SCHEDULE OF EVENTS

	Screening Period	Treatment Period Clinic Period (Day 1 to Day 3)															Follow-up Period	
Visit Days	**Screening D-5 to -1**	**D1 H0***	**D1 H2**	**D1 H4**	**D1 H8**	**D1 H12**	**D1 H18**	**D1 H24**	**D2 H30**	**D2 H36**	**D2 H42**	**D2 H48**	**D3 H54**	**D3 H60**	**D3 H66**	**D3 H72**	**D7** (±1d)	**D30** (±3d)
Study Procedure																		
Informed Consent	X																	
Inclusion/Exclusion Criteria	X	X																
Demographics	X																	
Medical/Family History	X																	
Physical Examination	X															X	X	
Body Weight/Height	X																	
Clinical Lab Assessments [a]	X															X	X	
Urinalysis [a]	X																X	
Drug & Alcohol Screen [b]	X	X																
Pregnancy Test [c]	X	X																X
Hepatitis & HIV Screen	X																	
Genetic Sample [d]	O																	
Vital Signs [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse Oximetry								X										
12-Lead ECG [f]	X											X					X	
C-SSRS [g]		X						X						X		X	X	X
Confinement									X									
CGI-I [h]			X	X		X		X		X		X		X		X	X	X
CGI-S [h]	X	X																
HAMD [h]	X	X	X	X	X	X		X		X		X		X		X	X	X
IVR HAMD [h]	X	X						X				X		X		X	X	X
MADRS [h]	X	X						X				X		X		X	X	X
BIMF [h]		X															X	X
EPDS [h]		X												X			X	X
GAD-7 [h]		X												X			X	X
PHQ-9 [h]		X												X			X	X

	Screening Period	Treatment Period Clinic Period (Day 1 to Day 3)															Follow-up Period	
Visit Days	**Screening D-5 to -1**	**D1 H0***	**D1 H2**	**D1 H4**	**D1 H8**	**D1 H12**	**D1 H18**	**D1 H24**	**D2 H30**	**D2 H36**	**D2 H42**	**D2 H48**	**D3 H54**	**D3 H60**	**D3 H66**	**D3 H72**	**D7** (±1d)	**D30** (±3d)
Study Procedure																		
SSS [i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Plasma PK [j]		X		X	X	X		X	X	X		X		X		X		
Breast Milk PK [k]		X	X				X		X		X		X		X			
Study Drug Infusion		X																
Adverse Events	X																	
Concomitant Medications	X																	

O = optional * = All H0 procedures to be completed prior to dosing

a Safety laboratory tests will include hematology, serum chemistry, coagulation, and select hormone parameters. The urine test will include a urinalysis. Lab assessments are to be completed within ± 30 minutes of the scheduled timepoint.

b Urine for selected drugs of abuse and alcohol (serum or breath)

c Serum at Screening and urine for all other timepoints

d A blood sample for genetic testing, where consent is given

e Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing). Vital signs will be obtained within ± 30 minutes of the scheduled timepoint, unless the subject is asleep between the hours of 23.00h and 06.00h.

f Performed within ± 30 minutes of the scheduled time point on Day 2.

g The "Baseline" C-SSRS form will be completed on Day 1. The "Since Last Visit" C-SSRS form will be completed at all subsequent timepoints.

h To be completed within ± 30 minutes of the scheduled timepoint.

i To be completed within ± 15 minutes of the scheduled timepoint, unless the subject is asleep between the hours of 23.00h and 06.00h

j Blood samples for PK analysis will be collected at pre-infusion and at 4 (before change in infusion rate), 8, 12, 24 (before change in infusion rate), 30, 36, 48 60 (before end of infusion) and 72 hours after the start of the infusion. PK blood draws after the start of infusion will have a window of ± 10 minutes. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.

k Optional assessment per subject consent, breast milk will be collected and pooled over the following time periods of interest: 0, 1-12, 12-24, 24-36, 36-48, 48-60 and 60-72 hours after the start of the infusion.

BIMF = Barkin Index of Maternal Functioning; CGI-I = Clinical Global Impression of Improvement; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EPDS = Edinburgh Postnatal Depression Scale; GAD-7 = Generalized Anxiety Disorder 7-Item Scale; HAMD = Hamilton Rating Scale for Depression, 17-item; MADRS = Montgomery-Asberg Depression Rating Scale; PHQ-9 = Patient Health Questionnaire; PK = pharmacokinetic; SSS = Stanford Sleepiness Scale.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Definition of Terms
AE	adverse event
ALLO	allopregnanolone
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from time zero to infinity
AUC_{0-60}	area under the concentration-time curve from time zero to 60 hours
BIMF	Barkin Index of Maternal Functioning
BMI	body mass index
BMP	breast milk population
BUN	blood urea nitrogen
C_{avg}	average drug concentration in the plasma at steady-state during a dosing interval
CBC	complete blood count
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression–Improvement
CGI-S	Clinical Global Impression–Severity
cGMP	Current Good Manufacturing Practice
C_{max}	maximum (peak) plasma concentration of the drug
CMO	Chief Medical Officer
CNS	central nervous system
CRF	case report form
CS	clinically significant
CSF	cerebrospinal fluid
CSR	clinical study report
C_{ss}	Steady-state drug concentration in the plasma during constant-rate infusion
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	Cytochrome P450 enzyme involved in drug metabolism
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EEG	electroencephalography
EFF	efficacy population
Ph. Eur.	European Pharmacopeia
EPDS	Edinburgh Postnatal Depression Scale
ERα	estrogen receptor alfa
ERß	estrogen receptor beta

Abbreviation or Specialist Term	Definition of Terms
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
$GABA_A$	gamma-aminobutyric acid–gated chloride channel
GAD-7	Generalized Anxiety Disorder 7-Item Scale
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
h	hour
HAMD	Hamilton Rating Scale for Depression, 17-item
HBsAg	hepatitis B surface antigen
Hct	hematocrit
HCV	hepatitis C virus
HEENT	head, eyes, ears, nose, and throat
Hgb	hemoglobin
HPLC MS/MS	High-performance liquid chromatography tandem mass spectrometry
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	intention-to-treat population
IV	intravenous
IVR	interactive voice response
LFT	liver function test
MADRS	Montgomery-Asberg Depression Rating Scale
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
NCS	not clinically significant
NF	National Formulary
NIMH	National Institute of Mental Health
PHQ-9	Patient Health Questionnaire
PK	pharmacokinetic
PKP	pharmacokinetic population
PMID	PubMed identification
PP	per-protocol population
PPD	postpartum depression
PR	progesterone receptor
PT/INR	prothrombin time/international normalized ratio
RBC	red blood cell
RSE	refractory status epilepticus
SAE	serious adverse event

Abbreviation or Specialist Term	Definition of Terms
SAF	safety population
SAP	statistical analysis plan
SBECD	betadex sulfobutyl ether sodium
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SRSE	super refractory status epilepticus
SSRI	selective serotonin reuptake inhibitors
SSS	Stanford Sleepiness Scale
SWFI	sterile water for injection
$T_{1/2}$	half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum (peak) plasma concentration
TSH	thyroid stimulating hormone
US	United States
USP	United States Pharmacopeia
VAS	Visual analogue scale
V_d	volume of distribution
WBC	white blood cell

5 INTRODUCTION AND RATIONALE

This study is designed to evaluate the efficacy, safety, and pharmacokinetics (PK) of SAGE-547 (allopregnanolone) as a treatment for women with severe postpartum depression (PPD), an area of high unmet medical need.

PPD is considered to be moderate to severe depression in women who have recently given birth, otherwise defined as the occurrence of major depressive disorder (MDD) within 4 weeks of delivery (DSM V 2013) or up to a year after giving birth (Okun 2013). There are two entry criteria for the diagnosis of depression (depressed mood and/or loss of interest) and seven 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 five symptoms of depression (DSM V 2013), although this diagnosis may be confounded by the relative frequency of symptoms such as sleep disturbance or appetite problems in pregnant and postpartum women. Most women experience onset of symptoms within the first three months following delivery, and PPD is most prevalent at 10 to 14 weeks following childbirth (Okun 2013).

During pregnancy, estradiol and progesterone levels increase dramatically but then rapidly decline in the acute postpartum period (Gavin 2005). The onset of PPD symptoms coincides with the rapid decrease of the gonadal steroids postpartum. The duration of a PPD episode has been estimated as shorter than depressive episodes in the general population (approx. 5 months), while other studies indicate time to remission is approximately the same (Chaudron 2003).

PPD is common and has devastating consequences for the woman and for her family (Fihrer 2009; Verbeek 2012). Perinatal depression is reported to be the most underdiagnosed obstetric complication in America (Earls 2010). Furthermore, it is the most common psychiatric illness to occur in the puerperium (O'Hara 2014). A meta-analysis of 30 studies (Gaynes 2005) found that the point prevalence of major and minor depression ranged between 6.5% and 12.9% at different times during the first postpartum year. Overall incidence is estimated at around 15–20% with up to 10% being considered severe (Edge 2007, O'Hara 2014).

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 non-pharmacological 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.

5.1 Role of Allopregnanolone in Affective Disturbances

The neurosteroid metabolite of progesterone, allopregnanolone, acutely regulates neuronal function (Gangisetty 2010) and appears to play a significant role in affective disturbances that occur with changes in reproductive endocrine function, such as during the postpartum period (Amin 2006, Nappi 2001, Epperson 2006).

Neurosteroids are metabolites of cholesterol-derived steroid hormones that are synthesized in the brain and nervous system; they modulate the major inhibitory and excitatory central nervous system (CNS) neurotransmitter systems: γ-aminobutyric acid (GABA) and glutamate, respectively. Neurosteroids are among the most potent and effective modulators of $GABA_A$ receptors and augment GABAergic inhibition (Belelli 2005). The powerful anxiolysis that accompanies this potentiation of $GABA_A$ receptors has led to the speculation that neurosteroid dysregulation plays a central role in the etiology of affective disorders, including reproductive mood disorders, such as PPD (Amin 2006).

There is increasing evidence supporting the role of neurosteroids in affective dysregulation. Allopregnanolone and pregnanolone have been shown to modulate the GABA receptor positively (Majewska 1986). Several groups have demonstrated decreased allopregnanolone levels in MDD, with an increase seen in both plasma and cerebrospinal fluid (CSF) following successful antidepressant treatment (Uzunova 1998; Romeo 1998; Ströhle 1999; Schüle 2006; Eser 2006; Schüle 2007). In addition, allopregnanolone has demonstrated anxiolytic effects in several animal anxiety models (Bitran 1991; Wieland 1991; Bitran 1993).

Allopregnanolone may also exert antidepressant effects by reducing the physiological impact of stress, promoting neuroprotection, and protecting against the pro-inflammatory immune activation and cytokine hypersecretion associated with MDD. In animals, allopregnanolone increases in response to stress, reduces pain sensitivity, and is thought to restore physiologic homeostasis following stress (Frye 1994; Morrow 1995). Allopregnanolone also exerts neuroprotective effects by reducing the expression of pro-apoptotic proteins and apoptotic DNA fragmentation (Djebaili 2005; Sayeed 2009), thereby reducing the cell death and gliosis associated with depression (Glantz 2010; Shelton 2011). Neuroprotection is mediated by immune regulation in depression (Licinio 1999), and allopregnanolone reduces the expression of the pro-inflammatory cytokine TNF-α (He 2004), which is elevated in depressed individuals (Dowlati 2010). Thus, allopregnanolone modulates biological processes dysregulated in major depressive disorder.

5.1.1 Rationale for Allopregnanolone Treatment of PPD

Genetic susceptibility to affective dysregulation may be unmasked during periods of reproductive hormone change such as during pregnancy and postpartum (Maguire 2008). Maguire and Mody demonstrated that a GABA receptor subunit mutation was behaviorally silent until the animal was exposed to pregnancy and the postpartum state, at which time the dams showed depressive-like behaviors and cannibalized their offspring (Maguire 2008). During pregnancy, the expression of the $GABA_A$ receptor δ-subunit is down-regulated as allopregnanolone levels increase, and at parturition, the expression of the $GABA_A$ receptor δ-subunit is recovered in response to rapidly declining neurosteroid levels (Maguire 2009). In contrast, the $GABA_A$ receptor δ-subunit-deficient mice fail to adapt to the dramatic changes in allopregnanolone and experience depression-like and anxiety-like behavior and abnormal

maternal behaviors, which are reversed by administration of allopregnanolone (Maguire 2008). This model provides compelling support for the hypothesis that changes in neurosteroid concentrations during pregnancy and postpartum are capable of provoking affective dysregulation, particularly in those with a genetically-determined susceptibility. The capacity of changes in neurosteroids, such as allopregnanolone, to function as behavioral switches suggests a potentially important treatment role of this hormone metabolite in reproductive endocrine-related mood disorders such as PPD.

The onset of PPD symptoms coincides with the rapid decrease of the gonadal steroids postpartum and has been reproduced in a pivotal clinical study (Bloch 2000). The authors investigated the possible role of changes in gonadal steroid levels in PPD by simulating two hormonal conditions related to pregnancy and parturition in euthymic women, 8 with and 8 without a history of PPD. They induced hypogonadism with leuprolide, adding back supra-physiologic doses of estradiol and progesterone for 8 weeks to simulate pregnancy. They then withdrew both steroids under double-blind conditions to mimic the rapid decrease of sex steroids upon delivery. Five of the eight women with a history of postpartum depression (62.5%) and 0% of the comparison group developed significant mood symptoms typical of PPD during the withdrawal period.

Although progesterone levels were measured in this study, allopregnanolone was not. However, since allopregnanolone is the major active metabolite of progesterone, it can be assumed that the decrease in progesterone would cause a similar precipitate drop in allopregnanolone levels, as observed in the postpartum period (Gilbert Evans 2005, Paoletti 2006, Nappi 2001).These data provide direct evidence in support of the involvement of progesterone and its metabolites in the development of postpartum depression in a subgroup of women. Further, they suggest that women with a history of postpartum depression are differentially sensitive to mood-destabilizing effects of gonadal steroids (Bloch 2000).

Additional details regarding the role of allopregnanolone in the etiology of affective disorders and its nonclinical pharmacology and pharmacokinetics are presented in the Investigational Brochure.

5.2 SAGE-547 Injection (Allopregnanolone)

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex, and CNS (Holzbauer 1985; Ottander 2005; Paul 1992). It is a metabolite of progesterone created by the actions of 5-α reductase and 3-α hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic $GABA_A$ receptors.

SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), United States Pharmacopeia (USP), and 250 mg/mL betadex sulfobutyl ether sodium buffered with 10 mM citrate at a pH of 6.0, and will be administered intravenously. SAGE-547 Injection is also being developed for the treatment of adult patients with refractory status epilepticus (RSE), inclusive of super refractory status epilepticus (SRSE), who have not responded to standard treatment regimens, and investigated for the treatment of adults with essential tremor.

5.3 Summary of Nonclinical and Clinical Experience With Allopregnanolone or SAGE-547

5.3.1 Nonclinical Pharmacology

The primary pharmacological effects of allopregnanolone or SAGE-547 are described earlier in the rationale (Sections 5.1 and 5.1.1). Secondary pharmacologic effects comprise mainly the binding and consequent increased activity of steroid hormone receptors (androgen receptor [(AR], progesterone receptor [PR], and estrogen receptor beta [ERß]), with some evidence of inhibition at the highest doses (AR and estrogen receptor alfa [ERα]). These non-target effects may yield some adverse events in the clinic.

Nonclinical toxicology studies largely illustrate the sedative and anesthetic effects of allopregnanolone and/or SAGE-547 at higher equivalent doses than the proposed dose for the current study. PK data in animals indicate a short half-life and rapid clearance with a moderate volume of distribution and cerebral levels higher than plasma. See SAGE-547 Investigational Brochure for more details.

5.3.2 Clinical Experience

The clinical PK data with intravenous (IV) administration of allopregnanolone in healthy women, men, and women on oral contraceptives confirmed the PK observations in animals of a short half-life ($T_{1/2}$ 20-40 mins), C_{max} achievable at approximately 3rd trimester levels (150 nM), rapid clearance and moderate volume of distribution (V_d). See SAGE-547 Investigational Brochure for more details.

There are currently no double-blind, placebo-controlled clinical efficacy data for SAGE-547 in PPD. An open-label, proof-of-concept study (547-PPD-201) evaluating the safety, tolerability, pharmacokinetics, and efficacy of SAGE-547 Injection in the treatment of adult female subjects with severe postpartum depression was started in 2014. This was the first-ever study in this indication. Four women experienced significant improvement in depressive symptoms within 24 hours after administration of open-label intravenous SAGE-547. During the SAGE-547 treatment period, all four subjects rapidly achieved remission, as measured by the HAMD total score. All four subjects also demonstrated consistent improvement as measured by the CGI-I score. SAGE-547 was well-tolerated in all subjects treated with no serious adverse events observed during therapy or during the 30-day follow-up period. A total of 14 adverse events were reported in four subjects. The only adverse event reported in more than one subject was sedation, observed in two subjects. This trial was initially planned to enroll 10 women, however, due to the observed clinical activity, the 547-PPD-201 trial was stopped early with the plan to initiate a placebo-controlled clinical trial as rapidly as possible.

There are six reported studies of allopregnanolone, mainly in healthy individuals and none in PPD (Timby 2006; Timby 2011a and 2011b; van Broekhoven 2007; Kask 2008; Kask 2009; Navarro 2003). Data indicate that normal physiological allopregnanolone levels in women vary during the menstrual cycle up to a maximum of 6-10 nM, with lower levels present post-menopause (Genazzani 1998). The highest physiological levels observed are in the third trimester of pregnancy, up to around 160 nM at time of delivery (Luisi 2000). Levels drop precipitously to baseline (<10 nM) with removal of the placenta (Klak 2003).

One study demonstrated subjective improvements in contentedness in women (van Broekhoven 2007). The clinical safety data are presented below in the Risks and Benefits section (Section 5.4).

5.4 Potential Risks and Benefits

In the recently completed open-label clinical trial of SAGE-547 in PPD (547-PPD-201), a total of 14 adverse events were reported in four subjects. The only adverse event reported in more than one subject was sedation, observed in two subjects.

Consistent with these observations, published reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported adverse events (AEs) were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, vertigo, mild nausea, impaired episodic memory, and mild headache (Timby 2006 and 2011a and 2001b; van Broekhoven 2007). One subject experienced what was potentially a withdrawal effect, an anxiety attack (Timby 2011b). No serious AEs (SAEs) were reported in the six clinical studies conducted to date (Timby 2006; Timby 2011a and 2011b; van Broekhoven 2007; Kask 2008; Kask 2009; Navarro 2003). There is also a potential risk of supra-additive sedative effects with other drugs interacting with the $GABA_A$ receptor, such as benzodiazepines and anti-epileptic medications (Norberg 1999); therefore, the Investigator is advised to avoid co-medication if possible and to exercise caution with these drug classes. As this is one of the first clinical trials of SAGE-547 in PPD, the potential benefits in this population are unknown, although the risks are likely to be similar to those mentioned above. Given the nonclinical rationale and the fact that endogenous allopregnanolone in humans appears to play a role in psychiatric disorders such as major depression, premenstrual dysphoric disorder, and anxiety disorders, it is possible that subjects may have a clinical benefit at the exposures selected for this trial. In view of the limited nature of the demonstrated risks of exogenous allopregnanolone infusion and the potential for benefit in severe PPD, there is a favorable benefit-risk evaluation for the conduct of the present study.

5.5 Study No. 547-PPD-202

5.5.1 Study Population

This study will evaluate the efficacy, safety, and pharmacokinetics (PK) of SAGE-547 Injection in the treatment of adult female subjects diagnosed with severe postpartum depression.

5.5.2 Route of Administration, Dosage, Dosage Regimen, and Treatment Period

SAGE-547 Injection or placebo will be administered over a 60 hour period by an IV infusion according to the dose regimen shown in Table 2**.** (see Section 11.1.1).

The specific infusion dose of SAGE-547 Injection will be calculated based on weight for each subject. Infusion bags will be changed every 24 hours. Details about the preparation and administration of the study drug infusions will be included in the Pharmacy Manual.

5.5.3 Dose Rationale

The infusion rate of SAGE-547 to be studied in this trial was chosen to achieve a mean exposure of 150 nM, roughly equivalent to the highest endogenous concentrations measured in third trimester pregnancy at approximately 157 nM (Luisi 2000). Since pregnant women tolerate this level without apparent AEs, 150 nM was selected as the target exposure for this study. This level of exposure has already been achieved in 547-PPD-201 as well at higher levels in a study in subjects with essential tremor (547-ETD-201) and subjects with super refractory status epilepticus (547-SSE-201), with no drug-related SAEs reported. Since the most common adverse event in 547-ETD-201 was sedation, dose adjustment rules are included in this protocol to ensure that all subjects can remain on treatment for 60 hours. A similar C_{max} was also achieved in several other studies conducted with intravenous allopregnanolone (Timby 2011b), with excellent tolerability (see SAGE-547 IB 2014 for details of safety profile).

The selection of exposure in the current trial is based on a cautious approach adapted to the anticipated benefit-risk in the PPD patient population, and on previous experience from the ongoing clinical trials of SAGE-547 in adult subjects with SRSE (Protocol 547-SSE-201) and of SAGE-547 in female subjects with PPD (Protocol 547-PPD-201). In the ongoing SRSE trial, as determined by simulation, loading and maintenance infusions are required to achieve the target exposure. In contrast, in the current trial, subjects will instead begin treatment with a four-hour dose-titration phase. The starting dose is approximately 9- to 18-fold lower than the NOAEL observed in rats and dogs, although this is not the first in human study. Doses will be increased as follows: 30 µg /kg/hour [0-4 hours], then 60 µg/kg/hour [4-24 hours], then 90 µg/kg/hour [24-60 hours].

Subjects will be treated in an inpatient setting and continually monitored for safety, and if any severe tolerability issues arise, the infusion will be terminated. The Stanford Sleepiness Scale (SSS) will be regularly administered to monitor sedation and allow dose adjustment based on tolerability, with a formal dose interruption and reduction scheme implemented for this and other adverse events (Table 2).

6 ETHICS

6.1 Institutional Review Board or Independent Ethics Committee

This trial will be initiated only after the protocol has been reviewed and approved by the Institutional Review Board (IRB) where the study is to be conducted. The IRB must meet all US Food and Drug Administration (FDA) requirements governing IRBs (Code of Federal Regulations [CFR], Title 21, Part 56). The same applies for the implementation of changes introduced by an amendment.

6.2 Ethical Conduct of the Study

This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and the most recent amendment (2008).

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol, and must also conduct the study in accordance with International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP) standards as well as local regulations.

6.3 Subject Information and Informed Consent

Prior to subject participation in the trial, written informed consent must be obtained from each subject according to ICH GCP and in accordance with local regulations. Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests, SAGE-547 infusion, and study evaluations. Each subject's signature must be dated by each signatory and the informed consent form (ICF) retained by the investigator as part of the trial records. As an additional assessment, the ICF will contain a provision for optional consent for the collection of breast milk for the duration of the 60-hour SAGE-547 infusion and up to Day 3 for biobanking and PK analysis purposes. The ICF, as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the CFR, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject a copy of the signed and dated ICF. The ICF for subject participation must also be available as part of the subject's file for review by the site's dedicated study monitor.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

7 STUDY OBJECTIVES

7.1 Primary Objective

The primary objective of this study is to determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms in subjects with postpartum depression (PPD) compared to placebo injection as assessed by the change from baseline in Hamilton Rating Scale for Depression (HAMD) total score

7.2 Secondary Objectives

The secondary objectives of the study are:

- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces depressive symptoms compared to placebo injection as assessed by HAMD response, HAMD remission, change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score, change from baseline in Clinical Global Impression – Severity (CGI-S) score, Clinical Global Impression – Improvement (CGI-I) response, and changes from baseline in HAMD subscale and individual item scores.
- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces other mood symptoms compared to placebo injection as assessed by changes from baseline in the Generalized Anxiety Disorder 7-Item Scale (GAD-7) total score.
- To determine if SAGE-547 Injection infused intravenously for 60 hours increases sedation levels compared to placebo injection as assessed by the changes from baseline in Stanford Sleepiness Scale (SSS) score.
- To evaluate the safety and tolerability of SAGE-547 Injection compared with placebo as assessed by the incidence of adverse events, vital sign measurement, clinical laboratory evaluations, electrocardiogram (ECG) parameters, and the Columbia Suicide Severity Rating Scale (C-SSRS).

7.3 Exploratory Objectives

- To determine if SAGE-547 Injection infused intravenously for 60 hours reduces subject-reported depressive symptoms compared to placebo injection as assessed by the change from baseline in Edinburgh Postnatal Depression Scale (EPDS) total score, change from baseline in Patient Health Questionnaire (PHQ-9) total score, and change from baseline in Interactive Voice Response (IVR) HAMD total score.
- To determine if SAGE-547 Injection infused intravenously for 60 hours improves maternal behaviors compared to placebo injection as assessed by the change from baseline in Barkin Index of Maternal Functioning (BIMF) total and sub-scale scores.

7.4 Pharmacokinetic Objective

- To assess the pharmacokinetic (PK) profile of SAGE-547, metabolites of SAGE-547, and betadex sulfobutyl ether sodium (SBECD) and the concentration of SAGE-547 in breast milk, when possible.

8 INVESTIGATIONAL PLAN

8.1 Overview of Study Design

This is a multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the efficacy, safety, and pharmacokinetics of SAGE-547 Injection in adult female subjects diagnosed with severe PPD. The study design is presented in Figure 1. The study will consist of an up to 5-day Screening Period (Day -5 to -1), 3-day (60-hour) Treatment Period, and 30-day Follow-up Period; see Figure 2. Subjects must remain as in-patient during the study Treatment Period, which is approximately 60 hours/2.5 days in duration. The Screening Period assessments may be conducted on an in-patient or an out-patient basis. The Follow-Up Period assessments are conducted on an out-patient basis.

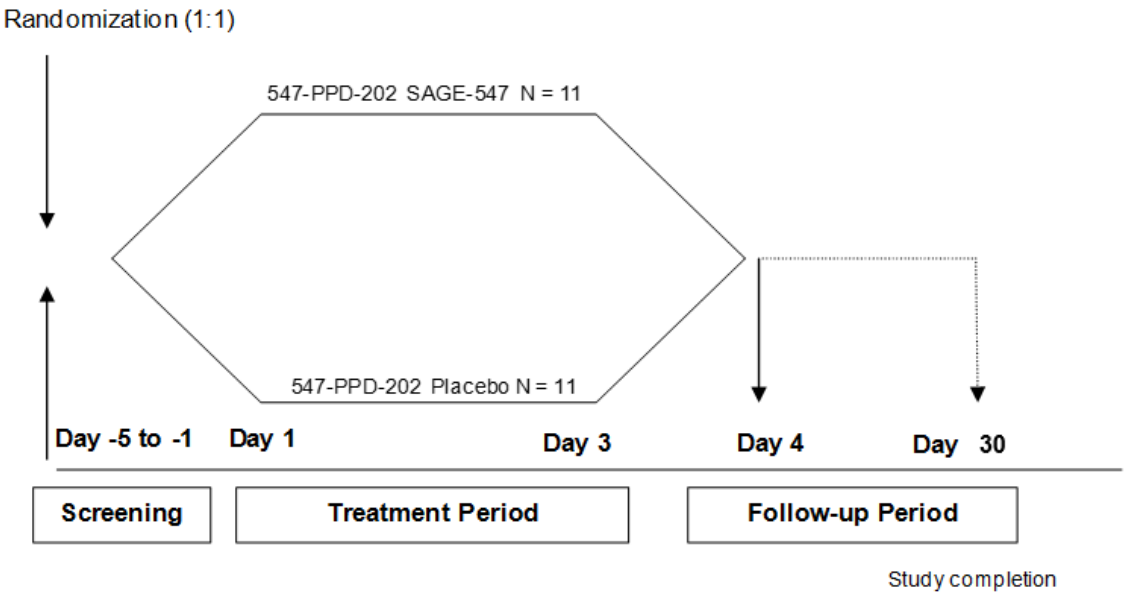

FIGURE 1: STUDY DESIGN

SAGE-547 Injection or placebo will be administered at the study center. Subjects will be monitored for safety during the Treatment and Follow-up Periods (through Study Day 30 ± 3 days) including monitoring for AEs/SAEs, routine clinical laboratory assessments, physical examination, vital signs, and ECG.

All study-related procedures will occur after written informed consent is obtained at the Screening Visit, which will occur on any one calendar day during the Screening Period window (Day -5 through 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.

The end of the Screening Period coincides with the beginning of the Treatment Period. The Treatment Period is the period of Day 1 of SAGE-547 IV infusion through completion of the infusion on Day 2 and up to Day 3. Subjects will be confined to the study center from the Screening Visit until after the 60-hour assessments have been conducted on Day 3. On the morning of dosing (Day 1), subjects will begin a 4-hour dose titration period 30µg/kg/hour [0-4 hours], then 60 µg/kg/hour [4-24 hours], then 90 µg/kg/hour [24-60 hours]); see dose regimen presented in Section 11.1.1. Total SAGE-547 Injection or placebo dosing will occur over 60 hours.

Trial-specific assessments for safety, PK, efficacy, and exploratory outcome measures will be completed at pre-specified times over a 72-hour period during the Treatment Period:

- The safety and tolerability of SAGE-547 Injection will be assessed by AEs, clinical laboratory measures, physical examinations (including cognitive and mental health examinations), vital signs, ECG, use of concomitant medication, and the Columbia Suicide Severity Rating Scale (C-SSRS) during the Screening, Treatment, and Follow-up Periods (through Study Day 30 ± 3 days).
- Plasma will be collected to formally assay for SAGE-547, metabolite, and SBECD levels prior to dosing through the treatment period and up to 12 hours post infusion on Day 3.
- Primary efficacy assessment of the HAMD will be completed as scheduled during the Screening, Treatment, and Follow-up Periods (through Study Day 30).
- Secondary efficacy assessments of MADRS, CGI-I, EPDS, Generalized Anxiety Disorder 7-Item Scale (GAD-7), PHQ-9 will be completed as scheduled during the Screening, Treatment, and Follow-up Periods (through Study Day 30).
- Concentrations of SAGE-547 in breast milk will be measured for those subjects who consent to giving breast milk samples.

The end of the Treatment Period coincides with the beginning of the Follow-up Period.

Subjects will attend the clinic for safety follow-up assessment at one week (7±1d) and one month (30±3d) after the initiation of the study drug infusion.

Scheduled assessments for all safety, PK, efficacy, and exploratory outcome measures planned for the trial are summarized in Table 1. All subjects who receive treatment with SAGE-547 are to complete all study assessments through Study Day 30 (±3d).

The Medical Monitor will review AEs on an ongoing basis.

8.2 Blinding and Randomization

This is a double-blind study. Subjects will be randomized to SAGE-547 or placebo; subjects, clinicians, and study team will be blinded to treatment allocation. The pharmacist, who will prepare the infusion bags according to the randomization schedule, and an unblinded Monitor, who will preform drug accountability during the study, will be unblinded.

Subjects will be randomly assigned to receive SAGE-547 Injection followed by placebo according to a computer-generated randomization schedule.

Only the clinic pharmacist, who is responsible for preparing the infusions, will be given a copy of the randomization schedule. In the event of a medical emergency, the pharmacist may reveal actual infusion contents to the primary investigator, who should also alert Sage of the emergency (see Section 15.4 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 have been unblinded, the subject will be terminated from the study.

9 SELECTION AND WITHDRAWAL OF SUBJECTS

9.1 Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial:

1. Subject has signed an ICF prior to any study-specific procedures being performed
2. Subject is an ambulatory female aged between 18 and 45 years of age
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 at Screening, must have already fully and permanently weaned their infant(s) from breastmilk; or if still actively breastfeeding at Screening, must agree to cease giving breastmilk to their infant(s) prior to receiving study drug. For the avoidance of doubt, subjects who are breastfeeding and do not agree to permanently wean their infant(s) from breastmilk at Screening are not eligible for the study.
6. Subject must have a negative pregnancy test at Screening and Day 1 prior to the start of study drug infusion
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, as diagnosed by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)
8. Subject has a HAMD total score of $\geq$26 at Screening and Day 1 (prior to randomization)
9. Subject is $\leq$ six months postpartum
10. Subject is willing to delay start of other antidepressant or anxiety medications and any new pharmacotherapy regimens, including prn benzodiazepine anxiolytics, until the study drug infusion and 72-hour assessments have been completed
11. Subject has no detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), and human immunodeficiency virus (HIV) antibody at Screening

9.2 Exclusion Criteria

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

1. Recent history or active clinically significant manifestations of metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, dermatological, urogenital, neurological, or eyes, ears, or nose and throat disorders, or any other acute or chronic condition that, in the Investigator's opinion, would limit the subject's ability to complete or participate in this clinical study
2. Known allergy to progesterone or allopregnanolone
3. Active psychosis per Investigator assessment
4. Attempted suicide associated with index case of postpartum depression

5. Medical history of seizures
6. Medical history of bipolar disorder
7. History of active alcoholism or drug addiction (including benzodiazepines) in the 12 months prior to Screening
8. Exposure to another investigational medication or device within 30 days prior to Screening
9. Administration of psychotropics that have been initiated within 14 days prior to Screening and are not being taken at a stable dose.

9.3 Subject Withdrawal/Study Termination

9.3.1 Withdrawal/Discontinuation of Individual Subjects

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

Subjects who do not have at least one efficacy observation after 12 hours of SAGE-547 infusion are not considered evaluable for the efficacy assessment and may be replaced.

9.3.2 Subject Withdrawal From the Study

Subjects may withdraw from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

9.3.3 Discontinuation of Study Drug by the Investigator

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

The Investigator may withdraw the subject from the study drug for any of the following reasons:

- The subject is unwilling or unable to adhere to the protocol
- The subject experiences an intolerable AE
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

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

9.3.4 Study Termination

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

10 INVESTIGATIONAL PRODUCT

10.1 Identity of Investigational Product

SAGE-547 Injection (allopregnanolone)

10.2 Clinical Supplies

10.2.1 SAGE-547

SAGE-547 Injection and ancillary supply kits containing IV administration bags, solution sets, and IV bag labels will be provided to the sites.

SAGE-547 Injection is a preservative-free, sterile, clear, colorless 5 mg/mL solution of SAGE-547 (allopregnanolone) and 250 mg/mL betadex sulfobutyl ether sodium buffered with 10 mM citrate at a pH of 6.0, intended for IV injection. All inactive excipients used in the formulation are compendial grade and conform to current United States Pharmacopeia (USP) and European Pharmacopeia (Ph. Eur.) standards. The product is aseptically processed, sterile filtered, and filled into 20 mL Type 1 parenteral glass vials with West FluroTec® coated stopper container closure systems, under current Good Manufacturing Practice (cGMP) conditions. SAGE-547 Injection is intended to be used as a single-use vial. An appropriate number of single-use vials to support the dosing duration of the study are packaged and delivered to the site. SAGE-547 Injection vials should be stored under refrigerated conditions (2–8 °C). Ancillary supply kits should be stored at controlled room temperature (20–25 °C).

All study drug labels will contain information to meet the applicable regulatory requirements.

10.2.2 Placebo

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and consisting of the same formulation without allopregnanolone. Placebo vials should be stored under refrigerated conditions (2–8 °C).

10.3 Preparation of SAGE-547 Injection or Placebo for Dosing

The pharmacy will be responsible for preparing SAGE-547 Injection or placebo for subject dosing. The prepared admixture will be administered at room temperature. The prepared admixture will be assigned a room temperature (20–25 °C) storage shelf life of 24 hours from time of compounding.

SAGE-547 Injection or placebo is not intended to be administered to subjects undiluted. Each single-use vial of SAGE-547 Injection, which is hypertonic, will require dilution with an appropriate volume of Sterile Water for Injection (SWFI) to render it isotonic. Refer to the Pharmacy Manual for specific instructions regarding infusion preparation and administration instructions.

10.4 Administration and Accountability

The pharmacy will maintain accurate records of all investigational drug product supplies received, stored, dispensed, and discarded. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate (or rates), and the date and time of preparation. Reasons for departure from the expected dosing regimen must be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication needs to be reconciled in full.

Refer to the Pharmacy Manual for complete details on preparation and administration.

11 TREATMENT OF SUBJECTS

11.1 Dosing Schedule

This is a double-blind study. Subjects will be randomized to receive 60 hours of intravenous treatment with either SAGE-547 Injection or placebo.

The timing of infusion relative to the overall trial design is shown in Figure 2.

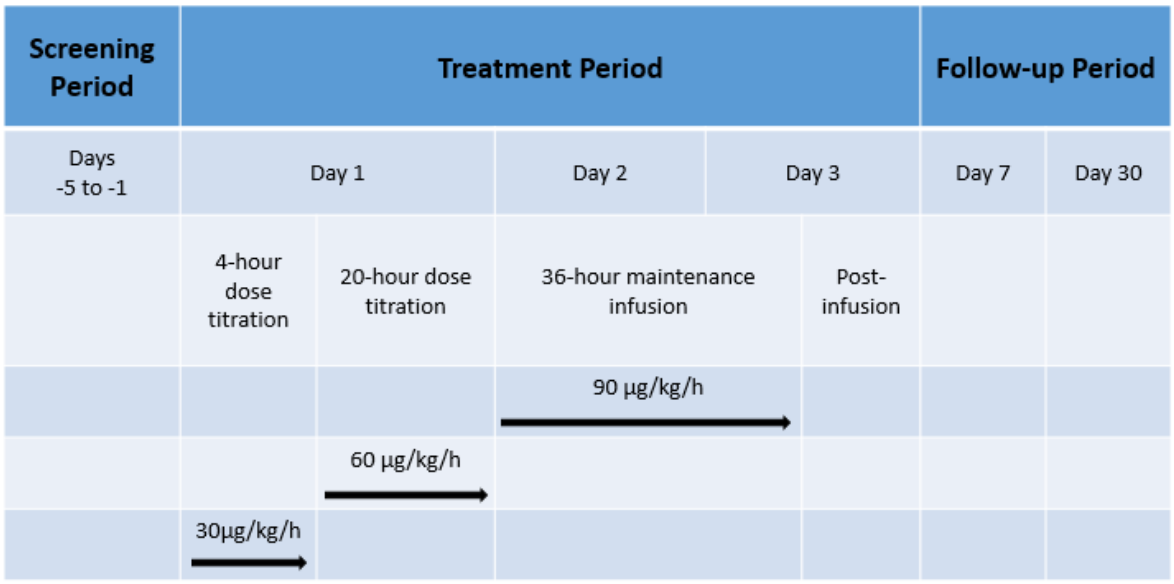

FIGURE 2: TRIAL DESIGN AND TIMELINE FOR DOSING

Clinical supply and preparation of SAGE-547 Injection for dosing is described Section 10.2 and Section 10.3, respectively.

11.1.1 Dose Regimen

The specific infusion dose of SAGE-547 Injection will be calculated based on weight (obtained at screening) for each subject and administered according to dose regimen shown in Table 2). The infusion rates are the same for all subjects within a particular dosing period (0-4 hours, 4-24 hours, etc.) (Table 2).

TABLE 2: INFUSION RATES

Timepoint	Day 1 0-4 hours	Day 1 4-24 hours	Day 2/3 24-60 hours
Infusion rates	30 µg/kg/hour	60 µg/kg/hour	90 µg/kg/hour

Dosing is to begin in the morning (on Day 1) to avoid awakening subjects during the night for completion of study assessments.

If any subject has an SSS score of ≥5 for two or more consecutive assessments or an SSS score of ≥6 for a single occurrence during normal waking hours, the infusion rate will be decreased to the next lowest infusion dose (or turned off if this occurs on the 30 µg/kg/hour dose level) for the remainder of the study. Please refer to Section 11.1.4 for more details.

11.1.2 Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line with the supplied study-specific IV administration bags and lines.

11.1.3 Treatment Period

Total dosing with SAGE-547 or placebo will occur over 60 hours, including a 24-hour dose titration and a 36-hour maintenance infusion.

11.1.4 Dosing of Intravenous SAGE-547 in the Case of AEs

Since allopregnanolone levels in the proposed clinical trial are similar to physiological levels seen in the third trimester of pregnancy, and all the AEs reported with SAGE-547 or allopregnanolone to date were mild and non-serious, it is anticipated that the AEs associated with SAGE-547 will be mild and manageable without dose interruption or reduction. Based on the observed adverse events to date, the adverse events most likely to result in AE are sedation with or without hypotension.

However, in the case of severe or life-threatening AEs occurring, the investigator is advised to interrupt infusion until regression of the AE to mild or resolution and only resume infusion if it is deemed in the best interest of the subject. Resumption of infusion at the next lowest dose (or turned off if this event occurs on the 30 µg/kg/hour dose level) for one hour, followed by re-escalation to the maintenance rate, may be considered to address potential recurrence of the AE. If the AE recurs infusion should be definitively discontinued.

11.2 Dosing Compliance

Investigational product will be prepared in the site pharmacy, administered as a continuous IV infusion by the study staff, and will be documented in the study record. There should be no adjustments in dosing except those described in Section 11.1.4.

11.3 Concomitant Medications and Restrictions

11.3.1 Concomitant Medications

Subjects will receive standard of care for adult female patients diagnosed with PPD. 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 11.3.2. All concomitant medications should be documented throughout the study from Screening through Day 30 (± 3 days) and recorded on the eCRF. Prior medications (i.e., those taken prior to signing of informed consent) that required wash-out for study entry will also be documented.

11.3.2 Prohibited 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 on this medication for at least 30 days prior to study enrollment.
- Benzodiazepines are to be avoided as much as possible. Eligible subjects taking a benzodiazepine at the time of study entry will 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. Particular attention should be paid to assessment of AEs and implementation of the dose interruption and reduction scheme in subjects on concomitant benzodiazepines since they have been shown to have a supra-additive effect with pregnenolone in an animal model of anesthesia (Norberg 1999).
- The use of hypnotics for sleep/insomnia such as Ambien® and trazodone are to be avoided.
- Anticonvulsants and atypical antipsychotics are to be avoided if possible and are not to be initiated at any time during active treatment period (60 hours). However, if a subject is taking one of these medications for at least 30 days prior to study admission, they will be permitted to remain on this medication, at their current dose (no dose adjustments are allowed).
- SAGE-547 has demonstrated inhibitory effects on cytochrome P-450 (CYP) 2C9 (CYP2C9). The following medications are primarily metabolized by CYP2C9 and therefore are prohibited during SAGE-547 administration: fluconazole and miconazole (antifungal), amentoflavone (constituent of Ginkgo biloba and St. John's Wort), sulfaphenazole (antibacterial), valproic acid (anticonvulsant, mood-stabilizing), and apigenin. See Appendix 10 for a more complete list.

12 STUDY ASSESSMENTS

12.1 Safety Assessments

The safety and tolerability of SAGE-547 Injection will be evaluated by summarization of AEs by frequency, severity and seriousness, mean changes from baseline in clinical laboratory measures, physical examination, vital signs, ECGs, and concomitant medication usage. Suicidality will be monitored using the C-SSRS. All safety assessments should be performed per the study center's standard of care and will be collected according to the Schedule of Events (Table 1). All safety assessments are to be completed within ± 30 minutes of the scheduled time point.

In addition to the schedule outlined in Table 1, completion of safety assessments including physical examination, vital signs, and clinical laboratory tests should occur in the event of an emergency or SAE, when possible.

12.1.1 Adverse Events

Adverse events will be collected after the ICF has been signed through the end of the study (see Section 15.2.1 for additional details). Medical conditions or adverse events that occur after the ICF has been signed and *prior to* completion of Screening will be captured on the Medical History eCRF.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (version 17.0 or higher), as described in Section 14.4.

12.1.2 Clinical Laboratory Tests

Blood samples will be collected for hematology, serum chemistry, coagulation, and specific hormone parameters, hepatitis, human immunodeficiency virus (HIV), pregnancy and genetic analysis. Urine samples for urinalysis and selected drugs of abuse will also be collected. These assessments will be performed in accordance with the Schedule of Events (Table 1) and as outlined individually below.

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 will be recorded as medical history. Clinical laboratory results that are Abnormal; CS during the study and indicate a worsening from baseline will be considered AEs, assessed according to Section 15, and recorded in the eCRF.

1. Hematology, Serum Chemistry, Coagulation

Blood samples will be collected for analysis of the following:

- **Hematology:** complete blood count (CBC) including white blood cell (WBC) count with differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils) platelet count, red blood cell (RBC) count, hemoglobin (Hgb) and hematocrit (Hct), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH)

- **Serum chemistry:** albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatinine, gamma glutamyl transferase (GGT), glucose phosphate, potassium, sodium, total protein and triglycerides (Screening only)
- **Coagulation:** activated partial thromboplastin time (aPTT), prothrombin time (PT), international normalized ratio (INR)

2. Hepatitis and HIV

Blood samples will be collected for analysis of the following:

- **Hepatitis**: hepatitis B virus surface antigen (HBsAg), antibody against hepatitis C virus (anti-HCV)
- **HIV**: antibody against human immunodeficiency virus type 1/2 (anti-HIV 1/2)

3. Hormones

Blood samples will be collected for analysis of thyroid stimulating hormone (TSH), estrogen, progesterone, progesterone metabolites and oxytocin.

4. Pregnancy Test

All subjects will be tested for pregnancy by serum hCG at Screening and urine hGC on Day 1 prior to administration of study drug. Subjects with a positive pregnancy test at Screening or Day 1will be ineligible for study participation.

5. Genetic Testing

A blood sample for genetic testing will be collected at screening, where consent is given. This sample will be used to test for the $GABA_A$ receptor δ-subunit. Genetic susceptibility to affective dysregulation may be unmasked during periods of reproductive hormone change such as during pregnancy and postpartum (Maguire 2008). Maguire and Mody demonstrated that a GABA receptor subunit mutation was behaviorally silent until the animal was exposed to pregnancy and the postpartum state, at which time the dams showed depressive-like behaviors and cannibalized their offspring (Maguire 2008).

6. Urinalysis

Urinalysis will include assessment of bilirubin, glucose, ketones, leukocytes, nitrite, pH, protein and specific gravity.

7. Drugs of Abuse and Alcohol

Urine assessment for selected drugs of abuse (including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine and propoxyphene). Use of benzodiazepines at screening is not necessarily exclusionary, as subjects will be allowed to take psychotropics that have been initiated at least 14 days prior to admission to the study center at a stable dose (see Section 11.3). Alcohol will be assessed in plasma at Screening and in serum, via breathalyzer or urine dipstick on Day 1.

12.1.3 Physical Examination

Body weight and height will be measured at Screening. Body mass index (BMI) will be programmatically calculated in the eCRF.

Any condition present at the post-treatment physical examination that was not present at or worsened since the baseline examination is to be documented as an AE. Whenever possible, the same individual is to perform all physical examinations. Physical examinations will include assessment of body systems (e.g., HEENT, heart, lungs, abdomen, and extremities) as well as cognitive and neurological examination and mental status examination.

12.1.4 Vital Signs

Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure (supine and standing) and pulse oximetry A full set of vital signs will be obtained at all specified timepoints (± 30 minutes), unless the subject is asleep between the hours of 23.00h and 06.00h each day. Additional measures of pulse oximetry will be collected during sleeping hours.

12.1.5 ECG

A baseline 12-lead ECG will be performed during Screening to assess the presence of any current or historical cardiovascular conditions. The following ECG parameters will be recorded: heart rate, PR, QRS, QT, and QTc. Subjects with clinically significant abnormalities should not be entered into the study.

12.1.6 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” C-SSRS form will be completed on Day 1 prior to dosing. The “Since Last Visit” C-SSRS form will be completed for all subsequent assessments.

Copies of the C-SSRS are provided in APPENDIX 1.

12.1.7 Stanford Sleepiness Scale (SSS)

The Stanford Sleepiness Scale is patient-rated scale designed to quickly assess how sedated or sleepy a patient is feeling. Degrees of sleepiness and alertness are rated on a scale of 1 to 7, where the lowest score of 1 indicates that the patient is “feeling active, vital, alert, or wide awake” and the highest score of 7 indicates that the patient is “no longer fighting sleep, sleep onset soon; having dream-like thoughts.” The SSS will be administered unless the subject is asleep between the hours of 23.00h and 06.00h each day. If the SSS is not scored due to a subject being asleep, a score of X will be reported in the CRF to indicate that the subject was asleep. All SSS assessments are to be completed within ± 15 minutes of the scheduled time point.

A copy of the SSS is provided in APPENDIX 5.

12.2 Efficacy Assessments

For all efficacy assessments, the baseline values will be calculated as the last recorded value prior to the start of infusion of randomized treatment. 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.

12.2.1 Primary Efficacy Outcome Measure

The primary outcome measure is the HAMD. The HAMD will be administered before, during, and after the infusion of blinded study drug.

8. Hamilton Rating Scale for Depression (HAMD)

The 17-item HAMD will be used to rate the severity of depression in subjects who are already diagnosed as depressed (Hamilton 1960). The 17-item HAMD is comprised of 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 HAMD assessments are to be completed within ± 30 minutes of the scheduled time point, but prior to starting dosing on D1 H0.

The HAMD total score will be calculated as the sum of the 17 individual item scores. Item 16 can be rated according to history (item 16A) or actual weight change (item 16B). The item 16 score is calculated as the item 16 response that is not equal to 3 (i.e., "Not assessed").

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

A copy of the HAMD is provided in APPENDIX 2.

12.2.2 Secondary Efficacy Outcome Measures

Secondary efficacy assessments include evaluation of depressive symptom severity by the MADRS and CGI, as described in Section 12.2.2.1. Additional assessments of depressive symptom severity and reproductive mood disorders will be measured by the following clinician- and subject-rated outcome measures: EPDS, GAD-7 and PHQ-9, as described in Sections 12.2.3.1 through 12.2.3.2.

9. Montgomery Asberg Depression Rating Scale (MADRS)

The MADRS is a ten-item diagnostic questionnaire which psychiatrists use to measure the severity of depressive episodes in patients with mood disorders. It was designed as an adjunct

to the HAMD which would be more sensitive to the changes brought on by antidepressants and other forms of treatment than the Hamilton Scale was.

Higher MADRS score indicates 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 1. Apparent sadness 2. Reported sadness 3. Inner tension 4. Reduced sleep 5. Reduced appetite 6. Concentration difficulties 7. Lassitude 8. Inability to feel 9. Pessimistic thoughts 10. Suicidal thoughts.

The MADRS total score will be calculated as the sum of the 10 individual item scores.

A copy of the MADRS is provided in APPENDIX 3.

10. Clinical Global Impression (CGI) Scale

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 patient's condition. The CGI scale is comprised of 3 items. Only the first two items are being used in this study.

The CGI-Severity (CGI-S) item uses a 7-point Likert scale to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating 1 = normal, not at all ill, 2 = borderline mentally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, and 7 = extremely ill. The CGI-S will be rated by the clinician at screening and on Day 1 (prior to dosing).

The CGI-Improvement (CGI-I) item employs a 7-point Likert scale to measure the overall improvement in the patient's condition post-treatment. The investigator will rate the patient's total improvement whether or not it is due entirely to drug treatment. Response choices include: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. The CGI-I is only rated at post-treatment assessments. By definition, all CGI-I assessments are evaluated against baseline conditions. CGI-I response will be defined as having a CGI-I score of "very much improved" or "much improved".

A copy of the CGI is provided in APPENDIX 4.

11. Generalized Anxiety Disorder 7-Item Scale (GAD-7)

The GAD-7 is a patient-rated depressive symptom severity scale (Spitzer 2006). Scoring for GAD-7 generalized anxiety is calculated by assigning scores of 0, 1, 2, and 3 to the response categories, respectively, of "not at all sure," "several days," "over half the days," and "nearly every day." GAD-7 total score for the seven items ranges from 0 to 21, where a score of 0 to 4 = minimal anxiety, 5 to 9 = mild anxiety, 10 to 14 = moderate anxiety, and 15 to 21 = severe anxiety. All assessments are to be completed within ± 30 minutes of the scheduled time point.

The GAD-7 total score will be calculated as the sum of the 7 individual item scores.

A copy of the GAD-7 is provided in APPENDIX 7.

12.2.3 Exploratory Patient Reported Outcome Measures

Exploratory efficacy assessments include evaluation of depressive symptom severity and reproductive mood disorders. These will be measured by the following clinician- and subject-rated outcome measures: EPDS, PHQ-9, BIMF and IVR HAMD.

12. Edinburgh Postnatal Depression Scale (EPDS)

The EPDS is a patient-rated depressive symptom severity scale specific to the perinatal period (Cox 1987). The EPDS total score will be calculated as the sum of the 10 individual item scores.

A copy of the EPDS is provided in APPENDIX 6.

13. Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a patient-rated depressive symptom severity scale. To monitor severity over time for newly diagnosed patients or patients in current treatment for depression, patients may complete questionnaires at baseline and at regular intervals thereafter. Scoring is total based on responses to specific questions, as follows: “not at all” = 0; “several days” = 1; “more than half the days” = 2; and “nearly every day = 3.” All assessments are to be completed within ± 30 minutes of the scheduled time point.

The PHQ-9 total score will be calculated as the sum of the 9 individual item scores. The PHQ-9 total score will be categorized as follows: 1-4 = minimal depression, 5-9 = mild depression, 10-14 = moderate depression, 15-19 = moderately severe depression; and 20-27 = severe depression.

A copy of the PHQ-9 is provided in APPENDIX 8.

14. Barkin Index of Maternal Functioning (BIMF)

The BIMF is a patient reported outcome scale BIMF covers a broad range of functional areas (self-care, infant care, mother-child interaction, psychological well-being of mother, social support, management, adjustment). This new application of maternal functional status is a robust construct where the physical and mental health of the mother is essential to optimal functioning. Each item is rated on a scale of 0 (strongly disagree) to 6 (strongly agree) , and subscales are drawn from these items.

A copy of the BIMF is provided in APPENDIX 9.

15. Interactive Voice Response (IVR) HAMD

The IVR HAMD is a validated patient reported version of the clinician rated HAMD. Similar total and subscale scores as described in Section 12.2.1.1 will be calculated for the IVR HAMD.

12.3 Pharmacokinetics

12.3.1 Plasma PK Samples

Blood samples for PK analysis will be collected in accordance with the Schedule of Events (Table 1). Scheduled time points for PK blood draws after the start of infusion will have a window of ± 10 minutes. Samples will be processed according to the PK Manual, and analyzed for concentrations of SAGE-547, metabolites of SAGE-547, and SBECD. Additionally, PK samples may be obtained outside the planned collection times if issues administering study drug are encountered, such as incorrect infusion rate, interrupted infusion, or other administration deviations where PK level assessment may be important in understanding subject state. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.

The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve (AUC) from time zero to 60 hours ($AUC_{0\text{-}60}$), AUC from time zero to infinity (AUC_{inf}), maximum (peak) plasma concentration (C_{max}), time at maximum (peak) plasma concentration (T_{max}), steady-state drug concentration in the plasma during constant-rate infusion (C_{ss}), and average drug concentration in the plasma at steady state during a dosing interval (C_{avg}).

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Subject-specific plasma PK kits for sampling including instructions on sample collection, processing methods, storage and shipping conditions, will be provided in the study PK Manual.

12.3.2 Breastmilk PK Samples

Women who are actively lactating at Screening, and who otherwise fulfill all of the inclusion and exclusion criteria for the study, will be asked if they will consent to pumping. Breastmilk will be collected and pooled at pre-defined intervals. The times of the first and last pumping of each collection period will be recorded. Breastmilk will be pooled within each collection period and the total volume will be measured. Detailed instructions for breastmilk PK sampling, processing methods, storage and shipping will be provided in the study PK Manual. After collection of the last breastmilk sample, women will reduce pumping to comfortably curtail breast milk production.

13 STUDY PROCEDURES

The study procedures listed below by study day reflect the data collection times for this protocol.

Scheduled assessments for all safety, efficacy, PK and exploratory outcome measures planned for the trial are summarized in Table 1 (Schedule of Events). All subjects who receive treatment with SAGE-547 should complete all study assessments through Study Day 30 (± 3 days).

Subjects who are evaluated at the Day 3 visit of the Treatment Period (i.e., all Hour 60 assessments are completed, post-infusion) and complete the Day 30 (± 3 days) visit during the Follow-up Period will be defined as study completers.

13.1 Screening Period

The Screening Period consists of a window from Day -5 through Day -1 prior to starting SAGE-547 treatment. The Screening Period begins with the signature of the ICF. Eligibility is determined by applying the inclusion/exclusion criteria. The diagnosis of PPD must be by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). A full medical and family history will be taken including recording of all depression, other Axis 1 and Axis 2 disorders and post-partum depression episodes in primary probands (who may be subject to a SCID-I interview).

The following assessments/procedures will be conducted at the Screening Visit, which will occur on any one calendar day of the Screening Period. 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 examinations, 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, and all screening assessments are completed, reviewed and approved by the Investigator prior to administration of SAGE-547.

Subjects will be confined to the study center from the Screening Visit until after the 60-hour assessments have been conducted on Day 3.

- Written informed consent, with optional provision for breast milk collection (see Section 6.3 for more information).
- Review of inclusion/exclusion criteria to determine subject eligibility.
- Demographic information and medical/family history collected.
- Blood will be collected for a pregnancy test.
- Blood will be collected to screen for hepatitis and HIV.
- Completion of physical examination, including body weight. Height should be recorded. BMI will be calculated.
- Vital signs.
- Blood and urine samples collected for clinical laboratory testing, including drug and alcohol screening.

- Blood sample will be taken for genetic analysis with subject consent.
- An ECG reading taken.
- Completion of the HAMD (including IVR HAMD), CGI-S and MADRS.
- Recording of concomitant medications.

13.2 SAGE-547 Treatment Period (Day 1 to Day 3, Hours 0-60)

All safety, efficacy, pharmacokinetic and other outcome assessments described in this section are to be completed within ± 30 minutes of the scheduled time points, unless otherwise stated. Windows for PK collection time points are specified by respective time point for Study Days 1 to 3 in Section 13.2.1 to Section 13.2.3, respectively (see Section 12.3 for additional details). Subjects will be confined to the study center from the Screening Visit until after the 60-hour assessments have been conducted on Day 3.

13.2.1 Day 1

- Review of inclusion/exclusion criteria to determine subject eligibility.
- Randomization (on a 1:1 basis: one group will receive SAGE-547 and one group will receive placebo).
- Urine will be collected for a pregnancy test.
- Begin study drug administration for dose titration in the morning followed by maintenance infusion.
- Vital signs and pulse oximetry will be recorded prior to infusion and at 2, 4, 8, 12, 18, and 24 hours on Day 1 (± 30 minutes), unless the subject is asleep between the hours of 23.00h and 06.00h each day. Additional measures of pulse oximetry will be collected during sleeping hours.
- Blood and urine samples collected for drug and alcohol screening.
- A blood sample for PK analysis will be collected prior to infusion (i.e., morning of Day 1 prior to dosing), and at Hours 4 (before change in infusion rate), 8, 12, and 24 (before change in infusion rate) after the start of the infusion. PK blood draws after the start of infusion will have a window of ± 10 minutes. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.
- Completion of the HAMD prior to dosing and at Hours 2, 4, 8, 12, and 24 on Day 1 (± 30 minutes).
- Completion of the IVR HAMD prior to dosing and at Hour 24 on Day 1 (± 30 minutes).
- Completion of the MADRS prior to dosing and at Hour 24 on Day 1 (± 30 minutes).
- Completion of the CGI-S prior to dosing and the CGI-I at Hours 2, 4, 12, and 24 on Day 1 (± 30 minutes).

- Completion of the following questionnaires prior to dosing: BIMF, EPDS, GAD-7, and PHQ-9 (± 30 minutes).
- Completion of the SSS prior to dosing and at Hours 2, 4, 8, 12, 18, and 24 on Day 1 (± 15 minutes) unless the subject is asleep between the hours of 23.00h and 06.00h each day.
- AEs will be monitored.
- Concomitant medications will be recorded.
- Completion of the "Baseline" C-SSRS form prior to dosing. Completion of the "Since Last Visit" C-SSRS form at Hour 24(± 30 minutes) .
- Per subject consent (optional), collection of breast milk at pre-infusion and at the following time periods of interest: 0, 1-12, 12-24, 24-36, 36-48, 48-60, and 60-72 hours after the start of the infusion.

13.2.2 Day 2

- Ongoing SAGE-547 maintenance infusion administration.
- Vital signs and pulse oximetry will be recorded at Hours 30, 36, 42, and 48 (± 30 minutes), unless the subject is asleep between the hours of 23.00h and 06.00h each day.
- Additional measures of pulse oximetry will be collected during sleeping hours.
- A blood sample for PK analysis will be collected at Hours 30, 36, and 48. PK blood draws will have a window of ± 10 minutes. In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.
- Completion of the HAMD at Hour 36 and Hour 48 (± 30 minutes).
- Completion of the IVR HAMD at Hour 48 (± 30 minutes).
- Completion of the CGI-I at Hour 36 and Hour 48 (± 30 minutes).
- Completion of the MADRS at Hour 48 (± 30 minutes).
- Completion of the SSS at Hours 30, 36, 42, and 48 on Day 2 (± 15 minutes) unless the subject is asleep between the hours of 23.00h and 06.00h each day.
- An ECG reading taken at Hour 48.
- AEs will be monitored.
- Concomitant medications will be recorded.
- Per subject consent (optional), ongoing collection of breast milk during the maintenance phase of infusion.

13.2.3 Day 3

- Ongoing SAGE-547 maintenance infusion administration until Hour 60.
- Completion of physical examination.
- Vital signs will be recorded at Hours 54, 60, 66, and 72 (± 30 minutes) .
- A blood sample for PK analysis will be collected at Hours 60 and 72 (± 10 minutes). In the event of an unplanned dose adjustment, an unscheduled PK sample should be collected just prior to the infusion rate change.
- Blood sample collected for clinical laboratory testing at Hour 72.
- Completion of the HAMD and MADRS at Hour 60 and 72 (± 30 minutes).
- Completion of the IVR HAMD at Hours 60 and 72 (± 30 minutes).
- Completion of the CGI-I at Hours 60 and 72 (± 30 minutes).
- Completion of the following questionnaires at Hour 60: EPDS, GAD-7, and PHQ-9 (± 30 minutes).
- Completion of the SSS at Hours 54, 60, 66, and 72 on Day 3 (± 15 minutes) unless the subject is asleep between the hours of 23.00h and 06.00h each day.
- AEs will be monitored.
- Concomitant medications will be recorded.
- Completion of the C-SSRS at Hours 60 and 72.
- Per subject consent (optional), ongoing collection of breast milk.

13.3 Follow-up Period (Day 7 through Day 60)

13.3.1 Day 7 (± 1 day)

The following assessments should be completed:

- Completion of physical examination.
- Vital signs.
- Blood and urine samples collected for clinical laboratory testing.
- An ECG reading taken.
- Completion of the C-SSRS, HAMD, IVR HAMD, MADRS, CGI-I, EPDS, GAD-7, PHQ-9 and BIMF.
- AEs will be monitored.
- Concomitant medications will be recorded.

13.3.2 Day 30 (± 3 days)

The following assessments should be completed:

- Urine will be collected for a pregnancy test.
- Vital signs.
- Completion of the C-SSRS, HAMD, IVR HAMD, MADRS, CGI-I, EPDS, GAD-7, PHQ-9 and BIMF.
- AEs will be monitored.
- Concomitant medications will be recorded.

14 STATISTICAL METHODS AND CONSIDERATIONS

In general, summary statistics for all study endpoints will be presented as mean, standard deviation (SD), median, and ranges for continuous endpoints, and as counts and percentages for categorical endpoints. For the purpose of all safety, efficacy, and exploratory analyses where applicable, baseline is defined as the last pre-dose measurement closest to the start of blinded study drug infusion.

A statistical analysis plan (SAP) will be generated and approved by a representative of Sage Therapeutics prior to database lock. All statistical analyses will be conducted using SAS for Windows (version 9.1.3, or higher; Cary, NC), unless otherwise specified.

Any deviations from the planned analyses will be described and justified in the final clinical study report (CSR).

14.1 Data Analysis Sets

The intent-to-treat (ITT) subject population in this study is adult female subjects who meet all eligibility criteria and who sign an informed consent to participate in this trial regardless whether or not study drug is administered.

Safety Population (SAF): All ITT subjects who begin receiving a study drug infusion will be included in the safety population. Subjects will be classified according to actual treatment received. This analysis population will be used for all safety analyses.

Efficacy Population (EFF): All SAF subjects who complete at least 12 hours of infusion and have efficacy evaluations through the 12-hour timepoint on Day 1. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

Per Protocol Population (PP): All EFF subjects who complete the full infusion with all efficacy assessments through hour 60, and without significant protocol violations or deviations. Subjects will be classified according to randomized treatment. This analysis population will be used for select sensitivity analyses of the primary and key secondary endpoints.

PK Population (PKP): All SAF subjects treated with SAGE-547 for whom at least one evaluable PK sample is available.

Breast Milk Population (BMP): All SAF subjects who begin receiving a study drug infusion and have at least one breast milk sample taken.

The number and percentage of subjects who receive SAGE-547 Injection or placebo, prematurely discontinue, and complete the study will be summarized. The number and percentage of subjects will also be summarized for each reason for premature discontinuation. In addition, the number of subjects whose data should be used for the planned analyses will be identified for each respective analysis population (i.e., SAF, EFF, PKP, PP, and BMP).

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 populations, using all non-missing data available. Any rules for the imputation of missing data will be described in the SAP.

14.3 Demographics and Baseline Characteristics

Demographics such as age, race, and ethnicity will be summarized. In addition, baseline characteristics such as height, weight, and BMI will be summarized. Categorical summaries, such as race and ethnicity, will be summarized by frequency and percentage. Continuous summaries, such as age, height, weight, BMI and baseline vital signs, will be summarized using descriptive statistics such as n, mean, SD, median, minimum, and maximum.

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

Medical/family history will be collected and listed by subject.

14.4 Primary Endpoints

Change from baseline to each assessment in HAMD total score will be analyzed using a mixed effects repeated measures model (MMRM) including center, treatment, baseline HAMD total score, assessment timepoint, and timepoint-by-treatment. Center will be treated as a random effect while all other explanatory variables will be treated as fixed effects. The primary comparison will be between SAGE-547 and placebo at the 60 hour assessment. Model based point estimates (i.e., LS means), 95% confidence intervals, and p-values will be reported for each assessment.

Summaries of HAMD total scores and changes from baseline values will include n, mean, SD, median, minimum, and maximum.

14.5 Secondary Endpoints

Efficacy Analysis

MMRM methods similar to those described in Section 14.4 will be used for the analysis of the following variables: MADRS total score, CGI-S score, EPDS total score, GAD-7 total score, PHQ-9 total score, and select individual item and subscale scores. For each model, the comparison of interest will be between SAGE-547 and placebo at the 48 hour assessment. Model based point estimates (i.e., LS means), 95% confidence intervals, and p-values will be reported.

Logistic regression methods will be used for the analysis of the following response variables: HAMD response, HAMD remission, and CGI-I response. Logistic regression models will include terms for center, treatment, and baseline score. The comparison of interest will be the difference between SAGE-547 and placebo at the 60-hour assessment. Model based point estimates (i.e., 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 timepoint. Summaries will include n, mean, SD, median, minimum, and maximum.

Safety Analysis

Safety and tolerability of SAGE-547 Injection will be evaluated by AEs, concomitant medications, changes from baseline in physical examination, vital signs, CBC, serum chemistry, urinalysis, and 12-lead ECG. Suicidality will be monitored by the C-SSRS. Sedation will be assessed using the SSS. Safety data will be listed by individual and summarized by treatment group. In addition, an analysis of SSS data will be performed comparing the treatment groups in the same way as for the primary endpoint. All safety summaries will be performed on the SAF population.

Safety data will be examined for possible relationships between subject characteristics and plasma allopregnanolone concentrations, as appropriate.

Scheduled visits for all safety assessments are described in Section 12.1 and summarized in Table 1.

Adverse events: The analysis of AEs will be based on the concept of treatment-emergent AEs (TEAEs). A TEAE is defined as an AE with onset after the start of SAGE-547 infusion, or any worsening of a pre-existing medical condition/AE with onset after the start of SAGE-547 infusion and until 7 days after the end of infusion (i.e., Day 10). A treatment-emergent serious AE (TESAE) is defined as an AE with onset after the start of SAGE-547 infusion, or any worsening of a pre-existing medical condition/AE with onset after the start of SAGE-547 infusion and until 30 days after the end of infusion (i.e., Day 33). All TEAEs will be summarized and grouped by MedDRA® System Organ Class (SOC) and specific AE preferred term (PT). Results will be displayed in order of decreasing frequency by SOC and PT. For presentation, AE verbatim text will be coded into a MedDRA term and classified by SOC and PT using MedDRA® version 17.0 or higher. In addition, summaries will be provided by severity (mild, moderate, severe) and by causality (related, not related) to study drug (see Section 15.2.2).

TEAEs and TESAEs leading to discontinuation will be summarized and listed.

Adverse events with onset after the completion of screening but prior to the start of SAGE-547 infusion (considered non-treatment emergent) will be listed by subject.

Clinical laboratory evaluations: Results will be listed by Subject ID and timing of collection. Mean changes from baseline in clinical laboratory measures will be evaluated.

Physical examinations: Physical examinations will be evaluated at Screening and Day 7. Any clinically significant change in physical examination compared to those observed at Screening should be noted as an AE.

Vital signs: Vital signs, including oral temperature (°C), respiratory rate, heart rate, blood pressure (supine and standing), and pulse oximetry will be obtained at the scheduled time points described in Section 12.1.4. Mean changes from baseline (pre-infusion) in vital signs will be evaluated.

12-Lead ECG: The following ECG parameters will be listed for each subject: heart rate, PR, QRS, QT, and QTc. Any clinically significant abnormalities or changes in ECGs should be listed as an AE. ECG findings will be listed by subject and visit.

Concomitant medications: A summary of all concomitant medications taken during the course of the study will be presented in tabular form by therapeutic drug class and generic drug name using the WHO Collaborating Centre for Drug Statistics Methodology Norwegian Institute of Public Health (http://www.whocc.no).

C-SSRS: 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.

SSS: Changes in score over time will be represented graphically, and change from baseline will be measured.

PK Analysis: Plasma will be collected to assay for concentrations of SAGE-547, metabolites of SAGE-547, and SBECD. The following PK parameters will be derived from the plasma concentrations (where evaluable): $AUC_{0\text{-}60}$, AUC_{inf}, C_{max}, time at maximum (peak) plasma concentration (T_{max}), steady-state drug concentration in the plasma during constant-rate infusion (C_{ss}), and average drug concentration in the plasma at steady state during a dosing interval (C_{avg}).

Plasma concentrations will be listed by subject and summarized by nominal collection timepoint. PK parameters will be listed by subject and summarized by collection timepoint. Correlations between concentrations and AEs or tolerability measures may be performed as deemed necessary.

In addition to typical descriptive statistics, summaries should include geometric mean, coefficient of variation, and geometric coefficient of variation.

14.6 Determination of Sample Size

Assuming a two-sided test at an alpha level of 0.10, a sample size of 10 evaluable subjects per group would provide 80% power to detect an effect size of 1.2 between the SAGE-547 and placebo groups with regard to the primary outcome variable of change from baseline in HAMD total score. An effect size of 1.2 corresponds to a placebo adjusted difference of 12 points in the change from baseline in HAMD total score at 60 hours with an assumed standard deviation of 10 points. By including two treatment groups and using a 1:1 randomization ratio, a total of 20 evaluable subjects are required. Assuming a non-evaluability rate of 10%, at least 22 subjects will be randomized.

Based on the results of the interim analysis (see Section 14.7), the sample size could be increased to a maximum of 32 randomized subjects. This adjustment to the sample size would allow for an effect size of 1.0 to be detected.

14.7 Interim Analysis

An interim analysis will be conducted by an independent DSMB for sample size re-estimation purposes when at least 16 subjects have completed efficacy assessments through 60 hours. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in an interim analysis plan.

14.8 Changes From Protocol Specified Analyses

Any changes from the analytical methods outlined in the protocol will be documented in the final SAP.

15 ADVERSE EVENTS

Section 15.1 lists important AE definitions.

Section 15.2 summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

Section 15.3 summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

15.1 Adverse Event Definitions

15.1.1 Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

15.1.2 Suspected Adverse Reaction

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

15.1.3 Life-Threatening

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

15.1.4 Serious

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE (see definition in Section 15.1.3)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- Other medically important condition (as described below)

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include

allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

15.1.5 Unexpected

An AE or suspected adverse reaction is considered "unexpected":

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

"Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

15.2 Investigator Responsibilities

15.2.1 Identification and Documentation of Adverse Events by Investigator

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected during subject preparation, study drug administration during Screening, after the initiation of study drug administration through to Day 3, and at the Follow-up Visits on Day 7 (± 1 day) and Day 30 (± 3 days). SAEs will continue to be collected until the Day 30 (± 3 days) follow-up visit. Medical conditions that occur prior to completion of the Screening Visit will be captured on the Medical History eCRF. Adverse events that occur after completion of the Screening Visit will be recorded on the AE page of the eCRF (AE eCRF).

All AEs revealed by observation, physical examinations, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the AE eCRF. Any clinically significant deterioration from baseline in laboratory assessments or other clinical findings is considered an AE and must be recorded on the AE eCRF, unless otherwise stated. AE information recorded on AE eCRF will be entered into the database on an ongoing basis. The database, including AE information, will be transferred to the Sponsor on a pre-defined schedule for review.

All AEs, 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.

For all SAEs, an SAE report form must be completed with as much information as possible and submitted in the time frame described in Section 15.2.3. When new significant information is obtained as well as when the outcome of an event is known, the SAE report form should be updated on a follow-up report. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject's medical file.

All SAEs will be followed until the events are resolved or improved, a stable status has been achieved, or the subject is lost to follow-up.

15.2.2 Adverse Event Classification

Definitions for the categories of AE classification are included in this section.

16. Relationship to Investigational Drug

Not Related:	The temporal relationship of the clinical event to study drug administration makes causal relationship unlikely AND other drugs, therapeutic interventions, or underlying conditions provide a plausible explanation for the observed event.
Related:	Reasonable temporal relationship of the clinical event to study drug administration AND cannot be reasonably explained by other factors (such as the subject's clinical state, concomitant therapy, and/or other interventions).
Possibly Related:	The temporal relationship of the clinical event to study drug administration makes causal relationship possible but not unlikely AND other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

17. Severity

The severity of an adverse experience will be defined as follows and reported as indicated on the AE eCRF:

Mild:	Discomfort noticed, but no disruption to daily activity.
Moderate:	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.
Severe:	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.

18. Action Taken With Investigational Drug

Action taken with regard to administration of SAGE-547 Injection for this trial will be recorded using the one of following categories (the category "dose increased" does not apply to this trial):

- Drug withdrawn: An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
- Dose not changed: An indication that a medication schedule was maintained.
- Drug interrupted: An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.
- Dose reduced: An indication that a medication schedule was modified to a reduced rate/dose.
- Unknown: Unknown, not known, not observed, not recorded, or refused.
- Not applicable: Determination of a value is not relevant in the current context.

19. Assessment of Outcome

Assessment of outcome of AEs will be categorized as one of the following:

- Recovered/Resolved: The event has improved or recuperated.
- Recovering/Resolving: The event is improving.
- Not Recovered/Not Resolved: The event has not improved or recuperated.
- Recovered/Resolved with Sequel: The subject recuperated but retained pathological conditions resulting from the prior disease or injury.
- Fatal: The termination of life as a result of an adverse event.
- Unknown: Not known, not observed, not recorded, or refused.

15.2.3 Investigator Reporting to Sponsor and Sponsor Emergency Contact

All SAEs that occur during the course of the study must be reported by the Investigator on the designated report form (study-specific SAE form or MedWatch 3500A form) and sent by facsimile to the medical monitor within 24 hours from the point in time when the Investigator becomes aware of the SAE. Investigators must report any SAE, whether or not considered drug related. The initial report must be as complete as possible, including assessment of the causal relationship (i.e., assessment of whether there is a reasonable possibility that the drug caused the event). The medical monitor will contact the investigator via telephone for follow-up information regarding the SAE, as appropriate.

Information not available at the time of the initial report must be documented on a follow-up report. As additional information becomes available, the designated report form must be updated and supporting information, including hospital records, laboratory and diagnostic testing results, etc. All supporting documentation must be de-identified. In addition, all SAEs that occur up to and including 30 days after administration of study drug must be reported within 1 working day from when the Investigator becomes aware of the SAE. A final report to document resolution of all SAEs is required.

In a medical emergency (i.e., an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care and contact the Medical Monitor.

15.2.4 Medical Monitor and Emergency Contact Information

[redacted], MD
[redacted]
Office (9-5 EST): [redacted]
24/7 Hotline: [redacted]

15.2.5 SAE Reporting Contact Information

Contact information and reporting instructions are provided in the Safety Management Plan.

15.2.6 Reporting to Institutional Review Boards (IRBs)

It is the responsibility of the Investigator to promptly notify the institution's IRB of all serious and unexpected suspected adverse reactions (see Section 15.3.2).

15.3 Sponsor/Medical Monitor Responsibilities

15.3.1 Monitoring of Adverse Event Data

The Medical Monitor or designee will review AEs on an ongoing basis.

15.3.2 Reporting to FDA

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32[c][1][i]). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the AE and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

15.4 Emergency Identification of Study Medication

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment from the pharmacist; this normally requires prior approval by the Medical Monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the Medical Monitor may take place after unblinding. The Investigator will not unblind the Medical Monitor during that discussion. The process of

unblinding will ensure that only the investigator is unblinded; the Medical Monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the Medical Monitor, study management team, and data management team.

16 STUDY ADMINISTRATION

16.1 Quality Control and Quality Assurance

The Investigators and institutions will permit trial-related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed ICFs, etc.) in addition to CRFs.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure that this trial 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, CRFs 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 the Sponsor with the Investigator/institution and any other parties involved with the clinical trial will be in writing in a separate agreement.

16.2 Data Handling and Recordkeeping

16.2.1 Data Handling

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

16.2.2 Case Report Form Completion

Electronic CRFs (eCRFs) 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, AEs, and subject status.

The Investigator will have access to the electronic data capture (EDC) 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.

16.2.3 Retention of Study Records

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least two years after the last marketing application approval and until there are no pending or contemplated marketing applications or two years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

16.3 Confidentiality

To maintain subject privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the CRFs 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 the Sponsor. It is understood that there is an obligation to provide the Sponsor 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 authority(ies), other Investigators, corporate partners, or consultants as required.

16.4 Publication Policy

All information concerning SAGE-547 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.

16.5 Protocol Amendments

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (e.g., change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

17 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.

Amin Z, Mason GF, Cavus I et al. The interaction of neuroactive steroids and GABA in the development of neuropsychiatric disorders in women. Pharmacol, Biochem and Behavior 2006;84:635-43.

Austin MP, Middleton P, Reilly NM, Highet NJ. Detection and management of mood disorders in the maternity setting: the Australian Clinical Practice Guidelines. Women Birth 2013;26(1):2-9. doi: 10.1016/j.wombi.2011.12.001. Epub 2012 Jan 2.

Belelli D, Lambert JJ. Neurosteroids: endogenous regulators of the GABA(A) receptor. Nat Rev Neurosci 2005; 6(7):565-75. PMID: 15959466.

Bitran D, Hilvers RJ, Kellogg CK. Anxiolytic effects of 3α-hydroxy-5α[β]-pregnan-20-one: endogenous metabolites of progesterone that are active at the GABAA receptor. Brain Res 1991;561(1):157-161. PMID: 1686744.

Bitran D, Purdy RH, Kellog CK. Anxiolytic effect of progesterone is associated with increases in cortical alloprenanolone and GABAA receptor function. Pharmacol Biochem Behav 1993;45(2):423-8. PMID: 8392205.

Bloch M, Schmidt PJ, Danaceau M, et al. Effects of gonadal steroids in women with a history of postpartum depression. Am J Psychiatry 2000;157(6):924-30. PMID: 10831472.

Chaudron L. Postpartum depression: what pediatricians need to know. Pediatr Rev 2003;24(5);154-61. PMID: 12728188.

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.

Djebaili M, Guo Q, Pettus EH, Hoffman SW, Stein DG. The neurosteroids progesterone and allopregnanolone reduce cell death, gliosis, and functional deficits after traumatic brain injury in rats. J Neurotrauma 2005;22(1):106-18. PMID: 15968816.

Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL. A meta-analysis of cytokines in major depression. Biol Psychiatry 2010;67(5):446-57. PMID: 20015486.

DSM V. Diagnostic and statistical manual of mental disorders (5th ed.). American Psychiatric Association 2013. Arlington, VA: American Psychiatric Publishing.

Earls MF; Committee on Psychosocial Aspects of Child and Family Health American Academy of Pediatrics. Incorporating recognition and management of perinatal and postpartum depression into pediatric practice. Pediatrics 2010;126(5):1032-9. doi: 10.1542/peds.2010-2348.

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. PMID: 17719367.

Epperson CN, Gueorguieva R, Czarkowski KA et al. Preliminary evidence of reduced occipital GABA concentrations in puerperal women: a 1H-MRS study. Psychopharmacol 2006; 186:425-433. PMID: 16724188.

Eser D, Schüle C, Baghai TC, Romeo E, Rupprecht R. Neuroactive steroids in depression and anxiety disorders: clinical studies. Neuroendocrinology 2006;84(4):244-54. PMID: 17159334.

Fihrer I, McMahon CA, Taylor AJ. The impact of postnatal and concurrent maternal depression on child behaviour during the early school years. J Affect Disord 2009;119(1-3):116-23. PMID: 19342104.

Fournier JC, DeRubeis RJ, Hollon SD et al. Antidepressant drug effects and depression severity—a patient-level meta-analysis. JAMA 2010;303:47-53. PMID: 20051569.

Frye CA, Duncan JE. Progesterone metabolites, effective at the GABAA receptor complex, attenuate pain sensitivity in rats. Brain Res 1994;643(1-2):194-203. PMID: 8032914.

Gangisetty O and Reddy DS. Neurosteroid withdrawal regulates GABA-A receptor α4-subunit expression and seizure susceptibility by activation of progesterone receptor-independent early growth response factor-3 pathway. Neuroscience 2010; 170:865-880. PMID: 20670676.

Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, and Swinson T. Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol 2005;106:1071-83. PMID: 16260528.

Gaynes BN, Gavin N, Meltzer-Brody S, Lohr KN, Swinson T, Gartlehner G, et al. Perinatal depression: prevalence, screening accuracy, and screening outcomes. Evid Rep Technol Assess (Summ) 2005;(119):1-8. PMID: 15760246.

Gilbert Evans SE, Ross LE, Sellers EM et al. 3alpha-reduced neuroactive steroids and their precursors during pregnancy and the postpartum period. Gynecol Endocrinol 2005 21, 268-279. PMID: 16373246.

Genazzani AR, Petraglia F, Bernardi F, Casarosa E, Salvestroni C, Tonetti A, et al. Circulating levels of allopregnanolone in humans: gender, age, and endocrine influences. J Clin Endocrinol Metab 1998;83(6):2099-103. PubMed PMID: 9626145.

Glantz LA, Gilmore JH, Overstreet DH, Salimi K, Lieberman JA, Jarskog LF. Pro-apoptotic Par-4 and dopamine D2 receptor in temporal cortex in schizophrenia, bipolar disorder and major depression. Schizophr Res 2010;118(1-3):292-9. PMID: 20067857.

Hamilton M: A rating scale for depression. Journal Neurol Neurosurg Psychiatry 1960; 23:56-62. PMID: 14399272.

He JQ, Tang XW, Chen HX, Xiang Z. [Study on treatment of climacteric depression with bushen tiaogan qingxin recipe]. Zhongguo Zhong Xi Yi Jie He Za Zhi 2004;24(10):889-92. [Article in Chinese]. PMID: 15553820.

Holzbauer M, Birmingham MK, De Nicola AF, Oliver JT. In vivo secretion of 3 alpha-hydroxy-5 alpha-pregnan-20-one, a potent anaesthetic steroid, by the adrenal gland of the rat. J Steroid Biochem. 1985 Jan;22(1):97-102. PubMed PMID: 3974231.

Kask K, Bäckström T, Lundgren P, Sundström Poromaa I. Allopregnanolone has no effect on startle response and prepulse inhibition of startle response in patients with premenstrual dysphoric disorder or healthy controls. Pharmacol Biochem Behav 2009;92(4):608-13. PubMed PMID: 19268499.

Kask K, Bäckström T, Nilsson LG, Sundström-Poromaa I. Allopregnanolone impairs episodic memory in healthy women. Psychopharmacology (Berl) 2008;199(2):161-8. PMID: 18551282.

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. PMID: 18303940.

Klak J, Hill M, Parízek A, Havlíková H, et al. Pregnanolone isomers, pregnenolone and their polar conjugates around parturition. Physiol Res 2003;52(2):211-21. PMID: 12678664.

Licinio J, Wong ML. The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. Mol Psychiatry 1999;4(4):317-27. PMID: 10483047.

Luisi S, Petraglia F, Benedetto C, Nappi RE, Bernardi F, Fadalti M, et al. Serum allopregnanolone levels in pregnant women: changes during pregnancy, at delivery, and in hypertensive patients. J Clin Endocrinol Metab 2000;85(7):2429-33. PMID: 10902789.

Maguire J, Mody I. GABA(A)R plasticity during pregnancy: relevance to postpartum depression. Neuron 2008;59(2):207-13. PMID: 18667149.

Maguire J, Ferando I, Simonsen C, Mody I. Excitability changes related to GABAA receptor plasticity during pregnancy. J Neurosci 2009;29(30):9592-601. PMID: 19641122.

Majewska MD, Harrison NL, Schwartz RD, Barker JL, Paul SM. Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor. Science 1986;232:1004-7. PMID: 2422758.

McDowell, I. Measuring Health: A guide to rating scales and questionnaires. 2006: 3rd Ed. New York: Oxford University Press.

Morrow AL, Devaud LL, Purdy RH, Paul SM. Neuroactive steroid modulators of the stress response. Ann N Y Acad Sci 1995;771:257-72. PMID: 8597405.

Müller-Thomsen T, Arlt S, Mann U, Maß R, Ganzer S. Detecting depression in Alzheimer's disease: evaluation of four different scales. Archives of Clinical Neuropsychology 2005;20:271-6. PMID: 15708735.

Nappi RE, Petraglia F, Luisi S et al. Serum allopregnanolone in women with postpartum "blues". Obstet Gynecol 2001;97 (1):77-80. PMID: 11152912.

Navarro PA, Kaddouz D, de Ziegler D, Silva de Sá MF, Ferriani RA. Vaginal administration of allopregnanolone to postmenopausal women undergoing estrogen replacement therapy: preliminary results. Maturitas 2003;46(2):147-52. PubMed PMID: 14559386.

Norberg L, Backstrom T and Wahlstrom G. Anaesthetic effects of pregnanolone in combination with allopregnanolone, thiopental, hexobarbital and flurazepam: an EEG study in the rat. Br J Anaesth 1999; 82(5):731-737. PMID: 10536552.

O'Hara MW, Wisner KL. Perinatal mental illness: definition, description and aetiology. Best Pract Res Clin Obstet Gynaecol 2014;28(1):3-12. doi: 10.1016/j.bpobgyn.2013.09.002.

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.

Ottander U, Poromaa IS, Bjurulf E, Skytt A, Bäckström T, Olofsson JI. Allopregnanolone and pregnanolone are produced by the human corpus luteum. Mol Cell Endocrinol 2005 Jul 15;239(1-2):37-44. PubMed PMID: 15935549.

Paoletti AM, Romagnino S, Contu R, et al. Observational study on the stability of the psychological status during normal pregnancy and increased blood levels of neuroactive steroids with GABA-A receptor agonist activity. Psychoneuroendocrinology 2006; 31(4): 485-492. PMID: 16406349.

Paul SM, Purdy RH. Neuroactive steroids. FASEB J 1992;6(6):2311-22. PMID: 1347506.

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. doi: 10.1176/appi.ajp.2011.10111704.

Romeo E, Ströhle A, Spalletta G, di Michele F, Hermann B, Holsboer F, Pasini A, Rupprecht R. Effects of antidepressant treatment on neuroactive steroids in major depression. Am J Psychiatry 1998;155(7):910-3. PMID: 9659856.

Sayeed I, Parvez S, Wali B, Siemen D, Stein DG. Direct inhibition of the mitochondrial permeability transition pore: a possible mechanism for better neuroprotective effects of allopregnanolone over progesterone. Brain Res 2009;1263:165-73. PMID: 19368823.

Schüle C, Romeo E, Uzunov DP, Eser D, di Michele F, Baghai TC, et al. Influence of mirtazapine on plasma concentrations of neuroactive steroids in major depression and on 3α-hydroxysteroid dehydrogenase activity. Mol Psychiatry 2006;11(3):261-72. PMID: 16344854.

Schüle C, Baghai TC, di Michele F, Eser D, Pasini A, Schwarz M. Effects of combination treatment with mood stabilizers and mirtazapine on plasma concentrations of neuroactive steroids in depressed patients. Psychoneuroendocrinology 2007;32(6):669-80. PMID: 17560730.

Shelton RC, Trivedi MH. Moderators of antidepressant response in major depression. J Clin Psychiatry 2011;72(10):e32. PMID: 22075105.

Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. Arch Intern Med 2006; 166(10):1092-1097. doi: 10.1001/archinte.166.10.1092.

Timby E, Balgård M, Nyberg S, Spigset O, Andersson A, Porankiewicz-Asplund J, et al. Pharmacokinetic and behavioral effects of allopregnanolone in healthy women. Psychopharmacology (Berl) 2006 Jun;186(3):414-24. PMID: 16177884.

Timby E, Hedström H, Bäckström T, Sundström-Poromaa I, Nyberg S, Bixo M. Allopregnanolone, a GABAA receptor agonist, decreases gonadotropin levels in women A preliminary study. Gynecol Endocrinol 2011 Dec;27(12):1087-93. PMID: 21190418. (Timby 2011a)

Timby E. Allopregnanolone effects in women. Clinical studies in relation to the menstrual cycle, premenstrual dysphoric disorder and oral contraceptive use. Umea University Medical Dissertation 2011; New Series No. 1459. (Timby 2011b)

Uzunova V, Sheline Y, Davis JM, Rasmusson A, Uzunov DP, Costa E, et al. Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine. Proc Natl Acad Sci 1998;95(6):3239-44. PMID: 9501247.

van Broekhoven F, Bäckström T, van Luijtelaar G, Buitelaar JK, Smits P, Verkes RJ. Effects of allopregnanolone on sedation in men, and in women on oral contraceptives. Psychoneuroendocrinology. 2007 Jun;32(5):555-64. PMID: 17470385.

Verbeek T, Bockting CL, van Pampus MG et al. Postpartum depression predicts offspring mental health problems in adolescence independently of parental lifetime psychopathology. J Affect Disord 2012;136(3):948-54. doi: 10.1016/j.jad.2011.08.035.

Wieland S, Lan NC, Mirasedeghi S, Gee KW. Anxiolytic activity of the progesterone metabolite 5α-pregnan-3α-ol-20-one. Brain Res 1991;565(2):263-8. PMID: 1688192.

18 APPENDICES

Copies of the rating scales and questionnaires included in APPENDIX 1 through APPENDIX 9 are for reference only.

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APPENDIX 1. Columbia Suicide Severity Rating Scale (C-SSRS)

The “Baseline” and “Since Last Visit” versions of the C-SSRS begin on the next full page (Posner et al. 2011).

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***) Past X Months - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103-130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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APPENDIX 2. Hamilton Rating Scale for Depression, 17-Item (HAMD)

The HAMD presents on the next full page (Hamilton 1960).

The HAMD total score will be calculated as the sum of the 17 individual item scores. Item 16 can be rated according to history (item 16A) or actual weight change (item 16B). The item 16 score is calculated as the item 16 response that is not equal to 3 (i.e., “Not assessed).

Patient Name:_____ Date:_____

Hamilton Rating Scale for Depression (17-items)

Instructions: For each item select the "cue" which best characterizes the patient during the past week.

1. **Depressed Mood**
(sadness, hopeless, helpless, worthless)
0 Absent
1 These feeling states indicated only on questioning
2 These feeling states spontaneously reported verbally
3 Communicates feeling states nonverbally, i.e., through facial expression, posture, voice and tendency to weep
4 Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and nonverbal communication

2. **Feelings of Guilt**
0 Absent
1 Self-reproach, feels he has let people down
2 Ideas of guilt or rumination over past errors or sinful deeds
3 Present illness is a punishment. Delusions of guilt
4 Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. **Suicide**
0 Absent
1 Feels life is not worth living
2 Wishes he were dead or any thoughts of possible death to self
3 Suicide ideas or gesture
4 Attempts at suicide (any serious attempt rates 4)

4. **Insomnia - Early**
0 No difficulty falling asleep
1 Complains of occasional difficulty falling asleep i.e., more than ½ hour
2 Complains of nightly difficulty falling asleep

5. **Insomnia - Middle**
0 No difficulty
1 Patient complains of being restless and disturbed during the night
2 Waking during the night – any getting out of bed rates 2 (except for purposes of voiding)

6. **Insomnia - Late**
0 No difficulty
1 Waking in early hours of the morning but goes back to sleep
2 Unable to fall asleep again if gets out of bed

7. **Work and Activities**
0 No difficulty
1 Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
2 Loss of interest in activity; hobbies or work – either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
3 Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores.
4 Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores, or if patient fails to perform ward chores unassisted.

8. **Retardation**
(slowness of thought and speech; impaired ability to concentrate; decreased motor activity)
0 Normal speech and thought
1 Slight retardation at interview
2 Obvious retardation at interview
3 Interview difficult
4 Complete stupor

9. **Agitation**
0 None
1 "Playing with" hand, hair, etc.
2 Hand-wringing, nail-biting, biting of lips

10. **Anxiety - Psychic**
0 No difficulty
1 Subjective tension and irritability
2 Worrying about minor matters
3 Apprehensive attitude apparent in face or speech
4 Fears expressed without questioning

11. **Anxiety - Somatic**
0 Absent
1 Mild
2 Moderate
3 Severe
4 Incapacitating
Physiological concomitants of anxiety such as:
Gastrointestinal - dry mouth, wind, indigestion, diarrhea, cramps, belching
Cardiovascular – palpitations, headaches
Respiratory - hyperventilation, sighing
Urinary frequency
Sweating

12. **Somatic Symptoms - Gastrointestinal**
0 None
1 Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
2 Difficulty eating without staff urging. Requests or requires laxatives or medications for bowels or medication for G.I. symptoms.

13. **Somatic Symptoms - General**
0 None
1 Heaviness in limbs, back or head, backaches, headache, muscle aches, loss of energy and fatigability
2 Any clear-cut symptom rates 2

14. **Genital Symptoms**
0 Absent
1 Mild
2 Severe
0 Not ascertained
Symptoms such as: loss of libido, menstrual disturbances

15. **Hypochondriasis**
0 Not present
1 Self-absorption (bodily)
2 Preoccupation with health
3 Frequent complaints, requests for help, etc.
4 Hypochondriacal delusions

16. **Loss of Weight**
A. When Rating by History:
0 No weight loss
1 Probable weight loss associated with present illness
2 Definite (according to patient) weight loss

B. On Weekly Ratings by Ward Psychiatrist, When Actual Changes are Measured:
0 Less than 1 lb. weight loss in week
1 Greater than 1 lb. weight loss in week
2 Greater than 2 lb. weight loss in week

17. **Insight**
0 Acknowledges being depressed and ill
1 Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2 Denies being ill at all

Total Score:_____

APPENDIX 3. Montgomery Asberg Depression Rating Scale (MADRS)

The MADRS presents on the next full page. (McDowell 2006, Müller-Thomsen 2005).

Montgomery-Åsberg Depression Rating Scale (MADRS)

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5) and then report the appropriate number. The items should be rated with regards to how the patient has done over the past week.

1. Apparent sadness

Representing despondency, gloom and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

0 = No sadness.
2 = Looks dispirited but does brighten up without difficulty.
4 = Appears sad and unhappy most of the time.
6 = Looks miserable all the time. Extremely despondent

2. Reported sadness

Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope.

0 = Occasional sadness in keeping with the circumstances.
2 = Sad or low but brightens up without difficulty.
4 = Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
6 = Continuous or unvarying sadness, misery or despondency.

3. Inner tension

Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 = Placid. Only fleeting inner tension.
2 = Occasional feelings of edginess and ill-defined discomfort.
4 = Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
6 = Unrelenting dread or anguish. Overwhelming panic.

4. Reduced sleep

Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

0 = Sleeps as normal.
2 = Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
4 = Moderate stiffness and resistance
6 = Sleep reduced or broken by at least 2 hours.

5. Reduced appetite

Representing the feeling of a loss of appetite compared with when-well. Rate by loss of desire for food or the need to force oneself to eat.

0 = Normal or increased appetite.
2 = Slightly reduced appetite.
4 = No appetite. Food is tasteless.
6 = Needs persuasion to eat at all.

6. Concentration difficulties

Representing difficulties in collecting one's thoughts mounting to an incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.
0 = No difficulties in concentrating.
2 = Occasional difficulties in collecting one's thoughts.
4 = Difficulties in concentrating and sustaining thought which reduced ability to read or hold a conversation.
6 = Unable to read or converse without great difficulty.

7. Lassitude

Representing difficulty in getting started or slowness in initiating and performing everyday activities.
0 = Hardly any difficulty in getting started. No sluggishness.
2 = Difficulties in starting activities.
4 = Difficulties in starting simple routine activities which are carried out with effort.
6 = Complete lassitude. Unable to do anything without help.

8. Inability to feel

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.
0 = Normal interest in the surroundings and in other people.
2 = Reduced ability to enjoy usual interests.
4 = Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
6 = The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. Pessimistic thoughts

Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.
0 = No pessimistic thoughts.
2 = Fluctuating ideas of failure, self-reproach or self- depreciation.
4 = Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
6 = Delusions of ruin, remorse or irredeemable sin. Self- accusations which are absurd and unshakable.

10. Suicidal thoughts

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicide attempts should not in themselves influence the rating.
0 = Enjoys life or takes it as it comes.
2 = Weary of life. Only fleeting suicidal thoughts.
4 = Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intenstion.
6 = Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

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APPENDIX 4. Clinical Global Impression–Improvement Scale (CGI-I) and Severity Scale (CGI-S)

The CGI-I and CGI-S presents on the next full page. For the purposes of Protocol 547-PPD-202, only Items 1 and 2, Severity of Illness and Global Improvement, will be assessed in subjects enrolled in the study.

1. **Severity of illness**
   Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?
   0 = Not assessed
   1 = Normal, not at all ill
   2 = Borderline mentally ill
   3 = Mildly ill
   4 = Moderately ill
   5 = Markedly ill
   6 = Severely ill
   7 = Among the most extremely ill patients

2. **Global improvement:** Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.
   Compared to his condition at admission to the project, how much has he changed?
   0 = Not assessed
   1 = Very much improved
   2 = Much improved
   3 = Minimally improved
   4 = No change
   5 = Minimally worse
   6 = Much worse
   7 = Very much worse

3. **Efficacy index:** Rate this item on the basis of **drug effect only**.
   Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.
   EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		**Side effects**			
		None	*Do not significantly interfere with patient's functioning*	*Significantly interferes with patient's functioning*	*Outweighs therapeutic effect*
Marked	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
Moderate	Decided improvement. Partial remission of symptoms	05	06	07	08
Minimal	Slight improvement which doesn't alter status of care of patient	09	10	11	12
Unchanged or worse		13	14	15	16

Not assessed = 00

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

APPENDIX 5. Stanford Sleepiness Scale (SSS)

The SSS presents on the next full page.

Stanford Sleepiness Scale

This is a quick way to assess how alert you are feeling. If it is during the day when you go about your business, ideally you would want a rating of a one. Take into account that most people have two peak times of alertness daily, at about 9 a.m. and 9 p.m. Alertness wanes to its lowest point at around 3 p.m.; after that it begins to build again. Rate your alertness at different times during the day. If you go below a three when you should be feeling alert, this is an indication that you have a serious sleep debt and you need more sleep.

An Introspective Measure of Sleepiness
The Stanford Sleepiness Scale (SSS)

Degree of Sleepiness	**Scale Rating**
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

APPENDIX 6. Edinburgh Postnatal Depression Scale (EPDS)

The EPDS presents on the next full page (Cox et al. 1987).

Study ID:

Edinburgh Postnatal Depression Scale

As you are pregnant or have recently had a baby, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**, not just how you feel today.

Here is an example, already completed.

I have felt happy:
☐ Yes, all the time
☒ Yes, most of the time This would mean: "I have felt happy most of the time" during the past week.
☐ No, not very often
☐ No, not at all

Please complete the other questions in the same way.

In the past 7 days:

1. I have been able to laugh and see the funny side of things
☐ As much as I always could
☐ Not quite so much now
☐ Definitely not so much now
☐ Not at all

2. I have looked forward with enjoyment to things
☐ As much as I ever did
☐ Rather less than I used to
☐ Definitely less than I used to
☐ Hardly at all

***3. I have blamed myself unnecessarily when things went wrong**
☐ Yes, most of the time
☐ Yes, some of the time
☐ Not very often
☐ No, never

4. I have been anxious or worried for no good reason
☐ No, not at all
☐ Hardly ever
☐ Yes, sometimes
☐ Yes, very often

***5 I have felt scared or panicky for no very good reason**
☐ Yes, quite a lot
☐ Yes, sometimes
☐ No, not much
☐ No, not at all

***6. Things have been getting on top of me**
☐ Yes, most of the time I haven't been able to cope at all
☐ Yes, sometimes I haven't been coping as well as usual
☐ No, most of the time I have copied quite well
☐ No, I have been coping as well as ever

***7 I have been so unhappy that I have had difficulty sleeping**
☐ Yes, most of the time
☐ Yes, sometimes
☐ Not very often
☐ No, not at all

***8 I have felt sad or miserable**
☐ Yes, most of the time
☐ Yes, quite often
☐ Not very often
☐ No, not at all

***9 I have been so unhappy that I have been crying**
☐ Yes, most of the time
☐ Yes, quite often
☐ Only occasionally
☐ No, never

***10 The thought of harming myself has occurred to me**
☐ Yes, quite often
☐ Sometimes
☐ Hardly ever
☐ Never

APPENDIX 7. Generalized Anxiety Disorder 7-Item Scale (GAD-7)

The GAD-7 presents on the next full page (Spitzer 2006).

Generalized Anxiety Disorder 7-item (GAD-7) scale

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	
Total Score *(add your column scores)* =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all _____
Somewhat difficult _____
Very difficult _____
Extremely difficult _____

APPENDIX 8. Patient Health Questionnaire (PHQ-9)

The PHQ-9 presents on the next full page.

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

APPENDIX 9. Barkin Index of Maternal Functioning (BIMF)

The BIMF is presented on the next full page.

Barkin Index of Maternal Functioning

Please **circle the number** that best represents how you have felt **over the past two weeks**. Please try to answer each question as honestly as possible as your responses will help us to better understand the postpartum experience.

	Strongly Disagree	Disagree	Somewhat Disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
1. I am a good mother.	0	1	2	3	4	5	6
2. I feel rested.	0	1	2	3	4	5	6
3. I am comfortable with the way I've chosen to feed my baby (either bottle or breast, or both).	0	1	2	3	4	5	6
4. My baby and I understand each other.	0	1	2	3	4	5	6
5. I am able to relax and enjoy time with my baby.	0	1	2	3	4	5	6
6. There are people in my life that I can trust to care for my baby when I need a break.	0	1	2	3	4	5	6
7. *I am comfortable* allowing a trusted friend or relative to care for my baby (can include baby's father or partner).	0	1	2	3	4	5	6
8. I am getting enough adult interaction.	0	1	2	3	4	5	6
9. I am getting enough encouragement from other people.	0	1	2	3	4	5	6
10. I trust my own feelings (instincts) when it comes to taking care of my baby.	0	1	2	3	4	5	6
11. I take a little time each week to do something for myself.	0	1	2	3	4	5	6
12. I am taking good care of my baby's physical needs (feedings, changing diapers, doctor's appointments).	0	1	2	3	4	5	6
13. I am taking good care of my physical needs (eating, showering, etc).	0	1	2	3	4	5	6
14. I make good decisions about my baby's health and well being.	0	1	2	3	4	5	6
15. My baby and I are getting into a routine.	0	1	2	3	4	5	6
16. I worry about how other people judge me (as a mother).	0	1	2	3	4	5	6
17. I am able to take care of my baby and my other responsibilities.	0	1	2	3	4	5	6
18. Anxiety or worry often interferes with my mothering ability.	0	1	2	3	4	5	6
19. *As time goes on*, I am getting better at taking care of my baby.	0	1	2	3	4	5	6
20. I am *satisfied* with the job I am doing as a new mother.	0	1	2	3	4	5	6

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APPENDIX 10. Selected Inducers, Inhibitors, and Substrates of CYP2C9

Inhibitors of CYP2C9 can be classified by their potency, such as:

- **Strong** being one that causes at least a 5-fold increase in the plasma AUC values, or more than 80% decrease in clearance.
- **Moderate** being one that causes at least a 2-fold increase in the plasma AUC values, or 50-80% decrease in clearance.
- **Weak** being one that causes at least a 1.25-fold but less than 2-fold increase in the plasma AUC values, or 20-50% decrease in clearance.

Substrates	Inhibitors	Inducers

• NSAIDs (analgesic, antipyretic, anti-inflammatory)
  ○ celecoxib
  ○ lornoxicam
  ○ diclofenac
  ○ ibuprofen
  ○ naproxen
  ○ ketoprofen
  ○ piroxicam
  ○ meloxicam
  ○ suprofen
• phenytoin (antiepileptic)
• fluvastatin (statin)
• sulfonylureas (antidiabetic)
  ○ glipizide
  ○ glibenclamide
  ○ glimepiride
  ○ tolbutamide
  ○ glyburide
• angiotensin II receptor antagonists (in hypertension, diabetic nephropathy, CHF)
  ○ irbesartan
  ○ losartan
• S-warfarin (anticoagulant)
• sildenafil (in erectile dysfunction)
• terbinafine (antifungal)
• amitriptyline (tricyclic antidepressant)
• fluoxetine (SSRI antidepressant)
• nateglinide (antidiabetic)
• rosiglitazone (antidiabetic)
• tamoxifen (SERM)
• torasemide (loop diuretic)
• ketamine
• THC
• JWH-018
• AM-2201
	Strong
	• fluconazole (antifungal)
	• miconazole (antifungal)
	• amentoflavone (constituent of Ginkgo biloba and St. John's Wort)
	• sulfaphenazole (antibacterial)
	• valproic acid (anticonvulsant, mood-stabilizing)
	• apigenin
	
	Moderate
	• amiodarone (antiarrhythmic)
	
	Unspecified potency
	• antihistamines (H_1 receptor antagonists)
	  ○ cyclizine
	  ○ promethazine
	• chloramphenicol
	• fenofibrate (fibrate)
	• flavones
	• flavonols
	• fluvastatin (statin)
	• fluvoxamine (SSRI)
	• isoniazid (in tuberculosis)
	• lovastatin (statin)
	• phenylbutazone (NSAID)
	• probenecid (uricosuric)
	• sertraline (SSRI)
	• sulfamethoxazole (antibiotic)
	• teniposide (chemotherapeutic)
	• voriconazole (antifungal)
	• zafirlukast (leukotriene antagonist)
	• quercetin (anti-inflammatory)
		Strong
		• rifampicin (bactericidal)
		• secobarbital (barbiturate)