Official Title: **A Multicenter, Open-label Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Brexanolone in the Treatment of Adolescent Female Subjects With Postpartum Depression**

NCT Number: NCT03665038

Document Date: Protocol Version 4.0: 20 December 2019

1. PROTOCOL AND AMENDMENTS

Version Number	Date	Title
Initial	**Version 1.0, 23 January 2018**	A Multicenter, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of Brexanolone in the Treatment of Adolescent Female Subjects with Postpartum Depression
Amendment 1	**Version 2.0, 11 September 2018**	A Multicenter, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of Brexanolone in the Treatment of Adolescent Female Subjects with Postpartum Depression
Amendment 2	**Version 3.0, 03 June 2019**	A Multicenter, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of Brexanolone in the Treatment of Adolescent Female Subjects with Postpartum Depression
Amendment 3	**Version 4.0, 20 December 2019**	A Multicenter, Open-Label Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Brexanolone in the Treatment of Adolescent Female Subjects with Postpartum Depression

A MULTICENTER, OPEN-LABEL STUDY EVALUATING THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF BREXANOLONE IN THE TREATMENT OF ADOLESCENT FEMALE SUBJECTS WITH POSTPARTUM DEPRESSION

PROTOCOL NUMBER: 547-PPD-304

IND NUMBER: 122,279

EUDRACT NUMBER: 2017-004356-34

Study drug	Brexanolone
Clinical Phase	3
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sage Contact and Sage Medical Monitor	[redacted], MD [redacted] Cambridge, MA 02142 Phone: [redacted]
Date of Original Protocol	Version 1.0, 23 January 2018
Date of Amendment 1	Version 2.0, 11 September 2018
Date of Amendment 2	Version 3.0, 03 June 2019
Date of Amendment 3	Version 4.0, 20 December 2019

PROTOCOL SIGNATURE PAGE

Protocol Number:	547-PPD-304
Product:	Brexanolone
IND No.:	122,279
EudraCT No.:	2017-004356-34
Study Phase:	3
Sponsor:	Sage Therapeutics
Protocol Date:	Version 4.0 20 December 2019

Sponsor Approval

[redacted] MD [redacted]

20 DEC 2019

Date (DD Month YYYY)

[redacted] PhD

20 Dec 2019

Date (DD Month YYYY)

[redacted]

20 Dec 2019

Date (DD Month YYYY)

[redacted] PhD [redacted]

20 DEC 2019

Date (DD Month YYYY)

[redacted] MS [redacted]

20 Dec 2019

Date (DD Month YYYY)

[redacted] DVM, MS, MPH [redacted]

20 DEC 2019

Date (DD Month YYYY)

INVESTIGATOR'S AGREEMENT

I have read the Clinical Protocol 547-PPD-304 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (DD Month YYYY)

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Sage Study Physician and 24-Hour Emergency Contact	[redacted], MD	Cambridge, MA 02142 Phone: [redacted]
Worldwide Clinical Trials Medical Monitor	[redacted], MD	1000 Continental Drive King of Prussia, PA 19406, Mobile: [redacted] Office: [redacted]
SAE Reporting Information	IQVIA Lifecycle Safety (LS)	4820 Emperor Boulevard Durham, NC 27703 Email: [redacted] Fax: [redacted] SAE Hotline: [redacted]
Product Complaint Contact	Sage Therapeutics	e-mail: [redacted] Phone: [redacted]

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics
215 First Street
Cambridge, MA 02142

Name of Study drug:
Brexanolone

Name of Active Ingredient:
Brexanolone (USAN), also known as allopregnanolone (scientific name)

Title of Study: A Multicenter, Open-Label Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Brexanolone in the Treatment of Adolescent Female Subjects with Postpartum Depression

Study center(s): A global study at up to 50 sites

Phase of development: 3

Objectives:

Primary Objective:

- The primary objective of the study is to evaluate the safety and tolerability of brexanolone when administered to adolescent female subjects diagnosed with PPD.

Secondary Objectives:

- To assess the plasma pharmacokinetic (PK) profile of brexanolone and, when appropriate, metabolites of brexanolone
- [redacted]
- [redacted]

Methodology:

In previous Versions 1 through 3 of this protocol, subjects were randomly assigned to active or placebo study drug in a blinded manner. With the current Amendment 3/Version 4, the study has been converted to an open-label study where all subjects will receive brexanolone.

This is a Phase 3, open-label study designed to evaluate the safety, tolerability and PK, of brexanolone in adolescent female subjects diagnosed (by Structured Clinical Interview for DSM-5 Axis I Disorders [SCID-5]) with PPD. Subjects will be administered a single, 60-hour continuous IV infusion of brexanolone.

Screening Period:

The Screening Period begins with the informed consent process at the Screening Visit, which can occur on any one calendar day of a 14-day window (from Day -14 through Day -1, inclusive). Subjects will undergo procedures at the Screening Visit to determine eligibility, including completion of the [redacted]

Treatment Period:

The Treatment Period is the period from the start of the assessments on Day 1 prior to initiation of brexanolone through the 72-hour assessments on Day 3. The 60-hour infusion will be administered as follows: 30 mcg/kg/hour (Hour 0 to 4), then 60 mcg/kg/hour (Hour 4 to 24), then 90 mcg/kg/hour (Hour 24 to 52), followed by 60 mcg/kg/hour (Hour 52 to 56), and 30 mcg/kg/hour (Hour 56 to 60). A programmable peristaltic infusion pump will be used to ensure accurate delivery of brexanolone.

Due to the risk of excessive sedation and sudden loss of consciousness, for the duration of the infusion, subjects will be monitored for hypoxia using continuous pulse oximetry equipped with an alarm, and will be assessed for excessive sedation by a healthcare provider every 2 hours during planned, non-sleep periods. Subjects must not be the primary caregiver of dependents and must be accompanied during any interactions with their child(ren) that occur during the infusion.

If excessive sedation occurs at any time during the infusion, the infusion will be stopped until the symptoms resolve. The infusion may be resumed at the same or lower dose as clinically appropriate. The infusion will be immediately stopped if pulse oximetry reveals hypoxia. After an episode of hypoxia, the infusion should not be resumed. Subjects will remain confined through the completion of the brexanolone infusion and Hour 72 assessments. If deemed medically appropriate by the investigator, subjects may be discharged after completing the Hour 72 assessments. Subjects will be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving, until any sedative effects have dissipated.

For lactating subjects, the investigator and subject should weigh the developmental and health benefits of breastfeeding during the infusion against any potential adverse effects on the breastfed child from brexanolone or from the underlying maternal condition. Subjects may continue to breastfeed or express milk to feed their infant during the infusion if the benefit is deemed to outweigh the risk. During the study, a qualified lactation consultant will be made available to subjects upon request.

Safety and efficacy assessments will be performed as outlined in the Schedule of Assessments (Table 2); blood samples will be collected and will be analyzed for concentrations of brexanolone and may be analyzed for concentrations of brexanolone metabolites.

Follow-up Period: Follow-up visits will be conducted through Day 30. Psychiatric review for worsening symptoms of depression will be available during the study and psychiatric follow-up after the end of the study will be arranged as needed by the Investigator and will be documented.

An independent data safety monitoring board will monitor the clinical data for safety signals throughout the study. In order to perform their monitoring function, the board will have access to all safety data as necessary.

Number of subjects (planned):

Qualified subjects 15 to 17 years old (inclusive) will be enrolled in the study. Enrollment will continue until approximately 20 subjects have been treated with brexanolone. The planned sample size of 20 includes those subjects who received brexanolone as blinded study drug during earlier versions of the protocol when the study was a randomized, double-blind, placebo-controlled study.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Subject (and parent/guardian, per local regulations) has signed the appropriate informed consent form prior to any study-specific procedures being performed.
2. Subject is ambulatory, female, and it is confirmed that she will be 15 to 17 years of age (inclusive) through completion of study drug infusion.
3. Subject agrees to adhere to the study requirements.
4. (Removed)
5. 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 SCID-5.
6. Subject has a [redacted] total score of ≥20 at screening and Day 1 (prior to initiation of the study drug infusion).
7. Subject is ≤6 months postpartum at screening.
8. Subject is willing at screening to delay the start of any new pharmacotherapy regimens, including antidepressant or antianxiety medication until the study drug infusion and 72-hour assessments have been completed.
9. If the subject is taking medications administered to treat the symptoms of depression or anxiety (such as anxiolytics or antidepressants), these must be at a stable dose from 30 days prior to dosing until the completion of the 72-hour assessments.
10. Subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the end of the study drug infusion, unless she is surgically sterile (either bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or does not engage in sexual relations which carry a risk of pregnancy:
    - Combined oral, intravaginal, or transdermal (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation
    - Oral, injectable, or implantable progesterone-only hormonal contraception associated with inhibition of ovulation
    - Intrauterine device
    - Intrauterine hormone-releasing system
    - Bilateral tubal occlusion
    - Vasectomized partner
11. Subject agrees not to be the primary caregiver of any dependents during the infusion.

Exclusion criteria:

1. Subject has a positive pregnancy test at screening or Day 1 (prior to initiation of the study drug infusion).
2. Subject's most recent pregnancy resulted in a miscarriage, still birth, or neonatal death; or subject has terminated parental rights (eg, child has been placed for adoption).
3. Subject has end stage renal disease.
4. Subject is in hepatic failure.
5. Subject is anemic (hemoglobin ≤10 g/dL).

6. Subject has untreated or inadequately treated hypothyroidism or hyperthyroidism.
7. Subject has known allergy to progesterone or allopregnanolone.
8. Subject has active psychosis per Investigator assessment.
9. Subject has attempted suicide during current episode of PPD.
10. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
11. Subject has current/active alcohol or drug abuse (including benzodiazepines) within the 30 days prior to screening as assessed by the Investigator. A positive urine drug screen is exclusionary unless deemed by the investigator to reflect a prescribed medication.
12. Subject has exposure to another investigational medication or device within 30 days prior to screening.
13. Subject has previously participated in this study or any other study employing brexanolone, SAGE-217, ganaxolone, any other compound containing allopregnanolone, or has received treatment with ZULRESSO™.
14. Subject is investigative site personnel, sponsor personnel, or an immediate member of their family (spouse, parent, child, or sibling whether biological or legally adopted).
15. Subject has received electroconvulsive therapy within 14 days prior to screening and/or plans to receive electroconvulsive therapy before the Study Day 7 visit.

Study drug, Dosage and Mode of Administration:

Brexanolone will be administered as a single, continuous, 60-hour intravenous (IV) infusion, administered according to the following dose regimen.

Time point	**Day 1 0 to 4 hours**	**Day 1 4 to 24 hours**	**Day 2-3 24 to 52 hours**	**Day 3 52 to 56 hours**	**Day 3 56 to 60 hours**
Dose	30 mcg/kg/hour	60 mcg/kg/hour	90 mcg/kg/hour	60 mcg/kg/hour	30 mcg/kg/hour

Reference therapy, dosage and mode of administration:

This is an open-label study with no control group.

Duration of participation: Each subject's involvement is up to 47 days, including a maximum 14-day Screening Period, a 3-day Treatment Period (60 hours of treatment and an additional 12 hours for completion of 72-hour assessments), and a Follow-up Period through Day 30 (±3 days).

Criteria for evaluation:

Primary Endpoint

- Incidence of treatment-emergent adverse events

Secondary Endpoints

- PK parameters derived from plasma concentrations of brexanolone and, when appropriate, metabolites of brexanolone

[redacted]

- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Mean changes from baseline in clinical laboratory measures, vital signs, ECGs and concomitant medication usage. [redacted]

Statistical methods:

General Considerations

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

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

Analysis Sets and Methods

Efficacy Set

The Efficacy Set will be defined as all subjects who initiate study drug infusion and have at least one post-baseline efficacy evaluation. Efficacy data will be analyzed using appropriate descriptive statistics and pre-specified statistical methods; subject listings will be provided for all efficacy data.

The change from baseline in [redacted] total score and binary efficacy endpoints, including Responder and Remission, will be appropriately summarized.

Safety Set

The Safety Set, defined as all subjects administered study drug, will be used to provide descriptive summaries of safety data. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA™). The overall incidence of treatment-emergent adverse events (TEAEs) will be displayed by treatment group and by System Organ Class and preferred term. The incidence of TEAEs will also be presented by maximum severity and relationship to study drug and by treatment group. Vital signs, clinical laboratory measures, ECG, and [redacted] data will be summarized by treatment group. Out-of-range safety endpoints may be categorized as low or high, where applicable.

Pharmacokinetic Set

The PK Set is defined as all subjects in the Safety Set for whom at least one evaluable post-baseline PK sample is available. The PK parameters, which will include AUC_{0-60}, AUC_{∞}, C_{max}, t_{max}, C_{ss}, and C_{avg}, will be summarized by descriptive statistics, including n, mean, SD, median, minimum, and maximum values, and listed by subject. In addition, PK data collected in this study may be combined with data from other studies in adolescent and adult subjects for population-PK and exposure-response analyses.

PK analyses may include determination of plasma concentration of brexanolone if a serious AE occurs.

Sample Size Calculation

No formal sample size calculation was made for this study. The planned sample size of 20 adolescent subjects treated with brexanolone should be appropriate to characterize the PK and safety profile.

Table 2: Schedule of Assessments

Study Procedure	Screening Period	Treatment Period/Inpatient Stay (Day 1 to Day 3)												Follow-up Period			
Visit Days	**D -14 to -1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D2**	**D2**	**D2**	**D3**	**D3**	**D3**	**D7 (±1d)**	**D14 and/or ET (±2d)**	**D21 (±3d)**	**D30 (±3d)**
Hour		**H0***	**H2**	**H4**	**H8**	**H12**	**H24**	**H30**	**H36**	**H48**	**H54**	**H60**	**H72**				
Informed consent process [a]	X																
Inclusion/exclusion criteria	X	X															
Demographics	X																
Medical history	X																
Height	X																
SCID-5	X																
Physical examination [b]	X												X		X		
Body weight	X												X		X		X
Clinical laboratory assessments [c]	X												X		X		
Drug and alcohol test [d]	X	X															
Pregnancy test[e]	X	X													X		X
Vital signs [f]	X	X[g]	X	X	X	X	X[g]	X[g]	X	X	X	X	X	X	X[g]		
12-lead ECG	X	X											X [h]		X		
[redacted]																	

Study Procedure	Screening Period	Treatment Period/Inpatient Stay (Day 1 to Day 3)												Follow-up Period			
Visit Days	D -14 to -1	D1	D1	D1	D1	D1	D1	D2	D2	D2	D3	D3	D3	D7 (±1d)	D14 and/or ET (±2d)	D21 (±3d)	D30 (±3d)
Hour		H0*	H2	H4	H8	H12	H24	H30	H36	H48	H54	H60	H72				
[redacted]																	
Plasma PK [k]		X		X	X	X	X	X	X	X		X	X				
Continuous pulse oximetry[l]		X											X				
Monitor for excessive sedation		X (Q2 hours during planned non-sleep periods)											X				
Study drug infusion		X											X				
Adverse events		X															
Prior/concomitant medications [m]		X															
Nonpharmacological interventions [n]		X															

[redacted]; D = day; ECG = electrocardiogram; [redacted]; ET = early termination; H = hour; [redacted]; PK = pharmacokinetic; Q = every; SCID-5 = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

* = All H0 procedures to be completed prior to dosing

a Depending on age at screening and local regulations, subjects will either sign an informed consent form, or will sign an adolescent assent form and their parent/guardian will sign a parental informed consent form.

b Full physical examination at screening. Symptom-directed physical examination may be conducted at subsequent time points.

c Safety laboratory tests will include hematology, serum chemistry, exploratory biochemistry, and hormone parameters at all scheduled time points. Coagulation to be assessed at screening only. Laboratory assessments are to be completed within ±30 minutes of the scheduled time point.

d Drug and alcohol testing will occur at screening and Day 1 (predose; H0) (see Section 12.1.6.2 for a list of analytes). Drug testing will be via urine dipstick; alcohol use will be tested via urine dipstick or breath test.

e Serum pregnancy test at screening and serum or urine pregnancy test at all other scheduled time points.

f At all time points, vital signs to include oral temperature (°C), respiratory rate, heart rate, and blood pressure. Heart rate and blood pressure to be collected in supine position at all scheduled time points. Vital signs collected after the initiation of brexanolone will be obtained within ±30 minutes of the scheduled time point, unless the subject is asleep between 23:00 h and 06:00 h. Predose (Hour 0) vital signs to be collected within 30 minutes prior to dosing.

g At the indicated time points additional heart rate and blood pressure measurements to be collected in the standing position.
h Performed within ±1 hour of the scheduled time point on Day 3.
[redacted]
k Pharmacokinetic blood draws after the start of infusion will have a window of ±10 minutes. In the event of an unplanned dose adjustment, if feasible, an unscheduled PK sample should be collected just prior to the infusion rate change. PK collection should also occur as soon as is feasible in the case of overdose.
l Continuous pulse oximetry to occur for the duration of the infusion. Oxygen saturation need only be recorded in the event of hypoxia, in which case, the event is to be recorded as an AE
m At screening to include all medications taken within 60 days, all psychotropic medications taken within 6 months, and all medications used to treat the current episode of PPD regardless of timing. At visits subsequent to screening all changes to any medication should be captured.
n All nonpharmacological interventions (eg, psychosocial, psychotherapeutic) used to treat the current episode of PPD should be captured at screening, and all changes should be captured at subsequent visits.

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

TABLE OF CONTENTS

[redacted]

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 3: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	adverse event
AESI	adverse event of special interest
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CS	clinically significant
[redacted]	[redacted]
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
[redacted]	[redacted]
ET	early termination
$GABA_A$	γ-aminobutyric acid-ligand gated chloride channel
GCP	Good Clinical Practice
[redacted]	[redacted]
[redacted]	[redacted]
ICD	International Classification of Diseases
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
[redacted]	[redacted]
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic(s)
PPD	postpartum depression
SAE	serious adverse event

Abbreviation or Specialist Term	Explanation
SAP	statistical analysis plan
SBECD	sulfobutylether-β-cyclodextrin
SCID-5	Structured Clinical Interview for DSM-5 Axis I Disorders
SD	standard deviation
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event

5. INTRODUCTION

5.1. Background of Postpartum Depression and Unmet Medical Need

Postpartum depression (PPD) is a serious mood disorder estimated to affect approximately 10 to 20 percent of women giving birth globally. In the United States, estimates of new mothers identified with PPD each year vary by state from 8 to 20 percent with an overall average of 11.5 percent (Ko et al 2017). Postpartum depression is defined in both the International Classification of Diseases (ICD)-10 and Diagnostic and Statistical Manual of Mental Disorders (DSM-5 2013) as a major depressive episode in the postpartum period with marked impairment in functioning. PPD often co-occurs with anxiety. PPD is a leading cause of maternal mortality (Savitz 2011) and, by affecting maternal functioning, poses serious risks to the emotional, cognitive, behavioral, and physical development of the infant and siblings (CPS 2004; Noorlander 2008). Findings from several studies implicate that peripartum fluctuations in reproductive hormones (in particular, the major progesterone metabolite, allopregnanolone) have a pivotal pathophysiological role in PPD. There is no evidence that the pathophysiology of PPD in adolescents differs from that in adults.

Current standard of care for PPD includes pharmacological therapies, most often antidepressants approved for major depressive disorder (MDD), combined with counseling, behavioral, and other nonpharmacological interventions (Altshuler 2001). While tricyclic antidepressants and/or selective serotonin reuptake inhibitors (SSRIs) are both commonly used, SSRIs tend to be preferred due to better safety data while breastfeeding (Altshuler 2001). However, the evidence for efficacy of MDD antidepressants in PPD is generally based on data from the MDD population (Austin 2013). Limited randomized data are available evaluating the effectiveness of MDD antidepressants in PPD (De Crescenzo, 2014). Thus, based on the level of available evidence, there is a considerable need for improved pharmacological therapy for PPD.

Allopregnanolone is a potent positive allosteric modulator of synaptic and extrasynaptic γ-aminobutyric acid-ligand gated chloride channel ($GABA_A$) receptors. Plasma allopregnanolone concentrations rise in concert with progesterone throughout pregnancy, reaching the highest physiological concentrations in the third trimester (Maguire 2009). After childbirth, these concentrations decrease abruptly (Nappi 2001). Failure of $GABA_A$ receptors to adapt to these changes at parturition has been postulated to have a role in triggering postpartum depression (Maguire 2008). Allopregnanolone and pharmacologically similar compounds have been shown to have profound effects on anxiety and depression in animal models (Paul 1992; Maguire 2008).

5.2. Brexanolone

The brexanolone drug product is a proprietary formulation of brexanolone drug substance (also referred to as allopregnanolone) and excipients. Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex, and central nervous system (Holzbauer 1985; Paul 1992; Ottander 2005). 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.

Nonclinical toxicology studies largely illustrate the sedative and anesthetic effects of allopregnanolone and/or brexanolone at higher equivalent doses than the proposed dose for the current study. Pharmacokinetic data in animals indicate a short half-life of brexanolone and rapid clearance with a moderate volume of distribution and cerebral levels higher than plasma. Clinical evidence to date demonstrates a clinically meaningful improvement in depressive symptoms in subjects with PPD following a 60-hour infusion of brexanolone compared with placebo.

Brexanolone (brand name ZULRESSO^{TM}) was approved by the US Food and Drug Administration on 19 March 2019 for the treatment of PPD in adults. Refer to the Investigator's Brochure for detailed description of clinical and nonclinical studies with brexanolone.

5.3. Dose Justification

Sage has completed three placebo-controlled studies of brexanolone in adult women with PPD, all of which demonstrated statistical improvement in depressive symptoms for brexanolone as compared with placebo (see Investigator's Brochure). All three studies employed a maintenance dose of 90 mcg/kg/h and this dose was well tolerated. Because the 90 mcg/kg/h maintenance dose was safe and effective in adult women with PPD, this dose has been chosen for this study of brexanolone in adolescents with PPD.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of brexanolone when administered to adolescent female subjects diagnosed with PPD.

6.2. Secondary Objective

The secondary objective of the study is:

- To assess the plasma pharmacokinetic (PK) profile of brexanolone and, when appropriate, metabolites of brexanolone

[redacted]

6.4. Endpoints

6.4.1. Primary Endpoint

The primary endpoint of this study is:

- Incidence of treatment-emergent adverse events

6.4.2. Secondary Endpoints

The secondary endpoint of this study is:

- PK parameters derived from plasma concentrations of brexanolone and, when appropriate, metabolites of brexanolone

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Mean changes from baseline in clinical laboratory measures, vital signs, ECGs and concomitant medication usage. [redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

In previous Versions 1 through 3 of this protocol, subjects were randomly assigned to active or placebo study drug in a blinded manner. With the current Amendment 3/Version 4, the study has been converted to an open-label study where all subjects will receive brexanolone.

This is a Phase 3, open-label study designed to evaluate the safety, tolerability, and PK, of brexanolone in adolescent female subjects diagnosed (by Structured Clinical Interview for DSM-5 Axis I Disorders [SCID-5]) with PPD. Subjects will be administered a single, 60-hour continuous IV infusion of brexanolone. Each subject's involvement is up to 47 days, including a maximum 14-day Screening Period, a 3-day Treatment Period (60 hours of treatment and an additional 12 hours for completion of 72-hour assessments), and a Follow-up Period through Day 30 (± 3 days).

The Screening Period begins with the informed consent process at the Screening Visit, which can occur on any one calendar day of a 14-day window (from Day -14 through Day -1, inclusive). Depending on age at screening and local regulations, subjects will either sign an informed consent form, or will sign an adolescent assent form and their parent/guardian will sign a parental informed consent form. Subjects will undergo procedures at the Screening Visit to determine eligibility, including completion of the [redacted].

The Treatment Period is the period from the start of the assessments on Day 1 prior to initiation of the brexanolone intravenous (IV) infusion through the 72-hour assessments on Day 3. The 60-hour infusion will be administered as follows: 30 mcg/kg/hour (Hour 0 to 4), then 60 mcg/kg/hour (Hour 4 to 24), then 90 mcg/kg/hour (Hour 24 to 52), followed by 60 mcg/kg/hour (Hour 52 to 56), and 30 mcg/kg/hour (Hour 56 to 60). A programmable peristaltic infusion pump will be used to ensure accurate delivery of brexanolone.

Due to the risk of excessive sedation and sudden loss of consciousness, for the duration of the infusion, patients will be monitored for hypoxia using continuous pulse oximetry equipped with an alarm, and will be assessed for excessive sedation by a healthcare provider every 2 hours during planned, non-sleep periods. Subjects must not be the primary caregiver of dependents and must be accompanied during any interactions with their child(ren) that occur during the infusion.

If excessive sedation occurs at any time during the infusion, the infusion will be stopped until the symptoms resolve. The infusion may be resumed at the same or lower dose as clinically appropriate. See Section 7.4 for details on dose adjustment criteria. The infusion will be immediately stopped if pulse oximetry reveals hypoxia. After an episode of hypoxia, the infusion should not be resumed.

Subjects will remain confined through the completion of the brexanolone infusion and Hour 72 assessments. If deemed medically appropriate by the investigator, subjects may be discharged after completing the Hour 72 assessments. Subjects will be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving, until any sedative effects have dissipated.

For lactating subjects, the investigator and subject should weigh the developmental and health benefits of breastfeeding during the infusion against any potential adverse effects on the

breastfed child from brexanolone or from the underlying maternal condition. Subjects may continue to breastfeed or express milk to feed their infant during the infusion if the benefit is deemed to outweigh the risk. During the study, a qualified lactation consultant will be made available to subjects upon request.

Safety and efficacy assessments will be performed as outlined in the Schedule of Assessments (Table 2). Blood samples will be collected and will be analyzed for concentrations of brexanolone and may be analyzed for concentrations of brexanolone metabolites.

Follow-up visits will be conducted on Day 7, Day 14, Day 21, and Day 30. Psychiatric review for worsening symptoms of depression will be available during the study and psychiatric follow-up after the end of the study will be arranged as needed by the Investigator and will be documented.

An independent data safety monitoring board (DSMB) will monitor the clinical data for safety signals throughout the study. In order to perform their monitoring function, the DSMB will have access to all safety data as necessary.

7.2. Number of Subjects

Qualified subjects 15 to 17 years old (inclusive) will be enrolled in the study. Enrollment will continue until approximately 20 subjects have been treated with brexanolone. The planned sample size of 20 includes those subjects who received brexanolone as blinded study drug during earlier versions of the protocol when the study was a randomized, double-blind, placebo-controlled study.

7.3. Treatment Assignment

In this open-label study, subjects will be administered a single, continuous, 60-hour intravenous (IV) infusion of brexanolone starting on Day 1.

7.4. Dose Adjustment Criteria

If excessive sedation occurs at any time during the infusion, the infusion will be stopped until the symptoms resolve. The infusion may be resumed at the same or lower dose as clinically appropriate. The infusion will be immediately stopped if pulse oximetry reveals hypoxia. After an episode of hypoxia, the infusion should not be resumed.

- For subjects who do not tolerate the 90 mcg/kg/hour dose, a reduction to 60 mcg/kg/hour may be considered during the time period when the 90 mcg/kg/hour is scheduled to occur.

Any sedation-related AEs that lead to dose interruption, termination, or reduction should be recorded as AEs of special interest (AESIs), and should be reported in an expedited manner as outlined in Section 12.2.7.

If other intolerable adverse events occur, the infusion will be stopped until the symptoms resolve. The infusion may be resumed at the same or lower dose as clinically appropriate.

A plasma sample for PK analysis should be drawn at the time that the dose is adjusted or the pump is stopped.

7.5. Study Termination

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

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

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

1. Subject (and parent/guardian, per local regulations) has signed the appropriate informed consent form prior to any study-specific procedures being performed.
2. Subject is ambulatory, female, and it is confirmed that she will be 15 to 17 years old (inclusive) through completion of study drug infusion.
3. Subject agrees to adhere to the study requirements.
4. (Removed)
5. 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 SCID-5.
6. Subject has a [redacted] total score of ≥20 at screening and Day 1 (prior to initiation of the study drug infusion).
7. Subject is ≤6 months postpartum at screening.
8. Subject is willing at screening to delay the start of any new pharmacotherapy regimens, including antidepressant or antianxiety medication until the study drug infusion and 72-hour assessments have been completed.
9. If the subject is taking medications administered to treat the symptoms of depression or anxiety (such as anxiolytics or antidepressants), these must be at a stable dose from 30 days prior to dosing until the completion of the 72-hour assessments.
10. Subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the end of the study drug infusion, unless she is surgically sterile (either bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or does not engage in sexual relations which carry a risk of pregnancy:
    - Combined oral, intravaginal, or transdermal (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation
    - Oral, injectable, or implantable progesterone-only hormonal contraception associated with inhibition of ovulation
    - Intrauterine device
    - Intrauterine hormone-releasing system
    - Bilateral tubal occlusion
    - Vasectomized partner
11. Subject agrees not to be the primary caregiver of any dependents during the infusion.

8.2. Subject Exclusion Criteria

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

1. Subject has a positive pregnancy test at screening or Day 1 (prior to initiation of the study drug infusion).
2. Subject's most recent pregnancy resulted in a miscarriage, still birth, or neonatal death; or subject has terminated parental rights (eg, child has been placed for adoption).
3. Subject has end stage renal disease.
4. Subject is in hepatic failure.
5. Subject is anemic (hemoglobin ≤10 g/dL).
6. Subject has untreated or inadequately treated hypothyroidism or hyperthyroidism.
7. Subject has known allergy to progesterone or allopregnanolone.
8. Subject has active psychosis per Investigator assessment.
9. Subject has attempted suicide during current episode of PPD.
10. Subject has a medical history of bipolar disorder, schizophrenia, and/or schizoaffective disorder.
11. Subject has current/active alcohol or drug abuse (including benzodiazepines) within the 30 days prior to screening as assessed by the Investigator. A positive urine drug screen is exclusionary, unless deemed by the investigator to reflect a prescribed medication.
12. Subject has exposure to another investigational medication or device within 30 days prior to screening.
13. Subject has previously participated in this study or any other study employing brexanolone, SAGE-217, ganaxolone, any other compound containing allopregnanolone, or has received treatment with ZULRESSO™.
14. Subject is investigative site personnel, sponsor personnel, or an immediate member of their family (spouse, parent, child, or sibling whether biological or legally adopted).
15. Subject has received electroconvulsive therapy within 14 days prior to screening and/or plans to receive electroconvulsive therapy before the Study Day 7 visit.

8.3. Subject Withdrawal, Early Discontinuation of Study Drug, and Study Termination

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded on the appropriate 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.

8.3.1. 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 for safety, behavioral,

compliance, or administrative reasons or upon termination of the study. Subjects who withdraw should, if possible, complete an early termination visit, which includes the assessments for the Day 14 visit (see Table 2).

8.3.2. Discontinuation of Study Drug

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

8.3.3. Replacement of Subjects

Subjects who initiate the study drug infusion and who subsequently withdraw for any reason will not be replaced.

9. TREATMENT OF SUBJECTS

9.1. Study Drug

Subjects will be administered a single continuous 60-hour infusion of brexanolone.

9.2. Prior/Concomitant Medications and Restrictions

Subjects may receive standard of care for adolescent patients diagnosed with PPD, including psychosocial interventions. Any concomitant medication determined medically necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. Where feasible, changes to psychotropic medications may be made only as outlined in the paragraph below.

Concomitant use of opioids, CNS depressants, such as benzodiazepines, or other drugs interacting with the $GABA_A$ receptor are permitted if on stable recommended dose but should be used with caution during infusions of brexanolone, as there may be an increased risk of sedation-related events. Subjects that are receiving medications administered to treat the symptoms of depression or anxiety (such as anxiolytics or antidepressants) must have been initiated at least 30 days prior to dosing and must remain at a stable dose until completion of the 72-hour assessments. Any new medication for depression or anxiety initiated after the 72-hour assessments are completed must be preceded by a discussion between the investigator and the Medical Monitor.

Subjects on high doses of benzodiazepines may be at increased risk for sedation-like AEs if administered concomitantly with brexanolone. These subjects may be considered for eligibility based on specific discussions between the Investigator and the Medical Monitor. All patients should be monitored during the infusion for any events of excessive sedation.

The following interventions will be recorded on the appropriate eCRF:

- All medications taken from 60 days prior to informed consent through the final study visit
- All psychoanaleptic and psycholeptic medications (including anxiolytics or antidepressants) taken in the previous 6 months prior to informed consent through the final study visit
- All medications used to treat the current episode of PPD regardless of timing through the final study visit
- All nonpharmacological interventions used to treat the current episode of PPD regardless of timing through the final study visit

9.3. Treatment Adherence

Study drug will be prepared by a pharmacist or designee, administered as a continuous IV infusion, and the dose actually received will be documented in the study record. There should be no adjustments in dosing except as described in Section 7.4.

9.4. Blinding and Randomization

This is an open-label study. This study was previously conducted (in Protocol Versions 1 through 3) as a randomized placebo-controlled double-blind study. An independent DSMB will have access to all safety data as necessary.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Description of Study Drug

As supplied, the brexanolone drug product is a sterile, clear, colorless 5 mg/mL solution of brexanolone and 250 mg/mL sulfobutyl-ether-beta-cyclodextrin buffered with 10 mM citrate at a pH of 6.0, supplied in single-dose 20 mL vials for IV administration. The composition and pharmaceutical quality of the study drug will be maintained according to the current Good Manufacturing Practice and Good Clinical Practice (GCP) guidelines and available for review in the study medication documentation.

10.2. Study Drug Packaging and Labeling

Brexanolone will be provided to the sites.

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 conditions. Brexanolone is intended to be used as a single-use vial.

Study drug labels with all required information and conforming to all applicable regulatory requirements will be prepared by the Sponsor.

10.3. Study Drug Storage

The investigator or designee should refer to the Pharmacy Manual for instructions on acknowledging receipt of study drug.

Study drug vials should be stored under refrigerated conditions (2 to 8°C). The vials must be carefully stored safely and separately from other drugs. The study drug may not be used for any purpose other than the present study.

The Investigator or designee will be responsible for ensuring appropriate storage, dispensing, inventory, and accountability of all clinical supplies. An accurate, timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory must be available for inspection by the designated representatives of the Sponsor or the Sponsor's representatives on request, and must include the information below:

- The identification of the subject to whom the drug was dispensed
- The date(s) and quantity of the drug dispensed to the subject
- The product lot/batch number

The preparation of the study drugs must be documented on a 'Drug Preparation and Dispensing Log Form' or similar form.

The drug inventory and any clinical supplies that have been destroyed must be documented. This documentation must include at least the information below or as agreed with the Sponsor:

- The number of prepared units
- The number of administered units
- The number of unused units

- The number of units destroyed at the end of the study
- The date, method, and location of destruction

10.4. Preparation of Study Drug for Dosing

The Pharmacist or designee will be responsible for preparing study drug (brexanolone) for subject dosing. The prepared admixture will be administered at room temperature.

Refer to the Pharmacy Manual for specific instructions regarding requirements for IV bags and labeling, infusion sets, infusion preparation and administration instructions.

10.5. Study Drug Administration

Subjects will receive a 60-hour continuous IV infusion of brexanolone.

The specific infusion dose of study drug will be calculated based on weight (obtained at screening) for each subject and administered according to the dose regimen in Table 4.

Table 4: Infusion Rate

Time point	Day 1 0 to 4 hours	Day 1 4 to 24 hours	Day 2 to 3 24 to 52 hours	Day 3 52 to 56 hours	Day 3 56 to 60 hours
Dose	30 mcg/kg/hour	60 mcg/kg/hour	90 mcg/kg/hour	60 mcg/kg/hour	30 mcg/kg/hour

Dosing should begin in the morning (on Day 1) to avoid the dose increase to 90 mcg/kg/hour late in the day, and to avoid awakening subjects during the night for completion of study assessments.

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

10.6. Study Drug Accountability

The Pharmacist or designee will maintain accurate records of all investigational drug product supplies received, stored, dispensed, and discarded. Accurate records will be kept regarding the volume of study drug used for each IV preparation, as well as the required infusion dose (or doses), 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.

10.7. Study Drug Handling and Disposal

The pharmacist or designee for drug accountability is to document the date and time of preparation of test article and for which subject the study drug was intended (ie, record subject initials and birth date or another unique identifier).

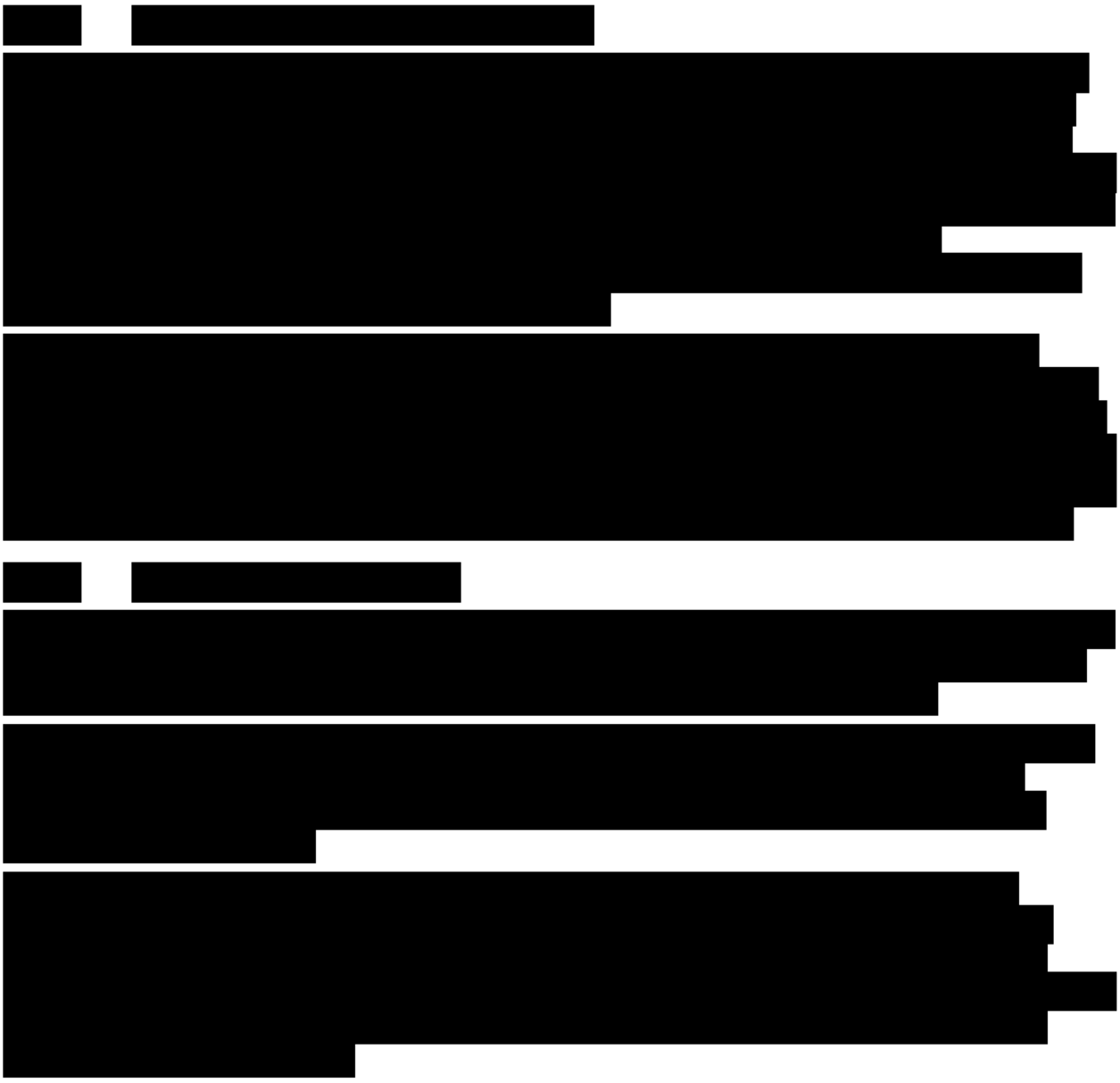
At the end of the study, any unused study drug will be retained or returned to the Sponsor for destruction or destroyed locally per the Sponsor's directions; disposition of study drug will be documented.

11. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

11.1. Efficacy Assessments

For all efficacy assessments, the baseline value will be defined as the last measurement prior to the start of the study drug infusion. Change from baseline will be calculated as the assessment score minus the baseline value.

The following assessments will be performed at the time points specified in the Schedule of Assessments (Table 2).



[redacted]

11.2. Pharmacokinetic Assessments

Blood samples for PK analysis will be collected in accordance with the Schedule of Assessments (Table 2). Samples will be processed according to the PK Manual, and may be analyzed for concentrations of brexanolone, metabolites of brexanolone, and sulfobutyl-ether-beta-cyclodextrin. 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. ASSESSMENT OF SAFETY

12.1. Safety and Tolerability Assessments

Safety and tolerability of study drug will be evaluated by incidence of treatment-emergent adverse events as well as changes from baseline in vital signs measurements, clinical laboratory measures, ECGs, concomitant medication usage, and [redacted]

The following assessments will be performed at the time points specified in the Schedule of Assessments (Table 2).

12.1.1. Demographic/Medical History

Medical history will be collected and listed by subject. Age, race, and ethnic origin will be recorded. The diagnosis of PPD will be determined using the SCID-5. Subjects will be specifically asked about the following depression, anxiety, and other diagnoses per DSM-5: generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, major depressive disorder, persistent depressive disorder, postpartum depression, bipolar disorder, seasonal affective disorder, psychotic depression, premenstrual dysphoric disorder, situational depression, atypical depression, menstrual migraine, other Axis 1 and Axis 2 disorders, pregnancy history (including number of pregnancies, number of births, methods of delivery, and birth complications) and PPD episodes.

12.1.2. Vital Signs

Vital signs include oral temperature (°C), respiratory rate, heart rate, and blood pressure. Heart rate and blood pressure to be collected in supine position at all scheduled time points as well as in the standing position at specific time points listed in Table 2.

Additionally, respiratory rate, heart rate, and blood pressure should be collected for any subject that experiences an AESI (defined in Section 12.2.7) as soon as is feasible after the onset of the event and recorded as unscheduled in the eCRF. Collection of vital signs should occur per local clinical practice, at a minimum until the subject regains consciousness.

12.1.3. Weight, Height and Body Mass Index

Body weight and height will be measured; body mass index will be programmatically calculated in the eCRF.

12.1.4. Physical Examination

Physical examinations of major body systems will be undertaken and recorded. Any clinically significant finding present at the post-screening physical examination that was not present at or worsened since the screening examination will be documented as an AE. Major body systems to be included in the screening physical examination are head, eye, ear, nose and throat, heart, lungs, abdomen, and extremities; as well as cognitive and neurological examination, and mental status examination. Post-screening physical examinations may be symptom directed.

12.1.5. Electrocardiogram

Twelve-lead ECGs will be performed. The Investigator will record if the ECG is normal; abnormal, not clinically significant; or abnormal, clinically significant (CS). If Abnormal, details of the abnormality will be provided (ie, first-degree AV block, bundle branch block). The standard intervals (heart rate, PR, QRS, QT, and QTcF) will be recorded for all ECGs.

12.1.6. Laboratory Assessments

Blood samples will be collected for hematology, serum chemistry, and coagulation. Analytes to be evaluated are summarized in Table 5.

All blood samples will be sent to the central laboratory. Subjects may be considered eligible for the study based on results reported by a local laboratory; however, screening samples must also be sent to the central laboratory. Both local and central screening laboratories must adhere to the visit window provided in Table 2.

Table 5: Summary of Laboratory Analytes

Hematology	complete blood count (red blood cells, white blood cells with differentiation and absolute values, hemoglobin, hematocrit, reticulocytes, and platelets)
Coagulation (at Screening only)	activated partial thromboplastin time, prothrombin time, and international normalized ratio
Biochemistry	serum electrolytes (sodium, potassium, chloride, bicarbonate or total carbon dioxide, calcium, and phosphorus) renal function tests (creatinine and blood urea nitrogen); liver function tests (total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase); thyroid stimulating hormone; total protein; albumin and glucose (fasting or non-fasting)

All clinical laboratory test results outside the reference range will be interpreted by the Investigator as abnormal, not clinically significant; or abnormal, CS. Screening results considered abnormal and CS at the Screening Visit may make the subject ineligible for the study pending review by the Investigator or Medical Monitor. Clinically significant abnormal results after screening will be considered and reported as AEs.

12.1.6.1. Pregnancy Test

All subjects will be tested for pregnancy by serum human chorionic gonadotropin at the Screening Visit and by serum or urine human chorionic gonadotropin at other scheduled time points. Subjects may be considered eligible for the study based on serum pregnancy test results reported by a local laboratory; however, screening samples must also be sent to the central laboratory. Both local and central screening laboratories must adhere to the visit window provided in Table 2.

12.1.6.2. Drugs of Abuse and Alcohol

Urine assessment for select drugs of abuse will be performed (including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and phencyclidine). A positive urine drug screen is exclusionary, unless deemed by the investigator to reflect a prescribed medication. Alcohol will be assessed via breathalyzer or urine dipstick.

12.1.6.3. Hormones and Exploratory Biochemistry

Blood samples will be collected and may be analyzed for estrogen, progesterone, progesterone metabolites, oxytocin, tryptophan, kynurenine, and markers of inflammation.

12.1.7. Continuous Pulse Oximetry

Subjects will be monitored for hypoxia using continuous pulse oximetry equipped with an alarm. Oxygen saturation need only be recorded in the event of hypoxia, in which case, the event is to be recorded as an AE. The infusion will be immediately stopped if pulse oximetry reveals hypoxia. After an episode of hypoxia, the infusion should not be resumed.

12.1.8. Monitoring for Excessive Sedation

For the duration of the infusion, subjects must be assessed for excessive sedation by a healthcare provider every 2 hours during planned, non-sleep periods. If excessive sedation occurs at any time during the infusion, the infusion will be stopped until the symptoms resolve. The infusion may be resumed at the same or lower dose as clinically appropriate (see Section 7.4), and an AESI is to be reported (see Section 12.2.7).

[redacted]

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational)

product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

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

Laboratory abnormalities and changes from baseline in vital signs (including ECGs) are considered AEs if they result in discontinuation or interruption of study treatment, are clinically significant and require therapeutic medical intervention, meet protocol specific criteria (if applicable) and/or if the Investigator considers them to be clinically significant and adverse events. Laboratory values and vital signs that meet the criteria for a serious adverse event (SAE) should be reported in an expedited manner.

Laboratory values and vital signs that are clearly attributable to another AE do not require discrete reporting (e.g. electrolyte disturbances in the context of dehydration, chemistry and hematologic disturbances in the context of sepsis, etc.).

12.2.1.2. Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening (Note: The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above. (Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

All SAEs that occur from the signing of the consent form(s) through the end of study participation, whether or not they are related to the study drug, must be recorded on forms provided by Sage Therapeutics. Serious adverse events occurring *after* the subject's final study visit should be reported to the Sponsor or Sponsor's designee only if the investigator considers the SAE to be related to study drug.

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

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.

- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress, in the opinion of the Investigator, between the subject's consent to participate in the study and at the time of the procedure or treatment.
- The prescheduled or elective procedure or a routinely scheduled treatment is the sole reason for the intervention or hospital admission.

If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements above is met.

12.2.2. Relationship to Study Drug

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

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

If the relationship between the AE/SAE and the study drug is determined to be "possible" or "probable", the event will be considered related to the study drug for the purposes of expedited regulatory reporting.

12.2.3. Recording AEs

Information about AEs will be collected from the signing of the consent form(s) until the final visit of the study for that subject. All AEs will be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant.

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

Intensity will be assessed according to the following scale:

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

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

12.2.4. Pregnancy

Based on findings from animal studies of other drugs that enhance GABAergic inhibition, brexanolone may cause fetal harm. Should a pregnancy occur, it must be reported within 24 hours of identification and recorded on the Sage Therapeutics pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

12.2.5. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in protocol. Overdoses are not considered AEs and should not be recorded as an AE on the eCRF; however, all overdoses must be recorded on an Overdose form and sent to Sage or designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Sage or designee even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded.

12.2.6. Immediate Reporting SAEs

All SAEs (regardless of causality) will be recorded from the signing of the consent form(s) until the final visit of the study for that subject. Serious adverse events occurring *after* the subject's final study visit should be reported to the Sponsor or Sponsor's designee only if the investigator considers the SAE to be related to study drug.

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

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

Sage Therapeutics, or designee, is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB/EC of all SAEs that occur at his or her site. Investigators will also be notified of all suspected, unexpected, serious, adverse reactions (SUSARs) that occur during the clinical study or from other studies with brexanolone. Each site is responsible for notifying its ethics committee of these SUSARs. Sage or designee will submit SUSARs to regulatory agencies according to local law.

12.2.7. Adverse Events of Special Interest

The following events are considered AESIs and should be reported on the AESI form within 72 hours.

- Excessive sedation
- Loss of consciousness
- Any sedation-related AE that leads to dose reduction, interruption, or termination

If the AESI also qualifies as an SAE an SAE form should be submitted per the guidelines per Section 12.2.6.

13. STATISTICS

Planned statistical analyses are provided in brief below. A separate statistical analysis plan (SAP) will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock.

13.1. Data Analysis Sets

The Efficacy Set will be defined as all subjects who initiate study drug infusion and have at least one post-baseline efficacy evaluation. Efficacy data will be analyzed using appropriate descriptive statistics and pre-specified statistical methods; subject listings will be provided for all efficacy data.

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

The PK Set is defined as all subjects in the Safety Set for whom at least one evaluable post-baseline PK sample is available.

13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis sets, using all non-missing data available.

13.3. General Considerations

Except where noted, baseline is defined as the last measurement prior to the start of study drug infusion.

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

13.4. Demographics and Baseline Characteristics

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

Pregnancy results will be listed but not summarized.

Medical history will be listed by subject. Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 or higher.

13.5. Preliminary Analyses

In order to conduct the preliminary analyses, the sponsor may lock and unblind the data from subjects enrolled during earlier versions of the protocol when the study was a randomized, double-blind, placebo-controlled study, before the open-label study finishes.

13.6. Efficacy Analyses

The change from baseline in [redacted] total score and binary efficacy endpoints, including Responder and Remission, will be appropriately summarized.

13.7. Safety Analyses

13.7.1. Adverse Events

The analysis of AEs will be based on the concept of TEAEs, as defined in Section 12.2.1.1. The incidence of TEAEs will be summarized overall and by MedDRA Version 19.1 or higher, System Organ Class, and preferred term. In addition, summaries will be provided by severity (mild, moderate, severe) and by causality (related, not related) to study drug.

TEAEs leading to study drug discontinuation, study withdrawal, or dose modifications will also be summarized. All SAEs will be summarized.

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

13.7.2. Clinical Laboratory Evaluations

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

13.7.3. Physical Examinations

The study date of physical examinations will be listed. Any clinically significant finding present at the post-screening physical examination that was not present at or worsened since the screening examination will be documented as an AE.

13.7.4. Vital Signs

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

13.7.5. 12-Lead Electrocardiogram

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

13.7.6. Prior and Concomitant Medications

Medications will be recorded at each study visit during the study and will be coded using World Health Organization-Drug dictionary enhanced September 2016, or later.

Those medications taken prior to the initiation of the study drug infusion but not continuing beyond the initiation of the study drug infusion will be denoted “Prior”. Those medications taken prior to the initiation of the study drug infusion and continuing beyond the initiation of the study drug infusion will be denoted “Prior” and “Concomitant (ie, those with a start date before the first dose of study drug that are ongoing or with a stop date on or after the first dose of study

drug). Those medications started at the same time or after the initiation of the study drug infusion will be denoted "Concomitant" (ie, those with a start date on or after the first dose of study drug).

Medications will be summarized by ATC level 2 term and preferred term, separately for "Prior" or "Concomitant" medications as defined above.

Baseline antidepressant will be defined as medications belonging to Anatomical Therapeutic Chemical (ATC) 3 term N06A or N05A, or with an indication containing terms depression, postpartum depression, major depression, PPD, major depressive disorder, or mood.

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

Nonpharmacological interventions for PPD will be listed and summarized.

[redacted]

13.8. Determination of Sample Size

No formal sample size calculation was made for this study. The planned sample size of 20 adolescent subjects treated with brexanolone should be appropriate to characterize the PK and safety profiles.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Audits and Inspections

Authorized representatives of Sage Therapeutics, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sage Therapeutics or designee audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Council on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency about an inspection.

14.2. Institutional Review Board/ Independent Ethics Committee

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

14.3. Data Safety Monitoring Board

An independent DSMB will monitor the clinical data for safety signals throughout the study. In order to perform their monitoring function the DSMB will have access to all safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

14.4. Study Monitoring

A representative of Sage Therapeutics or designee will visit the investigational study site to:

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

During the study, a monitor from Sage Therapeutics or designee will have regular contacts with the investigational site in order to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that study drug accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records

relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).

- Record and report any protocol deviations not previously sent to Sage Therapeutics or designee; and
- Confirm AEs, AESIs, and SAEs have been properly documented on eCRFs and confirm AESIs and SAEs have been forwarded to Sage Therapeutics or designee in the protocol specified timelines and those SAEs that met criteria for reporting have been forwarded to the IRB.

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator and institution will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections as requested by Food and Drug Administration or other regulatory agencies, 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 consent form(s)) in addition to eCRFs.

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

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

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

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

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

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

16. ETHICS

16.1. Ethics Review

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

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

The Principal Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. 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.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and its most recent amendment (2008) and are consistent with ICH/GCP and other applicable regulatory requirements.

16.3. Written Informed Consent

All subjects will complete an informed consent process. Depending on age at screening and local regulations, the process will either require the subject to sign an informed consent form, or for the subject to sign an adolescent assent form and a parent/guardian to sign a parental informed consent form.

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

The consent forms, as specified by the clinical site's IRB/IEC, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

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

The Investigator(s) must maintain the original, signed consent form(s). A copy of the signed consent form(s) must be given to the subject and/or parent/guardian.

17. DATA HANDLING AND RECORDKEEPING

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

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

The Investigator will have access to the electronic data capture system and will receive a copy of the subject eCRF data at the end of the study. For subjects who discontinue or terminate from the study, the eCRFs will be completed as outlined in the eCRF completion guidelines.

17.1. Inspection of Records

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

17.2. Retention of Records

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

17.3. Confidentiality

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

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

All information regarding the study drug 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 study drug and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

18. PUBLICATION POLICY

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

19. REFERENCES

Altshuler LL, Cohen LS, Moline ML, et al. Treatment of depression in women: a summary of the expert consensus guidelines. J Psychiatr Pract. 2001;7(3):185-208.

Austin MP, 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.

[redacted]

CPS. Maternal depression and child development. Paediatr Child Health. 2004;9(8):575–98.

De Crescenzo F. Selective serotonin reuptake inhibitors (SSRIs) for post-partum depression (PPD): A systematic review of randomized clinical trials. J Affective Disorders. 2014; 152-154: 39044.

DSM-5. Diagnostic and statistical manual of mental disorders (5th ed.). American Psychiatric Association.

[redacted]

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;22(1):97-102.

[redacted]

Ko J, Rockhill K, Tong V, Morrow B, Farr S. Trends in Postpartum Depressive Symptoms – 27 States, 2004, 2008, and 2012. Morbidity and Mortality Weekly Report. 2017; 66(6): 153-158.

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

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

[redacted]

Nappi RE, Petraglia F, Luisi S, Polatti F, Farina C, Genazzani AR. Serum allopregnanolone in women with postpartum “blues”. Obstet Gynecol 2001; 97: 77–80.

Noorlander Y, Bergink V, van den Berg MP. Perceived and observed mother-child interaction at time of hospitalization and release in postpartum depression and psychosis. Arch Womens Ment Health. 2008;11(1):49–56.

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;239(1-2):37-44.

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

[redacted]

Savitz DA, Stein CR, Ye F, Kellerman L, Silverman M. The epidemiology of hospitalized postpartum depression in New York State, 1995-2004. Ann Epidemiol. 2011;21(6):399–406.

[redacted]