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9. DOCUMENTATION OF STATISTICAL METHODS

547-PPD-304 SAP v1.0 05 March 2021

SAGE THERAPEUTICS INCORPORATED

Statistical Analysis Plan

Methods

Protocol Number 547-PPD-304

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

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Version: Version 1.0

Date of SAP: 05 March 2021

Authorization Signature Page

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

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1 TABLE OF CONTENTS

[redacted]

2 LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
AUC	area under the concentration-time curve
AUC_{∞}	area under the concentration-time curve from time zero to infinity
[redacted]	[redacted]
BMI	body mass index
bpm	beats per minute
[redacted]	[redacted]
[redacted]	[redacted]
C_{max}	maximum (peak) plasma concentration
CS	clinically significant
C_{ss}	steady-state drug concentration in the plasma during oral intake
C_{avg}	steady-state drug concentration in the plasma
[redacted]	[redacted]
CV	coefficient of variation
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
[redacted]	[redacted]
ET	early termination
FCS	fully conditional specification
GEE	Generalized Estimating Equation
[redacted]	[redacted]
[redacted]	[redacted]
HCG	human chorionic gonadotropin
HCRU	healthcare resource utilization
IV	intravenous
kg	kilogram
m	meter
[redacted]	[redacted]
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
mmHg	millimeter of mercury
MMRM	mixed effects model for reported measures
msec	millisecond
n	number
NCS	not clinically significant
PCS	potentially clinically significant
PCSC	potentially clinically significant change

PHQ-9	Patient Health Questionnaire
PK	pharmacokinetic(s)
PPD	postpartum depression
PT	preferred term
QTcF	QT corrected with Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
[redacted]	[redacted]
SI	International System of Units
SOC	system organ class
ss	steady state
TEAE	treatment-emergent adverse event
Tmax	time at maximum (peak) plasma concentration
WHO	World Health Organization
WHO-DDE	World Health Organization-Drug Dictionary Enhanced

3 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the approved clinical study protocol Version 4.0 dated 20 December 2019.

The purpose of the SAP is to describe in detail the statistical methodology and the statistical analyses to be conducted for data presentation for Study 547-PPD-304, a multicenter, open-label study evaluating doses up to 90 mcg/kg/h of brexanolone in adolescent female subjects with postpartum depression.

All patients who received the active study treatment brexanolone will be presented, which includes patients who were randomized in the earlier versions of the protocol (Protocol Version 1.0, dated 23 January 2018, Version 2.0, dated 11 September, 2018, and Version 3.0 dated 03 June 2019), and received the active study treatment, as well as the patients who are enrolled under Protocol Version 4.0, the open-label study.

In addition, for the patients enrolled under the double blinded protocol versions (Protocol Version 1.0, dated 23 January 2018, Version 2.0, dated 11 September, 2018, and Version 3.0 dated 03 June 2019), all of their data will be presented according to their randomized treatment arms (placebo and brexanolone).

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

4 STUDY OBJECTIVES

4.1 Primary Objective

- To evaluate the safety and tolerability of brexanolone when administered to adolescent female subjects diagnosed with postpartum depression (PPD).

4.2 Secondary Objectives

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

[redacted]

5 STUDY ENDPOINTS

5.1 Primary Endpoint

- Incidence of treatment-emergent adverse events (TEAEs)

5.2 Secondary Endpoints

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

[redacted]

- Mean changes from baseline in clinical laboratory measures, vital signs, electrocardiogram (ECG) and concomitant medication use. [redacted]

6 STUDY DESIGN

6.1 Overall 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 (from Day -14 through day -1, inclusive), a 3-day (60 hours of treatment and an additional 12 hours for completion of 72-hour assessments), and a Follow-up Period through Day 30 ($\pm$ 3 days).

In Study 547-PPD-304, once subjects are confirmed as eligible for the study, subjects will be administered brexanolone. On the morning of dosing (Day 1), subjects will begin a 4-hour dose titration period of 30 mcg/kg/hour (0-4 hours), then 60 mcg/kg/hour (4-24 hours), then

90 mcg/kg/hour (24-52 hours); followed by a decrease to 60 mcg/kg/hour (52-56 hours), and 30 mcg/kg/hour (56-60 hours) as shown in Table 1.

Table 1: Infusion Rates for 547-PPD-304

	Infusion Rate (mcg/kg/hour)				
Time point	**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**
Dose(mcg)	30	60	90	60	30

Total brexanolone dosing will occur over 60 hours.

The end of the Treatment Period coincides with the beginning of the Follow-up Period. Follow-up visits will be conducted on Day 7, Day 14, Day 21, Day 30.

6.2 Sample Size and Power

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.

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.

6.3 Randomization and blinding

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

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.

7 MODIFICATIONS

7.1 Modifications from the Approved Clinical Study Protocol

Not applicable.

7.2 Modifications from the Approved Statistical Analysis Plan

Not applicable.

7.3 Modifications from the Approved DSMB Charter

DSMB Charter 1.0, dated 31 Oct 2018, specified periodic data review meetings to be scheduled quarterly after the first meeting.

DSMB Charter 2.0, dated 16 July 2019, updated the periodic data review meetings scheduled quarterly or when a minimum of five (5) new subjects are enrolled and 14-day visit data are available.

BREXANOLONE DSMB Charter Version 1.0, dated 20 October 2020, a brexanolone program-wide DMC charter has been created to cover all ongoing brexanolone studies: 547-PPD-304 and 547-ARD-301.

8 ANALYSIS SETS

8.1 All Subjects Set

The All Subjects Set will include every subject who has given written informed consent. This set will be used for subject disposition.

8.2 Randomized/enrolled Set

The Randomized/enrolled Set will include subjects who have been randomized in earlier double blinded versions of the protocol and subjects who are enrolled in the current open-label version of the protocol. Subjects will be classified according to randomized treatment for the double-blinded treatment and also for the active study treatment brexanolone they receive.

8.3 Safety Set

The Safety Set will include all randomized/enrolled subjects who start the infusion of study drug. Subjects will be classified according to actual treatment received. This analysis set will be used for subject demographics and baseline characteristic summaries and all safety analyses.

8.4 Efficacy Set

The Efficacy Set will include the subset of the Safety Set who have a valid baseline efficacy assessment and at least one post-baseline efficacy assessment.

8.5 Pharmacokinetics Set

The PK Set will include all subjects in the Safety Set who have at least one evaluable post-baseline PK sample. Subjects will be classified according to actual treatment received. This analysis set will be used for all PK analyses.

9 STATISTICAL ANALYSIS

9.1 General Considerations

Unless otherwise specified, continuous endpoints will be summarized with number (n), mean, standard deviation (SD), median, minimum (min) and maximum (max). The minimum and maximum will be reported with the same degree of precision (ie, the same number of decimal places) as the raw data. Measures of location (mean and median) will be reported to 1 degree of precision more than the raw data. Measures of spread (SD) will be reported to 2 degrees of precision more than the raw data. 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. Percentages will be presented to 1 decimal place except for 0%, which will be presented as "0", and 100%, which will be presented as "100".

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

All subject data, including those derived, will be presented in the subject data listings. The listings will display all subjects who were enrolled. In general, the subject data listings will be sorted by randomized treatment group, subject number and assessment visit and date (and time, if applicable). The summary tables will be presented descriptively by treatment group.

9.1.1 Study Day Definition

Study day is defined as follows:

- The day when the study drug infusion is started is designated as Day 1.
- For visit days after Day 1, study day = visit date – Day 1 date + 1.
- For visit days prior to Day 1, study day = visit date – Day 1 date. Thus, study days for the screening visit are negative numbers. There is no "Day 0".

9.1.2 Baseline Definition

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

9.1.3 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 of the available non-missing data. [redacted] subscales that were collected during protocol version 1.0-3.0 will be calculated, and the missing responses will be handled using the built-in scoring tool.

Safety data will not be subject to any imputation and will be summarized on an observed basis.

The following conventions will be used for missing adverse event (AE) dates (Section 9.1.3.1), and missing prior and concomitant medication dates (Section 9.1.3.2) for determining the TEAEs or for determining prior and concomitant medication. The actual date will not be replaced by the imputed date.

9.1.3.1 Adverse Events Onset Date

If the AE onset date is completely missing in which the day, month, and year are all missing, do not impute a date but consider it as TEAE, unless the AE end date is before the initiation of treatment, in which case the AE will be considered prior.
For the partial AE onset date and time,

- If the year is present, but the month and day are missing:
  - If year of AE onset = year of initiation of the treatment, then set the month and day to the month and day of initiation of the blinded treatment

- If year of AE onset < year of initiation of the treatment, then set the month and day to December 31.
- If year of AE onset > year of initiation of the treatment, then set the month and day to January 1.

- If the year and month are present, but the day is missing:
  - If year and month of AE onset = year and month of initiation of the treatment, then set the day to the day of initiation of the treatment.
  - If year and month of AE onset < year and month of initiation of the treatment, then set the day to the last day of month
  - If year and month of AE onset > year and month of initiation of the treatment, then set the day to the first day of the month
- If the year and day are present and the month is missing:
  - If year of AE onset = year of initiation of the treatment and
    - if day $\geq$ the day of initiation of the treatment, then set the month to the month of initiation of the treatment
    - if day < day of initiation of the treatment, and
      - If the month of initiation of the treatment = December, then set the month to the month of initiation of the treatment, i.e. December.
      - If the month of initiation of the treatment < December, then set the month = the month of initiation of the treatment +1.
  - If year of AE onset < year of initiation of the treatment, then set the month to December.
  - If year > year of initiation of the treatment, then set the month to January.
- If the year and day are present and the month is missing, then treat it as if the day is missing, and only the year is present. Follow the imputation rules for "year is known, but the month and day is unknown".
- When the year is missing, but the month and/or day is known, treat this date as missing; do not impute.

The general rule is to impute the AE onset date as close as to the initiation of treatment date, with a preference to after the initiation of the treatment date. If the imputed AE onset date is after the AE stop date, then set the onset date to the AE stop date.

9.1.3.2 Prior and Concomitant Medications Date

If the start date (or end date) of a medication is completely missing in which the year is unknown, then the start date (or end date) will not be imputed.

For the partial start date of medication,

- If the year is present and the month and day are missing, set the month and day to January 1.
- If the year and day are present and the month is missing, set the month to January.

- If the year and month are present and the day is missing, set the day to the first day of the month.
- If the imputed start date of medication is after the non-imputed end date of medication, then the start date will be set to the end date of medication.

For the partial end date of medication,

- If the year is present and the month and day are missing, set the month and day to December 31.
- If the year and day are present and the month is missing, set the month to December.
- If the year and month are present and the day is missing, set the day to the last day of the month.
- If the imputed end date of medication is before the non-imputed start date of medication, then the end date will be set to the start date of medication.

If both the start date and end date are imputed, and the imputed end date of medication contradicts with the imputed start date of medication, the general rule is to set the imputed month or day (either stop or start) to the non-imputed month and day (either stop or start) such that they will not contradict each other. Then consider the following:

- If the imputed end month = imputed start month, and
  - If the imputed end day < imputed start day, then the end day will be set to the start day of medication.
- If the imputed end month < imputed start month, and
  - If the imputed end day $\geq$ imputed start day, then the end month will be set to the start month of medication.
  - If the imputed end day < imputed start day
    - If the start month of the medication is not December, then the end month will be set to the start month of medication +1
    - If the start month of the medication = December, then the end month will be set to the start month of medication (December) and the end day will be the start day of the medication.

9.2 Background Characteristics

9.2.1 Subject Disposition

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

The summaries of subject disposition will include the number and percentage of subjects who were screened, screen failed, enrolled, randomized, received brexanolone injection or placebo, subjects who completed the study, who prematurely withdrew from the study, primary reasons for not completing the study, who completed infusion, who discontinued infusion prematurely, and primary reasons for discontinuing treatment. Study completion summary and treatment completion summary will be based on subjects who received study drug (Safety Set). Percentages will be calculated based on the Safety Set. These data will be

provided by randomized treatment groups. If a subject is rescreened because the subject has been a screen failure the first time, the status of the subject will be determined from the second screening. In the count of screened subjects, this subject will be counted only once.

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 set (ie, All Subject, Safety, Efficacy, and PK Sets).

Study completion and discontinuation details, eligibility, treatment allocation, population assignment, and protocol deviations will be presented in listings.

9.2.2 Protocol Deviations

Protocol deviations identified during site monitoring will be captured on an electronic case report form (eCRF) and categorized by the study team as major and minor deviations, without any unblinding information. The major deviations will be further categorized as major-efficacy, major-safety and major-Good Clinical Practice (GCP) deviations. The major deviations will be summarized by type and by actual treatment received using the Safety Set. The minor deviations will be included in the listing.

The list of protocol deviations that may affect efficacy will be identified and finalized by a study team review before database unblinding by a study team review, and will be documented as such.

Any violation of inclusion/exclusion criteria will be presented in a data listing using the Randomized Set.

9.2.3 Demographics and Baseline Characteristics

Demographic data, such as age, gender, race and ethnicity, and baseline characteristics, such as height, weight, body mass index (body mass index [BMI], calculated as weight (kg)/ [height $(m)^2$]), and baseline antidepressants use, will be listed and summarized using the Safety Set. For this summary, as well as for the subsequent analyses, baseline antidepressant use will be defined as taking any medications belonging to the anatomical therapeutic chemical (ATC) 3 term N06A or N05A, or contain terms as ‘depression’, ‘postpartum depression’, ‘major depression’, postpartum depression (‘PPD’), ‘major depressive disorder’, or ‘major depressive mood’.

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

9.2.4 Medical History

Medical history collected at screening will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 23.0. Medical history data will be summarized by system organ class (SOC) and preferred term (PT) and listed by subject using the Safety Set.

9.2.5 Study Drug Exposure and Compliance

Drug administration information collected on the eCRF will be listed by subject using the Safety Set. Details will include dose, infusion rate and unit, start date/time of dose, and end

date/time of dose. In Protocol Version 1.0-2.0, fusion administration sets were fully primed with admixture according to subject body weight, so the infusion rate for each infusion duration is fixed. In Protocol Version 3.0 and 4.0, the infusion administration set was set as the same, but the infusion rates vary depending on subject body weight, with the target 1mg/mL concentration to achieve the recommended dose for each infusion duration. The dose categories and infusion rate for given dose are listed in Table 2.

Table 2: Dose Categories and Infusion Rate for Given Dose of 547-PPD-304

Dose Category	**Infusion Rate for Given Dose (mcg/kg/hour)**	
Titration	30 (Day 1 0-4 hours)	60 (Day 1 4-24 hours)
Maintenance	90 (Day 2 24 hours - Day 3 52 hours)	
Taper	60 (Day 3 52-56 hours)	30 (Day 3 56-60 hours)

Overall exposure to study drug is defined as total number of hours treated with study drug during the study, which is calculated as the sum of actual exposure duration of each infusion segment. The exposure duration for a segment is defined as (end time of infusion – start time of infusion [in seconds])/3600.

Exposure to study drug in each planned infusion rate segment (titration dose, maintenance dose, and tapering dose) is defined as the sum of actual exposure duration of each infusion segment within the infusion rate segment.

Study drug compliance (%) is calculated as [actual total dose (in mcg/kg)/planned total dose (in mcg/kg)] x 100.

Overall exposure to study drug, exposure to study drug in each infusion rate segment and study drug compliance will be summarized using the Safety Set.

9.3 Efficacy Analysis

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

9.3.1 Definition of Efficacy Variables

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.3.3 Visit Windows

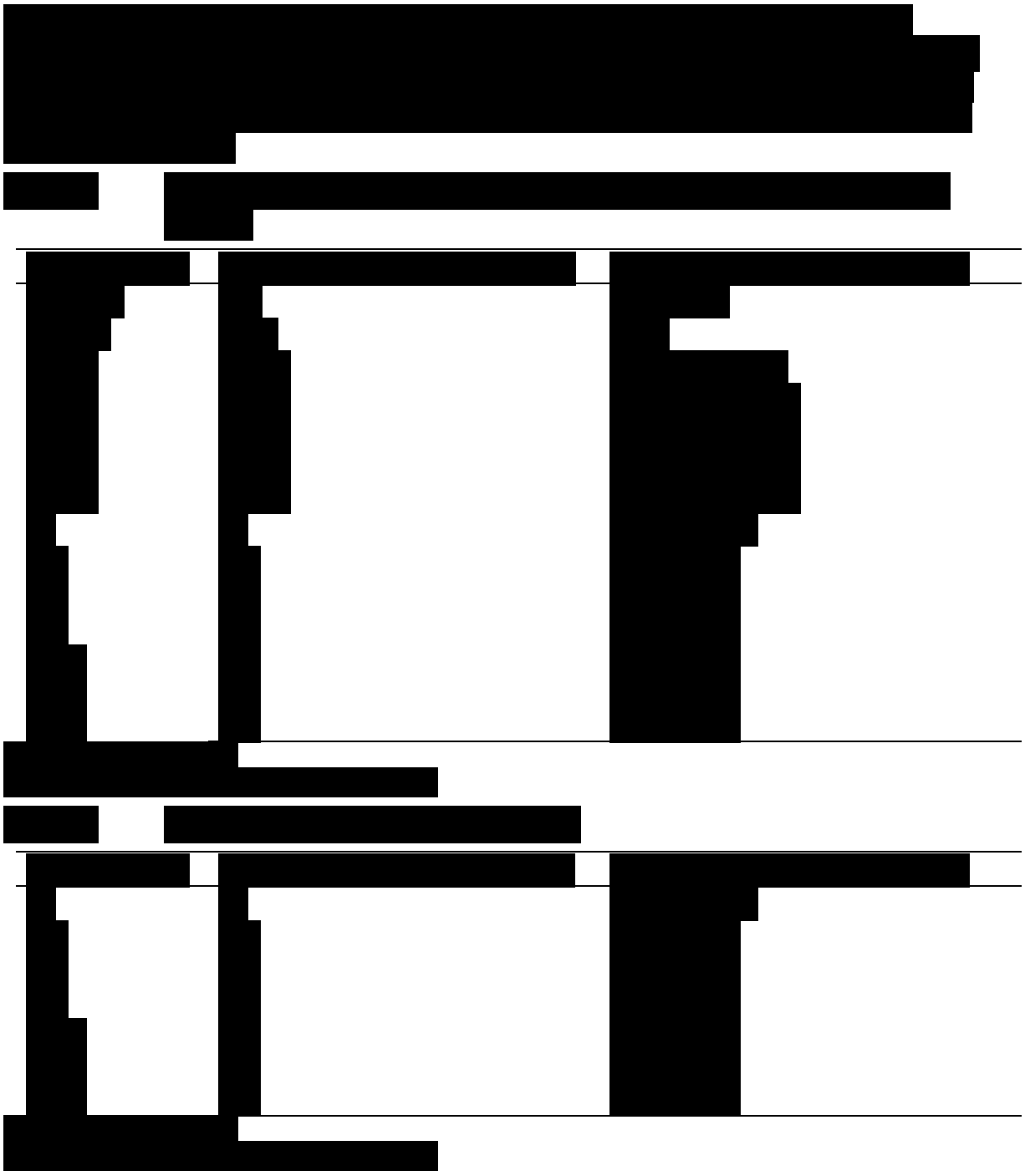
The unscheduled or early termination (ET) visit will be mapped to a scheduled visit for analysis using the date/time of collection/assessment as a basis to determine study day/hour and then study day/hour will be mapped to the intended visit. Once analysis visit windows get assigned, all visits, including scheduled visits, unscheduled visits, and ET visits will be eligible for being flagged as the "analyzed record" within the analysis window. A subject's individual analysis visit window could potentially contain more than 1 visit. In the event of multiple visits falling within an analysis window or in case of a tie, the following rules will be used in sequence to determine the "analyzed record" for the analysis visit window:

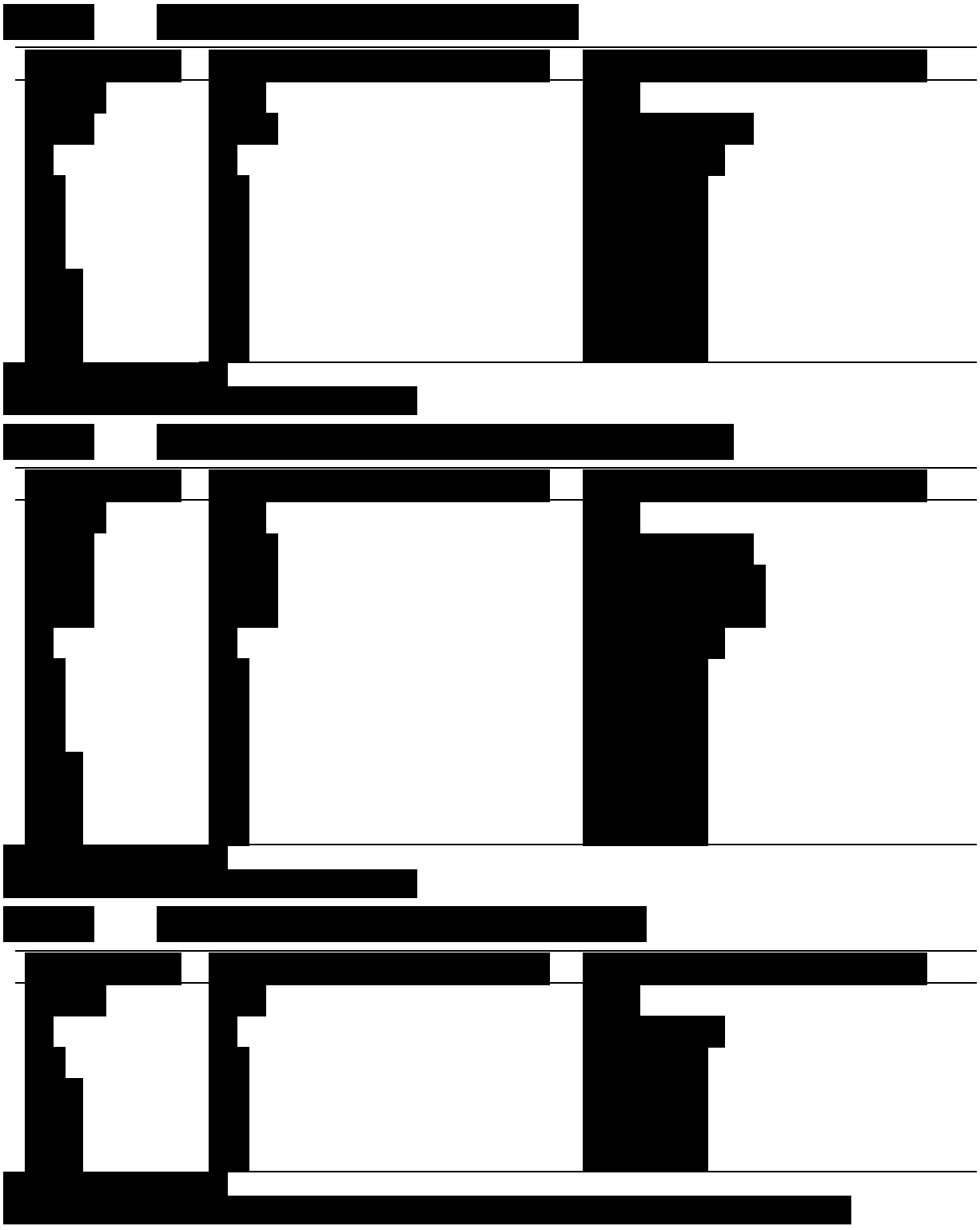
- If there is a scheduled visit/day for the analysis visit window, then the scheduled visit/day data will be used.
- If there is no scheduled visit/day for the analysis visit window, the data closest to the scheduled study day/hour will be used.
- If there is no scheduled visit/day for the analysis visit window and there are visits equally close to the day/hour of scheduled visit, the latest data will be used.

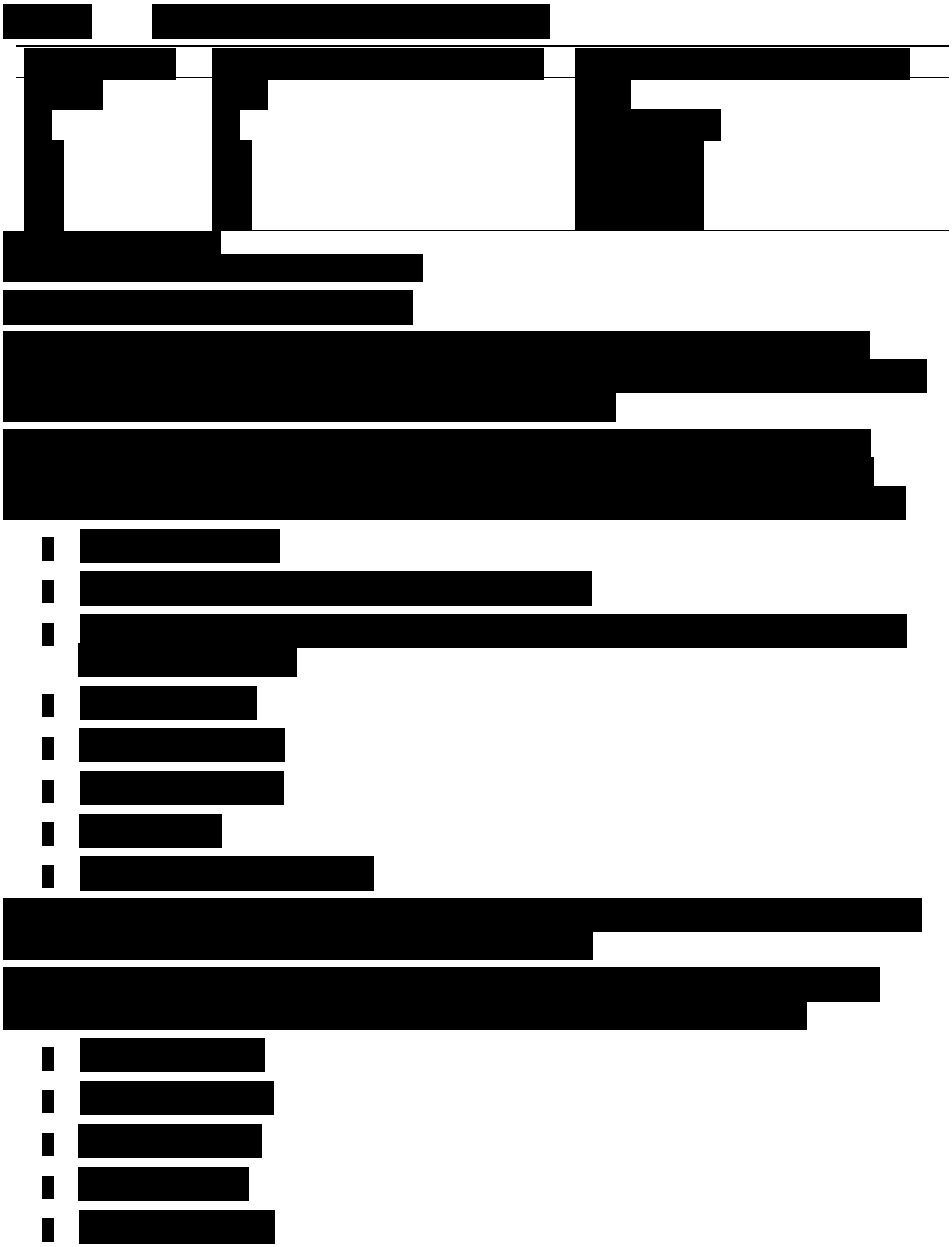
The data not flagged as the "analyzed record" will also be listed in subject listings.

The Follow-up Period in this version of the protocol was reduced from Day 90 ± 7 days to Day 30 ± 3 days for consistency with the Follow-up Period in the adult PPD studies for brexanolone.

Tables 4 – 8 summarize the visit window for all the efficacy endpoint under both follow up schedules.







[redacted]

9.4 Safety Analysis

The primary objective is the safety and tolerability of brexanolone, as evaluated by TEAEs. Other safety endpoints include clinical laboratory tests, vital signs, ECGs and concomitant medication usage. [redacted]

Safety data will be listed by subject and summarized descriptively by treatment group. All safety analyses will be performed on the Safety Set.

The safety endpoints and variables considered in the summary tables for this study are summarized in Table 10.

Table 10: Safety Endpoints and Variables in the Summary Tables and Listings

Safety Evaluation	Incidence	Actual Value	Change from Baseline	Abnormality/Clinical Significance (CS)
AEs	X	*		
Concomitant Medications	X	*		
Laboratory assessments		X	X	*
ECG		X	X	*
Vital Signs		X	X	*
[redacted]				

X = Safety Assessment will be summarized in tables
* = Safety Assessment will be presented in individual subject data listings
Abbreviations:AE=Adverse Event; ECG=electrocardiogram; [redacted]

9.4.1 Visit Windows

The mapping rule of unscheduled or early termination (ET) visit and the rule of flagging "analyzed record" are the same as described in Section 9.3.3.

Table 11 displays the visit windows for analysis of clinical laboratory parameters (including hematology, serum chemistry) parameters; Table 12 displays the visit windows for analysis of 12-lead ECG; Table 13 displays the visit windows for analysis of vital signs parameters; and Table 14 displays the visit windows for analysis of [redacted].

Table 11: Visit Windows for Analysis of Clinical Laboratory Parameters

Scheduled Visit	Study Day/Hour of Expected Visit	Study Day/Hour Window for Visit
Baseline	D -1	D -7 to D1H0
D3H72	D3H72	>D1H0, ≤ D3H72
D14	D14	>D4H0, ≤ D33

Note: D = Day, H = Hour.

Table 12: Visit Windows for Analysis of 12-lead Electrocardiogram Parameters

Scheduled Visit	Study Day/Hour of Expected Visit	Study Day/Hour Window for Visit
Screening	D-1	D-7 to D-1
Baseline	D1H0	D1H0
D3H72	D3H72	>D1H0, ≤ D3H72
D14	D14	>D4H0, ≤ D33

Note: D = Day, H = Hour.

Table 13: Visit Windows for Analysis of Vital Signs Parameters

Scheduled Visit	Study Day/Hour of Expected Visit	Study Day/Hour Window for Visit
Screening	D -1	D -7 to D-1
Baseline	D1H0	D1H0
D1H2	D1H2	>D1H0, ≤ D1H3
D1H4	D1H4	>D1H3, ≤ D1H6
D1H8	D1H8	>D1H6, ≤ D1H10
D1H12	D1H12	>D1H10, ≤ D1H18
D1H24	D1H24	>D1H18, ≤ D2H27
D2H30	D2H30	>D2H27, ≤ D2H33
D2H36	D2H36	>D2H33, ≤ D2H42
D2H48	D2H48	>D2H42, ≤ D3H51
D3H54	D2H54	>D3H51, ≤ D3H57
D3H60	D3H60	>D3H57, ≤ D3H66
D3H72	D3H72	>D3H66, ≤ D3H72
D7	D7	>D4H0, ≤ D10
D14	D14	>D10, ≤ D33

Note: D = Day, H = Hour.

[redacted]

9.4.2 Adverse Events

The analysis of AEs will be based on the concept of TEAEs. A TEAE is defined as an AE with onset on or after the start of study drug infusion, or any worsening of a pre-existing medical condition/AE with onset on or after the start of study drug infusion.

All adverse events will be coded using MedDRA version 23.0 or higher and summarized by SOC and PT. Multiple occurrences of an AE are counted only once per subject per SOC and per PT for summary tables. Incidences will be presented in order of decreasing frequency of the brexanolone group by SOC and PT. Incidences will also be presented in order of decreasing frequency of the brexanolone group by PT only. In addition, summaries will be provided by severity (mild, moderate, severe) and by causality (related, not related) to study drug (see protocol section 12.2.2 for definitions). TEAEs leading to treatment discontinuation and study discontinuation and Serious AEs (SAEs) (see protocol section 12.2.1.2 for definition) with onset after the start of randomized infusion will also be summarized.

Summary tables of TEAEs will be presented by treatment and will summarize the number and percentage of subjects for the following:

- Any TEAE
- TEAEs by maximum severity to study drug (mild, moderate, severe)
- Treatment-emergent serious AEs (SAEs)
- TEAEs leading to discontinuation of study drug
- TEAEs leading to withdrawal from study
- AEs of special interest (AESIs), which include:
    - Excessive sedation
    - Loss of consciousness
    - Any sedation-related AE that leads to dose reduction, interruption, or termination

Subjects will be counted only once within each SOC and PT at the maximum severity in the following order: severe, moderate, and mild. An AE with missing severity will be considered as a severe AE. The incidences will be presented by descending frequency of SOC and then, within a SOC, by descending frequency of PT based on the subject count, and in alphabetical order of PT if the incidence within a PT is a tie.

Subjects will be counted only once within each SOC and PT at the strongest relationship to study drug in the following order: related, not related to study drug. If the relationship between the AE and the study drug is determined to be “possible” or “probable”, the event will be considered as related to the study drug. An AE with missing relationship to study drug will be considered as related to study drug.

A summary of most frequent TEAE just by preferred term where the incidence is more than 5% in any treatment group will be provided, sorted by decreasing overall frequency.

All AEs, SAEs (including those with onset or worsening before the start of randomized infusion), AEs leading to study drug discontinuation and AEs leading to death through the Day 30 Follow-up Visit (±3 days), and all AESIs will be listed.

9.4.3 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 (WHO-DDE) dated March 2018, or later.

Medications will be presented according to whether they are being taken prior to and/or during the study (concomitant):

- Prior medications are defined as all medications taken prior to the infusion of study treatment.
- Concomitant medications are defined as all medications taken on or after the infusion of study treatment starts through the Day 30 (±3 days) visit. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

Note that medication that started prior to the infusion of study drug and continued after the start of infusion will be summarized as prior medication and separately as concomitant medication. Details of prior and concomitant medications will be listed by subject, start date, and verbatim term.

Medication summaries will be performed by ATC level 2 term and PT separately for “Prior” or “Concomitant” medications as defined above based on the Safety Set.

Nonpharmacological interventions for PPD will be listed and summarized.

9.4.4 Clinical Laboratory

9.4.4.1 Hematology, Serum Chemistry, Coagulation

Blood samples will be collected for coagulation at screening, and hematology and serum chemistry, throughout the study. Analytes to be evaluated are summarized in Table 15**.**

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 Appendix A.

Table 15: 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, clinically significant (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.

Summary tables will include descriptive statistics for the actual values and changes from baseline by scheduled time point in hematology, serum chemistry, and coagulation by treatment group. Frequency counts and percentages will be presented over time for these categorical data by treatment.

Shift analysis pre- and post-treatment will be presented for the following laboratory categories (low, normal and high).

Number and percent of subjects with liver injury as defined by Hy's law will be presented. Hy's law is defined as ALT or AST > 3 times of upper limit of normal; and total bilirubin > 2 times of upper limit of normal, and alkaline phosphatase < 2 time of upper limit of normal.

All parameters will be converted to consistent units according to the International System of Units (SI) before summarization.

All clinical laboratory results will be listed by subject and timing of collection. Out-of-range values will be flagged as low, high, or abnormal, where applicable.

The number and percentage of subjects with potentially clinically significant (PCS) values at any time after study drug infusion will be summarized by treatment group for the hematology and chemistry parameters defined in Table 16 and Table 17**.** PCS laboratory values will also be listed by subject.

Table 16: Hematology Potentially Clinically Significant Values

Laboratory Parameter	**Sex**	**Units**	**Criteria for PCS Values (Observed values)**	
			High	Low
Hemoglobin	Male	g/L	>185	<115
	Female	g/L	>170	<100
Hematocrit	Male	Fraction of 1	>0.55	<0.385
	Female	Fraction of 1	>0.49	<0.345
Platelet count		10^9/L	>600	<125
White blood cell		10^9/L	>15	<2.5
Basophils		10^9/L	>0.5	NA
Eosinophils		10^9/L	>1.5	NA
Neutrophils		10^9/L	NA	<1.5
Lymphocytes		10^9/L	>6.0	<0.5
Monocytes		10^9/L	>1.4	NA

Abbreviations: PCS = Potentially Clinically Significant

Table 17: Chemistry Potentially Clinically Significant Values

Laboratory Parameter	Units	Criteria for PCS Values (Observed values)	
		High	Low
Albumin	g/L	>70	<28
Blood urea nitrogen	mmol/L	>10.71	NA
Calcium	mmol/L	>2.75	<2.0
Chloride	mmol/L	>120	<90
Creatinine	mmol/L	>3xULN or >3x Baseline	
Gamma Glutamyl Transferase		>3xULN	
Glucose	mmol/L	>13.9	<2.8
Sodium	mmol/L	>150	<132
Potassium	mmol/L	>5.4	<3.3
Protein	g/L		<45
Bicarbonate	mmol/L	>34	<18
Chloride	mmol/L	>120	<90
Phosphorus	mmol/L	>1.94	<0.61
Liver Function Tests (LFT)			
Bilirubin	µmol/L	>2xULN	NA
Aspartate Aminotransferase	U/L	>3xULN	NA
Alanine Aminotransferase	U/L	>3xULN	NA
Alkaline Phosphatase	U/L	>1.5xULN	NA

Abbreviations: PCS = Potentially Clinically Significant

Liver function tests will be monitored closely for potentially clinically significant values, and will be summarized for occurrence any time post-baseline for the following parameters for these PCS threshold (for condition involving >1 parameter, the results need to be from the same timepoint):

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

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

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

Alkaline Phosphatase: >1.5xULN, >2xULN

Total Bilirubin: >1.5xULN, >2xULN

Total Bilirubin > 2xULN AND (Alanine Aminotransferase or Aspartate Aminotransferase >3xULN)

Total Bilirubin >2xULN AND Alkaline Phosphatase >2xULN AND (Alanine Aminotransferase or Aspartate Aminotransferase >3xULN)

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

9.4.4.2 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.

9.4.4.3 Pregnancy Test

All subjects will be tested for pregnancy by serum human chorionic gonadotropin (HCG) at the Screening Visit and by serum or urine HCG 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. Subjects with a positive pregnancy test at screening or Day 1 will be ineligible for study participation. Pregnancy test results will be listed by subject.

9.4.4.4 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. Drug screening and alcohol assessment results will be listed.

9.4.5 Electrocardiogram

A baseline 12-lead ECG will be performed during screening. The following ECG parameters will be recorded: heart rate (bpm), pulse rate (PR) (msec), QRS (msec), QT (msec), and QT corrected with Fridericia's formula (QTcF) (msec).

QTcF (msec) is calculated as: QT (msec) / $RR^{1/3}$, where RR = 60 / heart rate (bpm).

All ECG results will be interpreted by the Investigator as 'normal' 'abnormal, NCS'; or 'abnormal, CS'. If 'abnormal', details will be provided.

The actual value at each time point and change from baseline at each post-baseline time point will be summarized by treatment group. The number and percentage of subjects with 'normal', 'abnormal, not clinically significant' and 'abnormal, clinically significant' ECG results will be summarized at baseline and each post-baseline time point.

All ECG data will be listed by subject and time of measurement. Mean values of ECG parameters over time will be presented graphically by treatment group.

Additionally, the number and percentage of subjects with PCS and potentially clinically significant change (PCSC) values will be summarized for such occurrence any time post-baseline. Potentially clinically significant values will be identified for ECG parameters as outlined in the following table. This analysis includes triplicate values individually and is not based on average value. In addition, any PCS value at any time post-baseline will be summarized as shown in Table 18.

Table 18: ECG Potentially Clinically Significant Values

ECG	Units	Criteria for PCS Values (Observed values)		Criteria for PCSC values (Change from Baseline)	
		High	**Low**	**Increase**	**Decrease**
QTcF Interval	msec	>450 but ≤ 480 >480 but ≤ 500 >500	NA	≥ 30 to 60 >60	NA

Abbreviations: PCS = Potentially Clinically Significant; PCS = Potentially Clinically Significant Change; NA=Not Available

9.4.6 Vital Signs

Vital signs include oral temperature (°C), respiratory rate (breaths/min), heart rate (bpm), and blood pressure (mmHg). 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 Appendix A. 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 23.00 h and 06.00 h.

Additionally, respiratory rate, heart rate, and blood pressure should be collected for any subject that experiences an AESI 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.

Additionally, the number and percentage of subjects with PCS and PCSC values will be summarized for such occurrence any time post-baseline. Potentially clinically significant values will be identified for vital sign parameters as outlined in the Table 19.

Table 19: Vital Signs Potentially Clinically Significant Values

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

PCS = Potentially Clinically Significant; PCS = Potentially Clinically Significant Change; NA=Not Available

The change from supine to standing (Supine – Standing) vital signs – heart rate, systolic and diastolic blood pressure – will be summarized by scheduled assessment timepoint.
Any vital signs results considered clinically significant by the investigator will be captured as adverse events, hence will show up in AE displays.

9.4.7 Physical Examination

Body weight and height will be measured at screening. BMI will be programmatically calculated in the eCRF. The date of assessment and study day of physical examinations will be listed.

Note: 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 and will be presented in AE listings and tables.

[redacted]

[redacted]

9.5 Pharmacokinetic Analysis

Plasma will be collected to assay for concentrations of brexanolone. PK analyses will be performed using the PK set.

9.5.1 Collection schedule

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, 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.

9.5.2 Derived Pharmacokinetic parameters

The following PK parameters will be derived from the plasma concentrations of brexanolone (where evaluable):

Table 20: Pharmacokinetic Parameters and Definitions

$AUC_{0\text{-}60}$ (or AUC)	Area under the plasma concentration time curve from time 0 to 60 hours
AUC_{∞}	AUC from time 0 to infinity
C_{max}	Maximum (peak) plasma concentration
T_{max}	Time at maximum (peak) plasma concentration
C_{ss}	Steady-state drug concentration in the plasma during constant-rate infusion
T_{half}	Half-life of first elimination phase of brexanolone
CL/F	Clearance of brexanolone
Vss	Steady state volume of distribution
Vz/F	Volume of distribution

9.5.3 Handling of dropouts or missing data

PK parameters will be provided by qPharmetra, LLC. Please refer to the qPharmetra PK Analysis Plan for handling missing data.

9.5.4 Pharmacokinetic statistical analysis

The plasma concentrations along with time point deviation from scheduled time will be listed by subject.

PK will be summarized using appropriate descriptive statistics. PK plasma concentration equivalents that are BLQ will be set to zero. Plasma concentration values that are BLQ will be set to 0 for the calculation of descriptive statistics and the same will be considered for individual plots. If more than 50% of values at any given time point are BLQ, then only n, minimum, median and maximum will be reported.

All PK parameters will be summarized using n, geometric mean, geometric coefficient of variation (CV), CV, median, minimum, and maximum, all listed by subject.

9.5.5 Data presentation

Individual plasma PK concentrations and PK parameters will be presented with an appropriate number of significant figures as in the raw data. If the raw value has > 3 significant figures, use the following for representation.

- For values ≥ 100, display the whole number
- For values < 100, display 3 significant figures

The level of precision for each summary statistic will be presented as follows:

- n: integer
- Min, max: in same precision as individual data
- Arithmetic mean, median, geometric mean: in 1 more level of precision than min/max
- SD, standard error of mean (SEM): in 1 more level of precision than means/median
- CV% and geometric CV%: 1 decimal place.

The descriptive statistics will be generated as discussed above in Section 9.5.4. The following figures will be produced:

- Mean ± SD plasma concentration-time profiles through Day 3, 72 hours will be plotted on linear and semi-logarithmic scales
- Individual subject concentration-time profiles on linear and semi-logarithmic concentration scales
- Spaghetti plots for each treatment through Day 3, 72 hours (linear and semi-logarithmic scale)

10 SUMMARY OF INTERIM AND DATA SAFETY MONITORING BOARD ANALYSES

The interim DSMB analysis will be summarized in a separate SAP.

11 REFERENCES

Clinical Study Protocol: Version 4.0 (20 December 2019), Company: Sage Therapeutics Inc.

[redacted]

12 APPENDICES

12.1 Appendix A: 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															
Monitor for excessive sedation		X (Q2 hours during planned non-sleep periods)															
Study drug infusion		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]
Scale; 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.

Certificate Of Completion

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Source Envelope:
Document Pages: 40
Signatures: 5
Envelope Originator:
Certificate Pages: 2
Initials: 0
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Electronic Record and Signature Disclosure: Not Offered via DocuSign		
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Envelope Summary Events	Status	Timestamps
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Completed	Security Checked	10-Mar-2021 | 15:07

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