Official Title:	An Open-Label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Brexanolone in the Treatment of Adult Participants With Tinnitus
NCT Number:	NCT05645432
Document Date:	Final Version: 01 Feb 2024

Statistical Analysis Plan for Interventional Studies

Text only

Sponsor Name: Sage Therapeutics, Inc.

Protocol Number: 547-TRM-201
Protocol Title: An Open-Label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Brexanolone in the Treatment of Adult Participants with Tinnitus

Protocol Version and Date: Amendment 2.0, Version 3.0, dated 13-Oct-2023

Syneos Health Project Code: 7043647

Authors: [redacted]

Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
0.1	09-Dec-2022	[redacted]	Initial Release Version
0.2	23-Dec-2022		Updates based on internal review.
0.3	31-Jan-2023		Updates based on sponsor review.
1.0	27-Feb-2023		Updates based on sponsor review; Final version.
1.1	30-Nov-2023		Updates based on sponsor review.
1.2	12-Dec-2023		Updates based on sponsor review.
1.3	08-Jan-2024		Updates based on sponsor review.
1.4	18-Jan-2024		Updates based on sponsor review.
1.5	30-Jan-2024		Updates based on sponsor review.
2.0	31-Jan-2024		Final version.

I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

Name, Title	Signature	Date (DD-Mmm-YYYY)
[redacted]	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I am the author of this document Signing Time: 31-Jan-2024 | 19:01 EST 8E3348C12DAF475799A2A74F6F524EF9	31-Jan-2024 | 19:01 EST
[redacted]	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I have reviewed this document Signing Time: 01-Feb-2024 | 03:54 PST A9EFCEB136394EC48D3A1C13B23CD8DA	01-Feb-2024 | 03:54 PST

Sage Therapeutics Approval

Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)
[redacted]	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 31-Jan-2024 | 20:08 EST EBE3317E84BF496B857F15CC6D6E502A	31-Jan-2024 | 20:08 EST
[redacted]	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I have reviewed this document Signing Time: 01-Feb-2024 | 09:08 EST 2104CF00F3AF42A7B5FD5AAE857E3C85	01-Feb-2024 | 09:08 EST
[redacted]	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 01-Feb-2024 | 09:08 EST D1543B86AFEE4D57A3E89CEA14B6FF1C	01-Feb-2024 | 09:08 EST

[redacted]	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 31-Jan-2024 | 18:41 EST 9DE3C23A72CA4DF1B9A0BBD1CC8EB589	31-Jan-2024 | 18:42 EST
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)
[redacted]	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 01-Feb-2024 | 06:59 EST EA34638521424C2885BEC8F16850E54C	01-Feb-2024 | 06:59 EST
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)
[redacted]	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 31-Jan-2024 | 23:03 EST 6F1FC810D26B48578BAD92F70906BED1	31-Jan-2024 | 23:03 EST
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)

Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine Transaminase
AST	Aspartate Transferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CI	Confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
CS	Clinically Significant
[redacted]	[redacted]
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EOS	End of study
ICF	Informed consent form
IP	Investigational product
IV	Intravenous
LS	Least squares
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
[redacted]	[redacted]
NA	Not applicable
NCS	Not Clinically Significant
[redacted]	[redacted]
[redacted]	[redacted]
PT	Preferred Term
Q1	First quartile
Q3	Third quartile

Abbreviation	Description
QC	Quality Control
QTcF	QT corrected according to Fridericia's formula
RBC	Red Blood Cells
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
SOC	System organ class
SOP	Standard Operating Procedure
SPL	Sound pressure level
SS	Safety Set
TEAE	Treatment-emergent adverse event
[redacted]	[redacted]
TFL	Table, Figure and Listing
[redacted]	[redacted]
TMS	Transcranial magnetic stimulation
UN	Unstructured Covariance Matrix
VAS	Visual Analog Scale
VAS-A	VAS annoyance
VAS-L	VAS loudness
WOCBP	Woman of childbearing potential
WHO	World Health Organization

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control (QC) of all tables, figures and listings related to the safety, tolerability, and efficacy of Brexanolone in the treatment of adult participants with tinnitus. All clinical pharmacology assessments, including [redacted] assessments, will be detailed in a separate modeling and assessment plan. qPharmetra will prepare individual [redacted] estimates utilizing the existing [redacted] for Brexanolone and transfer to Sage. [redacted].

2.2. Timings of Analyses

The primary analysis of safety, tolerability, and efficacy is planned after all participants complete the final study visit or terminate early from the study.

3. Study Objectives

3.1. Primary Objective

The primary objective is to evaluate the safety and tolerability of brexanolone in adult participants with tinnitus.

3.2. Secondary Objectives

The secondary objectives are:

- To assess subjective tinnitus perception during brexanolone infusion based on Visual Analog Scales (VAS).
- To assess subjective tinnitus perception after brexanolone infusion based on VAS.

[redacted]

4. Study Details/Design

4.1. Brief Description

This is an open-label study to evaluate the safety, tolerability, [redacted], and efficacy of brexanolone in adults with tinnitus following a single 6-hour continuous intravenous (IV) infusion.

This study includes a Screening Period of up to 28 days, a 1-day Treatment Period, and a 6-day Follow-up Period. After providing informed consent, participants will undergo screening assessments as outlined in Study Protocol Table 2 to determine eligibility.

Screening Period:
The Screening Period begins with the signing of the informed consent form (ICF). Eligible participants will complete additional eligibility and baseline assessments as specified in the Schedule of Assessments (Study Protocol Table 2).

Starting 7 days before administration of investigational product (IP) (Day -7), participants will have twice daily remote predose assessments as indicated in Study Protocol Table 2. Participants will receive training on how to perform all remote assessments during Screening. The participant will be contacted by the site on Day -7 through Day -1 to remind them to begin remote assessments. Assessments will be performed remotely by the participant on Day -7 through Day -1. Ratings for both Visual Analog Scale-Loudness (VAS-L) and Visual Analog Scale-Annoyance (VAS-A) will be done twice daily, once each in the morning and evening. Participants will be excluded from dosing if they do not successfully perform at least 10 of the 14 remote VAS assessments.

Treatment Period:
A continuous, 6-hour IV infusion of IP will be administered at the Clinic Treatment Visit on Day 1. Assessments will be performed as indicated in Study Protocol Table 3.The participant will spend approximately 9 hours in the clinic on Day 1: 1 hour for setup of IV pump and assessments performed prior to administration of IP, 6 hours for the IP infusion, and 2 hours for safety observation at the conclusion of the IP infusion. At the discretion of the investigator, participants may stay in the clinic overnight after the end of infusion.

Follow-Up Period:

Assessments for the Follow-up Period will be performed as indicated in Study Protocol Table 3. The participant will be contacted by the site on Day 2 through Day 6 to remind them to begin remote assessments. Follow-up assessments will be conducted remotely on Day 2 through Day 6. Ratings for both VAS-L and VAS-A will be done twice daily, once each in the morning and evening.

Participants will return to the clinic approximately 6 days after the last dose of IP (Day 7±1 day) for efficacy and safety monitoring. The End of Study (EOS) Visit will be conducted at the time of discontinuation if this occurs at any time before Day 7±1 day (see Study Protocol Section 8.4.2).

4.2. Participant Selection

4.2.1. Inclusion Criteria

Participants must meet all of the inclusion criteria listed in Study Protocol Section 8.1 to qualify for participation in this study.

4.2.2. Exclusion Criteria

Participants who meet any of the exclusion criteria listed in Study Protocol Section 8.2 will be disqualified from participation in this study.

4.3. Determination of Sample Size

Up to 24 participants will be dosed to achieve approximately 20 study completers, assuming a 20% study discontinuation rate among dosed participants.

4.4. Treatment Assignment and Blinding

This is an open-label study in which all participants will receive a continuous, 6-hour IV infusion of brexanolone administered at the Clinic Treatment Visit on Day 1.

4.5. Administration of Study Medication

Participants will receive a 6-hour, continuous IV infusion of brexanolone on Day 1.

The specific infusion dose of IP will be calculated based on weight (obtained at Screening) for each participant and administered according to the dose regimen in Table 1.

Table 1. Infusion Rate

Time point	**Day 1** **0 to 0.5 hours**	**Day 1** **0.5 to 1 hour**	**Day 1** **1 to 6 hours**
Dose	30 mcg/kg/hour	60 mcg/kg/hour	90 mcg/kg/hour[a]

[a] reduction in dosage to 60 mcg/kg/hour should be considered for participants who do not tolerate 90 mcg/kg/hour. No reductions below 60 mcg/kg/hour are permitted.

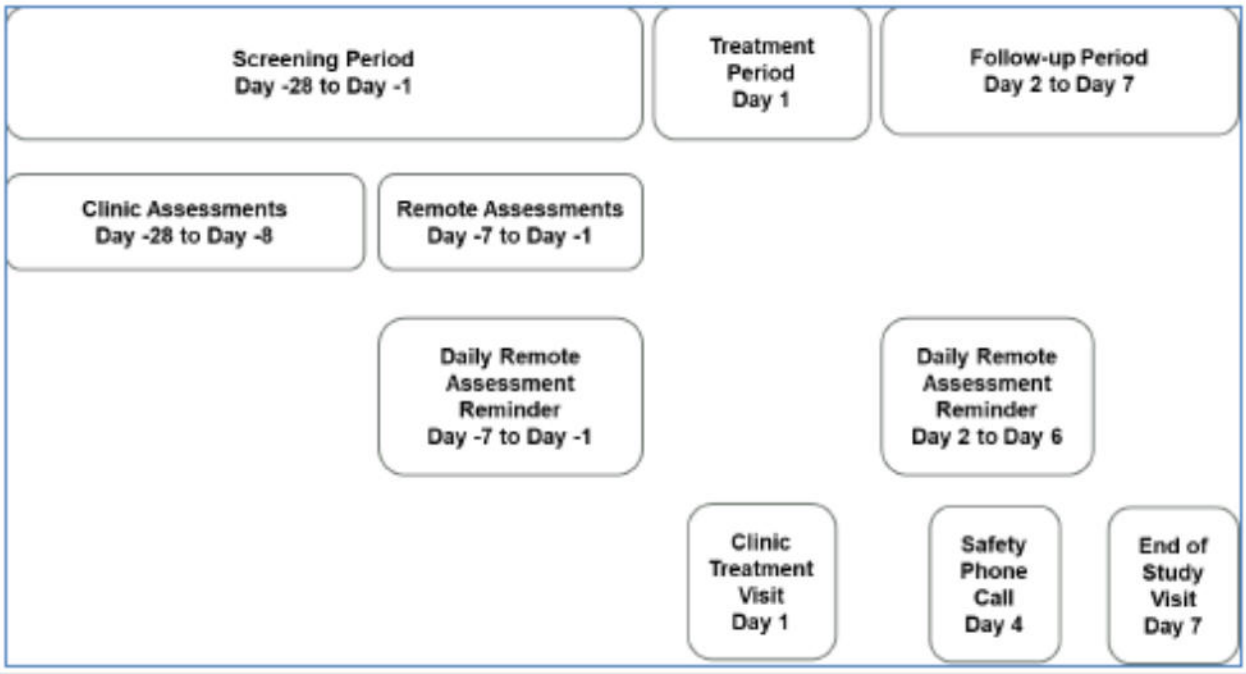
Due to the risk of excessive sedation and sudden loss of consciousness, for the duration of the infusion, participants will be monitored for hypoxia using continuous pulse oximetry equipped with an alarm and will be assessed for excessive sedation (with the [redacted]) by a healthcare provider. If excessive 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 per protocol guidance. The infusion will be immediately stopped if pulse oximetry reveals hypoxia. After an episode of confirmed hypoxia, the infusion should not be resumed.

In this study, excessive sedation, loss of consciousness, and any sedation-related adverse event (AE) that leads to dose reduction, interruption, or termination will be recorded as an adverse event of special interest (AESI).

4.6. Study Procedures and Flowchart

The study design is summarized in the flow chart below. Reference Protocol Schedule of Assessments (Tables 2 and 3) for the complete Schedule of Activities.

Figure 1. Study Design



5. Endpoints

5.1. Primary Endpoint

- Incidence of treatment-emergent adverse events (TEAEs)

5.2. Secondary Endpoints

- Change from baseline to Hour 6 of infusion in VAS-L ratings
- Change from baseline to Hour 6 of infusion in VAS-A ratings
- Change from baseline to post-infusion in VAS-L ratings measured via daily diary over multiple days
- Change from baseline to post-infusion in VAS-A ratings measured via daily diary over multiple days

[redacted]

- Change from baseline in vital signs, electrocardiogram (ECG), and clinical laboratory parameters

[redacted]

6. Analysis Sets

Details on the process for defining analysis datasets are located in the Data Review and Definition of Analysis Sets SOP (3911).

6.1. Screened Set

The Screened Set will include all participants who were screened for participation in this study.

6.2. Enrolled Set

The Enrolled Set will include all participants who provided written informed consent and passed the inclusion and exclusion criteria for study participation. Screen failures will not be included in this set.

6.3. Efficacy Set

The Efficacy Set will be defined as all participants who received any amount of IP and have at least one post-baseline efficacy evaluation.

6.4. Safety Set

The Safety Set (SS) will include all participants who received any amount of IP. The SS will be used for all analyses of safety endpoints.

6.5. Protocol Deviations

Protocol deviations identified during the study will be captured in the Electronic Data Capture (EDC) system. Protocol deviation management at Syneos Health is detailed in Protocol Deviation and Non-compliance Management (3101.W02).

7. General Aspects for Statistical Analysis

7.1. General Methods

- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, maximum, first quartile (Q1), and third quartile (Q3). In addition, change from baseline values will be calculated at each time point and summarized descriptively.
- For categorical variables, descriptive summaries will include counts and percentages.
- All relevant participant data will be included in listings. All participants entered into the database will be included in participant data listings

7.2. Key Definitions

7.2.1. Baseline

For in-clinic assessments, baseline is defined as the most recent value immediately prior to the start of IP infusion. For remote daily assessments, baseline is defined as the average of all available preinfusion values per participant. Change from Baseline is defined as the measurement at each timepoint minus the Baseline value.

7.2.2. Study Day

Study Day is calculated relative to the start date of study treatment and defined as follows:

- The day of participant receiving the IP infusion is designated as Day 1.
- For visit days after Day 1, study day = visit date – Day 1 date + 1.
- For visit days prior to Day 1, study day = visit date – Day 1 date. Thus, study days for screening visits are negative numbers. There is no “Day 0”.

7.3. Missing Data

All participants will be used in the analysis using all non-missing data available. No imputation process will be used to estimate missing data.

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

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

7.3.1. Adverse Events (AE)

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

For partial AE start dates:

- When the year is known but the month and day is unknown, then:
  - If the year matches the year of first dose and the end date (if present) is after first dose date, or AE is ongoing, then impute as the month and day of earlier date of (the first dose date + 1 day, last dose date).

  - If the year of AE onset < year of initiation of the treatment, then the month and day will be set to December 31st.
  - If the year of AE onset > the year of initiation of treatment, then the month and day will be set to January 1st.
- If the year and month are known, but the day is unknown, then:
  - If the year of AE onset = the year of initiation of the treatment and:
    - The month of AE onset = the month of initiation of the treatment, then the day will be set to the day of initiation of the treatment.
    - The month of AE onset < the month of initiation of the treatment, then the day will be set to the last day of month of the particular year.
    - If the month of AE onset > the month of initiation of the treatment, then the day will be set to the 1st day of month.
  - If the year of AE onset < the year of initiation of the treatment, then the day will be set to the last day of month of the particular year.
  - If the year of AE onset > the year of initiation of the treatment, then the day will be set to the 1st day of month.
- If the imputed AE onset date is after the AE stop date, then the onset date will be set to the stop date.
  - When the year and day are present and the month is missing, treat it as if the day is missing, and only year is present. Follow the imputation rules for "year is known, but the month and day is unknown."
  - When the year is missing, but the month and/or day is known, treat this date as missing; do not impute.

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

- If the year is present and the month and day are missing, then the month and day will be set to January 1.
- If the year and day are present and the month is missing, then the month will be set to January.
- If the year and month are present and the day is missing, then the day will be set to the 1st day of month.

7.3.3. Prior and Concomitant Medications

For the partial start date of medication:

- If the year is present and the month and day are missing, then the month and day will be set to January 1.
- If the year and day are present and the month is missing, then the month will be set to January.
- If the year and month are present and the day is missing, then the day will be set to the 1st day of month.
- If the imputed start date of medication is after the end date (imputed date if applicable) of medication, then the start date will be set to the end date of medication.

For the partial end date of medication:

- If the year is present and the month and day are missing, then the month and day will be set to either December 31 or date of death, whichever is earlier.
- If the year and month are present and the day is missing, then the day will be set to the last day of the month or month of death.

- If the year and day are present and the month is missing, then treat it as if the day is also missing. Set the month and day to be either December 31 or date of death, whichever is earlier.

7.4. Visit Windows

There will be no windowing for visits.

7.5. Pooling of Centers

Not applicable.

7.6. Subgroups

No subgroup analysis is planned for this study.

8. Demographic, Other Baseline Characteristics and Medication

8.1. Participant Disposition and Withdrawals

The summaries of participant disposition will include the number and percentages of participants who were screened, screen failed, treated, completed treatment, discontinued IP prematurely with primary reasons for discontinuing IP, completed the study, and prematurely withdrew from the study with primary reasons for not completing the study. All percentages will be calculated based on the participants who were enrolled, unless otherwise stated. If a participant is rescreened because the participant has been a screen failure the first time, the status of the participant will be determined from the second screening. In the count of screened participants, such a participant will be counted only once. Participants of all analysis sets will be summarized (eg, number and percentages of participants in Screening Set, Enrolled Set, Efficacy Set, and Safety Set)..

A listing will be provided for participants screen failed with primary reason and a disposition listing will be provided for all enrolled participants. A separate listing will be provided for the Safety Set and reported for participants who prematurely discontinued IP, prematurely withdrew from the study with reasons, and date of withdrawal from the study.

8.2. Protocol Deviations

All major protocol deviations will be summarized using the Safety Set. All protocol deviations (major and minor) will be included in a data listing for the Enrolled Set.

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

8.3. Demographic and Baseline Characteristics

Demographic data including age, sex, race, ethnicity, and baseline characteristics (e.g., weight, height, BMI, childbearing potential), will be summarized and listed using the Safety Set. The below conversions will be used if needed.

$$\text{Body mass index (BMI) } (kg/m^2) = \text{Weight}(kg)/[\text{Height}(m)^2]$$

8.4. Medical History

Medical history collected at screening will be analyzed using the Safety Set and coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The summary will be presented by primary system organ class (SOC) and preferred term (PT). A participant will be counted once within each level of summarization. Medical history will be presented in a corresponding listing.

8.5. Tinnitus Medical History

Tinnitus medical history will be analyzed for the Safety Set and will include at a minimum information related to initial onset, tinnitus pulse, perception, loudness, sound, awareness, conditions that worsen symptoms, hearing aid use, and sound tolerability. Tinnitus medical history will be tabulated and a corresponding listing provided.

8.6. Prior and Concomitant Medications

Medications will be recorded throughout the duration of the study and will be coded using World Health Organization (WHO) Drug Dictionary Global B3 September 2022, or later.

Medications taken prior to the initiation of the start of IP will be denoted “Prior”. Those medications taken prior to the initiation of the IP and continuing beyond the initiation of the IP, or those medications started at the same time or after the initiation of IP will be denoted “Concomitant”.

Both prior and concomitant medications will be separately summarized by anatomical therapeutic chemical (ATC Level 3) class and preferred term. Note that medication taken before the initial dosing of the IP and continued after the initial dosing will be categorized as a prior medication and, separately, as a concomitant medication. All prior and concomitant medications will be listed. Medications will be presented according to whether they are “Prior” or “Concomitant”, as defined above. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant. Missing date imputation rules are provided in Section 7.3.3.

Concomitant procedures are recorded on a separate electronic case report form (eCRF) page; this will be presented in a listing by participant.

The Safety Set will be used for all tables and listings.

8.7. Extent of Exposure

The number and percentage of treated participants receiving 6 hours of infusion will be tabulated. Detailed information regarding the infusion timepoints, planned doses, actual infusion rates, infusion interruptions, infusion discontinuations, and dose changes will be listed for each participant in the Safety Set.

Study drug exposure will be summarized using actual infusion duration, dose changes, infusion rate changes, and interruptions lasting more than 5 minutes. Actual infusion duration is the elapsed time between start time and stop time of study drug administration, defined as stop time (HH:MM) – start time (HH:MM), and will not include any dose interruptions lasting more than 5 minutes. Actual cumulative infusion duration is the sum of all actual infusion durations. The total length of interruption is the elapsed time between end time of one infusion and the start time of the next recorded infusion.

Detailed information regarding the infusion timepoints, planned dose, actual infusion rate, infusion interruption, and permanent infusion discontinuation will be listed for each participant in the Safety Set by timepoint. Actual cumulative infusion duration and cumulative length of infusion interruption lasting more than 5 minutes will be tabulated, along with number of unique infusion interruptions among treatment completers.

8.8. Treatment Compliance

The planned dose of 30, 60, or 90 mcg/kg/hour will be captured in the EDC system. The actual infusion rate will also be captured in the EDC in mL/hour, and converted to actual dose mcg/kg/hour using the following formula:

1000 mcg/hour * (actual flow rate from infusion pump in mL/hour) / (participant weight in kg)

Treatment compliance will be calculated as:

(actual dose / planned dose) * 100

Planned dose, actual infusion rate, actual dose, and percent compliance will be listed for each participant in the Safety Set by timepoint. Overall treatment compliance will be tabulated.

9. Efficacy

All efficacy analyses will be based on the Efficacy Set.

9.1. Visual Analog Scales

The VAS-L and VAS-A are participant-rated scales for evaluating tinnitus (Adamchic et al 2012). Scoring for both is along a linear horizontal scale, with the left side anchor (score of 0) representing the lowest severity and the right side anchor (score of 100) representing the highest severity of the rated tinnitus experience. Intermediate scores are determined by extrapolation between the two sides of the scales.

To assess tinnitus loudness (VAS-L), participants will answer the question “How loud is your tinnitus now?” on a horizontal scale anchored on left by “not audible” and on right by “extremely loud”. To assess tinnitus annoyance (VAS-A), participants will answer the question “How much is your tinnitus annoying you now?” on a horizontal scale anchored on left by “not annoying” and on right by “extremely annoying”.

The VAS-L and VAS-A will be administered both as remote and as in-clinic measures at different times of this study. Remote VAS data collection will occur from Day -7 to Day -1 (preinfusion) and from Day 2 to Day 7 (postinfusion). For remote assessments, ratings for both VAS-L and VAS-A will be obtained twice daily, once each in the morning and once in the evening. And the daily arithmetic means of VAS-L and VAS-A ratings will be computed separately for remote measures obtained during pre- and postinfusion periods. -. For remote assessments, the daily arithmetic mean will be calculated by averaging the morning and evening scores ([morning score + evening score] / 2). If a participant is missing either a morning or evening score, then the single available score will be used as the mean for that day.

The VAS-L and VAS-A will be obtained in-clinic during the treatment period (Day 1) , administered once prior to start of infusion and then repeated at hours 0.5, 1, 2, 3, 4, 5 and 6 of the infusion. .

For the treatment period (Day 1), baseline is defined as the most recent value immediately prior to the start of IP infusion, or predose. For the postinfusion remote assessment period (Days 2 through 7), baseline is defined as the average of all available preinfusion values per participant collected from Day -7 through Day -1. This will be calculated by summing the daily arithmetic means and dividing by the total number of non-missing days. If a participant is missing either a morning or evening score, then the single available score will be used as the mean for that day Missing day or partial missing day VAS ratings will not be imputed.

Descriptive statistics of both VAS component scores and VAS component change from baseline scores will be tabulated. Considering the small sample size, unbiased Hedge’s g will be used to compare the effect size of the post baseline score at each timepoint to the baseline score. Hedge’s g will be calculated for pre-post scores in one group using the following formula:

$$g = d \times J$$

Where $d = \frac{(post-baseline\ mean)-(baseline\ mean)}{SD_{within}}$ and $J = 1 - \frac{3}{4(2n-2)-1}$

SD_{within} can be computed from the standard deviation of the change from baseline (SD_{CFB}) as

$$SD_{within} = SD_{CFB}/\sqrt{2(1-r)},$$

r is the correlation between baseline and post-baseline, n is the number of pairs.

The 95% CI of Hedge's g will be calculated as

$$g \pm t(n-1,\ 0.025)\ \times\ SE(g);$$

Where $SE(g)\ =\ \sqrt{Var(g)} = \sqrt{Var(d)} \times J^2\ =\ \sqrt{\left(\frac{1}{n}+\frac{d^2}{2n}\right)2(1-r)}\left(1-\frac{3}{4(2n-2)-1}\right)^2$

(Borenstein et al 2009).

Each VAS component score will be analyzed separately; this will also be done separately for Day 1 (during treatment) and Days 2 to 7 (after treatment).

For each component, a mixed-effects model for repeated measures will be considered. Each repeated measures model will include (a) change from baseline scores as the dependent variable and (b) both baseline VAS component value and visit as fixed effect independent variables. The residual errors from the same participant across visits will be modeled using an unstructured covariance matrix (UN). If the model using an unstructured covariance matrix does not converge, compound symmetry (CS) and first order autoregressive (AR(1)) covariance structures may be used, in that order. Model-based point estimates (i.e., least squares means, their 95% confidence intervals (CIs), and standard errors (SEs) will be reported. For Day 1 the repeated timepoint will be hours and for Days 2 through 7 the repeated timepoint will be days.

Example SAS code:

```
proc mixed data=XXX;
  class subjid timepoint;
  model <change from baseline score> =
                <baseline> timepoint
                        / solution ddfm=KR;
    repeated timepoint / subject=subjid type=un;
run;
```

Line plots of least squares (LS) mean will be plotted with standard error bars. Q-Q plot for residuals will also be provided to assess normality assumptions.

Listings of observed raw scores and change from baseline values will be presented separately for each VAS component by participant.

[redacted]

[redacted]

[redacted]

10. Safety

The Safety Set (SS) will be used for all safety analyses. Safety and tolerability of brexanolone will be evaluated by incidence of treatment-emergent adverse events [redacted]. Listings for discharge and safety phone call will also be included.

10.1. Adverse Events

An Adverse Event (AE) is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of IP, whether or not related to IP. Adverse events will be coded using MedDRA Version 25.1 or higher.

10.1.1. Treatment-Emergent Adverse Event (TEAE)

A TEAE is defined as an AE with onset after the start of IP, or any worsening of a pre-existing medical condition/adverse event with onset after the start of IP and throughout the study. If the date of an adverse event is incomplete and an unambiguous determination could not be made with respect to its onset time versus administration of IP, the adverse event will be assumed to be a TEAE. For imputation of missing AE dates, please refer to Section 7.3.1.

An overview summary table of TEAEs will present the number and percentage of participants as well as the number of events for the following:

- TEAEs
- TEAEs by maximum severity (severe>moderate>mild)
- Study drug-related TEAEs
- Treatment-emergent serious adverse events (SAEs)
- TEAEs leading to interruption of IP
- TEAEs leading to withdrawal of IP
- TEAEs leading to discontinuation from the study
- Treatment-emergent AESIs
- TEAEs leading to death

Incidence of TEAEs in following categories will be provided by SOC and PT. A participant is counted only once under each SOC and PT in case of multiple occurrences of the same AE. These tables will be sorted by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

- TEAEs
- TEAEs by maximum severity (severe>moderate>mild)
- Study drug-related TEAEs
- Treatment-emergent SAEs
- TEAEs leading to interruption of IP
- TEAEs leading to withdrawal of IP
- TEAEs leading to discontinuation from the study
- TEAEs leading to death

For maximum severity, participants will be counted only once within each SOC and PT at the maximum severity in the following order: severe>moderate>mild; an AE with missing severity will be omitted from

severity presentation. For relationship to IP, participants will be counted only once within each SOC and PT at the strongest relationship to IP in the following order: related>not related; an AE with relationship missing is treated as related.

All AEs through the end of the study will be listed including, but not limited to, verbatim term, PT, SOC, relationship to study drug, start and end date, seriousness, action taken, and outcome. Separate listings will be provided for SAEs, AEs leading to death, AEs leading to treatment discontinuation, AEs leading to study withdrawal, and AEs leading to dose reduction. TEAEs will be flagged in the listing.

10.1.2. Adverse Event of Special Interest (AESI)

An AESI is an AE/SAE of scientific and/or medical concern, specific to the product or program for which ongoing monitoring and rapid communication by the investigator to the sponsor is required. The following events are considered AESIs and collected as an AESI:

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

Treatment-emergent AESIs will be summarized. All AESIs (including those with onset or worsening before the start of IP) will be separately listed, in addition to being included in the primary TEAE tables discussed above. Excessive sedation and loss of consciousness will be reported in a listing for the information including the timepoint, whether the participant was assessed for excessive sedation, and the date and time.

10.2. Laboratory Evaluations

Urinalysis samples will be collected. Blood samples will be collected for hematology, serum chemistry, and coagulation. Analytes to be evaluated are summarized in Table 2.

Table 2: Summary of Clinical Laboratory Analytes

Biochemistry	*Renal Panel*: glucose, calcium, phosphorus, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate *Hepatic Panel*: albumin, alanine transaminase (ALT), aspartate transferase (AST), total bilirubin and if elevated, reflex fractionation for direct and indirect bilirubin alkaline phosphatase, total protein, lactate dehydrogenase, gamma glutamyl transferase
Coagulation (Screening only)	Activated partial thromboplastin time, prothrombin time, and international normalized ratio only on participants determined to be high clinical risk for bleeding
Hematology	Red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell count with differential, and platelet count
Urinalysis	Specific gravity, pH, protein, glucose, ketones, occult blood, leukocyte esterase, nitrite, bilirubin, and urobilinogen. If protein, leukocyte, occult blood, and/or nitrites are positive, a microscopic examination will be performed

All clinical laboratory test results outside the reference range will be interpreted by the investigator as abnormal, not clinically significant (abnormal NCS) or abnormal, clinically significant (abnormal CS) in source documents. Clinically significant abnormal results after screening will be considered and reported as AEs.

Baseline value, post-baseline value and change from baseline in hematology, serum chemistry, and urinalysis lab results will be tabulated separately at screening and EOS visit. Coagulation will be tabulated at screening. Corresponding by participant listings will be presented. A shift table for hematology, serum chemistry and urinalysis lab shift from baseline to post-baseline values in abnormality of results will be provided. A summary table of potentially clinically significant values by visit will also be provided.

Follicle stimulating hormone testing will be conducted to confirm whether a participant with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being post-menopausal (see Study Protocol Section 8.1). Test results will be presented in a by participant listing.

A serum pregnancy test will be conducted for all woman of childbearing potential (WOCBP) at Screening; a urine pregnancy test will be conducted for all WOCBP at all other scheduled timepoints. Serum and urine pregnancy test results will be presented in a by participant listing.

Urine assessment for select drugs of abuse will be performed (including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and phencyclidine). Alcohol will be assessed via breathalyzer or urine dipstick. Drug and alcohol test results will be presented in a by participant listing.

Table 3: Criteria for Identifying PCS Values for Laboratory Evaluations

Laboratory Evaluation Parameter	Sex	Units	Criteria for PCS Values (Observed values)		Criteria for PCSC values (Change from Baseline)	Criteria for PCSC values (Change from Baseline)
Chemistry			High	Low		
Albumin	Both	g/L	>70	<28	NA	NA
Blood urea nitrogen (aka Urea Nitrogen and Nitrogen)	Both	mmol/L	>10.71	NA	NA	NA
Calcium	Both	mmol/L	>2.75	<2.0	NA	NA
Chloride	Both	mmol/L	>120	<90	NA	NA
Creatinine	Both	mmol/L	>3xULN or >3x Baseline		NA	NA
Gamma Glutamyl Transferase	Both		>3xULN		NA	NA
Glucose	Both	mmol/L	>13.9	<2.8	NA	NA

Sodium	Both	mmol/L	>150	<132	NA	NA
Potassium	Both	mmol/L	>5.4	<3.3	NA	NA
Protein (aka total protein) Chemistry results only	Both	g/L		<45	NA	NA
Bicarbonate (HCO3 may also be reported as CO2)	Both	mmol/L	>34	<18	NA	NA
Phosphorus (aka Phosphate)	Both	mmol/L	>1.94	<0.61	NA	NA
Bilirubin (total)	Both	µmol/L	>2xULN	NA	NA	NA
Aspartate Aminotransferase	Both	U/L	>3xULN	NA	NA	NA
Alanine Aminotransferase	Both	U/L	>3xULN	NA	NA	NA
Alkaline Phosphatase	Both	U/L	>1.5xULN	NA	NA	NA
Lactate Dehydrogenase	Both	U/L	>2xULN	NA	NA	NA
Coagulation						
Prothrombin time (PT)	Both	sec	>=1.11 x ULN	Not Specified	NA	NA
Partial thromboplastin time (PTT)	Both	sec	>1.5 xULN	Not Specified	NA	NA
Hematology			High	Low	NA	NA
Hemoglobin	Male	g/L	>185	<115	NA	NA
Hemoglobin	Female	g/L	>170	<100	NA	NA
Hematocrit	Male	Fraction of 1	>0.55	<0.385	NA	NA

Hematocrit	Female	Fraction of 1	>0.49	<0.345	NA	NA
Platelet count	Both	10^9/L	>600	<125	NA	NA
White blood cell	Both	10^9/L	>15	<2.5	NA	NA
Basophils	Both	10^9/L	>0.5	NA	NA	NA
Eosinophils	Both	10^9/L	>1.5	NA	NA	NA
Neutrophils	Both	10^9/L	NA	<1.5	NA	NA
Lymphocytes	Both	10^9/L	>6.0	<0.5	NA	NA
Monocytes	Both	10^9/L	>1.4	NA	NA	NA

10.3. Vital Signs, Weight, and Height

Vital signs (heart rate, respiratory rate, temperature, and blood pressure), weight, and height will be measured according to the Protocol Schedule of Assesments (Tables 2 and 3) and collected on the eCRF. BMI will be calculated and documented on the eCRF. Descriptive summaries (number of participants, mean, standard deviation, median, minimum, maximum, Q1, Q3) of actual values and changes from baseline of vital signs will be presented for each visit using the Safety Set.

Temperature will be summarized in Celsius (C) units.
Any abnormality in vital signs will be interpreted by an investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents.

Baseline for vital signs on Day 1 is defined as Day 1 pre-dose. Baseline for vital signs at EOS is defined as the screening values. Baseline value, post-baseline value and change from baseline in vital signs will be tabulated by visit. Vital sign data will be listed chronologically by participant and visit for each vital sign parameter. Potentially clinically significant values will be summarized by treatment. Weight, height, and BMI data will be listed by participant and visit. Pulse oximetry will be listed separately by participant and visit.

Table 4: Criteria for Identifying PCS Values for Vital Sign Parameters

Vital Sign Parameter	Sex	Units	Criteria for PCS Values (Observed values)		Criteria for PCSC values (Change from Baseline values)	
			High	Low	Increase	Decrease
Heart rate (supine and standing)	Both	Beats/min	>120	<40	NA	NA
Systolic Blood Pressure (supine and standing)	Both	mmHg	>180	<90	≥30	≥30
Diastolic Blood pressure (supine and standing)	Both	mmHg	>110	<50	≥20	≥20
Respiratory Rate	Both	breaths/min	>20	<8	NA	NA

10.4. ECG

A 12-lead ECG will be performed according to the Protocol Schedule of Assesments (Tables 2 and 3). The standard intervals (heart rate, PR, QRS, QT, and QT corrected according to Fridericia's formula [QTcF]), as well as any rhythm abnormalities, will be recorded.

All abnormal ECGs will be interpreted by an investigator as abnormal NCS or abnormal CS in source documents.

Baseline value, post-baseline value and change from baseline in ECG parameters will be tabulated at screening and EOS visit. A by participant listing will be provided, including each ECG parameter: ventricular heart rate (beats per minute [bpm]), PR Interval [msec], QT Interval [msec], QTcF Interval [msec], and central reader's interpretation, including clinical significance and abnormal description.

Table 5: Criteria for Identifying PCS Values for ECG Parameters

ECG Parameter			Criteria for PCS Values (Observed values)		Criteria for PCSC values (Change from Baseline)	Criteria for PCSC values (Change from Baseline)
	Sex	Units	High	Low	Increase	Decrease
QTcF Interval	Both	msec	>450 but <=480	NA	>=30 to 60	NA
QTcF Interval	Both	msec	>480 but <=500	NA	>60	NA

QTcF Interval	Both	msec	>500	NA	NA	NA

10.5. Physical Examination

Physical examinations will include assessments of body systems (e.g., head, eye, ear, nose, and throat; heart; lungs; abdomen; and extremities) as well as cognitive and neurological examination and mental status examination, as performed per local standard of care. Unscheduled physical examinations may also be conducted per the investigator's discretion.

Any abnormality in physical examinations will be interpreted by an investigator as abnormal NCS or abnormal CS in source documents.

Physical examination performed (Yes/No), not done reason, date and time of the examination will be listed.

11. Interim Analyses

There is no formal interim analysis planned for this study.

12. Changes from Analysis Planned in Protocol

Approximately 10 participants will be dosed instead of the expected 24 participants from the protocol.

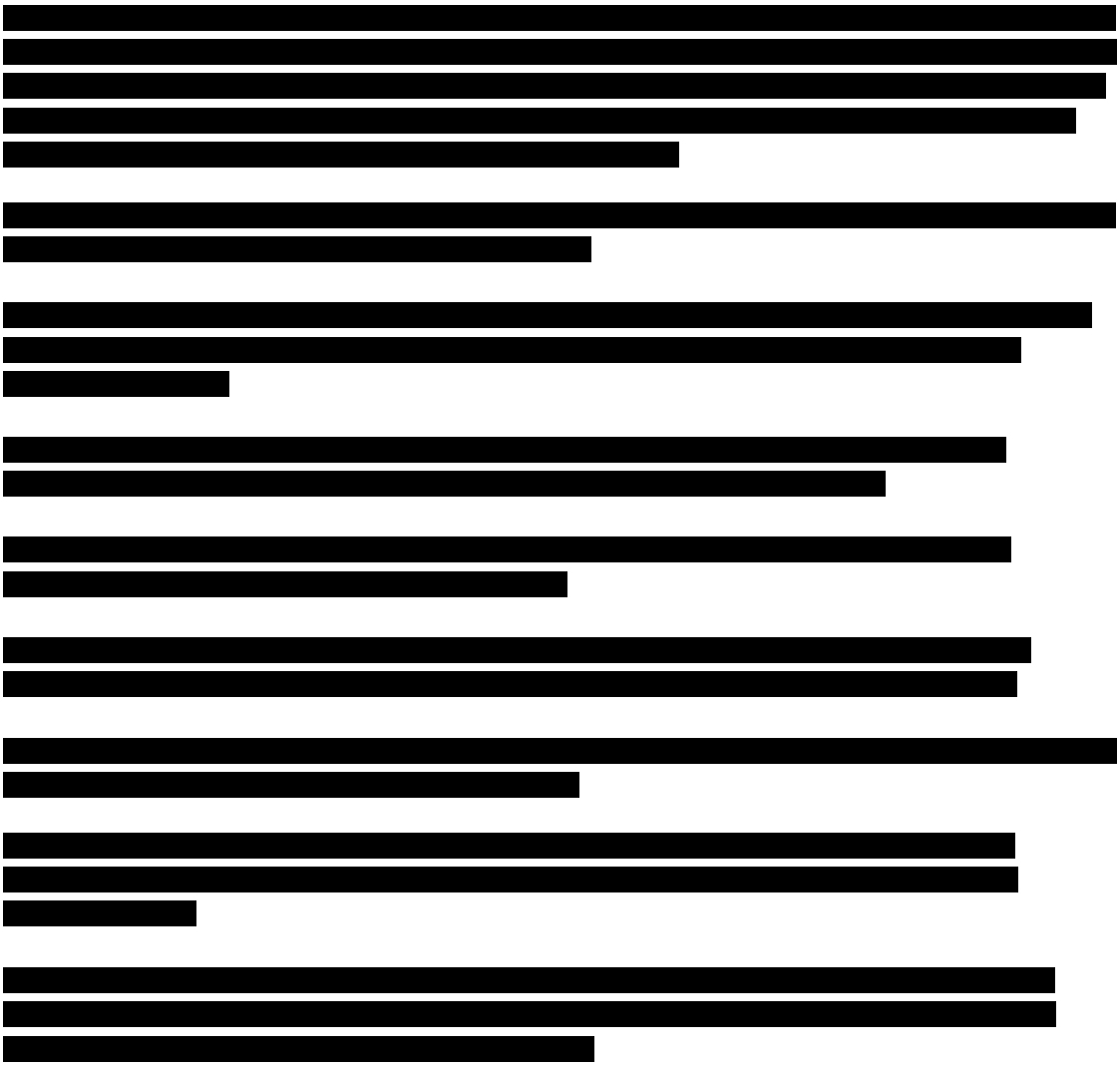
A screened analysis set will be identified to include all participants who were screened for participation in this study. This analysis set will be used in a listing of inclusion and exclusion criteria violations, including the primary reason for exclusion.

An enrolled analysis set will be identified to include all participants who provided written informed consent and passed the inclusion and exclusion criteria for study participation. Screen failures will not be included in this set. This analysis set will be used to list protocol deviations.

13. Reference List

Adamchic A, Langguth B, Hauptmann C, Tess PA. Psychometric Evaluation of Visual Analog Scale for the Assessment of Chronic Tinnitus. Am J Audiometry. 2012; 21:215-225.

Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Introduction to Meta-Analysis. 2009: Chapter 4, Effect Sizes Based on Means.



14. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. Syneos Health Standard Operating Procedure (SOPs) Developing Statistical Programming and Validation Plan (3920), End-to-End Process of the Production of Study Data Tabulation Model (SDTM) (3921), and End-to-End Process of the Production of Analysis Datasets and Tables, Figures, and Listings (3922) describe the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

15. Index of Tables, Figures, and Listings

Table, figure, and listing shells are provided in separate documents.

All tables, figures and listings (TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA). Computer-generated TFL output will adhere to the specifications detailed in the table, figure, and listing shell documents.

16. Appendices

16.1. Appendix A: Schedule of Assessments for Screening Period

Study Procedure	**Screening Period**							
	Clinic Assessments	**Remote Assessments**						
Visit Day	**-28 to -8**	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**
Clinic Visit	**X**							
Remote		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Informed consent process	X							
Inclusion/exclusion criteria	X							
Demographics	X							
Medical History [a]	X							
Height	X							
Physical examination [b]	X							
Body weight	X							
Clinical laboratory assessments [c]	X							
Drug and alcohol test [d]	X							
Pregnancy test (WOCBP only) [e]	X							
Vital signs [f]	X							
12-lead ECG [g]	X							
[redacted]								
Audiology Diagnostics [i]	X							
[redacted]								
VAS loudness and annoyance [j]		X	X	X	X	X	X	X
Remote Assessment Reminder [k]		X	X	X	X	X	X	X
[redacted]								
Participant training [l]	X							
Adverse events [m]	X							
Prior/concomitant medications [n]	X							
Nonpharmacological interventions [o]	X							

Abbreviations: [redacted]; ECG = electrocardiogram; [redacted]; TMS = transcranial magnetic stimulation; VAS = Visual Analogue Scale; VAS-A = VAS annoyance; VAS-L = VAS loudness; WOCBP = women of childbearing potential.
Note: Screening assessments must occur within 28 days prior to IP administration and results must be reported by Day -8.
Note: When scheduled at the same timepoint, assessments will be performed in the following order: vitals, VAS, [redacted].
[a] Tinnitus-related medical history will be obtained by structured interview.
[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, and urinalysis at all scheduled time points. Coagulation to be assessed at Screening only.
[d] Drug and alcohol testing will occur at Screening (see Study Protocol Section12.1.6 for a list of analytes). Drug testing will be on a urine specimen via urine dipstick. Alcohol use will be tested either on a urine specimen dipstick or breath test. A failed Screening drug or alcohol test does not exclude participation in the study if test is negative at Day 1.
[e] Serum pregnancy test at screening.
[f] Vital signs to include temperature (°C), respiratory rate, heart rate, and blood pressure. Heart rate and blood pressure to be collected in semi-inclined position.
[g] ECGs must be performed after the participant has been in a supine position for at least 5 minutes.
[redacted].
[i] A full audiological examination will be conducted at Screening including pure tone audiogram. The audiologist will perform a physical exam of ears and obtain clinical history to evaluate duration and quality (whether unilateral/bilateral, pulsatile/non-pulsatile). A healthcare professional trained to perform movement tests will evaluate whether tinnitus can be attributed to a somatosensory cause.

[j] Ratings for both VAS-L and VAS-A will be done twice daily, once each in the morning and evening, on Day -7 through Day -1.
[k] The participant will be contacted by the site on Day -7 through Day -1 to remind them to begin remote assessments.
[l] Participants will be trained by study personnel on the procedures for all remote assessments.
[m] A phone call to follow up on any AE(s) will be conducted, if deemed appropriate by the investigator, to review the current status of the participant.
[n] To include all medications taken within 60 days, all psychotropic medications taken within 6 months, and all medications used to treat tinnitus regardless of timing. Participants will be asked about any changes during clinic visits.
[o] Nonpharmacological interventions: eg, psychotherapy, sound therapy, masking, TMS. Participants will be asked about changes during clinic visits.

16.2. Appendix B: Schedule of Assessments for Treatment Period and Follow-up Period

Study Procedure	**Treatment Period**										**Follow-up Period**					
	Clinic Treatment Visit															**EOS Visit[a]**
Visit Day	**1**										**2**	**3**	**4**	**5**	**6**	**7±1**
Hour From Start of Infusion	**Pre-dose[b]**	**0**	**0.5**	**1**	**2**	**3**	**4**	**5**	**6**	**8**						
Clinic Visit	**X**															**X**
Remote											**X**	**X**	**X**	**X**	**X**	
Clinical laboratory assessments [c]																X
Pregnancy test (WOCBP only) [d]	X															X
Weight	X															
Vital signs [e]	X		X	X	X	X	X	X	X	X						X
Drug and alcohol test [f]	X															
12-lead ECG [g]																X
[redacted]																
VAS loudness and annoyance [j]	X		X	X	X	X	X	X	X		X	X	X	X	X	X
[redacted]																
Safety phone call													X			
Remote Assessment Reminder [l]											X	X	X	X	X	
Continuous pulse oximetry [m]					X											
IP infusion					X											
[redacted]																
Admission to clinic	X															
Discharge from clinic [o]										X						
Adverse events [p]	X															
Prior/concomitant medications [q]	X															
Nonpharmacoligical interventions [r]	X															

Abbreviations: [redacted]; EOS = End of Study; IP = investigational product; [redacted]

[redacted]; TMS = *t*ranscranial magnetic stimulation; VAS = Visual Analogue Scale; VAS-A = VAS annoyance; VAS-L = VAS loudness; WOCBP = women of childbearing potential.
Note: For Day 1 assessments, assessments at 0.5 and 1 hour must be collected within 10 minutes prior to the dose increase. Assessments at timepoints 2, 3, 4, 5, 6, and 8 hours may be completed within ±10 minutes of the scheduled time point.
Note: Preferred order of assessments at all timepoints: [redacted] VAS-L, VAS-A, vital signs (temperature [°C], respiratory rate, heart rate, and blood pressure), [redacted].
[a] The EOS Visit will be conducted at the time of discontinuation if this occurs at any time before Day 7 ±1 day.
[b] All predose assessments must be completed prior to IP administration.
[c] Safety laboratory tests will include hematology, serum chemistry, and urinalysis at all scheduled time points.
[d] Urine pregnancy test at all scheduled time points.
[e] Heart rate and blood pressure to be collected in semi-inclined position at all scheduled time points. Predose (Hour 0) vital signs will be collected within 60 minutes prior to dosing.
[f] Drug and alcohol testing will occur prior to dosing on Day 1(see Study Protocol Section 12.1.6 for a list of analytes). Drug testing will be on a urine specimen via urine dipstick. Alcohol use will be tested either on a urine specimen dipstick or breath test. Participants with a failed drug or alcohol test on Day 1 are excluded from participation in the study.
[g] ECGs must be performed after the participant has been in a supine position for at least 5 minutes.
[redacted]
[redacted]
[j] for both VAS-L and VAS-A will be done twice daily, once each in the morning and evening, on Day 2 through Day 6 and on the morning of Day 7.
[redacted]
[l] The participant will be contacted by the site on Day 2 through Day 6 to remind them to begin remote assessments.
[m] Continuous pulse oximetry to occur for the duration of the infusion. Oxygen saturation should be recorded prior to dose escalation at 0.5 hour and 1 hour. Otherwise, it need only be recorded in the event of confirmed hypoxia, in which case, the event is to be recorded as an AE.
[redacted]
[o] If deemed medically appropriate by the investigator, participants will be released from the clinic after the 2-hour safety assessments have been completed. Participants will be cautioned against engaging in potentially hazardous activities requiring mental alertness, including driving, until any sedative effects have dissipated. A designated companion must drive the participant when they are discharged from the clinic.
[p] A phone call to follow up on any AE(s) will be conducted, if deemed appropriate by the investigator, to review the current status of the participant.
[q] All changes to any medication should be captured. Participants will be asked about any changes during clinic visits.
[r] Nonpharmacological interventions: eg, psychotherapy, sound therapy, masking, TMS. Participants will be asked about any changes during clinic visits.

DocuSign

Certificate Of Completion

Envelope Id: 46D2B0897EC3428CBFF57B8925C5C3C1
Status: Completed
Subject: Complete with DocuSign: Sage_547-TRM-201_Statistical Analysis Plan_v2.0_31Jan2024.pdf
Source Envelope:
Document Pages: 40
Signatures: 8
Envelope Originator:
Certificate Pages: 7
Initials: 0
[redacted]
AutoNav: Enabled
IP Address: [redacted]
EnvelopeId Stamping: Enabled
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

Record Tracking

Status: Original
31-Jan-2024 | 18:00
Holder: [redacted]
Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] Sage Therapeutics - Part 11 Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 6F1FC810-D26B-4857-8BAD-92F70906BED1 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 31-Jan-2024 | 18:28 Viewed: 31-Jan-2024 | 23:02 Signed: 31-Jan-2024 | 23:03
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] Sage Therapeutics - Part 11 Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: D1543B86-AFEE-4D57-A3E8-9CEA14B6FF1C Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 31-Jan-2024 | 18:28 Viewed: 01-Feb-2024 | 09:05 Signed: 01-Feb-2024 | 09:08
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

Signer Events	Signature	Timestamp
[redacted] Security Level: Email, Account Authentication (Required)	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I have reviewed this document Signing Time: 01-Feb-2024 | 03:54 PST A9EFCEB136394EC48D3A1C13B23CD8DA Signature Adoption: Pre-selected Style Signature ID: A9EFCEB1-3639-4EC4-8D3A-1C13B23CD8DA Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 31-Jan-2024 | 18:28 Viewed: 01-Feb-2024 | 06:53 Signed: 01-Feb-2024 | 06:54
Electronic Record and Signature Disclosure: Accepted: 01-Feb-2024 | 06:53 ID: e9ad4edb-3e72-431c-8b7c-da8728842844		
[redacted] Sage Therapeutics - Part 11 Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Uploaded Signature Image Signature ID: EA346385-2142-4C28-85BE-C8F16850E54C Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 31-Jan-2024 | 18:28 Viewed: 01-Feb-2024 | 06:58 Signed: 01-Feb-2024 | 06:59
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 9DE3C23A-72CA-4DF1-B9A0-BBD1CC8EB589 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 31-Jan-2024 | 18:28 Viewed: 31-Jan-2024 | 18:40 Signed: 31-Jan-2024 | 18:42
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

Signer Events	Signature	Timestamp
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 8E3348C1-2DAF-4757-99A2-A74F6F524EF9 Using IP Address: [redacted] Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 31-Jan-2024 | 18:28 Viewed: 31-Jan-2024 | 18:59 Signed: 31-Jan-2024 | 19:01
Electronic Record and Signature Disclosure: Accepted: 13-Oct-2021 | 08:39 ID: dd681590-ccd9-4e80-bc6b-7e855f0cfc39		
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: EBE3317E-84BF-496B-857F-15CC6D6E502A Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 31-Jan-2024 | 18:28 Viewed: 31-Jan-2024 | 20:06 Signed: 31-Jan-2024 | 20:08
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 2104CF00-F3AF-42A7-B5FD-5AAE857E3C85 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 31-Jan-2024 | 18:28 Viewed: 01-Feb-2024 | 09:07 Signed: 01-Feb-2024 | 09:08
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	31-Jan-2024 | 18:28
Certified Delivered	Security Checked	01-Feb-2024 | 09:07
Signing Complete	Security Checked	01-Feb-2024 | 09:08
Completed	Security Checked	01-Feb-2024 | 09:08

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Sage Therapeutics - Part 11 (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Sage Therapeutics - Part 11:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: marcel@sagerx.com

To advise Sage Therapeutics - Part 11 of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at marcel@sagerx.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Sage Therapeutics - Part 11

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to marcel@sagerx.com and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Sage Therapeutics - Part 11

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to marcel@sagerx.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Sage Therapeutics - Part 11 as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Sage Therapeutics - Part 11 during the course of your relationship with Sage Therapeutics - Part 11.