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:	**Protocol** Amendment 2: 17 Oct 2023

AN OPEN-LABEL STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF BREXANOLONE IN THE TREATMENT OF ADULT PARTICIPANTS WITH TINNITUS

(AN OPEN-LABEL STUDY EVALUATING BREXANOLONE IN ADULTS WITH TINNITUS)

PROTOCOL NUMBER: 547-TRM-201

IND NUMBER: 162652

Investigational Product	Brexanolone
Clinical Phase	Phase 2
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted] Phone: [redacted] email: [redacted]
Sponsor Medical Monitor	[redacted], MD [redacted] Phone/text: [redacted] email: [redacted]
Sponsor Translational Lead	[redacted], PhD Phone: [redacted] email: [redacted]
Date of Original Protocol	31 August 2022
Date of Amendment 1	18 July 2023
Date of Amendment 2	13 October 2023

INVESTIGATOR'S AGREEMENT

I have received and read the investigator's brochure for brexanolone. I have read the 547-TRM-201 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (DD/MMM/YYYY)

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Sage Study Physician	[redacted], MD [redacted]	Phone/text: [redacted] email: [redacted]
24-Hour Emergency Contact	[redacted], MD [redacted]	E-mail: [redacted] Phone: Mobile: [redacted] Main Switchboard: [redacted]
Serious Adverse Event (SAE) Reporting Contact	IQVIA Lifecycle Safety	4820 Emperor Boulevard Durham, NC 27703 E-mail: Sage.Safety@iqvia.com Fax: +1-855-638-1674 SAE Hotline: +1-855-564-2229
	Sage Study Physician [redacted], MD [redacted]	E-mail: [redacted]
	[redacted] MD [redacted]	E-mail: [redacted] Phone: Mobile: [redacted] Main Switchboard: [redacted]
Product Complaint Contact	Sage Therapeutics	E-mail: productcomplaints@sagerx.com Phone: +1-833-554-7243

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics, Inc. (hereafter referred to as Sage Therapeutics, or Sage)

Name of Investigational Product:
Brexanolone

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

Protocol Number: 547-TRM-201

IND Number: 162652

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

Short Title: An Open-Label Study Evaluating Brexanolone in Adults with Tinnitus

Number of Sites and Study Location: This study will take place at a 1 to 2 sites in the US.

Phase of Development: 2

Planned Duration for Each Study Participant:
Each participant's involvement is up to 35 days, including a maximum 28-day Screening Period, a 1-day Clinic Treatment Visit, and a 6-day Follow-up Period.

Objectives and Endpoints:

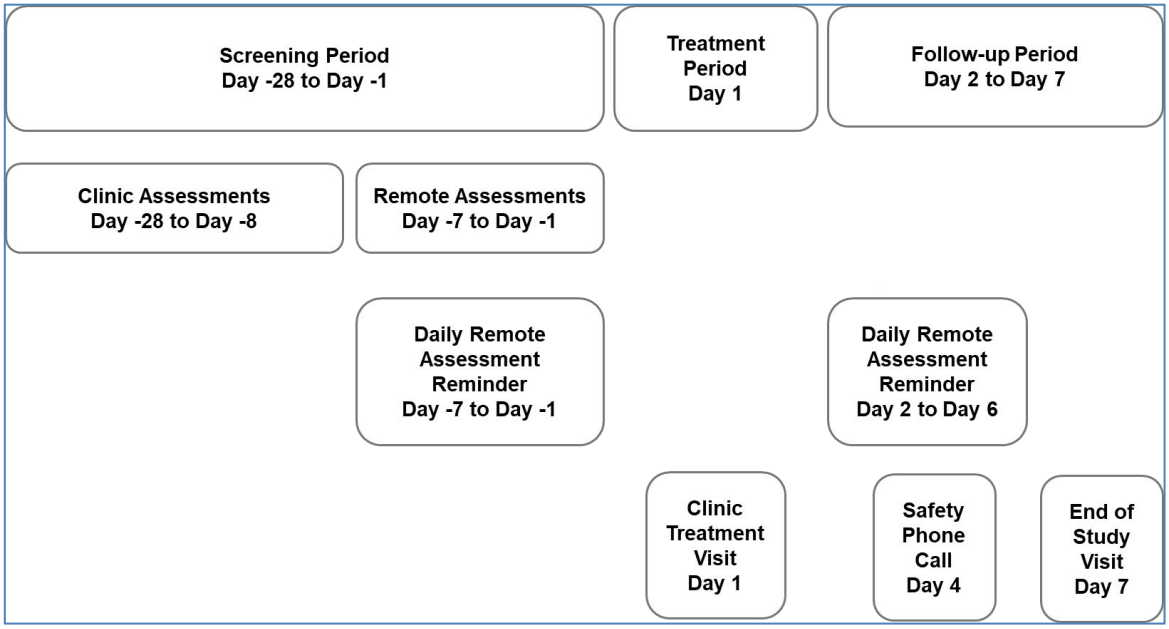
Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of brexanolone	• Incidence of treatment-emergent adverse events (TEAEs)
Secondary	
• To assess subjective tinnitus perception during brexanolone infusion based on Visual Analog Scales (VAS)	• Change from baseline to Hour 6 of infusion in VAS loudness (VAS-L) ratings • Change from baseline to Hour 6 of infusion in VAS annoyance (VAS-A) ratings
• To assess subjective tinnitus perception after brexanolone infusion based on VAS	• 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]	

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	• Change from baseline in vital signs, electrocardiogram (ECG), and clinical laboratory parameters [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Study 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. The study design is presented in Figure 1.

Figure 1: Study Design



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 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 (Table 2).

Starting 7 days before administration of investigational product (IP) (Day -7), participants will have twice daily remote predose assessments as indicated in 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 VAS-L and 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 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.

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 [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,

specifically if this occurs in the context of excessive sedation or sudden loss of consciousness. After an episode of confirmed hypoxia, the infusion should not be resumed.

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

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

A fall precaution protocol must be in place for the duration of the brexanolone infusion.

At the conclusion of the IP infusion, if deemed medically appropriate by the investigator, participants will be released from the clinic after the 2-hour safety observation period and completion of assessments. 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.

Follow-Up Period:

Assessments for the Follow-up Period will be performed as indicated in 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 EOS Visit will be conducted at the time of discontinuation if this occurs at any time before Day 7±1 day (see Section 8.4.2).

Number of Participants (planned): Up to 24 participants will be dosed to achieve approximately 20 study completers, assuming a 20% study discontinuation rate among dosed participants.

Eligibility Criteria:

Inclusion Criteria:

Participants must meet all of the following criteria to qualify for participation in this study:

1. Participant has signed an ICF before any study-specific procedure is started.
2. Participant is ambulatory and is 18 to 65 years of age, inclusive, at the time informed consent is obtained.
3. Participant has a designated companion for the Clinic Treatment Visit who will drive them when they leave the clinic.
4. Participant is in good physical health and has no clinically significant findings (excluding tinnitus), as determined by the investigator on medical history and physical examination, including neurologic and mental status examinations, 12-lead ECG, or clinical laboratory tests.
5. Participant has a diagnosis of subjective, idiopathic, unilateral or bilateral, non-pulsatile tinnitus (eg, not due to medical disease) of ≥6 months and <10 years duration.
6. Participant has mild to severe tinnitus distress according to Tinnitus Handicap Inventory (THI) score of 24 to 68 at Screening.
7. Participant is willing and able to safely discontinue the use of central nervous system (CNS) depressants (eg, opioids and benzodiazepines), antidepressants, anticonvulsants, CNS stimulants (with the exception of caffeine), aspirin, other nonsteroidal anti-inflammatory drugs, and

aminoglycosides at least 14 days or 5 half-lives (whichever is longer) prior to receiving IP and through completion of the study.

8. Female participant agrees to use at least one method of highly effective contraception during participation in the study and for 30 days following the last dose of IP, unless she is postmenopausal, permanently sterile, or does not engage in sexual relations which carry a risk of pregnancy (see Section 9.2.5).
9. Male participant with a partner who is of childbearing potential agrees to use an acceptable method of effective contraception for the duration of the study and for 13 weeks after receiving the IP, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy in his female partner(s). Acceptable methods of effective contraception are listed in Section 9.2.5.
10. Male participant is willing to abstain from sperm donation for the duration of the study and for 13 weeks after receiving the IP.

Exclusion Criteria:

Participants who meet any of the following criteria are disqualified from participation in this study:

1. Participant has history or presence of any neurologic disease or condition, including, but not limited to, unexplained loss of consciousness, seizure disorder including a prior nonfebrile seizure, and closed head trauma with clinically significant sequelae.
2. Participant has a history of sleep apnea or any clinically significant respiratory conditions that may predispose the participant to hypoxia during the infusion.
3. Participant intends to start or discontinue a pharmacological or nonpharmacological therapy (eg, psychotherapy, sound therapy, masking, transcranial magnetic stimulation [TMS]) for tinnitus during the course of the study.
4. Participant has currently active and medically significant or uncontrolled hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, metabolic disease (hypothyroidism with stable thyroid replacement is acceptable).
5. Participant's tinnitus can be modulated by maneuvers of the temporomandibular joint, head and neck, eyes, or limbs, or otherwise attributed to somatosensory cause or has had prior otoscopic surgeries or cholesteatoma.
6. Participants has current unilateral or bilateral hearing loss of 30 dB or greater (mild hearing loss) in one or more tested frequencies (500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz), 60 dB or greater at 6000 Hz and 8000 Hz, asymmetry of 30 dB or greater in two or more tested frequencies or uses a cochlear implant or hearing aid.
7. Participant has history of chronic otitis media (>3 per year during past 5 years).
8. Participant has a total score of 15 or greater (ie, moderately severe) on the Patient Health Questionnaire-9 (PHQ-9) at Screening.
9. Participant has diagnosis of moderate or severe substance use disorder (excluding nicotine dependence) within 12 months of Screening, has a positive screen for drugs of abuse including tetrahydrocannabinol (THC) on Day 1 prior to dosing, or has a positive screen for alcohol on Day 1 prior to dosing.
10. Participant has a known allergy to progesterone, allopregnanolone, or any IP excipient.
11. Female participant has a positive pregnancy test or a confirmed pregnancy at Screening or prior to dosing on Day 1
12. Participant has had exposure to another investigational drug or device within 30 days or 5 half-lives of the investigational drug, whichever is longer, prior to the Day 1 visit.

13. Participant has a history of suicidal behavior within 2 years or answers "YES" to Questions 3, 4, or 5 on the C-SSRS at Screening or at Day 1 or is currently at risk of suicide in the opinion of the investigator.
14. Participant has donated 1 or more units (1 unit = 450 mL) of blood or experienced acute loss of an equivalent amount of blood within 60 days prior to Day 1.
15. Participant has any condition, comorbidity, or lifestyle consideration that in the opinion of the investigator would limit or interfere with the participant's ability to complete or partake in the study.
16. Participant is unwilling or unable to comply with study procedures and the required training during the Baseline Period. The participant must complete 10 VAS assessments remotely prior to Day 1.
17. Participant is unable to complete participation in the study, eg, due to preplanned event including elective surgery.
18. Participant is investigative site personnel, sponsor personnel, or a member of their immediate families (spouse, parent, child, or sibling whether biological or legally adopted).

Investigational Product, Dosage and Mode of Administration:

Brexanolone will be administered as a single, continuous, 6-hour IV infusion, administered according to the following dosing regimen:

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] 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.

Duration of Treatment:

Each participant will receive a single 6-hour intravenous infusion of brexanolone.

Statistical Methods:

A detailed description of the analyses to be performed in the study will be provided in the statistical analysis plan (SAP). The SAP will be finalized and approved prior to database lock.

General Considerations

All participant data, including those that are derived, that support the tables and figures will be presented in the participant data listings. Some data may be presented only in participant listings, whereas other data may be presented in both listings and corresponding table(s) or figure(s).

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.

Continuous data will be summarized, at minimum, with number (n), mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. Categorical data will be summarized, at minimum, with counts and percentages. Change from baseline is calculated as the baseline value minus the post-baseline value, unless defined otherwise for specific assessments and/or endpoints.

Summary tables will generally summarize values at each timepoint and change from baseline at each post-baseline time point.

Analysis Sets

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.

[redacted]

Safety Set

The Safety Set is defined as all participants who received any amount of IP.

Statistical Methods

Statistical methods will be described in detail in the statistical analysis plan (SAP).

Descriptive statistics will be generated for safety, efficacy, and [redacted] data; participant listings will be provided in all cases.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA®). At minimum, TEAEs will be displayed by System Organ Class and preferred term. Vital signs, clinical laboratory measures, ECG, [redacted] data will be summarized. Out-of-range safety endpoints may be categorized as low or high, where applicable.

[redacted]

Table 2: Schedule of Assessments: 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

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**
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]; [redacted]; ECG = electrocardiogram; [redacted]; TMS = *t*ranscranial magnetic stimulation; VAS = Visual Analogue Scale; VAS-A = VAS annoyance; VAS-L = VAS loudness; WOCBP = women of childbearing potential.

Note: Clinic-based 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 Section 12.1.6 or 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.

Table 3: Schedule of Assessments – 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]																

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**	
[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															
Nonpharmacological interventions [r]	X															

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

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

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 4: Abbreviations and Specialist Terms

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
BMI	body mass index
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CNS	central nervous system
[redacted]	[redacted]
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IP	investigational product
IRB	institutional review board
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviation	Definition
QTcF	QT corrected according to Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SPL	sound pressure level
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
TMS	transcranial magnetic stimulation
UP	unanticipated problem
USM	urgent safety measure
VAS	Visual Analog Scale
VAS-A	VAS annoyance
VAS-L	VAS loudness
WOCBP	woman of childbearing potential

5. INTRODUCTION

Individuals with tinnitus hear sounds, ringing, buzzing, humming, clicking or other noises that usually originate in the auditory pathway rather than from an internal or external source. Tinnitus can be caused by either an underlying medical condition, such as noise trauma or age-related hearing loss, ear injury, or cardiovascular disease, or other causes, including medication use. Tinnitus is estimated to occur in approximately 1 in 10 adults in the US population (Bhatt et al 2016).

The presentation of tinnitus varies greatly among individuals. Most individuals with tinnitus experience subjective tinnitus, which is defined as the perception of sound(s) in the absence of a corresponding external or internal sound source. The duration of tinnitus symptoms after its initial onset is also used to classify the condition, and expert guidance defines tinnitus as acute if experienced for less than 3 months, as sub-acute after 3 months, and "chronic" for periods of 6 months or longer (Cima et al 2019). Tinnitus can also affect quality of life, and the term "bothersome" tinnitus designates cases in which the perception of the characteristic sound becomes very disturbing, and may be associated with anxiety, depression, sleep disturbances, and maladaptive psychological reactions that impede daily function (Cima 2018).

Disruption in γ-aminobutyric acid (GABA)ergic signaling affects the critical balance between excitatory and inhibitory inputs to central auditory pathways in both normal hearing and tinnitus. The $GABA_A$ receptor is expressed in the auditory system, particularly concentrated in the cochlea, and specific receptor subunits appear associated with long-term maintenance of hair cells and neurons in the inner ear (Maison et al 2006). Reductions in auditory cortex GABA levels occur with older age and correspond to elevated pure-tone hearing thresholds in humans (Gao et al 2015). The inhibitory function of the GABA-gated chloride channel ($GABA_A$) receptor is also thought to be critical for auditory processing, including sound segmentation and multi-sensory integration, by modulating input/output, frequency tuning, and temporal response accuracy (Wang et al 2008).

There are currently no Food and Drug Administration (FDA)-approved pharmacological or nonpharmacological treatments for tinnitus. However, attenuation of some tinnitus symptoms has been reported with a variety of GABAergic drugs, including benzodiazepine derivatives alprazolam (Johnson et al 1993) and clonazepam (Bahmad et al 2006), and the GABA homolog gabapentin (Zapp 2001; Shulman et al 2002; Bauer and Brozoski 2006) under select circumstances. Considering the inconsistent effects of conventional GABAergic drugs, agents that significantly potentiate extrasynaptic $GABA_A$ receptors may offer unique benefit in the management of tinnitus relative to drugs with low affinity at extrasynaptic $GABA_A$ receptors (Witkin et al 2022). Therefore, the investigation of the use of brexanolone, a positive allosteric modulator of synaptic and extra-synaptic $GABA_A$ receptors, in the treatment of tinnitus is supported by both nonclinical and clinical data.

5.1. Study Rationale

Brexanolone is a potent positive allosteric modulator of synaptic and extra-synaptic $GABA_A$ receptors and has potential to enhance both phasic and tonic inhibition in the brain. Brexanolone was formulated to be chemically identical to allopregnanolone, a metabolite of progesterone and endogenous neuroactive steroid.

Tonic conductance of extrasynaptic $GABA_A$ receptors is considered critical to producing shunting inhibition that regulates neuronal network excitability. By this rationale, it has been proposed that neurosteroids, including brexanolone, may show unique potential in the management of tinnitus when compared to drugs with selective affinity for synaptic $GABA_A$ receptors.

5.2. Effects of $GABA_A$ Receptors in the Auditory Pathway

GABA is an amino acid that functions as an important inhibitory neurotransmitter for the CNS (Watanabe et al 2002). Disruption in GABAergic signaling affects the critical balance between excitatory and inhibitory inputs to central auditory pathways in both normal hearing and tinnitus. The $GABA_A$ receptor is expressed in the auditory system, particularly concentrated in the cochlea, and specific receptor subunits appear associated with long-term maintenance of hair cells and neurons in the inner ear (Maison et al 2006). Reductions in auditory cortex GABA levels occur with older age and correspond to elevated pure-tone hearing thresholds in humans (Gao et al 2015). The inhibitory function of the $GABA_A$ receptor is also thought to be critical for auditory processing, including sound segmentation and multi-sensory integration, by modulating input/output, frequency tuning, and temporal response accuracy (Wang et al 2008).

Loss of inhibition in the GABA pathway and specific potassium pathways plays a role in the pathology of tinnitus in animal models (Yang et al 2011; Li et al 2013). Studies in humans support the findings in animal models. A significant decrease in $GABA_A$ receptor density in the medial temporal cortex in patients with severe disabling tinnitus and hearing loss was observed with single-photon emission computed tomography (Sedley et al 2015). An investigation using two-dimensional J-resolved spectroscopy identified lower glutamate and GABA concentrations in auditory cortices of tinnitus patients, as well as a correlation between glutamate concentration and perceived tinnitus loudness, suggesting the influence of excessive excitatory activity (Isler et al 2022).

5.3. Support for Use of Brexanolone in Tinnitus

Although no medications are approved for use in tinnitus management, and current guidelines discourage their use (Tunkel et al 2014), attenuation of some tinnitus symptoms has been reported with a variety of GABAergic drugs, including benzodiazepine derivatives alprazolam (Johnson et al 1993) and clonazepam (Bahmad et al 2006), and the GABA homolog gabapentin (Zapp 2001; Shulman et al 2002; Bauer and Brozoski 2006) under select circumstances.

Considering the inconsistent results for conventional GABAergic drugs in tinnitus, agents that significantly potentiate extrasynaptic $GABA_A$ receptors may offer unique benefit in the management of tinnitus relative to drugs with low affinity at extrasynaptic $GABA_A$ receptors (Witkin et al 2022). The GABAergic compound gaboxadol, which selectively activates extrasynaptic $GABA_A$ receptors, has successfully ameliorated tinnitus in animal studies (reviewed in Richardson et al 2012). This selective activation of extrasynaptic $GABA_A$ receptors by low concentrations of gaboxadol reduces spontaneous and evoked firing rates of sensory thalamic neurons involved in tinnitus. Such reductions in excitability of auditory thalamus/medial geniculate body (MGB) neurons following activation of extrasynaptic $GABA_A$ receptors in tinnitus could prove advantageous in reducing the transmission of hyperexcitability to the auditory cortex (Herd et al 2009).

While brexanolone is approved for the treatment of postpartum depression (PPD), its efficacy has also been examined in the management of super-refractory status epilepticus (SRSE). SRSE is a life-threatening form of status epilepticus that recurs despite 24 hours or more of continuous intravenous (IV) administration of anesthetic third-line agents. In a Phase 2, open-label study using a targeted burst-suppression regimen (the STATUS study), brexanolone was associated with a statistically significant increase in quantitative EEG suppression ratio (qSR) during the initial 1-hour loading infusion (which targeted a plasma concentration of 150 nM). Moreover, initial qSR increase was positively correlated with brexanolone plasma concentrations over first 9 hours of infusion (maintenance infusion of 86 mcg/kg/hour). These findings support the potential of brexanolone to enhance neural inhibition in presence of aberrant excitatory activity with brief exposure (Rosenthal et al 2015a; Rosenthal et al 2015b).

Based on the data for GABAergic compounds in tinnitus, suppression of aberrant excitatory activity by brexanolone in SRSE, and the potential role of GABA in the pathogenesis of this disorder, brexanolone, a positive allosteric modulator of synaptic and extra-synaptic $GABA_A$ receptors, is being evaluated in the treatment of patients with tinnitus.

5.4. Dose Justification

Brexanolone, administered as a 60-hour infusion, is approved for the treatment of postpartum depression (PPD) in patients 15 years and older with a maintenance infusion rate of 90 mcg/kg/hour for 28 hours. In the present study, a 5-hour duration infusion given at 90 mcg/kg/hour following a period of up-titration in otherwise healthy participants with tinnitus is thought to allow adequate time to approach steady-state levels of brexanolone and anticipated to rapidly achieve plasma concentrations of brexanolone in the range experienced during therapy for PPD and during a clinical study for burst suppression in patients with SRSE (Section 5.3). Moreover, 90 mcg/kg/hour given as a short-term infusion (ie, 4 hours) was generally well-tolerated in the brexanolone ADME/mass balance study (547-CLP-101).

6. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of brexanolone	• Incidence of treatment-emergent adverse events (TEAEs)
Secondary	
• To assess subjective tinnitus perception during brexanolone infusion based on Visual Analog Scales (VAS)	• Change from baseline to Hour 6 of infusion in VAS loudness (VAS-L) ratings • Change from baseline to Hour 6 of infusion in VAS annoyance (VAS-A) ratings
• To assess subjective tinnitus perception after brexanolone infusion based on VAS	• 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]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	• Change from baseline in vital signs, electrocardiogram (ECG), and clinical laboratory parameters [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

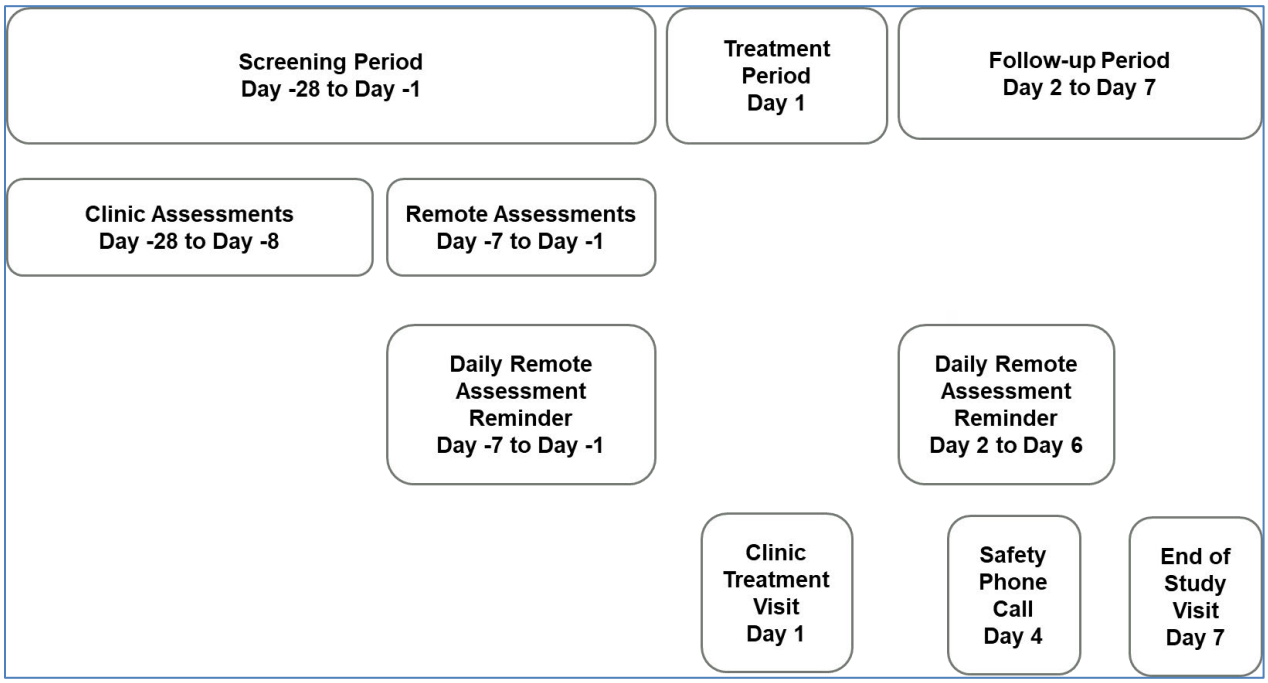
[redacted]	[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

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 IV infusion. The study design is presented in Figure 2.

Figure 2: Study Design



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 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 (Table 2).

Starting 7 days before administration of investigational product (IP) (Day -7), participants will have twice daily remote predose assessments as indicated in 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 VAS-L and 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 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.

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 [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, specifically if this occurs in the context of excessive sedation or sudden loss of consciousness. After an episode of confirmed hypoxia, the infusion should not be resumed.

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

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

A fall precaution protocol must be in place for the duration of the brexanolone infusion.

At the conclusion of the IP infusion, if deemed medically appropriate by the investigator, participants will be released from the clinic after the 2-hour safety observation period and completion of assessments. 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.

Follow-Up Period:

Assessments for the Follow-up Period will be performed as indicated in 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 at the EOS Visit. The EOS Visit will also be conducted at the time of study discontinuation if this occurs at any time before Day 7 ±1 day (see Section 8.4.2).

7.2. Number of Participants

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

7.3. Treatment Assignment

In this open-label study, all participants will receive a single 6-hour continuous IV infusion of brexanolone on Day 1.

7.4. Dose Escalation and Adjustment Criteria

[redacted]

If excessive sedation [redacted] 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.

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

For participants who do not tolerate the 90 mcg/kg/hour dose for reasons other than hypoxia, a reduction to 60 mcg/kg/hour should be considered. No reductions below 60 mcg/kg/hour are permitted.

Any sedation-related AEs that lead to dose interruption, termination, or reduction should be recorded as AESIs, and should be reported in an expedited manner as outlined in Section 12.2.3.

A plasma sample for [redacted] should be drawn during the time when the pump is stopped.

7.5. Criteria for Study Termination

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to participants, or for administrative reasons. In the event of study termination, Sage Therapeutics will provide written notification to the investigator. Investigational sites must promptly notify their institutional review board (IRB)/independent ethics committee (IEC), where required, and initiate withdrawal procedures for participating participants.

7.6. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed the EOS Visit.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Participant Inclusion Criteria

Participants must meet all of the following criteria to qualify for participation in this study:

1. Participant has signed an ICF before any study-specific procedure is started.
2. Participant is ambulatory and is 18 to 65 years of age, inclusive, at the time informed consent is obtained.
3. Participant has a designated companion for the Clinic Treatment Visit who will drive them when they leave the clinic.
4. Participant is in good physical health and has no clinically significant findings (excluding tinnitus), as determined by the investigator on medical history and physical examination, including neurologic and mental status examinations, 12-lead ECG, or clinical laboratory tests.
5. Participant has a diagnosis of subjective, idiopathic, unilateral or bilateral, non-pulsatile tinnitus (eg, not due to medical disease) of ≥6 months and <10 years duration.
6. Participant has mild to severe tinnitus distress according to Tinnitus Handicap Inventory (THI) score of 24 to 68 at Screening.
7. Participant is willing and able to safely discontinue the use of central nervous system (CNS) depressants (eg, opioids and benzodiazepines), antidepressants, anticonvulsants, CNS stimulants (with the exception of caffeine), aspirin, other nonsteroidal anti-inflammatory drugs, and aminoglycosides at least 14 days or 5 half-lives (whichever is longer) prior to receiving IP and through completion of the study.
8. Female participant agrees to use at least one method of highly effective contraception during participation in the study and for 30 days following the last dose of IP, unless she is postmenopausal, permanently sterile, or does not engage in sexual relations which carry a risk of pregnancy (see Section 9.2.5).
9. Male participant with a partner who is of childbearing potential agrees to use an acceptable method of effective contraception for the duration of the study and for 13 weeks after receiving the IP, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy in his female partner(s). Acceptable methods of effective contraception are listed in Section 9.2.5.
10. Male participant is willing to abstain from sperm donation for the duration of the study and for 13 weeks after receiving the IP.

8.2. Participant Exclusion Criteria

Participants who meet any of the following criteria are disqualified from participation in this study:

1. Participant has history or presence of any neurologic disease or condition, including, but not limited to, unexplained loss of consciousness, seizure disorder including a prior nonfebrile seizure, and closed head trauma with clinically significant sequelae.

2. Participant has a history of sleep apnea or any clinically significant respiratory conditions that may predispose the participant to hypoxia during the infusion.
3. Participant intends to start or discontinue a pharmacological or nonpharmacological therapy (eg, psychotherapy, sound therapy, masking, transcranial magnetic stimulation [TMS]) for tinnitus during the course of the study.
4. Participant has currently active and medically significant or uncontrolled hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, metabolic disease (hypothyroidism with stable thyroid replacement is acceptable).
5. Participant's tinnitus can be modulated by maneuvers of the temporomandibular joint, head and neck, eyes, or limbs, or otherwise attributed to somatosensory cause or has had prior otoscopic surgeries or cholesteatoma.
6. Participants has current unilateral or bilateral hearing loss of 30 dB or greater (mild hearing loss) in one or more tested frequencies (500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz), 60 dB or greater at 6000 Hz and 8000 Hz, asymmetry of 30 dB or greater in two or more tested frequencies or uses a cochlear implant or hearing aid.
7. Participant has history of chronic otitis media (>3 per year during past 5 years).
8. Participant has a total score of 15 or greater (ie, moderately severe) on the Patient Health Questionnaire-9 (PHQ-9) at Screening.
9. Participant has diagnosis of moderate or severe substance use disorder (excluding nicotine dependence) within 12 months of Screening, has a positive screen for drugs of abuse including tetrahydrocannabinol (THC) on Day 1 prior to dosing, or has a positive screen for alcohol on Day 1 prior to dosing.
10. Participant has a known allergy to progesterone, allopregnanolone, or any IP excipient.
11. Female participant has a positive pregnancy test or a confirmed pregnancy at Screening or prior to dosing on Day 1.
12. Participant has had exposure to another investigational drug or device within 30 days or 5 half-lives of the investigational drug, whichever is longer, prior to the Day 1 visit.
13. Participant has a history of suicidal behavior within 2 years or answers "YES" to Questions 3, 4, or 5 on the C-SSRS at Screening or at Day 1 or is currently at risk of suicide in the opinion of the investigator.
14. Participant has donated 1 or more units (1 unit = 450 mL) of blood or experienced acute loss of an equivalent amount of blood within 60 days prior to Day 1.
15. Participant has any condition, comorbidity, or lifestyle consideration that in the opinion of the investigator would limit or interfere with the participant's ability to complete or partake in the study.
16. Participant is unwilling or unable to comply with study procedures and the required training during the Baseline Period. The participant must complete 10 VAS assessments remotely prior to Day 1.

17. Participant is unable to complete participation in the study, eg, due to preplanned event including elective surgery.
18. Participant is investigative site personnel, sponsor personnel, or a member of their immediate families (spouse, parent, child, or sibling whether biological or legally adopted).

8.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently dosed. A minimal set of screen failure information will be collected, including demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who screen fail may not be rescreened except for failure of inclusion criterion 7 and/or exclusion criteria 12, 14, and 17 (after clinical recovery from the preplanned event). An individual who qualifies may only be rescreened once. Rescreened participants will be assigned a new participant number.

A failed Screening drug or alcohol test does not exclude participation in the study if test is negative at Day 1. However, participants with a failed drug or alcohol test on Day 1 are excluded from participation in the study and may not be rescreened.

8.4. Investigational Product Discontinuation and Early Termination from the Study

A participant may withdraw from the study at any time at his/her own request for any reason. The investigator may discontinue a participant from the study and/or from IP for safety, behavioral, compliance, or administrative reasons.

The investigator must notify the sponsor and/or the medical monitor when a participant discontinues IP and/or stops participation in the study for any reason.

8.4.1. Investigational Product Discontinuation

When a participant is discontinued from IP, the participant should continue, if willing, to participate in the remainder of the study by attending all scheduled visits per the SOA (Table 3).

The reason for IP discontinuation and/or the reason for early termination from the study must be documented in the participant's source documentation and recorded in the participant's electronic case report form (eCRF)

8.4.2. Early Termination from the Study

At the time of study withdrawal/stopping study participation, if possible, the EOS Visit should be conducted. The participant will be permanently discontinued both from the IP at that time.

If the participant withdraws consent for disclosure of future information, the sponsor will retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Reasons for study discontinuation include, but are not limited to, the following:

- Adverse event
- Pregnancy
- Protocol deviation
- Non-compliance with study drug
- Lost to follow-up
- Withdrawal by subject
- Screen failure
- Study terminated by sponsor

8.4.3. Loss to Follow-up

A participant will be deemed lost to follow-up after unsuccessful documented attempts to contact the participant.

8.4.4. Replacement of Participants

Participants who initiate the IP infusion and who subsequently withdraw for any reason will not be replaced. See Section 8.3 regarding rescreening of screen failure participants.

9. TREATMENT OF PARTICIPANTS

9.1. Description of Investigational Product

Participants will be administered a single continuous 6-hour IV infusion of brexanolone.

9.2. Prior and Concomitant Medications, Nonpharmacological Interventions, Restrictions, and Contraception Requirements

9.2.1. Prior and Concomitant Medications and/or Supplements

The start and end dates, route, dose/units, frequency, and indication for all medications and/or supplements taken within 60 days, all psychotropic medications taken within 6 months, and all medications used to treat tinnitus regardless of timing prior to signing the informed consent through the first dose of IP will be recorded.

All medications and/or supplements taken from the first dose of IP through the Day 7 (±1 days) visit (including start and end dates route, dose/units, frequency, and indication) will be recorded on the eCRF. Any concomitant medication determined necessary for the welfare of the participant may be given at the discretion of the investigator at any time during the study.

9.2.2. Nonpharmacological Interventions

The start and end dates for all nonpharmacological interventions for tinnitus prior to signing the informed consent will be recorded. Nonpharmacological interventions include, but are not limited to, psychotherapy, sound therapy masking, and transcranial magnetic stimulation (TMS).

9.2.3. Prohibited Medications

Participant must discontinue the use of central nervous system (CNS) depressants (eg, opioids and benzodiazepines), antidepressants, anticonvulsants, CNS stimulants (with the exception of caffeine), aspirin, other nonsteroidal anti-inflammatory drugs, and aminoglycosides at least 14 days or 5 half-lives (whichever is longer) prior to receiving IP and through completion of the study.

9.2.4. Other Restrictions

The participant should not engage in potentially hazardous activities requiring mental alertness and should not drive a car until after completion of the brexanolone infusion and until any feelings of sedation have dissipated. A designated companion must drive the participant when they are discharged from the clinic.

Alcohol consumption while receiving brexanolone is prohibited.

IV medications may not be coadministered with brexanolone in the same infusion line.

9.2.5. Acceptable Forms of Contraception

As per the Clinical Trials Facilitation and Coordination Group (CTFG), a woman is considered of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming

postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in females not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

A male is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Acceptable forms of highly effective contraception (ie, can achieve a failure rate of <1% per year when used consistently and correctly) for participants of childbearing potential or for a male participant's partner of childbearing potential include:

- Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion or bilateral tubal ligation (performed at least 3 months prior to screening)
- Vasectomized partner (performed at least 3 months prior to screening)
- Sexual abstinence (no sexual intercourse)

Acceptable forms of contraception for male participants include:

- Sexual abstinence (no sexual intercourse)
- History of vasectomy (performed at least 3 months prior to screening)
- Condom with spermicide used together with highly effective female contraceptive methods if the female partner(s) is of childbearing potential (see above for list of acceptable female contraceptive methods)

Acceptable forms of contraception which may not be considered as highly effective include:

- Oral progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide
- A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable

9.3. Intervention after the End of the Study

Not applicable

9.4. Treatment Adherence

Brexanolone will be administered to participants as a single 6-hour continuous IV infusion by site staff, as described in Section 10.5. The investigator(s) or designated staff will record the time and dose of IP administration in the source documents. Any reasons for non-adherence will also be documented. Deviation(s) from the prescribed dosage regimen will be documented. Details on IP accountability are included in Section 10.6.

9.5. Randomization and Blinding

This is an open-label study in which all participants will receive brexanolone.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

Brexanolone is a sterile, clear, colorless, and preservative-free solution. It is hypertonic and must be diluted prior to administration as an IV infusion. Each mL of solution contains 5 mg of brexanolone, 250 mg of betadex sulfobutyl ether sodium as a solubilizer, citric acid and sodium citrate as buffering agents, and Water for Injection, USP. Hydrochloric acid or sodium hydroxide may be used during manufacturing to adjust pH.

The composition and pharmaceutical quality of the study drug will be maintained according to the current Good Manufacturing Practice and Good Clinical Practice (GCP) guidelines and available for review in the IP documentation.

10.2. Investigational Product Packaging and Labeling

Brexanolone is sterile-filtered and aseptically filled into 20 mL Type 1 parenteral glass vials with West FluroTec® coated stopper container closure system under current Good Manufacturing Practice conditions. Brexanolone is intended to be used as a single-use vial.

IP labels with all required information and conforming to all applicable FDA Code of Federal Regulations and Good Manufacturing Practices/Good Clinical Practices (GCP) guidelines will be prepared by the sponsor.

Additional information regarding the packaging and labeling is provided in the pharmacy manual.

10.3. Investigational Product Storage

Upon receipt of the IP, the investigator, the responsible pharmacist, or designee will inspect the product and acknowledge receipt in accordance with the pharmacy manual.

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

10.4. Investigational Product Preparation

The pharmacist or designee will be responsible for preparing brexanolone for participant dosing. The prepared admixture will be administered at room temperature.

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

10.5. Investigational Product Administration

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 5.

Table 5: 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] 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.

10.6. Investigational Product Accountability, Handling, and Disposal

Upon receipt of IP, the investigator(s), or the responsible pharmacist or designee, will inspect the IP and complete and follow the instructions regarding receipt and storage in the investigator's brochure and (where applicable) in the pharmacy manual. A copy of the shipping documentation will be kept in the study files. The IP provided is for use only as directed in this protocol. The investigator or designee must keep a record of all IP received, used, and returned/discarded.

Accurate records will be kept regarding the volume of IP used for each IV preparation, as well as the required infusion dose (or doses), the date and time of preparation and for which participant the IP was intended (ie, record participant initials and birth date or another unique identifier). Reasons for departure from the expected dosing regimen must be recorded. Sage Therapeutics will be permitted access to the study supplies at any time with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

The investigator, pharmacist, or qualified designee is responsible for drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

At the end of the study, any unused IP will be returned to Sage Therapeutics for destruction or destroyed locally per the site's procedures; disposition of IP will be documented.

10.7. Product Complaints

A product complaint is any written, electronic, or verbal expression of dissatisfaction regarding the identity, quality, reliability, safety, purity, potency, effectiveness, or performance (applicable for approved marketed products) of a drug product after it is released for distribution.

In the course of conduct of the study, study personnel may become aware of a product complaint associated with the use of a Sage product. Personnel shall notify Sage within 24 hours by forwarding the product complaint information via the contact information listed in Table 1 and in the Pharmacy Manual. Where possible, personnel should segregate and retain any product, materials, or packaging associated with the product complaint until further instruction is provided by Sage or its designated representative(s).

11. EFFICACY [redacted]

11.1. Efficacy Assessments

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.

[redacted]

11.1.2. Visual Analog Scales

The VAS loudness (VAS-L) and annoyance (VAS-A) are subject-rated scales for evaluating tinnitus (Adamchic et al 2012). Scoring for both is along a linear vertical scale, with the left side being not audible/not annoying (score of 0) and the right side being extremely loud or annoying (score of 100). 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”.

[redacted]

[redacted]

[redacted]

12. SAFETY ASSESSMENTS

12.1. Safety and Tolerability Assessments

Safety and tolerability of brexanolone will be evaluated by incidence of treatment-emergent adverse events as well as changes from baseline in vital signs measurements, ECGs, and clinical laboratory parameters, [redacted].

The following assessments will be conducted according to the Schedules of Assessments (Table 2 and Table 3).

12.1.1. Demography and Medical History

Demographic characteristics (age, race, sex, ethnicity) and a full medical history will be documented. Tinnitus-related medical history will be obtained by structured interview. Mild to severe tinnitus will be determined using the [redacted] Participants will also be asked about unexplained loss of consciousness, seizure disorder including a prior nonfebrile seizure, and closed head trauma with clinically significant sequelae.

12.1.2. Weight and Height

Height and weight will be measured and documented. Body mass index (BMI) will be calculated and documented.

12.1.3. Physical Examination

Whenever possible, the same individual should perform all physical examinations. Physical examinations will include assessment of body systems (eg, 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, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents.

12.1.4. Vital Signs

Vital signs comprise heart rate, respiratory rate, temperature, and blood pressure. Heart rate and systolic and diastolic blood pressure are to be measured after the participant has been semi-inclined for at least 5 minutes prior to the measurement.

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.

12.1.5. Electrocardiogram

A 12-lead ECG will be performed. The standard intervals (heart rate, PR, QRS, QT, and QTcF) as well as any rhythm abnormalities will be recorded.

Electrocardiograms will be performed after the participant has been resting in a position for at least 5 minutes.

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

12.1.6. Laboratory Assessments

Blood samples will be collected for hematology, serum chemistry, and coagulation. Analytes to be evaluated are summarized in Table 6.

Table 6: Summary of Clinical Laboratory Analytes

Biochemistry	*Renal Panel*: glucose, calcium, phosphorus, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate *Hepatic Panel*: albumin, ALT, 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 subjects 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 NCS or abnormal CS in source documents. Screening results considered abnormal, 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.

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 (Section 8.1).

12.1.6.1. Drugs of Abuse, Alcohol, Cotinine

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.

12.1.6.2. Pregnancy Screen

A serum pregnancy test will be conducted for all WOCBP at Screening; a urine pregnancy test will be conducted for all WOCBP at all other scheduled timepoints.

12.1.7. Continuous Pulse Oximetry

Subjects will be monitored during the infusion for hypoxia using continuous pulse oximetry equipped with an alarm. 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 hypoxia, in which case,

the event is to be recorded as an AE. The infusion will be immediately stopped if pulse oximetry reveals hypoxia. After an episode of hypoxia, the infusion should not be resumed.

[redacted]

12.1.10. COVID-19 Procedures

The site should follow their internal plan, policies, and procedures for coronavirus disease 2019 (COVID-19).

The following information regarding diagnosis, isolation, and/or hospitalization due to COVID-19 will be documented as part of medical history, AE collection, and prior/concomitant medication/procedure collection at Screening and throughout the study.

Questions to be asked are as follows:

1. Were you diagnosed with COVID-19?
    - If the answer is “no”, no further questions.

- If the answer is “yes”, the following questions are asked:
  - Did you have a test? If yes, was the result positive, negative, or inconclusive?
  - Were you isolated? If yes, what were the dates of isolation?
  - Were you hospitalized? If yes, what were the dates of hospitalization?

2. Did you receive the COVID-19 vaccine?
   - If the answer is “no”, no further questions.
   - If the answer is “yes”, the following questions are asked:
     - What is the reported name of the COVID-19 vaccine you received?
     - Who is the manufacturer of the COVID-19 vaccine you received?
     - On what date(s) did you receive the COVID-19 vaccine?

12.2. Adverse and Serious Adverse Events

12.2.1. Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

A treatment-emergent adverse event (TEAE) is 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. The term IP includes any Sage IP, a comparator, or a placebo administered in a clinical study.

Laboratory abnormalities and changes from baseline in vital signs, and ECGs are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the investigator considers them to be clinically significant. Any abnormalities that meet the criteria for a serious adverse event (SAE) should be reported in an expedited manner. Laboratory abnormalities and changes from baseline in vital signs and ECGs that are clearly attributable to another AE do not require discrete reporting (eg, electrolyte disturbances in the context of dehydration, chemistry, and hematologic disturbances in the context of sepsis).

All AEs that occur after any participant has signed the informed consent and throughout the duration of the study, whether or not they are related to the study, must be reported to Sage Therapeutics.

Participants who discontinue the IP due to an AE, regardless of investigator-determined causality, should be followed until the event is resolved, considered stable, or the investigator determines the event is no longer clinically significant. Any AEs that are unresolved at the

participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The sponsor or its representative retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.2. Serious Adverse Event Definition

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

- Results in death
- Places the participant at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect

An SAE may also be any other medically important event that, in the opinion of the investigator may jeopardize the participant or may require medical intervention to prevent 1 of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

All SAEs that occur after any participant has signed the ICF and throughout the duration of the study, whether or not they are related to the study, must be recorded on the SAE report form provided by Sage Therapeutics. Any SAE that is ongoing when the participant completes their final study visit, will be followed by the investigator until the event has resolved, stabilized, returned to baseline status, or until the participant dies or is lost to follow up.

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

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or on a waiting list to be scheduled) prior to obtaining the participant's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress, in the opinion of an investigator, between the participant's consent to participate in the study and at the time of the procedure or treatment.

12.2.3. Definition of Adverse Events of Special Interest

An adverse event of special interest (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. Such adverse events normally require thorough documentation and investigation in order to characterize them.

The following events are considered AESIs and should be reported on the AESI form to Sage and designee within 72 hours:

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

If the AESI also qualifies as an SAE, an SAE form should be submitted per the guidelines per Section 12.2.7.

12.2.4. Definition of Urgent Safety Measure and Unanticipated Problem

In accordance with Article 10(b) of Directive 2001/20/EC, some reported events may result in an urgent safety measure (USM), defined as an action that the sponsor and investigator may take in order to protect the participants of a study against any immediate hazard to their health or safety. Examples of USMs include:

- Suspension of enrollment due to significantly higher incidence of death at one site
- Additional clinical or non-clinical investigations performed due to increased frequency of AEs
- Halting a clinical study for safety reasons

In accordance with FDA Guidance 21 CFR Part 312.66, some reported events may qualify as an unanticipated problem (UP), defined as any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (i) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (ii) the characteristics of the population being studied; related or possibly related to an individual's participation in the study; and
- Suggests the study may place the participant or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the study than was previously known or recognized.

Any UP must be reported within 24 hours of awareness via email to Sage and designee due to the urgent reporting requirements to regulators and IRB(s)/IECs(s).

12.2.5. Relationship to Investigational Product

The investigator must make the determination of relationship to the IP for each adverse event (not related, related). The following definitions should be considered when evaluating the relationship of AEs and SAEs to the IP.

Not Related	An AE will be considered "not related" to the use of the IP if there is not a reasonable possibility that the event has been caused by the IP. Factors pointing towards this assessment include but are not limited to: the lack of temporal relationship between administration of the IP and the event, the presence of biologically implausible

	relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE
Related	An AE will be considered "related" to the use of the IP if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point towards this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of alternative explanation for the AE

12.2.6. Recording Adverse Events

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

Intensity will be assessed according to the following scale:

- Mild: symptom(s) barely noticeable to participant or does not make participant uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s)
- Moderate: symptom(s) of a sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptom(s) may be needed
- Severe: symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause cessation of treatment with IP; treatment for symptom(s) may be given and/or participant hospitalized

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.2.2. An AE of severe intensity may not necessarily be considered serious.

12.2.7. Reporting Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE(s), the study site must notify Sage and designee within 24 hours of the study site staff becoming aware of the SAE(s). The investigator must complete, sign and date the SAE report form, verify the accuracy of the information recorded on the SAE report form with the corresponding source documents, and send a copy to Sage and designee.

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

Serious adverse events occurring after the designated follow up time for the study, should be reported to Sage and designee according to the timelines noted above only if the investigator considers the SAE related to IP.

Sage or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the principal investigator's responsibility to notify the IRB/IEC of all SAEs that occur at his or her site. Investigators will also be notified of all suspected unexpected serious adverse reactions (SUSARs) that occur during the clinical study. IRBs/IECs will be notified of SAEs and/or SUSARs as required by local law.

In addition, appropriate personnel in Sage Drug Safety and Pharmacovigilance or designee will unblind SUSARs for the purpose of regulatory reporting. Sage or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Sage, or designee, will submit SUSARS to investigators in a blinded fashion.

12.3. Pregnancy

If a participant becomes pregnant after the first administration of IP, pregnancy information must be collected and recorded on the Pregnancy form and submitted to Sage and designee within 24 hours of learning of the pregnancy. Details will be collected for all pregnancies for which conception was likely to have occurred after the start of IP administration until 5 terminal half-lives following the last administration of IP or until the completion of the study whichever is longer. Any pregnancy occurring in that time frame will be followed until delivery or termination of the pregnancy. The investigator will also attempt to collect pregnancy information on any participant's partner who becomes pregnant after the participant has received the first administration of IP. After obtaining the necessary signed informed consent from the pregnant partner directly, the investigator will follow the same pregnancy reporting procedures specified for pregnant participants.

The participant or participant's partner will be followed to determine the outcome of the pregnancy. The outcome of all pregnancies (eg, spontaneous abortion, elective abortion, normal birth) must be followed and documented even if the participant was discontinued from the study. The investigator will collect follow-up information on the participant or participant's partner and the neonate, and the information will be forwarded to Sage and designee within 24 hours of awareness. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication. Any complication during pregnancy (eg, anemia, infections, pre-eclampsia) should be reported as an AE/SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death,), the investigator should follow the procedures for reporting an SAE.

12.4. Overdose

Overdose is described in Section 12.5.

12.5. Special Considerations

Drug abuse is the persistent or sporadic, intentional excessive use of IP which is accompanied by harmful physical or psychological effects in the participant. If an event of drug abuse occurs during the study, it must be reported to the sponsor and/or designee using the Special Considerations Form within 24 hours of the site becoming aware of the event(s). If the drug abuse results in an AE or SAE, the AE or SAE must also be recorded and reported as described in Section 12.2.6 and Section 12.2.7, respectively.

Drug misuse refers to situations where IP is intentionally and inappropriately used not in accordance with the intended use as specified in the protocol. If an event of drug misuse occurs during the study, it must be reported to the sponsor and/or designee using the Special Considerations Form within 24 hours of the site becoming aware of the event(s). If the drug misuse results in an AE or SAE, the AE or SAE must also be recorded and reported as described in Section 12.2.6 and Section 12.2.7, respectively.

An overdose is any dose of study treatment given to a participant or taken by a participant that exceeds the dose described in the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on the Special Considerations Form and sent to Sage and/or designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Sage and designee even if the overdose does not result in an AE. If an overdose results in an AE or SAE, the AE or SAE must also be recorded and reported as described in Section 12.2.6 and Section 12.2.7, respectively.

A medication error is any preventable event that may cause or lead to inappropriate medication use or participant harm while the medication is in the control of the healthcare professional, participant, or consumer. All medication errors must be recorded on the Special considerations form and sent to the sponsor and/or designee within 24 hours of the site becoming aware of the medication error. The medication error must be reported to the sponsor and/or designee even if the medication error does not result in an AE. If a medication error results in an AE or SAE, the AE or SAE must also be recorded and reported as described in Section 12.2.6 and Section 12.2.7, respectively.

13. STATISTICS

A detailed description of the analyses to be performed in the study will be provided in the statistical analysis plan (SAP). The SAP will be finalized and approved prior to database lock.

13.1. Data Analysis Sets

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

[redacted]

The Safety Set is defined as all participants who received any amount of IP.

13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All participants will be used in the analyses, as per the analysis populations, using all non-missing data available. No imputation process will be used to estimate missing data.

13.3. General Considerations

All participant data, including those that are derived, that support the tables and figures will be presented in the participant data listings. Some data may be presented only in participant listings, whereas other data may be presented in both listings and corresponding table(s) or figure(s).

For the Screening period and Days 2-7, not more than one (1) set of remote morning VAS components and one (1) set of remote evening VAS components per timepoint will be used in the statistical analysis of data for a given study participant. However, morning and evening VAS component data may be displayed and descriptively summarized.

For in-clinic VAS component assessments (VAS-A and VAS-L, Section 11.1.2), baseline is defined as the most recent VAS component value immediately prior to the start of IP infusion.

For remote daily VAS-A assessments, baseline is defined as the arithmetic mean of Screening VAS-A values per participant; likewise, for remote daily VAS-L assessments, baseline is defined as the arithmetic mean of Screening VAS-L values per participant.

Continuous data will be summarized, at minimum, with number (n), mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. Categorical data will be summarized, at minimum, with counts and percentages. Change from baseline is calculated as the baseline value minus the post-baseline value, unless defined otherwise for specific assessments and/or endpoints.

Summary tables will generally summarize values at each timepoint and change from baseline at each post-baseline time point.

13.4. Demographics and Baseline Characteristics

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

Pregnancy test results and drug screen results will be listed but not summarized.

Medical history will be listed by participant.

13.5. Efficacy Analysis

Efficacy analyses will primarily be based on the Efficacy Set.

The two secondary endpoints of this study are (a) tinnitus perception during brexanolone infusion based on the VAS and (b) tinnitus perception after brexanolone infusion based on VAS. For remote assessments, ratings for both VAS-L and VAS-A will be obtained twice daily, once each in the morning and evening, during the both the Screening Period and on Day 2 to Day 7.

The daily arithmetic means of remote VAS-A and VAS-L ratings obtained during the Screening Period will be computed and used descriptively. The daily arithmetic means of remote VAS-A and VAS-L ratings obtained on Days 2-7 will be used both descriptively and in statistical modeling.

Each component of VAS for tinnitus will have change from baseline score (see Section 13.3 for a description of appropriate baseline for a given schedule of assessment timepoint) at each postbaseline assessment (whether during brexanolone infusion or post-brexanolone infusion) computed. Descriptive statistics of both VAS component scores and VAS component change from baseline scores will be summarized.

Each VAS component score will be analyzed separately for each secondary endpoint. This will be done separately for Day 1 (ie, during treatment) and Days 2 to 7 (ie, after treatment). The during-infusion Day 1 VAS component data will consist of VAS components obtained at 0.5, 1, 2, 3, 4, 5, and 6 hours. The post-infusion Days 2 to 7 VAS component data will consist of daily arithmetic component means.

Each analysis will utilize a mixed effects model for repeated measures. Each repeated measures model will include (a) the change from baseline score of the appropriate VAS component as the dependent variable and (b) both baseline VAS component value and visit as fixed effect independent variables. Participants will be treated as random effects.

Model- based point estimates (ie, least squares means, their 95% confidence intervals, and associated p-values) at each time point (visit) will be reported where applicable. Line plots of change from baseline scores will be plotted with standard error bars. Additional analyses will be detailed in the SAP.

13.5.1. Multiplicity Adjustment

Not applicable.

13.5.2. Sensitivity Analyses

Sensitivity analyses are not described in the protocol. Sensitivity analyses may be discussed in the SAP.

13.6. Safety Analyses

The primary endpoint of this study is the incidence of TEAEs. This will be primarily assessed with TEAE tables presenting per-participant frequency counts and percentages within each unique combination of System Organ Class and Preferred Term. Please see Section 13.6.1 for additional detail.

Generally, safety and tolerability of brexanolone will be evaluated by incidence of TEAEs and SAEs, as well as changes from baseline in vital signs measurements, ECGs, and clinical laboratory parameters, [redacted].

Safety data will be listed by participant and summarized by treatment group. All safety summaries will be performed on the Safety Set using treatment received.

13.6.1. Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0 or higher. A treatment-emergent adverse event (TEAE) is defined as an AE with onset or worsening of severity after the first dose of brexanolone.

The proportion of participants experiencing TEAEs will be displayed by treatment group and by system organ class and preferred term. Summaries will be provided by severity (mild, moderate, severe) and by causality (related, not related to IP). TEAEs leading to discontinuation or interruption of treatment or withdrawal from the study and any treatment-emergent SAEs will be summarized. All AEs and SAEs through the end of the study will be listed.

13.6.2. Clinical Laboratory Evaluations

Results of clinical laboratory parameters in each scheduled visit and mean changes from baseline will be summarized in standard units. Normal ranges for each parameter will be provided by the laboratory; shift from baseline to post-baseline values in abnormality of results will be provided. Potentially clinically significant values will be summarized by treatment. Clinical laboratory results will be listed by participant and timing of collection.

13.6.3. Physical Examinations

The occurrence of a physical examination (yes/no) and the date performed will be listed by participant.

13.6.4. Vital Signs

Vital sign results at each visit and mean changes from baseline will be summarized by scheduled visit. Potentially clinically significant values will be summarized by treatment. Vital sign results will be listed by participant and timing of collection.

13.6.5. 12-Lead Electrocardiogram

The following ECG parameters will be listed for ECGs for each participant: heart rate, PR, QRS, QT, and QTcF. ECG data will be summarized by visit. Electrocardiogram findings will be listed by participant and visit.

13.6.6. Prior and Concomitant Medications

Medications will be recorded at each study visit during the study and will be coded using World Health Organization-Drug dictionary version March 2022, or later.

All medications and/or supplements taken within 60 days, all psychotropic medications taken within 6 months, and all medications used to treat tinnitus regardless of timing prior to signing the informed consent will be recorded on the eCRF. Those 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 the IP will be denoted "Concomitant".

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.

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

[redacted]

13.8. Sample Size and Power

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

13.8.1. Interim and Data Monitoring Committee (DMC) Analyses

Not applicable

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Unless otherwise waived or addressed in another forum (eg, investigator meeting), before an investigational site can enter a participant into the study, a representative of Sage will visit the investigational study site to:

- Confirm the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, IP management, GCP/ International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP compliance, and the responsibilities of Sage or its representatives. Agreed upon site responsibilities will be documented in a Clinical Trial Agreement between Sage and the investigator.

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

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

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

14.2. Audits and Inspections

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

14.3. Institutional Review Board or Independent Ethics Committee

The principal investigator must obtain IRB (or IEC) approval for the clinical study prior to enrolling a participant. Initial IRB (or IEC) approval, and all materials approved by the IRB (or IEC) for this study including the participant consent form and recruitment materials must be maintained by the investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practice and all applicable regulatory requirements, Sage Therapeutics may conduct a quality assurance audit(s) at the clinical site. Please see Section 14.2 for more details regarding the audit process.

The investigator must have adequate quality control practices to ensure that the study is performed in a manner consistent with the protocol, GCP/ICH GCP guidelines, and applicable regulatory requirements. The investigator is responsible for reviewing all identified protocol deviations. Protocol deviations that harm or increase the possibility of harm to the rights and welfare of a participant, or a deviation made without prior IRB/IEC approval to eliminate an immediate hazard to the participant should be reported to the IRB/IEC per the IRB/IEC's written procedures.

The investigator is responsible for supervising any individual or party to whom the investigator delegates study-related duties and functions conducted at the study site. When the investigator retains the services of any individual or party to perform study-related duties and functions, the investigator must ensure the individual or party is qualified to perform study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed, and any data generated.

The investigator must maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained, if necessary to provide clarification.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be given a written and dated approval or favorable opinion by an IRB or IEC as appropriate. The investigator must obtain and document approval before he or she can enroll any participant into the study. The IRB or IEC must supply to the sponsor a list of the IRB/IEC membership and a statement to confirm that the IRB/IEC is organized and operates according to GCP and applicable laws and regulations.

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

The principal investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the IP. Sage Therapeutics will provide this information to the principal investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines. In addition, the principal investigator must inform the IRB/IEC and sponsor of any changes significantly affecting the conduct of the study and/or increasing the risk to participants (eg, violations to the protocol or urgent safety measures taken for participant safety).

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH and GCP guidelines, as well as all applicable regional or national regulatory requirements.

16.3. Written Informed Consent

Prior to enrolling a study participant, the investigator(s) will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Participants must also be notified that they are free to discontinue from the study at any time. The participant should be given the opportunity to ask questions and allowed time to consider the information provided.

When the participant decides to participate in the study, the participant (or the participant's, parent or legally authorized representative) must provide signed and dated informed consent. The written consent must be obtained before conducting any study procedures. The investigator must document the consent process in the participant's source documentation. The investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the participant or to the participant's parent or legally authorized representative.

Throughout the study, participants should be informed of any changes made to the study and as new safety and or risk information becomes known. The provision of this information will be

documented in the participant's source records, and when applicable, an updated ICF will be provided.

16.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data (including but not limited to, retained biological samples, images and/or recordings) will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Sage Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

Sage Therapeutics or its representative(s) will be allowed to conduct visits at the investigation site and/or supporting facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the facility, drug storage area, drug accountability records, participant medical records and study source documents, and other records relative to study conduct.

Inspection of the study by a Regulatory Authority may occur at any time. The investigator must agree to the inspection of study-related records and source documents by the Regulatory Authority representative(s).

17.2. Retention of Records

The principal investigator must maintain all documentation relating to the study for the period outlined in the site contract, or for a period of 2 years after the last marketing application approval, and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Sage is responsible to inform the investigator/institution as to when study documents no longer need to be retained.

18. PUBLICATION POLICY

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

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Signature Page for VV-CLIN-003013 v1.0

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Protocol 547-TRM-201, Amendment 1

Summary of Changes

Date of Amendment: 18 July 2023

An Open-Label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Brexanolone in the Treatment of Adult Participants with Tinnitus

Rationale for Protocol Amendment 1

Changes to the protocol include:

- Updated Inclusion Criterion #5 to increase the allowable duration of tinnitus diagnosis prior to Screening from <5 to <10 years (Synopsis, Section 8.1).
- Clarified schedule of assessments footnote a to state that clinic-based screening assessments must be reported by Day -8 (Table 2).
- Made minor editorial wording updates or clarifications to align with the protocol template (Synopsis, Section 8.1, Section 9.2.5, Section 12.2.7).
- Clarified that the infusion will be immediately stopped if pulse oximetry reveals hypoxia, specifically in the context of excessive sedation or sudden loss of consciousness (Synopsis, Section 7.1).
- Clarified that contact information in the event of a product complaint can be found in the Pharmacy Manual (Section 10.7).
- Updated Section 12.4 Overdose and added Section 12.5 Special Considerations with new language for “abuse” and “misuse” to align with the Regulation (EU) No 536/2014 Of the European Parliament and Of The Council (Section 12.4, Section 12.5).
- Moved language regarding medication errors from Section 10.7 to Section 12.5.

Administrative changes, including personnel updates, have also been made.

Protocol 547-TRM-201, Amendment 2

Summary of Changes

Date of Amendment: 13 October 2023

An Open-Label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Brexanolone in the Treatment of Adult Participants with Tinnitus

Protocol Amendment 2 reflects the following changes:

- The Sponsor Contact has changed from:

[redacted]
Phone: [redacted]
email: [redacted]

to:

[redacted]
Phone: [redacted]
email: [redacted]

- The Sponsor Medical Monitor and Study Physician have changed from:

[redacted], MD
[redacted]
Phone/text: [redacted]
email: [redacted]

to:

[redacted], MD
[redacted]
Phone/text: [redacted]
email: [redacted]

- The Sponsor Approval page was deleted to align with current Sage process and template.
- For clarity, editorial changes were made to a secondary endpoint (Section 6), the description of the Analysis Sets (Section 13.1), the description of the mixed effects model (Section 13.5) and corresponding sections of Section 2, Synopsis.
- Minor formatting changes