**Official Title:** **A Study of Brexanolone for Acute Respiratory Distress Syndrome due to COVID-19**

**NCT Number:** NCT04537806

**Document Date:** Protocol Version 5.0: 26 February 2021

# A STUDY OF BREXANOLONE FOR ACUTE RESPIRATORY DISTRESS SYNDROME DUE TO COVID-19

## PROTOCOL NUMBER: 547-ARD-301

| | |
|---|---|
| Investigational Product | Brexanolone |
| Clinical Phase | 3 |
| Sponsor | Sage Therapeutics, Inc.<br>215 First Street<br>Cambridge, MA 02142 |
| Sage Contact and Medical Monitor | [redacted] PhD<br>[redacted]<br>Phone: [redacted]<br>[redacted] |
| Date of Original Protocol | 07 April 2020; Version 1 |
| Date of Amendment 1 | 30 June 2020; Version 2 |
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| Date of Amendment 3 | 18 August 2020, Version 4 |
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# SPONSOR APPROVAL

| | |
|---|---|
| **Protocol Number:** | 547-ARD-301 |
| **Study Title:** | A Study of Brexanolone for Acute Respiratory Distress Syndrome Due to COVID-19 |
| **Protocol Version and Date:** | Version 5, 24 February 2021 |

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Signer Name: [redacted]
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Date

# INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for brexanolone. I have read the 547-ARD-301 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)

# CONTACT INFORMATION

**Table 1: Contact Information**

| Role in Study | Name | Address and Telephone Number |
|---|---|---|
| Sage Medical Monitor | [redacted], PhD | 215 First Street<br>Cambridge, MA 02142<br>Phone: [redacted]<br>email: [redacted] |
| | [redacted], MD | PrimeVigilance USA Inc.<br>100 Regency Forest Drive<br>Suite 160<br>Cary, NC 27518, USA<br>Phone: [redacted] |
| SAE Reporting | IQVIA Lifecycle Safety (LS) | 4820 Emperor Boulevard<br>Durham, NC 27703<br>e-mail: [redacted]<br>Fax: [redacted]<br>SAE Hotline: [redacted] |
| Product Complaint Contact | Sage Therapeutics | e-mail: [redacted]<br>Phone: [redacted] |

# 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), also known as allopregnanolone (scientific name)

**Title of Study:**
A Study of Brexanolone for Acute Respiratory Distress Syndrome Due to COVID-19

**Number of Sites and Study Location:** Up to 15 healthcare sites in the US

**Phase of Development:** 3

**Planned Duration for each Study Participant:**

The planned study period will be approximately 1 month. This includes up to 2 days for screening (Visit 1), a 60-hour treatment period (Visit 2 through Visit 6), and follow-up visits through Day 28 (Visit 11).

**Objectives and Endpoints**:

Primary Objective

- To evaluate the effect of brexanolone in participants on ventilator support for acute respiratory distress syndrome (ARDS) due to COVID-19

Secondary Objective

- To evaluate the safety of brexanolone in participants on ventilator support for ARDS due to COVID-19

[redacted]

Primary Endpoint

- Proportion of participants alive and free of respiratory failure at Day 28

Secondary Endpoint

- Incidence of treatment-emergent adverse events

- All-cause mortality through Day 28

[redacted]

- Change from baseline in vital signs, [redacted], clinical laboratory parameters, and 12-lead ECG

[redacted]

**Study Description**:

This is a randomized, double-blind, placebo-controlled study designed to evaluate treatment with brexanolone in approximately 100 participants with ARDS due to COVID-19. Participants and their family or caregivers, clinicians, site staff, and sponsor personnel will be masked to treatment allocation.

Patients with ARDS and SARS-CoV-2 infection who give informed consent (or for whom consent is given by a proxy) and who are currently intubated and receiving mechanical ventilation as part of standard of care for no longer than 48 hours before signing informed consent or who are on an immediate clinical plan to receive such intervention, will be eligible for screening. All participants must have mechanical ventilation in place prior to randomization, and randomization must occur within 48 hours of signing informed consent. Eligible participants will be stratified by age (<70 or ≥70 years) and randomized 1:1 within each stratum to receive either brexanolone plus standard of care or placebo plus standard of care.

Participants will receive continued standard of care in addition to a continuous intravenous (IV) infusion of brexanolone or placebo for 60 hours. The infusion must be initiated within 6 hours from the time of randomization. The blinded 60-hour infusion will be administered at a dose of 70 mcg/kg/h for 58 hours followed by a 2-hour taper at 35 mcg/kg/h. Transfer out of the ICU is not an indication to discontinue the infusion of investigational product (IP).

Because brexanolone is a $GABA_A$ receptor positive allosteric modulator, it is possible that the sedating properties of co-administered anesthetics may be potentiated in the presence of brexanolone. Thus, during brexanolone infusion, lower doses of co-administered sedative agents may achieve the same anesthetic effects. During IP infusion, if sedation levels are deeper than intended, the dose(s) of sedative anesthetics should be titrated to the desired effect rather than adjusting the dose of IP.

In the scenario that a participant is experiencing unplanned sedation/somnolence when no longer on any sedating agents, but still receiving blinded IP, the IP infusion may be stopped or the dose may be reduced to 35 mcg/kg/h until the symptoms resolve.

The IP infusion may also be stopped, or the dose may be reduced to 35 mcg/kg/h if the participant experiences an intolerable AE determined by the investigator to be related to IP.

If the infusion is stopped and symptoms resolve, the IP infusion may be resumed at the same or lower dose as clinically appropriate. Each time the decision is made to stop the IP infusion or reduce the dose for AEs, the Richmond Agitation Sedation Scale (RASS) will be administered and if RASS ≥ -3, the Confusion Assessment Method for the intensive care unit (CAM-ICU) will be administered as well.

In this study, reintubation events, delirium, unplanned sedation/somnolence, altered mental status, and sudden loss of consciousness will be recorded as adverse events of special interest (AESI) and should be reported in an expedited manner as outlined in Section 12.2.3.

Follow-up assessments will be conducted as summarized in Figure 1; limited assessments will be collected by phone if the participant has been discharged from inpatient care. All participants will have measures of pulmonary function assessed throughout the study. Unless the clinical condition of the participant dictates otherwise, ventilation guidelines for ARDS due to COVID-19 should be followed.

An independent data monitoring committee (DMC) will monitor the clinical data for safety and will meet at least monthly throughout the duration of the study. In order to perform their monitoring function, the DMC will have access to unblinded safety and efficacy data to ensure the safety of the participants in the study. The DMC will also review the results of the planned interim analysis and provide recommendations for continuing or stopping the study for safety and/or futility in accordance with the DMC charter.

**Number of Participants (planned):** Approximately 100 participants

**Eligibility Criteria:**

**Inclusion Criteria**

Each eligible participant must:

1. Be confirmed positive for SARS-CoV-2 infection as determined by polymerase chain reaction at screening or within 2 weeks prior to screening
2. Be aged 18 years or older
3. Be able to provide written informed consent, signed by participant or by proxy (legally acceptable representative)
4. Have a presumptive diagnosis of ARDS at screening and $PaO_2/FiO_2$ (PF ratio) <300 within 48 hours prior to randomization
5. Be intubated and receiving mechanical ventilation prior to randomization. Note that participants must have initiated mechanical ventilation within 48 hours prior to written informed consent, or have an immediate clinical plan for such intervention at time of written informed consent
6. Be likely to survive, in the opinion of the investigator, for at least 72 hours from the time of written informed consent

**Exclusion Criteria:**

Each eligible participant must not:

1. Be concurrently participating in another clinical study for an investigational product or device at screening
2. Be pregnant, based on a positive pregnancy test at screening
3. Be in fulminant hepatic failure at screening
4. Have end stage renal disease at screening
5. Have a known allergy to progesterone, allopregnanolone, or any excipients in the brexanolone injection

**Investigational Product Dosage and Mode of Administration:**

Brexanolone or placebo will be administered as a single, continuous, IV infusion for 60 hours at 70 mcg/kg/h for 58 hours followed by a 2-hour taper at 35 mcg/kg/h.

**Duration of Treatment:**

Each participant will receive a single IV infusion of brexanolone or placebo for 60 hours.

**Statistical Methods:**

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan, which will be finalized and approved prior to database lock for the planned interim analysis.

**General Considerations**

Unless otherwise specified in the statistical analysis plan, baseline is defined as the last measurement prior to the start of IP infusion.

Continuous variables will be summarized with n, mean, standard deviation, median, minimum and maximum, Q1, and Q3. Change from baseline values for continuous endpoints will be calculated at each time point and descriptively summarized as described above. For all categorical endpoints, summaries will include counts and percentages. Out of range safety endpoints may be categorized as low or high, where applicable.

**Analysis Sets**

The Randomized Set is defined as all randomized participants (based on treatment as randomized).

The Full Analysis Set is defined as all randomized participants who initiated IV infusion of brexanolone or placebo (based on treatment as randomized).

The Per Protocol (PP) Set is defined as all randomized participants (based on treatment as randomized) with no major protocol deviations. This is a subset of the Randomized Set.

The Safety Set will include all participants who initiated IV infusion of brexanolone or placebo (based on actual treatment received).

**Safety Analysis**

The incidence of treatment-emergent adverse events, changes from baseline in vital signs, [redacted], clinical laboratory evaluations, and 12-lead ECG will be summarized.

**Efficacy Analysis**

The primary endpoint of proportion of participants alive and free of respiratory failure at Day 28 will be summarized using a logistic regression, adjusting for age group. The odds ratio and difference in proportions will be estimated. The secondary endpoint of all-cause mortality through Day 28 will be analyzed using both the Kaplan-Meier method for time to death and the logistic regression model for the proportion of deaths. [redacted]

[redacted]

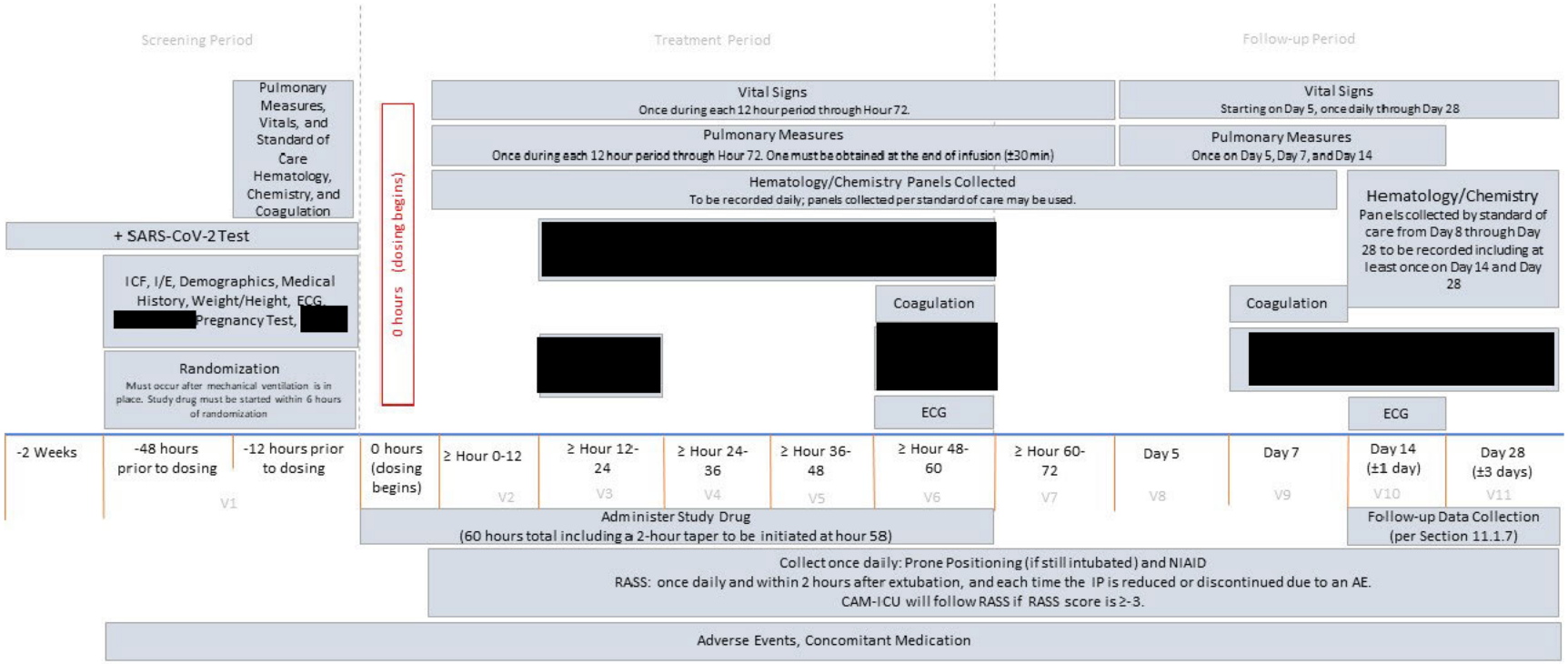
**Interim Analysis**

An interim analysis is planned when approximately 50% of the total planned number of participants have completed Day 28 (see Section 13.8.1.1).

**Sample Size**

The sample size of approximately 100 participants would provide 80% power to detect an absolute treatment difference of 27% in proportions of the primary endpoint of participants being alive and free of respiratory failure at Day 28, assuming the proportion is 50% for the placebo group and 77% for the brexanolone group.

**Figure 1: Schedule of Assessments**




NOTES:

[redacted]

- Following hospital discharge, only assessments that can be collected by phone should be conducted.
- For each 24-hour period of mechanical ventilation, the site will document whether prone positioning was conducted for at least 12 hours,
- For any AESI experienced during the infusion (Hour 0 through Hour 72), [redacted]

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

## TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES

# 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

| Abbreviation | Definition |
|---|---|
| AE | adverse event |
| AESI | adverse event of special interest |
| ARDS | acute respiratory distress syndrome |
| CAM-ICU | Confusion Assessment Method for the intensive care unit |
| CFR | Code of Federal Regulation |
| COVID-19 | A syndrome caused by infection with the SARS-CoV-2 virus |
| CRF | case report form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DMC | data monitoring committee |
| ECG | Electrocardiogram |
| ECMO | extracorporeal membrane oxygenation |
| ET | early termination |
| FDA | Food and Drug Administration |
| $FiO_2$ | fraction of inspired oxygen |
| GABA | gamma-aminobutyric acid |
| GCP | Good Clinical Practice |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ICU | Intensive care unit |
| IEC | Independent Ethics Committee |
| IP | investigational product |
| IRB | Institutional Review Board |
| IRT | interactive response technology |
| IV | Intravenous |
| LAR | legally authorized representative |
| [redacted] | [redacted] |
| MedDRA | Medical Dictionary for Regulatory Activities |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| $PaO_2$ | partial pressure of arterial oxygen |

| Abbreviation | Definition |
|---|---|
| [redacted] | [redacted] |
| PPD | postpartum depression |
| RASS | Richmond Agitation Sedation Scale |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SARS-CoV-2 | the novel coronavirus responsible for COVID-19 |
| [redacted] | [redacted] |
| SRSE | super-refractory status epilepticus |
| TEAE | treatment-emergent adverse event |

# 5. INTRODUCTION

Multiple approaches should be sought to mitigate the clinical and public health impact of COVID-19. While several approaches are being investigated with an aim to lower viral load and develop vaccines, an approach to improving respiratory function in COVID-19 patients with respiratory failure is urgently needed. Brexanolone (Zulresso™) is an FDA-approved intravenous (IV) infusion for the treatment of postpartum depression (PPD) in adults. Extensive safety experience in Intensive Care Unit (ICU) was gained during development of a separate indication for super-refractory status epilepticus (SRSE). Based on its unique pharmacology targeting multiple subtypes of $GABA_A$ receptors, brexanolone has the potential to attenuate the impact of COVID-19 in ventilated patients through multiple mechanisms of action. Preclinical evidence to date suggests that brexanolone is likely to have the following beneficial effects in the clinic: anti-inflammatory and fluid clearance effects via direct action on $GABA_A$ receptors located in human alveolar epithelial cells; anti-inflammatory and antiviral effects via inhibition of toll-like receptors and reduction in proinflammatory cytokines; and direct effects on pulmonary function through direct effects on smooth muscle in the lung, reducing shunting and improving partial pressure of arterial oxygen ($PaO_2$).

Severe forms of infection with SARS-CoV-2 produce significant impairment of respiratory function, including acute lung inflammation and acute respiratory distress syndrome (ARDS) (Wujtewicz 2020). Although epidemiological data are rapidly evolving, preliminary reports show that pulmonary impact severe enough to warrant critical care treatment is occurring in 3 to 6% of infected patients (CDC COVID-19 Response Team 2020; Wujtewicz 2020). Data from United Kingdom and from Seattle both suggest that of patients with COVID-19 in critical care, >75% require mechanical ventilation and up to approximately 50% do not survive (Bhatraju 2020; ICNARC 2020). The respiratory symptoms associated with morbidity are driven by factors including vasoconstriction, pulmonary edema, and inflammation secondary to cytokine activation. In addition to viral-induced respiratory trauma, ventilator support that is provided to address ARDS can also exacerbate lung damage and lead to a negative spiral that further contributes to morbidity and mortality.

Brexanolone is chemically identical to allopregnanolone, an endogenous member of a family of molecules known as neuroactive steroids. There is substantial literature suggesting that brexanolone could act to improve airway flow and overall lung function under pathological conditions, including those conditions associated with ARDS, namely an elevated inflammatory response and fluid accumulation in the lungs. Notably, a recent analysis of 323 hospitalized patients with COVID-19 found that patients receiving the $GABA_A$ receptor partial agonist zopiclone had significantly better survival. In critically ill patients in the study, the administration of zopiclone in addition to standard ventilator support was associated with a favorable clinical outcome in 67% of patients versus 13% of patients not on zopiclone (Hu 2020).

While approved for the treatment of PPD, brexanolone has been investigated for the treatment of several disorders, including SRSE. SRSE is status epilepticus that does not respond to standard treatments and which has a mortality rate of 30-40%. In the clinical development program for SRSE, the safety and tolerability of a 6-day continuous IV infusion of brexanolone with doses up to 150 mcg/kg/h was established in unconscious patients on mechanical ventilators in (neuro)critical care units. These patients had serious comorbidities, had been on mechanical

ventilation for several days to several weeks, and were receiving multiple concomitant medications including IV barbiturates, benzodiazepines, anticonvulsants, and general anesthetics. In the studies of patients with SRSE, no important risks or safety signals related to brexanolone infusion were observed and the safety profile was similar to placebo (ie, standard of care), supporting the potential for investigational use of brexanolone in patients with COVID-19-related ARDS.

In preclinical studies, IV-administered brexanolone distributed to all tissues, including lung, with a lung-to-plasma ratio of approximately 1.5 to 2.3. Other data showed good persistence in lung after systemic administration.

## 5.1. Dose Justification

The brexanolone dose regimen to be used in this study (70 mcg/kg/h for 58 hours followed by a 2-hour taper at 35 mcg/kg/h) was chosen for this patient population based on the following considerations:

- Acceptable safety and tolerability profile defined in pivotal nonclinical toxicology studies (see brexanolone Investigator's Brochure for additional details)
- Brexanolone is an endogenous compound that increases during pregnancy, culminating in plasma concentrations of approximately 150 nM at the end of the third trimester. These plasma concentrations are in a similar range as is predicted for an infusion of 70 mcg/kg/h of brexanolone.
- The dosing regimen approximates the total dose and duration approved for the treatment of postpartum depression
- The dosing regimen is intended to simplify dosing in intensive care units and to maintain steady-state plasma concentrations for the maximum amount of time over the course of the infusion in participants with ARDS due to COVID-19
- Participants will be already unconscious prior to or at start of the infusion; therefore, titration (intended to reduce the incidence of dizziness and somnolence in conscious patients) is not considered necessary
- Brexanolone is rapidly cleared; therefore, a short taper is incorporated to slow the decline in plasma concentrations during discontinuation

# 6. STUDY OBJECTIVES AND ENDPOINTS

## 6.1. Objectives

### 6.1.1. Primary Objective

- To evaluate the effect of brexanolone in participants on ventilator support for ARDS due to COVID-19

### 6.1.2. Secondary Objective

- To evaluate the safety of brexanolone in participants on ventilator support for ARDS due to COVID-19

[redacted]

## 6.2. Endpoints

### 6.2.1. Primary Endpoint

- Proportion of participants alive and free of respiratory failure at Day 28

### 6.2.2. Secondary Endpoint

- Incidence of treatment-emergent AEs
- All-cause mortality through Day 28

[redacted]

- [redacted]
- [redacted]
- Change from baseline in vital signs, [redacted], clinical laboratory parameters and 12-lead ECG
- [redacted]
- [redacted]

# 7. INVESTIGATIONAL PLAN

## 7.1. Overall Study Design

This is a randomized, double-blind, placebo-controlled study designed to evaluate treatment with brexanolone in approximately 100 participants with ARDS due to COVID-19. Participants and their family or caregivers, clinicians, site staff, and sponsor personnel will be masked to treatment allocation.

Patients with ARDS and SARS-CoV-2 infection who give informed consent (or for whom consent is given by a proxy) and who are currently intubated and receiving mechanical ventilation as part of standard of care for no longer than 48 hours before signing written informed consent or who are on an immediate clinical plan to receive such intervention will be eligible for screening. All participants must have mechanical ventilation in place prior to randomization, and randomization must occur within 48 hours of signing informed consent. Eligible participants will be stratified by age (<70 or ≥70 years) and randomized 1:1 within each stratum to receive either brexanolone plus standard of care or placebo plus standard of care.

Participants will receive continued standard of care in addition to a continuous IV infusion of brexanolone or placebo for 60 hours. The infusion must be initiated within 6 hours from the time of randomization. The blinded 60-hour infusion will be administered at a dose of 70 mcg/kg/h for 58 hours followed by a 2-hour taper at 35 mcg/kg/h. Transfer out of the ICU is not an indication to discontinue the infusion of IP.

Brexanolone may potentiate the sedative effects of co-administered anesthetics. During IP infusion, if sedation levels are deeper than intended, the dose(s) of sedative anesthetics should be titrated to the desired effect rather than adjusting the dose of IP (see Section 7.4 for additional details).

Dose adjustment is permitted in the event that a participant is experiencing unplanned sedation/somnolence when no longer on any sedating agents or if the participant experiences an intolerable AE determined by the investigator to be related to IP. Details regarding dose adjustment criteria and procedures are provided in Section 7.4.

Follow-up assessments will be conducted as summarized in Figure 1; limited assessments will be collected by phone if the participant has been discharged from inpatient care. All participants will have measures of pulmonary function assessed throughout the study. Unless the clinical condition of the participant dictates otherwise, the ventilation guidelines for ARDS due to COVID-19 should be followed.

An independent data monitoring committee (DMC) will monitor the clinical data for safety and will meet at least monthly throughout the duration of the study. In order to perform their monitoring function, the DMC will have access to unblinded safety and efficacy data to ensure the safety of the participants in the study. The DMC will also review the results of the planned interim analysis and provide recommendations for continuing or stopping the study for safety and/or futility in accordance with the DMC charter. Refer to Section 7.4.1 and Section 13.8.1.2 for additional details.

## 7.2. Number of Participants

Approximately 100 participants may participate.

## 7.3. Treatment Assignment

Eligible participants will be stratified by age (<70 or ≥70 years) and randomized 1:1 to receive either brexanolone plus standard of care or placebo plus standard of care. See Section 10.5 for details regarding IP administration. Additional details on randomization and blinding are provided in Section 9.5.

## 7.4. Dose Adjustment Criteria

Because brexanolone is a $GABA_A$ receptor positive allosteric modulator, it is possible that the sedating properties of co-administered anesthetics may be potentiated in the presence of brexanolone. Thus, during brexanolone infusion, lower doses of co-administered sedative agents may achieve the same anesthetic effects. During IP infusion, if sedation levels are deeper than intended, the dose(s) of sedative anesthetics should be titrated to the desired effect rather than adjusting the dose of IP.

After the anesthetic agents are stopped, patients will remain sedated for varying amounts of time as the anesthetic agents wash out of lipid tissues. Additionally, in patients who are candidates for extubation, it is common to continue mild sedation using drugs that do not affect respiratory drive (eg, dexmedetomidine) after discontinuing the anesthetic agent(s), in order to facilitate a spontaneous breathing trial.

In the scenario that a participant is experiencing unplanned sedation/somnolence when no longer on any sedating agents, but still receiving blinded IP, the IP infusion may be stopped or the dose may be reduced to 35 mcg/kg/h until the symptoms resolve.

The IP infusion may also be stopped or the dose may be reduced to 35 mcg/kg/h if the participant experiences an intolerable AE determined by the investigator to be related to IP.

If the infusion is stopped and symptoms resolve, the IP infusion may be resumed at the same or lower dose as clinically appropriate. Each time the decision is made to stop the IP infusion or reduce the dose for AEs, the Richmond Agitation Sedation Scale (RASS) will be administered, and if RASS ≥-3, the Confusion Assessment Method for the intensive care unit (CAM-ICU) will be administered as well (see Section 12.1.7).

### 7.4.1. Data Monitoring Committee

The DMC will review available unblinded safety data regularly (at least every month). The DMC will also have access to unblinded efficacy data as necessary. Refer to Section 13.8.1.2 for additional details. The DMC will be comprised of experienced members and will apply medical and statistical judgment during the performance of their activities according to a DMC charter.

The DMC will be provided with all SAEs (including fatalities) and AESIs on an ongoing basis.

### 7.4.2. Safety Criteria for Adjustment or Stopping Doses

Enrollment in the study will be discontinued if the DMC determines that any of the following criteria have been met:

1. there is an increased risk of mortality due to brexanolone
2. there is an increased risk of ICU delirium due to brexanolone
3. there is an increased risk of prolonged intubation due to brexanolone
4. there is an increased risk of reintubation due to brexanolone

After each data review, the DMC may recommend that the study continue without modifications, continue with modifications, or be terminated, or that study treatment or enrollment is suspended. The DMC may also recommend stopping the study for futility at the time of interim analysis.

## 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 SAEs 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 IRB/independent ethics committee (IEC), where required, and initiate withdrawal procedures for participants.

# 8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

Eligible participants must fulfill all inclusion criteria and none of the exclusion criteria. Results from standard of care assessments may be used for screening if they occur within the time windows specified in Figure 1.

## 8.1. Participant Inclusion Criteria

Each eligible participant must:

1. Be confirmed positive for SARS-CoV-2 infection as determined by polymerase chain reaction at screening or within 2 weeks prior to screening
2. Be aged 18 years or older
3. Be able to provide written informed consent, signed by participant or by proxy (legally acceptable representative)
4. Have a presumptive diagnosis of ARDS at screening and $PaO_2/FiO_2$ (PF ratio) <300 within 48 hours prior to randomization
5. Be intubated and receiving mechanical ventilation prior to randomization. Note that participants must have initiated mechanical ventilation within 48 hours prior to written informed consent, or have an immediate clinical plan for such intervention at time of written informed consent
6. Be likely to survive, in the opinion of the investigator, for at least 72 hours from the time of written informed consent

## 8.2. Participant Exclusion Criteria

Each eligible participant must not:

1. Be concurrently participating in another clinical study for an investigational product or device at screening
2. Be pregnant, based on a positive pregnancy test at screening
3. Be in fulminant hepatic failure at screening
4. Have end stage renal disease at screening
5. Have a known allergy to progesterone, allopregnanolone, or any excipients in the brexanolone injection

## 8.3. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) 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 their own request (or by proxy/legally authorized representative [LAR]) for any reason. The investigator may discontinue a participant from IP for safety, behavioral, compliance, or administrative reasons, however, participants will remain in the study unless they withdraw consent.

The reason for IP discontinuation and/or the reason for early termination from the study must be documented in the participant's study record and recorded in the participant's case report form (CRF).

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

### 8.4.1. Investigational Product Discontinuation

If it is necessary to discontinue the IP earlier than planned and consent is not withdrawn, participants will remain in the study and be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The reason for IP discontinuation must be documented in the participant's study record and recorded in the appropriate CRF.

### 8.4.2. Early Termination from the Study

At the time of early study termination/stopping study participation, if possible, an early termination visit should be conducted. The participant will be permanently discontinued both from the IP and from the study 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.

### 8.4.3. Loss to Follow-up

A participant will be deemed lost to follow-up after 3 attempts at contacting the participant have been unsuccessful.

### 8.4.4. Replacement of Participants

Participants will not be replaced.

# 9. TREATMENT OF PARTICIPANTS

## 9.1. Description of Investigational Product

Brexanolone is a sterile, clear, colorless solution that must be diluted prior to administration as an IV infusion. Placebo will be identical to brexanolone without the active ingredient. In this study, brexanolone or placebo will be administered as a single, continuous, IV infusion for 60 hours. Additional details on IP administration are in Section 10.5 and additional IP description details can be found in Section 10 and in the brexanolone IB.

## 9.2. Prior Medications, Concomitant Medications and Restrictions

### 9.2.1. Prior and Concomitant Medications and/or Supplements

Participants should receive standard of care treatment for ARDS due to COVID-19, and any concomitant medication deemed medically necessary for the welfare of the participant may be given at the discretion of the investigator at any time during the study. All concomitant medications, including central nervous system (CNS) depressants, agents employed to sedate participants and drugs administered to treat or prevent ICU delirium, administered from the time of informed consent through the end of the study should be recorded on the appropriate CRF. Details such as the start and stop dates and times, dose, and indication will be recorded.

As noted in Section 7.4, brexanolone may potentiate the sedative effects of anesthetic drugs such as propofol and midazolam; the doses of these drugs should be titrated to the desired level of sedation during the infusion of brexanolone. Any change to dose(s) of sedative drugs, CNS depressants, and drugs administered to treat or prevent ICU delirium, in addition to the date and time of each dosage change, will be recorded throughout the duration of the study.

Brexanolone contains betadex sulfobutyl ether sodium (SBECD) as a solubilizer. SBECD relies on renal clearance for elimination and may accumulate in participants with decreased renal function. Total daily dose of SBECD should be taken into consideration when other agents containing SBECD (including certain antifungals and antivirals, including remdesivir) are coadministered with IP.

### 9.2.2. Prohibited Medications

Not applicable

### 9.2.3. Other Restrictions

Participants may not participate in another clinical trial for an investigational product or device through the end of the study.

Phenytoin or propofol may not be coadministered with IP in the same line. For other IV medications, infusion may occur via a port system, with separate ports for each infusion to avoid mixing medications in the long lines from the bags.

## 9.3. Intervention after the End of the Study

Not applicable

## 9.4. Treatment Adherence

IP will be administered to participants 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 nonadherence 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 a randomized, double-blind, placebo-controlled study. Participants and their family or caregivers, clinicians, site staff, and sponsor personnel will be blinded to treatment allocation. An independent DMC (see Section 13.8.1) will have access to unblinded safety data monthly and efficacy data as necessary. Participants who meet the eligibility criteria will be randomized in a stratified manner based on age (<70 or ≥70 years). Participants will be randomized 1:1 within each stratum to receive brexanolone plus standard of care or placebo plus standard of care. Randomization will be performed centrally via an interactive response technology (IRT) system. Randomization schedules will be generated by an independent statistician. The allocation to treatment group will be based on the randomization schedule. The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding. The blinding of the study will be broken after the database has been locked.

Randomization must occur within 48 hours of written informed consent.

### 9.5.1. Emergency Unblinding

During the study, the blind is to be broken only when the safety of a participant is at risk and the treatment plan is dependent on the study treatment received. Unless a participant is at immediate risk, the investigator should make attempts to contact Sage prior to unblinding the study treatment administered to a participant. Requests from the investigator about the treatment administered to study participants should be discussed with the Sage medical monitor. If the unblinding occurs without Sage's knowledge, the investigator must notify Sage within 24 hours of breaking the blind. All circumstances surrounding a premature unblinding must be clearly documented in the source records.

In all cases where the IP allocation for a participant is unblinded (such as for SUSARs), pertinent information (including the reason for unblinding) must be documented in the participant's records and on the CRF.

# 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 (SBECD) as 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.

Placebo will be identical to brexanolone and provided in identical vials. Placebo will be manufactured in a similar way to brexanolone and will consist of the same formulation without the active ingredient.

## 10.2. Investigational Product Packaging and Labeling

Brexanolone and placebo will be provided to the sites.

The IP is sterile-filtered and aseptically filled into 20 mL clear glass vials with a stopper container closure system. IP is intended to be used as a single-use vial.

Blinded IP labels with all required information and conforming to all applicable FDA Code of Federal Regulations and Good Manufacturing Practices/Good Clinical Practices 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

IP vials should be stored under refrigerated conditions (2 to 8°C) and suitably protected from light. 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.

Additional information regarding IP storage is provided in the brexanolone Investigator's Brochure.

## 10.4. Investigational Product Preparation

The pharmacist or designee will be responsible for preparing IP for 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

IP will be administered as a single, continuous, IV infusion for 60 hours. Initiation of the infusion must occur within 6 hours of randomization.

The specific infusion dose of IP will be calculated based on weight (obtained at screening) for each participant and will be administered as a single continuous IV infusion for 60 hours at 70 mcg/kg/h for 58 hours followed by a 2-hour taper at 35 mcg/kg/h. Placebo infusion rates will be matched to the brexanolone infusion rates.

Transfer out of the ICU is not an indication to discontinue the infusion of IP. The IP infusion may be stopped or the dose reduced due to an AE as described in Section 7.4.

## 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. 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 AND CLINICAL PHARMACOLOGY ASSESSMENTS

## 11.1. Efficacy Assessments

The primary endpoint is the proportion of participants alive and free of respiratory failure at Day 28. Respiratory failure is defined based on resource utilization, requiring at least one of the following:

- Endotracheal intubation and mechanical ventilation
- Oxygen delivered by high-flow nasal cannula (heated, humidified oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ≥0.5)
- Noninvasive positive pressure ventilation
- Extracorporeal membrane oxygenation (ECMO)

The data relating to this endpoint is collected as described in Section 11.1.7 below.

[redacted]

[redacted]

### 11.1.6. Prone Positioning

Prone positioning is recommended in guidelines for the management of severe ARDS (Howell and Davis 2018). For each 24-hour period of mechanical ventilation, the site will document whether prone positioning was conducted for at least 12 hours, and if not, the reason will be documented.

### 11.1.7. Data Collection at Follow-Up

As applicable, the following will be documented during the follow-up visit(s):

- Dates and times of extubation and discontinuation of mechanical ventilation
    - The duration of time on mechanical ventilation will be calculated

[redacted]

- Dates and times of reintubation and re-initiation of mechanical ventilation
- Whether or not the participant requires oxygen delivered by high-flow nasal cannula (heated, humidified oxygen delivered via reinforced nasal cannula at flow rates >20L/min with fraction of delivered oxygen ≥0.5), and if so the date and time of initiation of oxygen delivery by high-flow nasal cannula
- Whether or not the participant requires noninvasive positive pressure ventilation and if so, the date and time of initiation of noninvasive positive pressure ventilation
- Whether or not the participant progressed to ECMO, and if so, the date and time of initiation and (as applicable) completion of ECMO

[redacted]

- Whether or not the participant progressed to tracheostomy, and if so, the date and time of the tracheostomy procedure
- Whether or not the participant died, and if so, the date, time, and cause of death

[redacted]

[redacted]

# 12. SAFETY ASSESSMENTS

## 12.1. Safety Parameters

All safety assessments will be conducted according to the Schedule of Assessments (Figure 1).

Abnormalities in vital signs, ECGs, and out of range values in laboratory test results will be interpreted by an investigator as abnormal, not clinically significant or abnormal, clinically significant in the source documents.

### 12.1.1. Demography and Medical History

Demographic characteristics (age, race, sex, ethnicity) and brief medical history will be documented.

Disease-specific medical history including onset date of COVID-19 symptoms will be documented as well as the date of admission to the ICU, date of diagnosis of ARDS, severity of ARDS at screening (per Berlin Criteria; ARDS Definition Task Force), date and time of initial intubation, and the date and time of initiation of mechanical ventilation. Note that the results of the imaging diagnostic test conducted per Berlin Criteria may be obtained from the participant's medical record after screening if necessary.

Lifetime history of COVID-19 vaccination, including dates of administration and manufacturer, will be recorded as part of the participant's disease-specific medical history.

### 12.1.2. Weight and Height

Height and weight will be documented in the CRF.

### 12.1.3. Vital Signs

Vital signs include systolic and diastolic blood pressure, heart rate, temperature, and respiratory rate (if not on mechanical ventilation) and are to be recorded for the times specified in Figure 1. Systolic and diastolic blood pressure and heart rate are to be collected supine or prone. Respiratory rate and temperature are collected once in any position.

Additionally, respiratory rate, heart rate, and blood pressure should be recorded for any participant who experiences an AESI (defined in Section 12.2.3) as soon as is feasible after the onset of the event and recorded as unscheduled on the CRF.

[redacted]

### 12.1.5. Electrocardiogram

A 12-lead ECG will be recorded at all scheduled time points. The standard intervals (heart rate, PR, QRS, QT, and QTcF) as well as any rhythm abnormalities will be recorded. Brief descriptive text should be included if the trace morphology is abnormal.

### 12.1.6. Laboratory Assessments

Hematology, clinical chemistry, and coagulation panels collected are to be recorded at the timepoints specified in Figure 1 and as noted below.

#### 12.1.6.1. Screening

Standard of care hematology, clinical chemistry, and coagulation panels are to be collected within 12 hours prior to initiating IP.

#### 12.1.6.2. Visit 2 (Hour 0) through Visit 9 (Day 7)

Hematology and clinical chemistry panels are to be recorded daily; panels collected per standard of care may be used. Additionally, coagulation parameters should be recorded at the time points indicated in Figure 1.

#### 12.1.6.3. After Visit 9 (Day 8 through Day 28)

Hematology and clinical chemistry panels are to be recorded on Day 14 and Day 28; panels collected per standard of care may be used. Additional hematology and clinical chemistry panels collected per standard of care between Day 8 and Day 28 should also be recorded.

#### 12.1.6.4. Pregnancy Screen

A serum or urine pregnancy test will be conducted for all female participants at screening.

### 12.1.7. Richmond Agitation Sedation Scale

The RASS is a tool validated to assess sedation and agitation in ICU patients (Sessler 2002). RASS is a 10-point scale, with 4 levels of anxiety or agitation (+1 to +4 [combative]), one level to denote a calm and alert state (0), and 5 levels of sedation (-1 to -5) culminating in unarousable (-5).

The RASS will be administered once daily at the scheduled time points. In addition, the RASS will be administered within 2 hours after extubation. The RASS will also be administered each time the decision is made to stop the IP infusion or reduce the dose (see Section 7.4).

### 12.1.8. Confusion Assessment Method for the Intensive Care Unit

The CAM-ICU score is a validated score to assess delirium in mechanically ventilated patients using standardized nonverbal assessments (Ely 2001).

The CAM-ICU will be administered every time RASS is assessed if RASS score ≥-3.

## 12.2. Adverse and Serious Adverse Events

Nonserious AEs will be collected per the procedure described in Section 12.2.1. AESIs will be collected per the procedures described in Section 12.2.3.

SAEs will be collected per the procedures described in Section 12.2.2 and Section 12.2.6.

### 12.2.1. Adverse Event Definition

An 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 TEAE is defined as an adverse event 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 trial.

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 an 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).

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 CRF. The sponsor or its representative retains the right to request additional information for any participant with ongoing AE(s)/SAE(s)/AESIs 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).

Except as noted in Section 12.2.6 and below, all SAEs that occur from the time of consent and throughout the duration of the study, whether or not they are related to IP, must be recorded on the SAE reporting form provided by Sage Therapeutics, unless the event appears in the list of common ICU comorbidities (Table 3). If the event is included on the list, refer to the procedures described in Section 12.2.6. 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.

### 12.2.3. Definition of Adverse Events of Special Interest (AESI)

An AESI is an AE/SAE of scientific and/or medical concern, specific to the product or program for which ongoing monitoring and rapid communication by the Investigator to the sponsor is required. Such AEs normally require thorough documentation and investigation in order to characterize them.

The following events are considered AESIs in this study:

- reintubation events
- delirium
- unplanned sedation/somnolence
- altered mental status
- sudden loss of consciousness

Such events should be reported on the AESI form to Sage or designee within 72 hours. If the AESI also qualifies as an SAE, an SAE form should be submitted per the guidelines per Section 12.2.6.

The investigator should provide additional details on the AESI form for the following AESIs as specified below:

- for reintubation events, include the reason for reintubation
- for delirium, document whether the participant had regained an appropriate state of orientation at some point after being extubated prior to onset of delirium

[redacted]

### 12.2.4. Relationship to Investigational Product

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

For AESIs deemed "not related" to IP, the suspected cause of the event should be recorded on the AESI form.

### 12.2.5. Recording Adverse Events

Adverse events spontaneously reported by the participant and/or in response to an open question from the study personnel or observed 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 and resolution (date and time), intensity, causality, seriousness criterion(ia), action taken, and outcome (if applicable), and whether the AE resulted in IP dose reduction, discontinuation of the IP or withdrawal from the study.

Intensity will be assessed according to the guidelines for the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The CTCAE provides a grading (severity) scale for AEs, with unique clinical descriptions of severity based on the general guidance listed below:

**Table 2: Common Terminology Criteria for Adverse Events**

| Grade | Criteria |
|---|---|
| 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| 2 | Moderate; minimal, local, or noninvasive intervention such as packing or cautery indicated, limiting age-appropriate instrumental activities of daily living (ADL) |
| 3 | Severe; or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL |

| Grade | Criteria |
|---|---|
| 4 | Life-threatening consequences; urgent indications indicated |
| 5 | Death related to adverse event |

It is important to distinguish between seriousness and severity. 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.

### 12.2.6. Reporting Serious Adverse Events

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

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

SAEs occurring after the designated follow-up time for the study, should be reported to Sage or 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.

**Exceptions to the Standard SAE Reporting Requirements**

Unless otherwise noted below, if the event is included in Table 3, an SAE reporting form does not need to be completed, but the event should be recorded on the CRF. The following exceptions apply:

- Please Note: If the event is on the list and if the event was considered by the investigator to be related to IP then the SAE reporting form will be completed, and the SAE will be reported to Sage per standard SAE reporting requirements. The SAE form for such an event has to be sent to Sage or designee within 24 hours of the site becoming aware of the SAE.
- Please Note: If the event is on the list, but the outcome is fatal, the mortality CRF will be completed, the SAE reporting form will be completed, and the SAE will be reported to Sage per standard SAE reporting requirements. The SAE form for such an event has to be sent to Sage or designee within 24 hours of the site becoming aware of the SAE. The mortality CRF will capture the actual cause of death as well as the category of the cause of death.

**Table 3: List of Common ICU Comorbidities**

| **Complications of Mechanical Ventilatory Support** | **Infectious Complications** |
|---|---|
| Pulmonary barotrauma / pneumothorax | Skin and soft tissue infection |
| Ventilator associated pneumonia | Sepsis or bacteremia |
| **Cardiac and Vascular Events** | Septic shock |
| Tachyarrhythmias such as: | Pneumonia |
| Atrial fibrillation | Urinary tract infection or urosepsis |
| Ventricular tachycardia | Catheter site infections |
| Ventricular fibrillation | **Gastrointestinal** |
| Pulmonary embolism | Esophageal, gastric or duodenal ulcer |
| Thromboembolic event (other than pulmonary) | Gastrointestinal bleeding |
| Myocardial infarction | **Other** |
| Stroke / cerebrovascular accident | Acute renal failure |
| Hypotension | Complications of procedures |

## 12.3. Pregnancy

If a participant becomes pregnant after initiating IP, pregnancy information must be collected and recorded on the pregnancy form and submitted to the sponsor 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 participant 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 and the neonate, and the information will be forwarded to Sage or designee. 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

An overdose will be considered to have occurred if the infusion rate exceeds the recommended rate by 10% at any point during the infusion and/or the total dose administered exceeds 10% of the protocol-defined total dose. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and sent to Sage or designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Sage or designee even if the overdose does not result in an AE.

# 13. STATISTICS

Detailed description of the interim and final analyses to be performed in the study will be provided in the statistical analysis plan (SAP). To avoid a potentially biased estimate of the event rate in each arm at the time of the interim analysis, both the interim analyses and final analysis will incorporate all available data from all participants in the study in the analysis population, regardless of whether participants have reached Day 28. The SAP will be finalized and approved prior to database lock of the interim analysis. Any changes/additions to the SAP following database lock will be described in detail in the clinical study report.

## 13.1. Data Analysis Sets

The Randomized Set is defined as all randomized participants (based on treatment as randomized).

The Full Analysis Set is defined as all randomized participants who initiated IV infusion of brexanolone or placebo (based on treatment as randomized).

Per Protocol (PP) Set is defined as all randomized participants (based on treatment as randomized) with no major protocol deviations. This is a subset of the Randomized Set.

The Safety Set will include all participants who initiated IV infusion of brexanolone or placebo (based on actual treatment received).

## 13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All participants, including those with missing data, will be used in the analyses, as per the analysis sets defined in Section 13.1. The primary analysis method will use all nonmissing data available. In addition, tipping-point analyses will be conducted as sensitivity analyses to assess the impact of 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 data listing, some may be presented with a corresponding table or figure; these will be indicated in relevant sections below. Unless otherwise specified in the SAP, baseline is defined as the last measurement prior to the start of IP infusion.

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

## 13.4. Demographics and Baseline Characteristics

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

Medical history will be listed by participant.

### 13.5. Efficacy Analysis

The primary endpoint of proportion of participants alive and free of respiratory failure at Day 28 will be summarized using a logistic regression, adjusting for age group. The odds ratio and difference in proportions will be estimated. The secondary endpoint of all-cause mortality through Day 28 will be analyzed using both the Kaplan-Meier method for time to death and the logistic regression model for the proportion of deaths. [redacted] All efficacy summaries will be performed on the Full Analysis Set. In addition, if over 5% of randomized participants do not receive IP, a sensitivity analysis of the primary endpoint will be conducted on the Randomized Set.

## 13.6. Safety Analyses

Safety and tolerability of brexanolone will be evaluated by the incidence of treatment-emergent AEs, changes from baseline in vital signs, [redacted], clinical laboratory evaluations, and 12-lead ECG. Safety data will be listed by participant and summarized by treatment. All safety summaries will be performed on the Safety Set.

### 13.6.1. Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher. A treatment-emergent adverse event (TEAE) is defined as an AE with onset after the start of IP. The analysis of AEs will be based on the concept of TEAEs. The incidence of TEAEs will be summarized by System Organ Class and preferred term. In addition, summaries will be provided for TEAEs Grade 3 and above per CTCAE guidelines and by causality (related, not related) to IP.

Any TEAEs leading to IP discontinuation, dose reduction, or study withdrawal and any treatment-emergent SAEs and AESIs will be summarized.

All AEs, SAEs, and AESIs (including those with onset or worsening before the start of IP) through the end of the study will be listed.

### 13.6.2. Clinical Laboratory Evaluations

Laboratory parameters in Table 4 will be summarized in standard units and mean changes from baseline will be presented.

**Table 4: Summary of Clinical Laboratory Analytes**

| | |
|---|---|
| **Biochemistry** | *Renal Panel*: glucose, calcium, phosphorus, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate<br>*Hepatic Panel*: albumin, alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, total protein, lactate dehydrogenase, gamma glutamyl transferase, c-reactive protein |
| **Hematology** | red blood cell count, hemoglobin, hematocrit, white blood cell count with differential, platelet count, erythrocyte sedimentation rate |
| **Coagulation** | Activated partial thromboplastin time and prothrombin time |

Normal ranges for each parameter in Table 4 will be provided by the laboratory; shift from baseline to postbaseline values and 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. 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.

### 13.6.4. 12-Lead Electrocardiogram

Mean ECG data will be summarized by visit. Electrocardiogram findings will be listed by participant and timing of collection.

[redacted]

### 13.6.6. Prior and Concomitant Medications

Medications will be recorded at each study visit during the study and may be coded using World Health Organization-Drug dictionary Global B3 March 2020, or later.

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

Data summarized for the following classes of medications will include the dose, duration, total dose over the hospitalized study period, and indication for use:

- CNS depressants (eg, benzodiazepines, opioids/opiates, barbiturates, propofol)

- other agents utilized for sedation effects (eg, dexmedetomidine)
- drugs administered to treat or prevent ICU delirium (eg, antipsychotics, atypical antipsychotics, or other agents intended for delirium treatment)

[redacted]

## 13.8. Sample Size and Power

The sample size of approximately 100 participants would provide 80% power to detect a treatment difference of 27% in proportions of the primary endpoint of participants being alive and free of respiratory failure at Day 28, assuming the proportion is 50% for the placebo group and 77% for the brexanolone group.

### 13.8.1. Interim and Data Monitoring Committee Analyses

#### 13.8.1.1. Interim Analysis

An interim analysis is planned when about 50% of the total planned number of participants have completed Day 28. This will include summary statistics on the primary endpoint, conducted by a statistical group independent of Sage. The interim data, including safety data will be reviewed by the DMC to evaluate the possibility of stopping the study for futility or safety. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study.

Upon review of data collected at Day 28 for 25 participants in each arm (50 participants total), the statistical rules are:

- **to stop the study for safety** if the difference in the observed mortality rate is more than 4% greater in the brexanolone arm compared to placebo.
- **to stop the study for futility** if the observed difference in the response rates of the primary endpoint (brexanolone response rate – control response rate) is less than 4%.

The aim of the stopping rule for safety is to ensure that there is a reasonably high probability of stopping the study when there is a true underlying excess risk of mortality with the use of IP, and a reasonably low probability of stopping the study when there is no such risk.

The aim of the stopping rule for futility is to ensure that there is a reasonably high probability of stopping the study when IP is ineffective, and a reasonably low probability of stopping the study when IP is efficacious.

[redacted]

To avoid potentially biased estimates of the event rate in each arm at the time of the interim analysis, all available data for the selected variables will be incorporated from all participants in the analysis population, regardless of whether participants have reached Day 28.

A detailed description of the interim analysis is included in the SAP.

#### 13.8.1.2. Data Monitoring Committee Analysis

An independent DMC will monitor the clinical data for safety and will meet at least monthly throughout the duration of the study. The DMC will provide recommendations for continuing or stopping the study for safety in accordance with the DMC charter. Stopping criteria are presented in Section 7.4.2 and Section 13.8.1.1.

In order to perform their monitoring function, the DMC will have access to unblinded safety data to ensure the safety of the participants in the study. Efficacy data will also be delivered to the DMC as needed to perform their functions. The DMC will also review the results of the planned interim analysis (see Section 13.8.1.1).

Only descriptive analysis will be performed (ie, no statistical hypothesis testing will be performed). All analyses will be performed by a designated clinical research organization independent of Sage.

# 14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

## 14.1. Study Monitoring

During the COVID-19 pandemic, travel and site visit restrictions are in place to protect the safety of participants, staff, and to minimize the spread of disease. While these COVID-19 restrictions are in place, oversight of the study sites will comprise phone calls and information provided by sites to Sage, as appropriate. Once the travel and site visit restrictions are lifted, Sage or a Sage representative may conduct in-person site visits, as appropriate.

Before an investigational site can enter a participant into the study, a representative of Sage Therapeutics may visit or otherwise contact the investigational study site to:

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

During the study, a monitor from Sage Therapeutics 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 case report forms, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms 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, clinic charts).
- Record and report any protocol deviations not previously sent to Sage Therapeutics
- Confirm AEs have been properly documented on CRFs and confirm any AESIs and SAEs have been forwarded to Sage Therapeutics as specified in Section 12.2.3 and Section 12.2.6, respectively, 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 IEC or an IRB 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 (GCP) 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. Significant protocol deviations 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 trial-related duties and functions conducted at the trial site. When the investigator retains the services of any individual or party to perform trial-related duties and functions, the investigator must ensure the individual or party is qualified to perform trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed, and any data generated.

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial 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 ICF, 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 trial 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 trial participant, the investigator(s) will ensure that the participant and/or the legally authorized representative is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Participants and/or their representatives must also be notified that they are free to discontinue from the study at any time. The participant and/or their representative should be given the opportunity to ask questions and allowed time to consider the information provided.

When the participant decides to participate in the trial, the participant (or the participant's LAR) 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 records. 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 LAR.

Participants may be unable to give consent. Therefore, consent will be given by proxy by a LAR. Should a participant gain the ability to sufficiently comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required

or recommended by the institution's IRB. The form of consent to be obtained will depend on the condition of the participant as determined by the principal investigator.

Throughout the trial, 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.

# 17. DATA HANDLING AND RECORDKEEPING

## 17.1. Inspection of Records

Sage Therapeutics or its representative(s) will be allowed to conduct site visits at the investigation facilities for the purpose of monitoring any aspect of the study (Section 14.1). The investigator agrees to allow the monitor to inspect the facility, drug storage area, drug accountability records, participant charts 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 IP. 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.

# 19. LIST OF REFERENCES

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