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

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STATISTICAL ANALYSIS PLAN
METHODS
PROTOCOL NUMBER 547-ARD-301

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

Author of SAP: [redacted]

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

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1. LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this Statistical Analysis Plan.

Table 1: Abbreviations and Specialist Terms

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
COVID-19	a syndrome caused by infection with the SARS-CoV-2 virus
CRF	case report form
DMC	data monitoring committee
ECG	Electrocardiogram
ET	early termination
eCRF	electronic case report form
FAS	full analysis set
FiO2	fraction of inspired oxygen
IP	investigational product
ICU	intensive care unit
IRT	interactive response technology
IV	Intravenous
LSM	least squares means
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PaO2	partial pressure of arterial oxygen
[redacted]	[redacted]
[redacted]	[redacted]
PP	per protocol
PCS	potentially clinically significant
PCSC	potentially clinically significant change
RASS	Richmond Agitation Sedation Scale
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Definition
SARS-CoV-2	the novel coronavirus responsible for COVID-19
[redacted]	[redacted]
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event

2. INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analyses and data presentations for the final analysis of the 547-ARD-301 study and is based on the study protocol, version 5.0, dated 24 February 2021. This study is being terminated early due to Sponsor decision, not for safety reasons. Please see Section 6.1 for additional details.

All analyses and data presentations will be generated using SAS® Version 9.4 or higher Software (SAS Institute, Cary, North Carolina, USA). This SAP will be finalized and approved before the clinical database lock for the planned final analysis. Any changes made to the SAP after the clinical database lock for the final analysis has occurred will be documented and discussed in the clinical study report for this study.

3. STUDY OBJECTIVES

3.1. Primary Objective

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

3.2. Secondary Objective

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

4. STUDY ENDPOINTS

4.1. Efficacy Endpoints

4.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of participants alive and free of respiratory failure at Day 28.

4.1.2. Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the all-cause mortality through Day 28.

4.1.3. Estimand for the Primary and Key Secondary Efficacy Endpoints

The estimand for the primary and key secondary efficacy endpoints is defined as follows:

1) There are two treatment regiments for participants to be evaluated: brexanolone or placebo.
2) The target population consists of participants age 18 years or older who are confirmed positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as determined by polymerase chain reaction, who have a presumptive diagnosis of ARDS at screening and PaO_2/FiO_2 (PF ratio) <300 prior to randomization, who are intubated and receiving mechanical ventilation prior to randomization.
3) The outcome for the primary efficacy endpoint is the proportion of participants alive and free of respiratory failure at Day 28. The outcome for the key secondary efficacy endpoint is the proportion of participants with all-cause mortality at Day 28.
4) The population-level summary measure is the difference in response probabilities between the two groups (brexanolone and placebo treatments).
5) The treatment policy strategy will be adopted for the primary and key secondary endpoints. That is the difference between two arms will be computed and analyzed including all observed on-study data, regardless of the occurrence of the intercurrent event, such as use of additional medication, premature discontinuation of treatment for any reason, investigational product discontinuation, or other protocol violations.

[redacted]

[redacted]

4.2. Safety Endpoints

- Incidence of treatment-emergent adverse events (TEAE)
- Change from baseline in vital signs, [redacted], clinical laboratory parameters, and 12-lead electrocardiogram (ECG)

[redacted]

5. STUDY DESIGN

5.1. Overall 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.

Participants 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 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. 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 investigational product (IP) – 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.

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 of the study protocol 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 adverse event (AE) determined by the investigator to be related to IP. Details regarding dose adjustment criteria and procedures are provided in Section 7.4 of the study protocol.

Follow-up assessments will be conducted as summarized in the Protocol, 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 data to ensure the safety of the participants in the study. The DMC will provide recommendations for continuing or stopping the study for safety or futility in accordance with the DMC charter. Refer to Section 7.4.1 and Section 13.8.1.2 of the study protocol for additional details.

5.2. Sample Size and Power

The sample size of approximately 100 participants would provide 80% power to detect a treatment difference of 27% in proportion of participants alive and free of respiratory failure at Day 28. The sample size is computed assuming proportion of 50% for the placebo group and 77% for the brexanolone group using Chi-square test with a two-sided Type I error rate (alpha) of 0.05.

5.3. Randomization

This is a randomized, double-blind, placebo-controlled study. Participants who meet the eligibility criteria will be randomized in a stratified manner based on age (<70 or ≥70 years). Participants will be randomized in a 1:1 ratio 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 system. Randomization schedules will be generated by an independent statistician outside Sage.

5.4. Blinding and Unblinding

Participants and their family or caregivers, clinicians, site staff, and sponsor personnel will be blinded to treatment allocation. An independent DMC will have access to unblinded data as described in the DMC charter.

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.

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 suspected unexpected serious adverse reactions (SUSARs)), pertinent information (including the reason for unblinding) must be documented in the participant's records.

6. MODIFICATIONS

6.1. Modifications from the Approved Clinical Study Protocol

The modifications presented in this section are intended to either clarify some aspects of the Protocol-specified analyses, modify them, or drop them entirely.

The Sponsor decided to terminate the study early due to a very challenging patient recruitment environment – the majority of residents in North America have now been vaccinated against n-Cov-19. This decision was not due to DMC recommendation and not due to safety reasons.

Modifications were made to both the overall concomitant medication analysis and the Midazolam/Propofol analysis to accommodate the nature of the collected data. Due to Sponsor decision to terminate the study early some analyses were dropped for simplicity and/or untenability (Kaplan-Meier analysis of all-cause mortality, tipping point analysis, interim analysis).

6.1.1. Per-Protocol Analysis Population

The Per-Protocol analysis population will not be used for any listing, tabulation, or figure generation and is therefore not used in any analyses specified in this SAP. However, the definition of the Per-Protocol analysis population is retained for consistency with the Protocol. Major deviations will flagged in protocol deviation listings.

6.1.2. Concomitant Medications

Protocol Section 13.6.6 states that "Data summarized for the following classes of medications will include the dose, duration, total dose over the hospitalized study period, and indication for use:" with respect to CNS Depressants, other agents utilized for sedation effects, and drugs administered to treat or prevent ICU delirium. The concomitant medication data for these classes of medications will not be summarized this way. A standard concomitant medication tabulation will be generated in which medication class replaces ATC Level 3 categories. See Sections 8.2.6 and 8.4.2.

[redacted]

6.1.4. Efficacy Analyses

Protocol Section 13.5 requires an odds ratio analysis of the primary endpoint and a Kaplan-Meier time to event analysis of the key secondary endpoint (all-cause mortality). Neither of these analyses will be performed.

6.1.5. Tipping Point Analyses

Protocol Section 13.2 requires a set of tipping point analyses to assess the impact of missing data. This will not be done.

6.1.6. Interim Analysis

Protocol Section 13.8.1.1 requires an interim analysis when approximately 50% of the planned participants have completed Visit 11 (Day 28 ± 3 days). This will not be done.

[redacted]

6.2. Modifications from the Approved Statistical Analysis Plan

Not applicable. There are no previous approved SAPs.

6.3. Modifications from the Approved DMC Charter

None.

7. ANALYSIS SETS

7.1. Efficacy Analysis Sets

The Randomized Set is defined as all randomized participants. Unless specified otherwise, a participant will be allocated to their randomized treatment in this analysis set.

The Full Analysis Set (FAS) is defined as all randomized participants who initiated IP (brexanolone or placebo). Unless specified otherwise, a participant will be allocated to their randomized treatment in this analysis set.

The Per-Protocol Set (PP) is defined as all randomized participants not having any major protocol deviations. Unless specified otherwise, a participant will be allocated to their randomized treatment in this analysis set.

7.2. Safety Analysis Set

The Safety Set will include all participants who initiated IP (brexanolone or placebo). Unless specified otherwise, a participant will be allocated to the treatment actually given in this analysis set.

8. STATISTICAL ANALYSIS

8.1. General Considerations

Unless otherwise specified, continuous endpoints will be summarized with n, mean, standard deviation (SD), median, minimum (min) and maximum (max). The min and max will be reported with the same number of decimal places as the source (raw) data. Mean and median will be reported to 1 decimal place more than the source (raw) data and standard deviation will be reported to 2 decimal places more than the source (raw) data, but no more than 4 decimal places. Any values that require transformation to standard units (metric or SI) will be converted with the appropriate corresponding precision.

Categorical variables (eg, presence of an AE) will be summarized using counts and percentages. Percentages will be presented to 1 decimal place unless otherwise specified.

All participant data, including those 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 with an underlying table or figure; these will be indicated in relevant sections below.

All summaries will be provided by treatment – either by treatment assigned at randomization, or actual treatment received. Actual treatment is defined as:

- Brexanolone – if the participant was exposed to brexanolone;
- Placebo – if the participant received placebo and not a single dose of brexanolone.

For the purpose of all safety and efficacy analyses, baseline is defined as the last non-missing measurement on or prior to the initiation of IP, unless stated otherwise.

P-values will be reported to four decimal places, with p-values less than 0.0001 reported as "<0.0001". P-values larger than 0.9999 will be reported as ">0.9999".

8.1.1. Definition of Study Day

For the purpose of the efficacy and safety data summaries, Study Day 1 is defined as the date of first dose of study treatment. For visits (or events) that occur on or after the date of first dose of study treatment, Study Day is defined as:

(date of visit [event] − date of first dose of study treatment + 1).

For visits (or events) that occur prior to the date of first dose of study treatment, Study Day is defined as:

(date of visit [event] − date of first dose of study treatment). There is no Study Day 0.

8.1.2. Visit Windows

Visit windows are defined in Table 2. It is noted that certain specific endpoints might have slightly different analysis visit rules. If an endpoint will be analyzed using the visit windows, as specified in the corresponding sections of the applicable endpoints, all assessments within the window, regardless if the assessment is scheduled or unscheduled, will be included. A

participant's individual analysis visit window could potentially contain more than 1 visit. In the event of multiple visits falling within an analysis window, the latest data will be used.

The summary by analysis visit will use the "analyzed records" only – at most one per participant within each window. The data not flagged as the "analyzed record" will be included in listings. A visit that does not fall under any analysis window will remain in the database and will be included in the listings. The visit window does not apply to the baseline assessment.

Table 2: Visit Windows

Scheduled Visit	Assessment Window	Analysis Visit Window	Study Day
V2	0 to 12h	>0 to ≤12h	1
V3	12h to 24h	>12h to ≤24h	1
V4	24h to 36h	>24h to ≤36h	2
V5	36h to 48h	>36h to ≤48h	2
V6	48h to 60h	>48h to ≤60h	3
V7	60h to 72h	>60h to ≤72h	3
Day 5 (V8)	Day 5	>72h to Day 5	3-5
Day 7 (V9)	Day 7	≥ Day 6 to Day 10	6-10
Day 14 (V10)	Day 14	≥ Day 11 to Day 17	11-17
Day 28 (V11)	Day 28	>= Day 25 to Day 31	25-31

Because endpoints are collected with different assessment schedules, some endpoint specific rules will be used:

[redacted]

- The clinical status assessed by RASS, and CAM-ICU in situations where RASS indicates appropriate subject alertness, will be administered daily and therefore will be windowed daily, from Day 1 through the end of study per-participant. If there is more than one assessment time point within the same day, the later assessment(s) will be used in the analysis.
- Hematology/Chemistry will be windowed according to the scheduled visits in the Protocol (Figure 1, page 11 – Visits 2 through 11). If there is more than one assessment within the scheduled visit, the later assessment will be used in the analysis.
- Vital signs will be windowed using the 12-hour interval as presented in Table 2 above, up to Hour 72 (i.e., Visits 2 through 7). Starting from Day 5, it will be windowed daily, with the exception that Day 5 will be windowed as 72 hours –

Day 5. If there is more than one assessment within the same windowed time interval, the later assessment will be used in the analysis.

- Coagulation data is collected at Screening (Baseline), Visit 6, and Visit 9. Visit 6 will be windowed as 42 hours to 72 hours, and Visit 9 will windowed as 72 hours to Day 10.

[redacted]

- ECG is collected at Screening (Baseline), Visit 6, and Visit 10. Visit 6 will be windowed as 42 hours to 72 hours, and Visit 10 will windowed as Day 11 to Day 17

[redacted]

8.2. Background Characteristics

8.2.1. Participant Disposition

The analyses of participant disposition will use all participants who provided written informed consent to the study, or for whom consent was given by a proxy.

The summaries of participant disposition will include the number of participants who were screened, who were not randomized and reasons for not having been randomized, who were randomized, who received IP, who did not receive IP, the number and percentage of participants who completed the study, who prematurely withdrew from the study, primary reasons for not completing the study, who completed treatment, who discontinued treatment prematurely, including primary reasons for discontinuing treatment, and who discontinued treatment but completed study. For participants completed/discontinued the treatment, percentages will be calculated based on the number of participants who received IP in the randomized group. Othe percentages will be calculated based on the participants who were randomized; treatment assignment will be taken as planned.

A completer for the study is defined as one who completed the last follow up visit (Visit 11, Day 28±3) based on the study completion case report form (CRF) page with the completion question answered Yes.

A participant is marked as completing the treatment if the complete treatment question on the study treatment completion CRF page is answered Yes.

The number of participants in each analysis set will be provided. Using Randomized Set, the reason for not being included in other analysis sets will be summarized.

Screen failure participants will be listed in a data listing.

8.2.2. Protocol Deviations

Protocol deviations identified during the study will be captured and categorized by the study team review as major or minor deviations in blinded fashion on an ongoing basis until database lock.

The major protocol deviations will be summarized for all randomized participants using the FAS. All protocol deviations (major and minor) will be included in a data listing.

8.2.3. Demographics and Baseline Characteristics

The following analyses will be provided separately for the Safety Analysis Set (using actual treatment received), and the FAS (using randomized treatment).

Demographic data (age at informed consent date, race, sex, ethnicity) and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized by treatment group (randomized for FAS and actual for Safety Analysis Set) and overall.

8.2.4. Pregnancy Tests

A serum or urine pregnancy test will be conducted for all female participants at screening. These data will be listed by participant.

8.2.5. Medical/Surgical History

Listings and tabulations associated with Medical and/or Surgical History will use the Safety Analysis Set.

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

In addition to medical/surgical history collected at screening, listings will also include COVID-19 symptom onset date, COVID-19 vaccination history (including dates of administration and manufacturer), [redacted] 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. Protocol version will be included in these listings.

8.2.6. Prior and Concomitant Medications

Listings and tabulations associated with Prior and Concomitant Medications will use the Safety Analysis Set.

All medications taken and procedures undergone during the study will be recorded. All medications will be coded using World Health Organization-Drug (WHO) Global B3 September 2020 or later.

Medications will be presented according to whether they are being taken prior to and/or during the study (concomitant). Prior medications are defined as those taken prior to the initiation of the IP. Concomitant medications are defined as those with a start date and time on or after the initiation of IP or those with a start date and time before the initiation of IP

that are ongoing or with a stop date/time on or after the initiation of IP. If medication date/time is incomplete and it is not clear whether the medication was concomitant, it will be assumed concomitant. For imputation of missing concomitant medication dates, please refer to Appendix A. Note that it is possible for a medication to be both 'prior' and 'concomitant' when a medication has start date and time before the initiation of IP and end date and time either missing or after the initiation of IP.

Concomitant procedures are recorded on a separate electronic case report form (eCRF) page; this will be presented in a listing by participant. The study day for the end date of the procedure will be provided, when a complete end date is available.

Concomitant medication data will be tabulated for the following classes of medications using a standard concomitant medication table format. Medications in the following categories will also be listed:

- 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).

Please see Section 8.4.2 for details regarding the ATC Level 3 codes corresponding to these medication classes. There will be no prohibited medications defined for this study.

8.2.7. Investigational Product Exposure

The total exposure (in mcg/kg) to IP is defined as the total mcg/kg for brexanolone that was received during the study. Total drug exposure for participants randomized to placebo is zero, unless the participant received brexanolone by mistake, in which case the total exposure comes from brexanolone exposure.

The exposure duration to IP is defined as total number of hours treated with study drug during the study, which is calculated as (end time of infusion – start time of infusion [in seconds])/3600. Note that this does not exclude the time when the dose has been interrupted.

The total exposure and exposure duration to IP will be summarized by descriptive statistics, using the Safety Analysis Set.

8.2.8. Investigational Product Adherence

IP adherence (%) is calculated as [Actual total dose (in mcg/kg)/Planned total dose (in mcg/kg) x 100]. Actual total dose will account for the tapering period. IP adherence will be summarized using the Safety Analysis Set.

8.3. Efficacy Analysis

The Full Analysis Set will be used for all efficacy analyses. When referencing "Day 28" in efficacy analyses, it is understood that this refers to Visit 11.

8.3.1. Definition of Efficacy Endpoints

8.3.1.1. Proportion of participants alive and free of respiratory failure at Day 28

The primary efficacy 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:

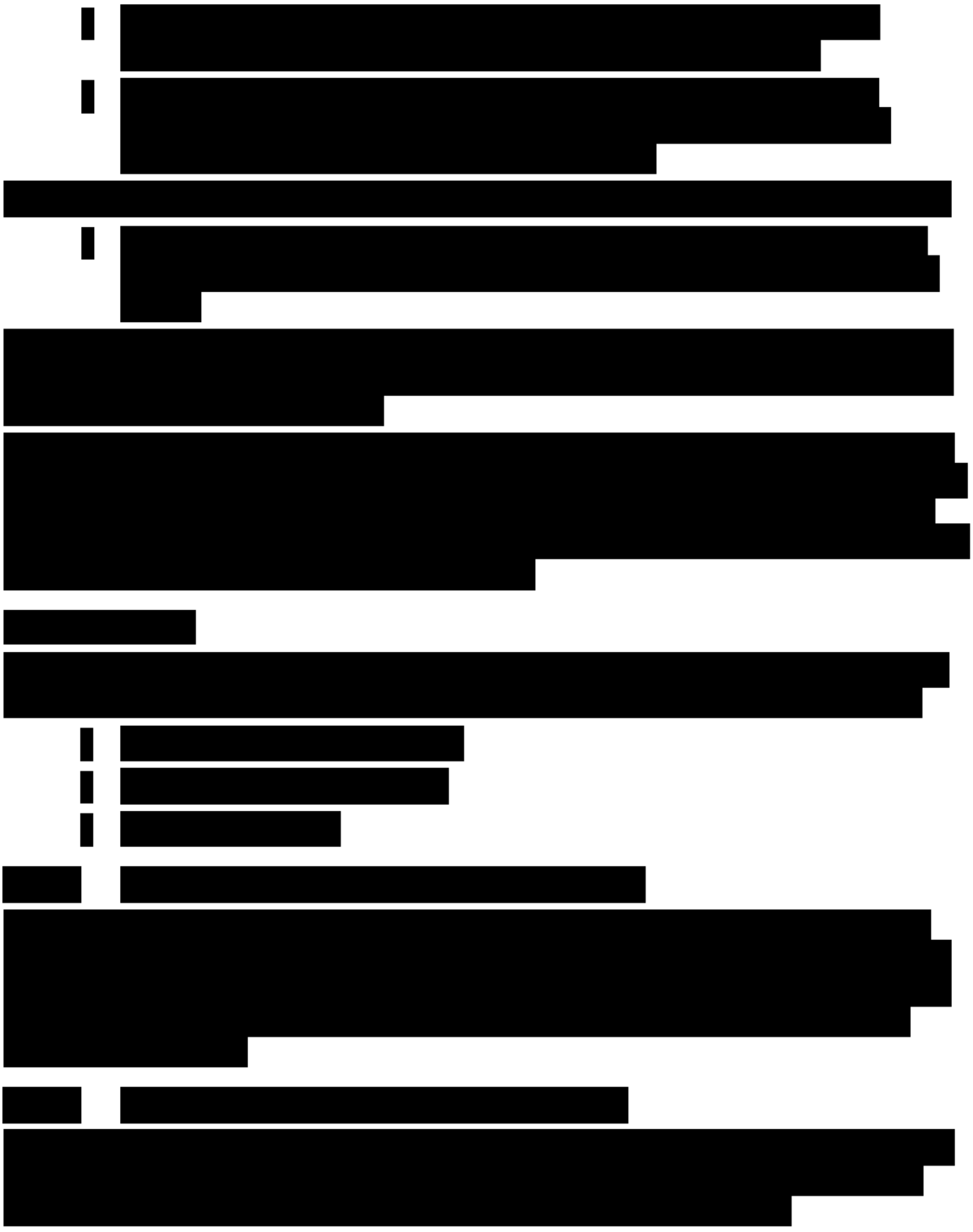
- Endotracheal intubation and mechanical ventilation
- Oxygen delivered by high-flow nasal cannula (heated, humidified oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ≥0.5)
- Noninvasive positive pressure ventilation
- Extracorporeal membrane oxygenation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

Please see Appendix D for a detailed breakdown of the Procedural terms used to identify subjects with respiratory failure.

8.3.1.2. All-cause mortality

The key secondary efficacy endpoint is the all-cause mortality, measured by proportion of participants who die due to any cause through Day 28.

[redacted]



[redacted]

8.3.2. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of participants alive and free of respiratory failure at Visit 11 (Day 28 ± 3 days). [1]

- If a participant dies prior to Visit 11, the participant will be assigned a value of "no" for the primary endpoint.
- Participants discontinuing the study for reasons other than death and prior to Visit 11 will not be included in the primary analysis.

The difference in the proportions between brexanolone and placebo will be analyzed using the SAS procedure GENMOD. In this model, the proportion will be the response variable, and the predictor variables will be treatment arm and age group (<70 or ≥70 years). Participants will be analyzed according to their actual age group, regardless of the age group used for randomization purposes. The proportion will be directly modeled using the binomial distribution with identity link. The point estimate, confidence interval, and p-value for the difference in the fitted proportions will be obtained using the "LSMEANS" statement to

[1] Lack of endotracheal intubation, for purposes of the Primary Efficacy Endpoint, does not require a subsequent >48 hour period of time without need for reintubation or noninvasive ventilation.

produce estimated treatment differences (ie, differences in proportions). A sample SAS code is as follows:

```
proc genmod data=indata;
         class trt01p agegr1;
         model aval = trt01p agegr1 / dist=binomial link=identity;
         lsmeans trt01p / diff cl;
run;
```

Please see Appendix D for a detailed breakdown of the Procedural terms used to identify subjects with lack of respiratory failure.

8.3.3. Analysis of Key Secondary Efficacy Endpoint

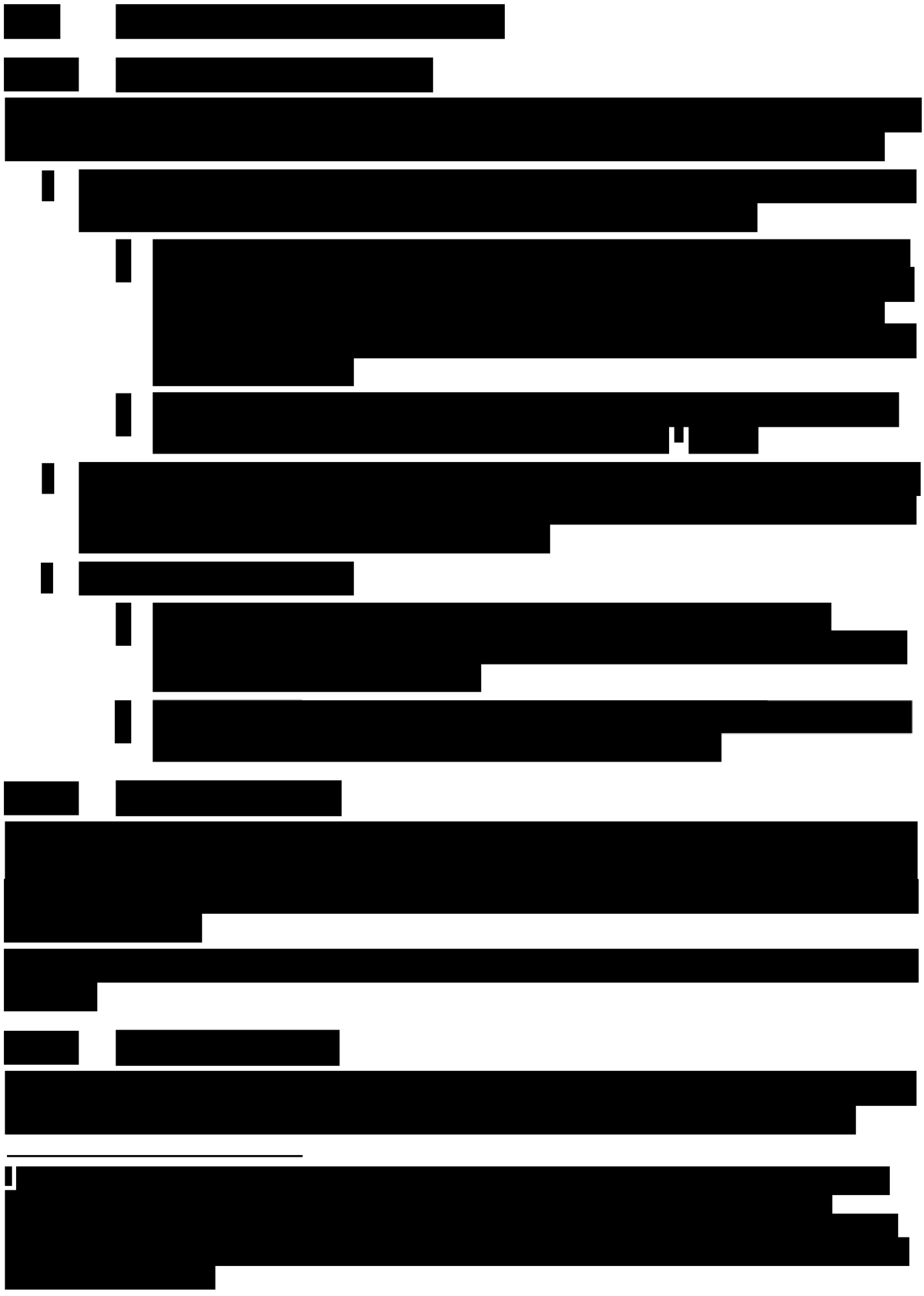
The proportion of participants who died for any cause (all-cause mortality) by Visit 11 (Day 28 ± 3 days) is the key secondary endpoint.

- If a participant dies prior to Visit 11, the participant will be assigned a value of "yes" for the key secondary endpoint
- Participants having Visit 11 (either in-person or via phone call) will be assigned a value of "no" for the key secondary endpoint
- Participants having follow-up assessments on/after Day 25 and known to be alive for those assessments and for whom Visit 11 was not performed will be assigned a value of "no" for the key secondary endpoint
- Participants with early study termination (ET) for reasons other than death and prior to Visit 11 will not be included in the primary analysis.

The difference in the proportions between brexanolone and placebo will be analyzed using the SAS procedure GENMOD. In this model, the proportion will be the response variable, and the predictor variables will be treatment arm and age group (<70 or ≥70 years). Participants will be analyzed according to their actual age group, regardless of the age group used for randomization purposes. The proportion will be directly modeled using the binomial distribution with identity link. The point estimate, confidence interval, and p-value for the difference in the fitted proportions will be obtained using the "LSMEANS" statement to produce estimated treatment differences (ie, differences in proportions). The sample SAS code presented in Section 8.3.2 will be adapted for this purpose.

8.3.3.1. Multiplicity Adjustment

No adjustment for multiplicity will be done.



[redacted]

8.4. Safety Analysis

Safety and tolerability of brexanolone will be evaluated by adverse events, concomitant medication usage, changes from baseline in vital signs, [redacted], clinical laboratory evaluations, RASS, CAM-ICU, and 12-lead ECG. Safety data, including adverse events of special interest (AESI), will be listed by participant and summarized by treatment group. All safety summaries will be performed on the Safety Analysis Set using actual treatment received. Assessments will be mapped to windows, with the choice of the record following the same rule as described in Section 8.1.2.

The safety endpoints and variables considered in the summary tables for this study are summarized in Table 3.

Table 3: Safety Endpoints and Variables in the Summary Tables

Safety Evaluation	Incidence	Raw Value	Change from Baseline	Normal Range Shift from Baseline	Potentially Clinically Significant (PCS)	Abnormality/ Clinical Significance
AEs	X					
Labs		X	X	X	X	*
ECG		X	X		X	*
Vital Signs		X	X		X	
<define all abbreviations and shorthand (eg, "labs") used in the table> X = Safety Assessment will be summarized in tables * = Safety Assessment will be summarized in individual participant data listings						

8.4.1. Adverse Events

Adverse events 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 adverse event with onset after the initiation of IP. The analysis of adverse events will be based on the concept of TEAEs.

If the date of an adverse event is incomplete and an unambiguous determination could not be made with respect to its onset time versus the first dose of IP and/or last dose of IP, the adverse event will be assumed to be a TEAE and a treatment period TEAE. For imputation of missing AE dates, please refer to Appendix A.

The incidence of all TEAEs and non-serious TEAE's will be separately summarized by SOC and preferred term PT. In addition, summaries will be provided by maximum severity (mild, moderate, severe, life-threatening, death) and by relationship (related, not related) to IP. Any TEAEs leading to discontinuation of treatment or withdrawal from the study and any treatment-emergent serious adverse events will also be summarized, sorted by descending frequency in SOC and PT.

For maximum severity, participants will be counted only once within each SOC and PT at the maximum severity in the following order: severe > moderate > mild; an AE with missing severity will be omitted from severity presentation. A participant will be counted only once within each SOC and PT at the strongest relationship to IP in the following order: related > not related. The incidences will be presented by descending frequency of SOC in the brexanolone group and then, within a SOC, by descending frequency of PT based on the participant count, and in alphabetical order of PT if the incidence within a PT is a tie.

The following table documents events considered to be AESI in this study, and the MedDRA preferred terms and lower-level terms (i.e., LLTs) in the right-hand column will be used to screen adverse events for possible AESI status. Where LLTs are specified, they take precedence in the determination of AESI's; when LLTs are left unspecified, it is understood that MedDRA preferred terms will take precedence:

AESI Term	MedDRA Preferred Term(s)
Loss of Consciousness	1. Loss of consciousness 2. Altered state of consciousness 3. Syncope
Excessive sedation	1. Sedation 2. Somnolence 3. Sedation complication (note: this corresponds to the LLT of "Sedation excessive)
Reintubation events	1. Endotracheal intubation (note: this corresponds to the LLT of "Reintubate") 2. Endotracheal intubation complication (note: this corresponds to the LLT of "endotracheal reintubation")
Delirium	1. Delirium 2. Intensive care unit delirium 3. Anesthetic complication neurological (note: this corresponds to the LLT of "Delirium on emergence")
Altered mental status	1. Mental status changes (note: this corresponds to the LLTs of "Acute mental status changes" and "Mental status changes" 2. Mini mental status examination abnormal

The process for identification of AESI is to screen for MedDRA terms in the right-hand column and to query once any adverse events have been identified as meeting these broad criteria. AESI's will be tabulated separately from all TEAE's, using the same SOC x PT format.

All AEs, AESI and SAEs (including those with onset or worsening before the start of IP) through the end of the study will be listed. In addition, a listing containing individual participant's AE data for participants who died, and participants with SAEs leading to treatment discontinuation will be provided, separately.

8.4.2. Concomitant Medications

Concomitant medications will be coded using WhoDD dictionary Global B3 September 2020 or later.

Concomitant medications are defined as those with a start date and time on or after the initiation of IP or those with a start date and time before the initiation of IP that are ongoing or with a stop date/time on or after the initiation of IP. If medication date/time is incomplete and it is not clear whether the medication was concomitant, it will be assumed concomitant. For imputation of missing concomitant medication dates, please refer to Appendix A.

A standard table of concomitant medications will be generated, showing both treatment groups as well as a total column, for the Safety Population. This table will show ATC Level 3 x Preferred Name and participants with multiple occurrences of a drug class or drug will be counted only once in the specific ATC classification or preferred name, respectively. Concomitant medications will also be listed.

Additionally, the following overlapping classes of medications will be separately tabulated using the same format as a standard concomitant medication table and will be restricted to the study days associated with ICU stay for each participant. Days in ICU occurring during any long-term safety follow-up will be included. For this purpose, medications of special interest are all qualifying medications with start dates that not only occur on or after the initiation of investigational product but also must occur during an ICU stay. There are no restrictions on medication stop date(s):

- 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).

These classes of medications will be identified via the following ATC Level 3 codes:

- N01A (anesthetics, general)
- N02A (opiods)
- N03A (antiepileptics)
- N05A (antipsychotics)
- N05B (anxiolytics)
- N05C (hypnotics and sedatives)

A separate listing of these medications will be generated and will at minimum include dose, dose frequency, route of administration, and duration.

8.4.3. Clinical Laboratory

The clinical laboratory tests to be performed in this study are listed in Table 4.

Table 4: Summary of Clinical Laboratory Analytes

Biochemistry	*Renal Panel*: glucose, calcium, phosphorus, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate *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 (i.e., leukocytes) with differential, platelet count, erythrocyte sedimentation rate
Coagulation	Activated partial thromboplastin time, prothrombin time, and international normalized ratio (INR)

For the laboratory results that is "< or = *x*", where *x* is a number as collected in the data, the numeric part of the result will be used in the calculation in the summary tables. The same is true if the result is presented as below limit of quantification (BLQ) and a lower limit of quantification (LLOQ) value is provided – LLOQ value will be used for calculation in the summary tables. The actual results as collected will be presented in the listings. The analysis summary will be performed for the scheduled laboratory values only. The unscheduled laboratory values will be presented in the listings.

All statistical analyses of laboratory values will be performed using SI units. Numerical values and change from baseline values will be summarized by actual treatment group at each windowed visit. If a normal range is provided for the parameter, the out-of-range values will be flagged as low or high, where applicable, in the participant data listings. Shift tables will also be generated.

The number and percentage of participants with potentially clinically significant (PCS) values will be provided in separate listings in hematology, serum chemistry, and liver function tests. PCS values will be identified for specific laboratory parameters as outlined in Table 5. The summaries will be based on all post-baseline values, including both scheduled and unscheduled data. Percentages for PCS tables will be based on the number of subjects contributing observations.

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

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

Any lab results considered clinically significant by the investigator will be captured as adverse events, hence will show up in AE listings and/or tabulations.

Table 5: Potentially Clinically Significant Values for Specific Laboratory Parameters

Laboratory Parameter	**Units**	**Criteria for PCS Values (Observed values)**	
		High	**Low**
Hemoglobin -male	g/L	>185	<115
Hemoglobin -female	g/L	>170	<100
Hematocrit-male	Fraction of 1	>0.55	<0.385
Hematocrit-female	Fraction of 1	>0.49	<0.345
Platelet count	10^9/L	>600	<125
Leukocytes	10^9/L	>15	<2.5
Basophils	10^9/L	>0.5	NA
Eosinophils	10^9/L	>1.5	NA
Neutrophils	10^9/L	NA	<1.5
Lymphocytes	10^9/L	>6.0	<0.5
Monocytes	10^9/L	>1.4	NA
Albumin	g/L	>70	<28
Blood urea nitrogen	mmol/L	>10.71	NA
Calcium	mmol/L	>2.75	<2.0
Chloride	mmol/L	>120	<90
Creatinine	mmol/L	>3xULN or >3x Baseline	
Gamma Glutamyl Transferase	U/L	>3xULN	
Glucose	mmol/L	>13.9	<2.8
Sodium	mmol/L	>150	<132
Potassium	mmol/L	>5.4	<3.3
Protein	g/L		<45
Bicarbonate	mmol/L	>34	<18
Phosphorus	mmol/L	>1.94	<0.61
Liver Function Tests (LFT)			

Laboratory Parameter	**Units**	**Criteria for PCS Values (Observed values)**	
		High	**Low**
Bilirubin	µmol/L	>2xULN	NA
Aspartate Aminotransferase	U/L	>3xULN	NA
Alanine Aminotransferase	U/L	>3xULN	NA
Alkaline Phosphatase	U/L	>3xULN	NA
Coagulation			
International Normalized Ratio (INR)	NA	>1.5x ULN	NA
Partial thromboplastin time (PTT)	sec	>1.5x ULN	NA

8.4.4. Vital Signs

Vital signs include systolic and diastolic blood pressure, heart rate, temperature, and respiratory rate (if not on mechanical ventilation). 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. Descriptive summaries of observed values and changes from baseline will be provided for vital sign parameters - by windowed visit and treatment group.

Additionally, the number and percentage of participants with PCS and PCS values will be summarized. PCS values will be identified for vital sign parameters as outlined in Table 6.

Table 6: Potentially Clinically Significant Values for Vital Sign Parameters

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

8.4.5. Electrocardiogram

A 12-lead ECG will be performed 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.

Example:

The observed value at each windowed visit and change from baseline at each post-baseline windowed visit will be summarized. Each ECG is evaluated by investigator as 'normal', 'abnormal, not clinically significant' and 'abnormal, clinically significant' in the eCRF; the number and percentage of participants with 'abnormal, clinically significant' or 'abnormal, not clinically significant' will be provided at baseline and each post-baseline windowed visit.

The number and percentage of participants with PCS and PCSC values will be summarized. PCS values will be identified for ECG parameters as outlined in Table 7. In addition, the maximum value of QTcF if within any of the PCS criteria will be summarized.

Table 7: Potentially Clinically Significant Values and Change for ECG Parameters

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

8.4.6. Richmond Agitation Sedation Scale

The RASS is a tool validated to assess sedation and agitation in ICU participants. 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 to all participants at the scheduled time points. In addition, the unscheduled RASS will be administered within 2 hours after each extubation. The unscheduled RASS will also be administered each time the decision is made to stop the IP infusion or reduce the dose.

Descriptive summaries of observed values will be provided for RASS- by windowed visit, and summarized by timepoint and treatment group. The unscheduled values will be presented in the listings.

8.4.7. Confusion Assessment Method for the Intensive Care Unit

The CAM-ICU score is a validated score to assess delirium in mechanically ventilated participants using standardized nonverbal assessments. The overall score is either "CAM-ICU Positive" or "CAM-ICU Negative". The CAM-ICU will be administered every time RASS is assessed if RASS score ≥-3.

The listings of the observed values will be provided for CAM-ICU.

8.4.8. Prone Positioning

During the period of mechanical ventilation, it will be documented whether or not at least 12 hours of prone positioning was conducted on each day. Descriptive summaries of the percent of days in prone position for at least 12 hours during intubation will be presented in a table.

9. SUMMARY OF INTERIM AND DMC ANALYSES

9.1.1.1. Interim Analysis

The originally planned Interim Analysis will not be performed due to Sponsor decision to stop the study early.

9.1.1.2. Data Monitoring Committee Analysis

An independent DMC will monitor the clinical data for safety and efficacy 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 or futility in accordance with the DMC charter. Stopping criteria are prespecified in study protocol 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 to ensure the safety of the participants in the study. Efficacy data will be delivered to the DMC as needed to perform their functions. The DMC will also review the results of the planned interim analysis.

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.

Sage team will remain blinded for all the DMC and interim analysis data until the end of study.

Please refer to the DMC Charter for additional details.

10. REFERENCES

Include a list of references, as appropriate.

Beigel JH, Tomashek, KM, Dodd, LE, Mehta, AK, Zingman, BS, et al. Remdesivir for the Treatment of COVID-19 – Preliminary Report. NEJM. 2020. DOI: 10.1056/NEJMoa2007764.

11. LIST OF APPENDICES

APPENDIX A. HANDLING OF MISSING DATES

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

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

Adverse Events

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

For partial AE start dates:

- When the year is known, but the month and day is unknown, then:
  - If the year matches the year of initiation of study drug and the end date (if present) is after the initiation of study drug, or AE is ongoing, then impute as the month and day of the initiation of the study drug date + 1 day.
  - If the year of AE onset < year of initiation of the treatment, then the month and day will be set to December 31st.
  - If the year of AE onset > the year of initiation of treatment, then the month and day will be set to January 1st.
- If the year and month are known, but the day is unknown, then:
  - If the year of AE onset = the year of initiation of the treatment and:
  - the month of AE onset = the month of initiation of the treatment, then the day will be set to the day of initiation of the treatment.
  - the month of AE onset < the month of initiation of the treatment, then the day will be set to the last day of month.
  - if the month of AE onset > the month of initiation of the treatment, then the day will be set to the 1st day of month.
  - If the year of AE onset < the year of initiation of the treatment, then the day will be set to the last day of month.
  - If the year of AE onset > the year of initiation of the treatment, then the day will be set to the 1st day of month.

If the imputed AE onset date is after the AE stop date, then the onset date will be set to the stop date.

- When the year and day are present and the month is missing, treat it as if the day is missing, and only year is present. Follow the imputation rules for "year is known, but the month and day is unknown".
- When the year is missing, but the month and/or day is known, treat this date as missing; do not impute.

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

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

Prior and Concomitant Medications

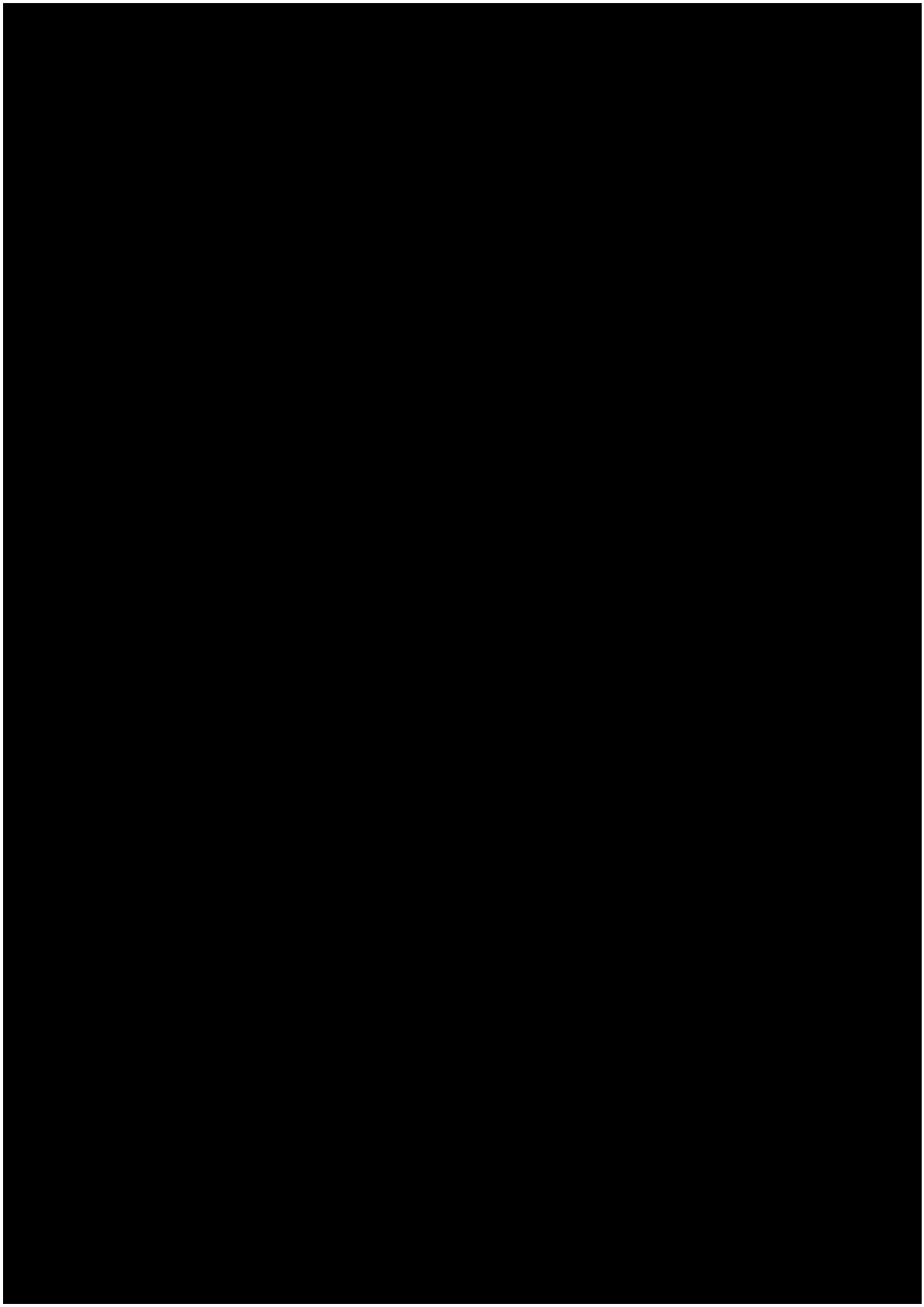
For the partial start date of medication:

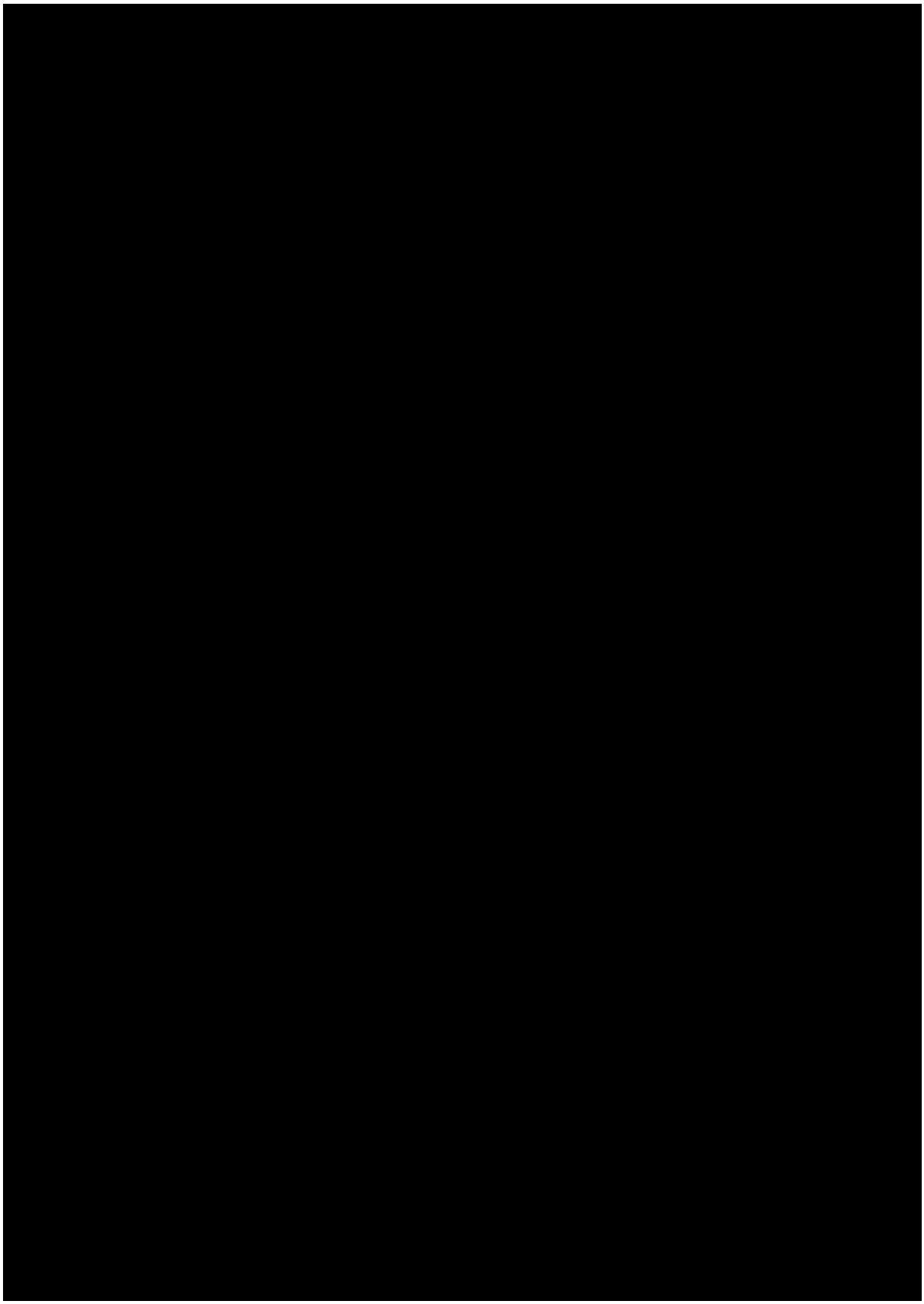
- If the year is present and the month and day are missing, then the month and day will be set to January 1.
- If the year and day are present and the month is missing, then the month will be set to January.
- If the year and month are present and the day is missing, then the day will be set to the 1st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

For the partial end date of medication:

- If the year is present and the month and day are missing, then the month and day will be set to December 31.
- If the year and day are present and the month is missing, then the month will be set to December. If the year and month are present and the day is missing, then the day will be set to the last day of the month.
- If the year and day are present and the month is missing, then treat it as if the day is also missing. Set the month and day to be December 31.

APPENDIX B. LIST OF DISPLAYS





APPENDIX D. PROCEDURAL TERMS USED IN THE IDENTIFICATION OF RESPIRATORY FAILURE AND UNSUCCESSFUL EXTUBATION

Verbatim Procedural Term †	Interpretation Relative to Respiratory Failure	Interpretation Relative to Extubation
1. Bronchoscopy	No impact on determination of respiratory failure	No impact on determination of unsuccessful extubation
2. Chest Tube Insertion	No impact on determination of respiratory failure	No impact on determination of unsuccessful extubation
3. CPR	No impact on determination of respiratory failure	No impact on determination of unsuccessful extubation
4. ECMO	Respiratory failure	Extubation considered unsuccessful if within 48 hours of extubation
5. Initiation of Non-Invasive Positive Pressure Ventilation	Respiratory failure	Extubation considered unsuccessful if within 48 hours of extubation
6. Initiation of Oxygen Delivery by High-Flow Nasal Cannula	Respiratory failure	No impact on determination of unsuccessful extubation
7. Intubation	Respiratory failure	Extubation considered unsuccessful if within 48 hours of extubation

8. Intubation/ Brochoscopy/ Cauterization	Respiratory failure	Extubation considered unsuccessful if within 48 hours of extubation
9. Mechanical Ventilation	Respiratory failure	Extubation considered unsuccessful if within 48 hours of extubation
10. None: Extubated to 4L NC	Respiratory failure	No impact on determination of unsuccessful extubation
11. Pneumothorax, Right	No impact on determination of respiratory failure	No impact on determination of unsuccessful extubation
12. PS/CPAP	Respiratory failure	Extubation considered unsuccessful if within 48 hours of extubation
13. Reintubation	Respiratory failure	Extubation considered unsuccessful if within 48 hours of extubation
14. Tracheostomy	No impact on determination of respiratory failure	No impact on determination of unsuccessful extubation

†Mis-spellings present in the clinical database are displayed as-is in this table

DocuSign

Certificate Of Completion

Envelope Id: 13C3E8B4E9954D1E89E1CADE1F9A1C15
Status: Completed
Subject: Please DocuSign: 2021_11_19 Sage SAP Methods 547-ARD-301 v1.0 FINAL.docx
Source Envelope:
Document Pages: 47
Signatures: 5
Envelope Originator:
Certificate Pages: 2
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Enabled
IP Address:
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

Record Tracking

Status: Original
19-Nov-2021 | 10:04
Holder
Location: DocuSign

Signer Events	Signature	Timestamp
Sage Therapeutics - Part 11 Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signature ID: 451F6B06-1474-4006-8EEE-0D4811AAF0DC Using IP Address: With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 19-Nov-2021 | 10:23 Viewed: 19-Nov-2021 | 14:22 Signed: 19-Nov-2021 | 14:23
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signature ID: 82D64825-6718-4EDD-9060-087B09B23F7B Using IP Address With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 19-Nov-2021 | 10:23 Viewed: 19-Nov-2021 | 10:25 Signed: 19-Nov-2021 | 10:26
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Sage Therapeutics - Part 11 Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signature ID: 460ADE93-CBF6-4E9A-90A9-AEF133BC820F Using IP Address: With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 19-Nov-2021 | 10:23 Viewed: 19-Nov-2021 | 11:06 Signed: 19-Nov-2021 | 11:08
Electronic Record and Signature Disclosure:		

Signer Events	Signature	Timestamp
Not Offered via DocuSign		
[redacted] [redacted] Sage Therapeutics - Part 11 Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Uploaded Signature Image Signature ID: EA346385-2142-4C28-85BE-C8F16850E54C Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 19-Nov-2021 | 10:23 Resent: 22-Nov-2021 | 14:44 Viewed: 22-Nov-2021 | 09:22 Signed: 23-Nov-2021 | 06:16
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] [redacted] Sage Therapeutics - Part 11 Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 89BBDD29-A7B4-4DDA-8896-FB74228A3343 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 19-Nov-2021 | 10:23 Viewed: 22-Nov-2021 | 13:29 Signed: 22-Nov-2021 | 13:29
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
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Certified Delivered	Security Checked	22-Nov-2021 | 13:29
Signing Complete	Security Checked	22-Nov-2021 | 13:29
Completed	Security Checked	23-Nov-2021 | 06:16

Payment Events	Status	Timestamps