Official Title:	**Assessment of Safe-Use Conditions for Administration of ZULRESSO in a Home Setting**
NCT Number:	NCT05059600
Document Dates:	Protocol Version 2.0: 28 June 2021

ASSESSMENT OF SAFE-USE CONDITIONS FOR ADMINISTRATION OF ZULRESSO IN A HOME SETTING

PROTOCOL NUMBER: 547-PPD-404

Investigational Product	ZULRESSO
Clinical Phase	Phase 4
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Medical Monitor	[redacted], MD [redacted] Phone: [redacted] [redacted]
Date of Original Protocol	27 October 2020
Date of Amendment 1	23 June 2021

Confidentiality Statement

The confidential information in this document is provided to you as an investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from Sage Therapeutics, Inc.

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SPONSOR APPROVAL

Protocol Number:	547-PPD-404
Study Title:	Assessment of Safe-Use Conditions for Administration of ZULRESSO in a Home Setting
Protocol Version and Date:	Version 2, 23 June 2021

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[redacted] for [redacted], PharmD, MS, RPh
[redacted]

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[redacted], PhD
[redacted]

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[redacted], MD

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INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for brexanolone injection. I have read the 547-PPD-404 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 AND ROLES AND RESPONSIBILITIES OF STUDY PERSONNEL

Table 1: Contact Information

Role in Study	Name	Address and Telephone Number
Sage Study Physician	[redacted], MD, [redacted]	Cambridge, MA 02142 Phone: [redacted]
SAE reporting	IQVIA Lifecycle Safety (LS)	4820 Emperor Boulevard Durham, NC 27703 e-mail: Sage.Safety@iqvia.com Fax: 1-855-638-1674 SAE Hotline: 1-855-564-2229
Product Complaint Contact	Sage Therapeutics	e-mail: productcomplaints@sagerx.com Phone: 1-833-554-7243

Table 2: Study Personnel Roles and Responsibilities

Role	Key Responsibilities
Investigator	Individual responsible for conduct of the clinical study
Home Infusion Provider	Company responsible for implementing the safe-use conditions for administering ZULRESSO in the home setting and providing, overseeing, and training all staff involved in dispensing and administering ZULRESSO
Home Healthcare Provider	Individual healthcare professional responsible for general care of the participant during infusion; present in the participant's home for the duration of study participation; multiple individuals will work in shifts to care for the same participant
Pharmacist or Qualified Designee	Individual(s) responsible for preparation and dispensing of investigational product (IP) and preprogramming the infusion pump

2. SYNOPSIS

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

Name of Investigational Product:
ZULRESSO®

Name of Active Ingredient:
brexanolone (previously referred to as SAGE-547)

Title of Study:
Assessment of Safe-Use Conditions for Administration of ZULRESSO in a Home Setting

Number of Sites and Study Location: This is a multicenter study that will take place in the United States.

Phase of Development: Phase 4

Planned Duration for each Study Participant:
The total duration of participation may be up to 31 days, including a screening period of up to 28 days, and a 60-hour infusion of ZULRESSO on Day 1 through Day 3.

Objectives and Endpoints:

Primary

- To evaluate whether the safe-use conditions for administration of ZULRESSO can be implemented in a home setting

Secondary

- To identify any process and procedural changes to be implemented for ZULRESSO administration at home

[redacted]

- [redacted]

Endpoints

Primary

- Incidence of treatment-emergent adverse events (TEAEs) leading to dose interruption/discontinuation

Secondary

- Incidence of nonadherence with the safe-use conditions for administration of ZULRESSO
- Incidence of use-related issues related to the home administration of ZULRESSO
- Incidence of all TEAEs
- Incidence of medication error

[redacted]

- [redacted]
- [redacted]

[redacted]

Study Description:

This is an open-label, multicenter study designed to assess the safe-use conditions for administration of ZULRESSO in a home setting to women with postpartum depression (PPD) with the overall goal to improve patient access to ZULRESSO treatment. The safety monitoring plan for this study incorporates safe-use conditions that are aligned with that of the FDA-approved ZULRESSO Risk Evaluation and Mitigation Strategy (REMS) and ZULRESSO prescribing information. A home infusion provider is responsible for implementing the safe-use conditions for administering ZULRESSO in the home setting.

This study consists of a screening period of up to 28 days and a 60-hour home infusion of ZULRESSO (Days 1 through 3). A home infusion provider will provide, oversee, and train pharmacy staff, home healthcare providers, and other home healthcare provider staff involved in dispensing and administering ZULRESSO in this study. All investigators and all pharmacy and home healthcare provider staff involved in dispensing and administering ZULRESSO will be trained regarding the risk of serious harm resulting from excessive sedation and sudden loss of consciousness during the administration of ZULRESSO. Home healthcare providers will also counsel participants regarding this risk and the importance of reporting any symptoms to a healthcare provider. Use of telehealth by the investigator is permitted for screening and remote assessments for monitoring or oversight of participants during the ZULRESSO infusion, as required.

All necessary equipment and supplies (eg, pulse oximeter, body weight scale, etc) used to conduct the study will be delivered by a home healthcare provider or shipped to the participant's home.

The screening period begins with the informed consent process, which may be conducted electronically. Consented participants will undergo remote or in-person screening procedures to determine eligibility.

During the treatment period, a home healthcare provider will arrive at the eligible participant's home on Day 1 to initiate the 60-hour intravenous (IV) infusion of ZULRESSO. The home healthcare provider must confirm that the participant continues to meet all of the eligibility criteria and complete any predose assessments per Table 3 prior to administering the infusion.

The open-label 60-hour infusion will be administered as follows: 30 mcg/kg/hour (Hour 0 to 4), then 60 mcg/kg/hour (Hour 4 to 24), then 90 mcg/kg/hour (Hour 24 to 52), followed by 60 mcg/kg/hour (Hour 52 to 56), and 30 mcg/kg/hour (Hour 56 to 60). A programmable peristaltic infusion pump with alarm is to be used to ensure accurate delivery of ZULRESSO. The pump will be preprogrammed by home infusion provider pharmacy staff. If necessary, the home healthcare provider may reprogram the pump in consultation with home infusion provider pharmacy staff for any issues unrelated to safety. If the pump must be reprogrammed during the infusion due to safety, the home healthcare provider must consult the investigator and if necessary, the pharmacist or qualified designee.

Due to the risk of excessive sedation and sudden loss of consciousness, for the duration of the infusion, participants must be monitored for hypoxia using continuous pulse oximetry equipped with an alarm and must be assessed for excessive sedation by a home healthcare provider every 2 hours during planned nonsleep periods. At least one home healthcare provider must be continuously available on site in the participant's home for the duration of the ZULRESSO infusion to monitor the participant and intervene as necessary. The participant must not be the primary caregiver of her dependent(s) and must be accompanied by another adult (other than the home healthcare provider) during any interactions with their child(ren) that occur during the infusion. If the participant becomes

the primary caregiver of dependent(s) at any point during the infusion, the infusion must be stopped and will not be resumed.

All home healthcare providers will have 24 hour/day access to home infusion nursing and pharmacy staff via telephone for any problems with the infusion pump, IV lines, or other equipment malfunctions. The investigator will be available 24 hour/day to address protocol -related queries/issues in addition to safety-related concerns.

If excessive sedation or loss of consciousness occur at any time during the infusion, the infusion will be stopped until the symptoms resolve. The infusion may be resumed at the same or lower dose as deemed clinically appropriate by the investigator.

The infusion will be immediately stopped if pulse oximetry reveals hypoxia. After an episode of hypoxia, the infusion should not be resumed. For any potentially serious adverse reaction, the home healthcare provider must assess the participant, administer oxygen in case of hypoxia, and should contact local emergency services and the investigator, if warranted.

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

For lactating participants, the investigator and participant should weigh the developmental and health benefits of breastfeeding against any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition. Participants may continue to breastfeed or express milk to feed their infant during the infusion if the benefit is deemed to outweigh the risk.

Participants will also be monitored during the infusion for worsening of depressive symptoms or emergent suicidal thoughts and behaviors.

In addition to local monitoring in the home, oxygen saturation, respiratory rate, blood pressure, and heart rate will also be remotely monitored throughout the duration of the infusion using a wearable device.

Compliance to safe-use conditions, processes, and procedures will be assessed by human factors (HF) researchers. Throughout the duration of the infusion, home healthcare provider staff will complete checklists and/or journals at the end of each day and/or shift to document any use-related issues. Any use-related issues determined to be critical in nature will be followed up immediately by an HF team member so that the information is recent and can be reported and root caused adequately.

Upon completion of the infusion, an HF team member will conduct a post-infusion remote interview with the home healthcare provider to assess their comprehension of and compliance to processes and procedures and to identify potential procedural changes specifically for ZULRESSO administration in a home setting, with the goal of further mitigating any use-related issues or errors from occurring in the home setting. Situations such as difficulties performing the tasks required to administer the infusion, procedural challenges, and unforeseen circumstances (eg, childcare issues, participant attempts to drive) will be documented.

After completing or discontinuing the ZULRESSO infusion, the participants' level of sedation should be assessed. Participants will be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving, until any sedative effects have dissipated. The home healthcare provider who completes the infusion must not leave the participant's home until she or he, in consultation with the investigator as needed, determines that any sedative effects have resolved and there are no safety risks to the participant. The home healthcare provider must also ensure that the SAE/AESI form(s), if applicable, have been completed and submitted to the investigator prior to leaving the participant's home.

[redacted]

[redacted]

Number of Participants (planned): Up to 50 participants.

Eligibility Criteria:

Inclusion Criteria:

1. Ambulatory female ≥18 years of age
2. Participant has a current diagnosis of PPD, as confirmed by the investigator
3. Participant agrees not to be the primary caregiver of any dependents during the infusion and must be accompanied by another adult (other than the home healthcare provider) during interactions with their child(ren)
4. Participant has no history of sleep apnea or any clinically significant respiratory conditions
5. Participant agrees to refrain from the use of central nervous system depressants, such as opioids, benzodiazepines, sleep aids and from drinking alcohol during the infusion
6. Participant is suitable for administration of ZULRESSO in a home setting, as per the judgement of the investigator
7. Participant's home is suitable and has necessary provisions for administration of ZULRESSO and meets the following criteria:
   - safe environment for the home infusion provider staff
   - access to a working telephone
   - electricity and grounded electrical outlets
   - running water
   - access to back-up emergency services (911 service or ambulance availability)
   - sanitary environment
8. Participant agrees to stay at home until the end-of-study visit has been completed, except for a medical emergency
9. Participant must have a negative pregnancy test at screening and on Day 1 prior to the start of the ZULRESSO infusion

Exclusion criteria:

1. Participant has end stage renal failure
2. Participant has known allergy to progesterone or allopregnanolone or any excipients in the brexanolone injection
3. Participant is currently at risk of suicide, as judged by the investigator, or has attempted suicide associated with the current episode of PPD

Investigational Product, Dosage and Mode of Administration:

ZULRESSO will be administered as a single, continuous, 60-hour IV infusion, administered according to the following dose regimen.

Time point	Day 1 0 to 4 hours	Day 1 4 to 24 hours	Day 2-3 24 to 52 hours	Day 3 52 to 56 hours	Day 3 56 to 60 hours
Dose	30 mcg/kg/h	60 mcg/kg/h	90 mcg/kg/h [a]	60 mcg/kg/h	30 mcg/kg/h

[a] A reduction in dosage to 60 mcg/kg/h may be considered during this time period for participants who do not tolerate 90 mcg/kg/h

Duration of Treatment:

Each participant will receive a single 60-hour IV infusion of ZULRESSO.

Statistical Methods:

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

General Considerations

For the purpose of all primary and secondary analyses where applicable, baseline is defined as the last measurement prior to initiation of the 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.

Analysis Sets

The Safety Set will include all participants administered IP.

All statistical analyses will be based on summarized data.

Safety Analysis

Incidence of TEAEs will be summarized using descriptive statistics. All analysis will be based on the Safety Set.

Sample Size Calculation

The sample size is based on assuming a 7% incidence rate of TEAEs leading to IP discontinuation or interruption, which is the rate observed in the post-marketing setting. With 50 participants who receive ZULRESSO, the probability is 0.87 for observing at least 2 events; 0.69 for observing at least 3 events, and 0.47 for observing at least 4 events.

Table 3: Schedule of Assessments

	Screening/ Baseline (Remote or In-person)	**60-Hour ZULRESSO Home Infusion**	**Post-Infusion/ET**
Study Procedure	**Day -28 to Day -1**	**Days 1 to 3 (0 to 60 hours)**	**Day 3 (>60 hours)**
Informed consent	X		
Inclusion/exclusion criteria	X	X (confirm participant continues to meet eligibility criteria prior to start of infusion)	
Demographics/medical and surgical history	X		
Body weight/height [1]	X	X (prior to start of infusion)	
Pregnancy test (urine)	X	X (prior to start of infusion)	
Participant training by home healthcare provider		X (prior to start of infusion)	
Vital signs [2]		X	
ZULRESSO infusion at home		X	
Continuous pulse oximetry (local monitoring) [3]		X	
Remote monitoring of oxygen saturation and heart rate via wireless pulse oximeter		X	
Monitoring for excessive sedation		X (every 2 hours during planned nonsleep periods)	
Daily and/or end-of-shift checklist/journal completed by home healthcare providers to document any use-related issues	X		X

	Screening/ Baseline (Remote or In-person)	60-Hour ZULRESSO Home Infusion	Post-Infusion/ET
Study Procedure	**Day -28 to Day -1**	**Days 1 to 3 (0 to 60 hours)**	**Day 3 (>60 hours)**
Post-infusion interview of home healthcare provider(s) conducted by HF researchers			X
Home healthcare provider to complete and submit SAE/AESI form(s), if applicable			X (prior to leaving participant's home)
[redacted]			
Adverse events[4]	X		
Prior/concomitant medications[4,5]	X		

Abbreviations: BP = blood pressure; ET = early termination; HF = human factors; HR = heart rate; RR = respiratory rate.

Note: Use of telehealth by the investigator is permitted for the screening visit, in addition to remote assessments conducted during the ZULRESSO infusion, as required.

[1] After the participant provides informed consent, a body weight scale will be delivered to the participant's home. The participant will weigh herself on the scale approximately 7 days prior to Day 1 and report her body weight to study personnel. Body weight at screening/baseline is used to calculate ZULRESSO dose and to be confirmed by the home healthcare provider on Day 1 to determine whether any change to ZULRESSO dose is required. Height will be collected at Day 1.

[2] Vital signs include BP, RR, HR, and oxygen saturation. o Oxygen saturation, RR, and HR collection will begin immediately prior to the start of the infusion and will be monitored continuously through a wearable device. BP will be collected prior to the start of the infusion, and all vital signs will be recorded in the event of excessive sedation, loss of consciousness, or any other adverse event of special interest.

[3] Oxygen saturation will only be recorded in the event of excessive sedation, loss of consciousness, hypoxia, or adverse event of special interest (AESI).

[4] Information regarding diagnosis, isolation, and/or hospitalization due to COVID-19 will be documented as part of medical history, AE collection, and prior/concomitant medication/procedure collection at screening and throughout the study.

[5] Prior medications will be collected at screening and concomitant medications and/or procedures will be collected thereafter.

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

TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 4: Abbreviations and Specialist Terms

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
eCRF	electronic case report form
FDA	Food and Drug Administration
$GABA_A$	γ-aminobutyric acid-ligand gated chloride channel
GCP	good clinical practice
HF	human factors
ICD-10	International Classification of Diseases
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PPD	postpartum depression
REMS	Risk Evaluation and Mitigation Strategies
SAE	serious adverse event
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event

5. INTRODUCTION

Postpartum depression (PPD) is a serious mood disorder estimated to affect approximately 10% to 20% of women giving birth globally. In the United States, estimates of new mothers identified with PPD each year vary by state from 10% to 24% with an overall average of 13.2% (Bauman 2020). PPD is defined in both the International Classification of Diseases (ICD)-10 (World Health Organization 2010) and Diagnostic and Statistical Manual of Mental Disorders (DSM-5 2013) as a major depressive episode in the postpartum period with marked impairment in functioning. PPD often co-occurs with anxiety. PPD is a leading cause of maternal mortality (Savitz 2011) and, by affecting maternal functioning, poses serious risks to the emotional, cognitive, behavioral, and physical development of the infant and siblings (CPS 2004; Noorlander 2008). Findings from several studies implicate that peripartum fluctuations in reproductive hormones (in particular, the major progesterone metabolite, allopregnanolone) have a pivotal pathophysiological role in PPD (Bloch 2000; Kanes 2017; Shule 2014).

Allopregnanolone is a metabolite of progesterone created by the actions of 5-α reductase and 3-α hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of synaptic and extrasynaptic γ-aminobutyric acid-ligand gated chloride channel ($GABA_A$) receptors. Plasma allopregnanolone concentrations rise in concert with progesterone throughout pregnancy, reaching the highest physiological concentrations in the third trimester (Maguire 2009). After childbirth, these concentrations decrease abruptly (Nappi 2001). Failure of $GABA_A$ receptors to adapt to these changes at parturition has been postulated to have a role in triggering PPD (Maguire 2008). Allopregnanolone and pharmacologically similar compounds have been shown to have profound effects on anxiety and depression in animal models (Paul 1992; Maguire 2008).

5.1. Brexanolone (ZULRESSO®)

Brexanolone injection is approved by the US FDA under the trade name ZULRESSO for the treatment of PPD in adults.

The brexanolone drug product is a proprietary formulation of brexanolone drug substance (chemically identical to endogenous allopregnanolone) and excipients.

In clinical studies with ZULRESSO, rapid improvements in depressive symptoms were observed by the end of a 60-hour infusion, and these improvements were observed out to 4 weeks beyond the end of the infusion. For details on the pharmaceutical properties of brexanolone, and results from nonclinical and clinical studies, see the brexanolone Investigator's Brochure.

5.2. Study Rationale

In the US, ZULRESSO is available commercially only through a restricted program called the ZULRESSO Risk Evaluation and Mitigation Strategy (REMS) due to the risk of serious harm resulting from excessive sedation or sudden loss of consciousness during the infusion. The requirement for ZULRESSO to be administered only to patients in a medically supervised healthcare setting limits patient access to ZULRESSO for the treatment of PPD. There is, therefore, a need to increase patient access to ZULRESSO while assuring safe use. Use of ZULRESSO in the home setting has the potential to increase patient access to ZULRESSO while

maintaining the appropriate REMS requirements with elements to assure safe use in the home (eg, education of patients and healthcare providers on the risk of excessive sedation and loss of consciousness, monitoring of patients for excessive sedation by a healthcare provider, and collection of safety data for any events of excessive sedation or loss of consciousness).

5.3. Dose Justification

The dose for this study is consistent with the recommended dose in the FDA-approved US Prescribing Information, which is a continuous 60-hour IV infusion, administered as follows:

- 0 to 4 hours: Initiate with a dosage of 30 mcg/kg/h
- 4 to 24 hours: Increase dosage to 60 mcg/kg/h
- 24 to 52 hours: Increase dosage to 90 mcg/kg/h (a reduction in dosage to 60 mcg/kg/h may be considered during this time period for participants who do not tolerate 90 mcg/kg/h)
- 52 to 56 hours: Decrease dosage to 60 mcg/kg/h
- 56 to 60 hours: Decrease dosage to 30 mcg/kg/h

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective

The primary objective of the study is to evaluate whether the safe-use conditions for administration of ZULRESSO can be implemented in a home setting.

6.2. Secondary Objective

The secondary objective of the study is:

- To identify any process and procedural changes to be implemented for ZULRESSO administration at home

[redacted]

6.4. Endpoints

6.4.1. Primary Endpoint

- Incidence of treatment-emergent adverse events (TEAEs) leading to dose interruption/discontinuation.

6.4.2. Secondary Endpoints

- Incidence of nonadherence with the safe-use conditions for administration of ZULRESSO
- Incidence of use-related issues related to the home administration of ZULRESSO
- Incidence of all TEAEs
- Incidence of medication error

[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is an open-label, multicenter study designed to assess the safe-use conditions for administration of ZULRESSO in a home setting to women with PPD with the overall goal to improve patient access to ZULRESSO treatment. The safety monitoring plan for this study incorporates safe-use conditions that are aligned with that of the FDA-approved ZULRESSO REMS and ZULRESSO prescribing information. A home infusion provider is responsible for implementing the safe-use conditions for administering ZULRESSO in the home setting. An overview of roles and responsibilities of study personnel is provided in Table 2.

This study consists of a screening period of up to 28 days and a 60-hour home infusion of ZULRESSO (Days 1 through 3). A home infusion provider will provide, oversee, and train pharmacy staff and home healthcare provider staff involved in dispensing and administering ZULRESSO in this study. All investigators and all pharmacy and home healthcare provider staff involved in dispensing and administering ZULRESSO will be trained regarding the risk of serious harm resulting from excessive sedation and sudden loss of consciousness during the administration of ZULRESSO. Home healthcare providers will also counsel participants regarding this risk and the importance of reporting any symptoms to a healthcare provider. Use of telehealth by the investigator is permitted for screening and remote assessments for monitoring or oversight of participants during the ZULRESSO infusion, as required.

All necessary equipment and supplies (eg, pulse oximeter, body weight scale, etc) used to conduct the study will be delivered by a home healthcare provider or shipped to the participant's home.

The screening period begins with the informed consent process, which may be conducted electronically. Consented participants will undergo remote or in-person screening procedures to determine eligibility.

During the treatment period, a home healthcare provider will arrive at the eligible participant's home on Day 1 to initiate the 60-hour intravenous (IV) infusion of ZULRESSO. The home healthcare provider must confirm that the participant continues to meet all of the eligibility criteria and complete any predose assessments per Table 3 prior to administering the infusion.

The open-label 60-hour infusion will be administered as follows: 30 mcg/kg/hour (Hour 0 to 4), then 60 mcg/kg/hour (Hour 4 to 24), then 90 mcg/kg/hour (Hour 24 to 52), followed by 60 mcg/kg/hour (Hour 52 to 56), and 30 mcg/kg/hour (Hour 56 to 60). A programmable peristaltic infusion pump with alarm is to be used to ensure accurate delivery of ZULRESSO. The pump will be preprogrammed by home infusion provider pharmacy staff. If necessary, the home healthcare provider may reprogram the pump as described in Section 10.5.

Due to the risk of excessive sedation and sudden loss of consciousness, for the duration of the infusion, participants must be monitored for hypoxia using continuous pulse oximetry equipped with an alarm and must be assessed for excessive sedation by a home healthcare provider every 2 hours during planned nonsleep periods. At least 1 home healthcare provider must be continuously available on site in the participant's home for the duration of the ZULRESSO infusion to monitor the participant and intervene as necessary. The participant must not be the primary caregiver of her dependent(s) and must be accompanied by another adult (other than the

home healthcare provider) during any interactions with her child(ren) that occur during the infusion. If the participant becomes the primary caregiver of dependent(s) at any point during the infusion, the infusion must be stopped and will not be resumed.

All home healthcare providers will have 24 hours/day access to home infusion nursing and pharmacy staff via telephone for any problems with the infusion pump, IV lines, or other equipment malfunctions. The investigator will be available 24 hours/day to address protocol-related queries/issues in addition to safety-related concerns.

If excessive sedation or loss of consciousness occur at any time during the infusion, the infusion will be stopped until the symptoms resolve. The infusion may be resumed at the same or lower dose as deemed clinically appropriate by the investigator.

The infusion will be immediately stopped if pulse oximetry reveals hypoxia. After an episode of hypoxia, the infusion should not be resumed. For any potentially serious adverse reaction, the home healthcare provider must assess the participant, administer oxygen in case of hypoxia, and should contact local emergency services and the investigator, if warranted.

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

For lactating participants, the investigator and participant should weigh the developmental and health benefits of breastfeeding against any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition. Participants may continue to breastfeed or express milk to feed their infant during the infusion if the benefit is deemed to outweigh the risk.

Participants will also be monitored during the infusion for worsening of depressive symptoms or emergent suicidal thoughts and behaviors (see Section 12.1.7).

In addition to local monitoring in the home, oxygen saturation and heart rate will also be remotely monitored throughout the duration of the infusion using a wearable device.

Compliance to safe-use conditions, processes, and procedures will be assessed by human factors (HF) researchers through evaluation of daily and/or end-of-shift checklists and/or journals completed by home healthcare provider staff (see Section 12.1.10).

Upon completion of the infusion, an HF team member will conduct a post-infusion remote interview with the home healthcare provider to assess their comprehension of and compliance to processes and procedures and to identify potential procedural changes specifically for ZULRESSO administration in a home setting, with the goal of further mitigating any use-related issues or errors from occurring in the home setting (see Section 12.1.11).

After completing or discontinuing the ZULRESSO infusion, the participants' level of sedation should be assessed. Participants will be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving, until any sedative effects have dissipated. The home healthcare provider who is present when the participant completes the infusion must not leave the participant's home until she or he, in consultation with the investigator as needed, determines that any sedative effects have resolved and there are no safety risks to the participant. The home healthcare provider must also ensure that the SAE/AESI form(s), if applicable, have been completed and submitted to the investigator as described in Section 12.2.3 prior to leaving the participant's home.

[redacted]

7.2. Number of Participants

Up to 50 participants may participate.

7.3. Treatment Assignment

In this open-label study, participants will be administered a single, continuous, 60-hour, IV infusion of ZULRESSO starting on Day 1.

7.4. Dose Adjustment Criteria

If excessive sedation occurs at any time during the infusion, the infusion will be stopped until the symptoms resolve. The infusion may be resumed at the same or lower dose as clinically appropriate. The infusion will be immediately stopped if pulse oximetry reveals hypoxia. After an episode of hypoxia, the infusion should not be resumed.

For participants who do not tolerate the 90 mcg/kg/hour dose for reasons other than hypoxia, a reduction to 60 mcg/kg/hour may be considered during the time period that the 90 mcg/kg/hour is scheduled to occur.

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

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

7.5. Criteria for Study Termination

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

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Participant Inclusion Criteria

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

1. Ambulatory female ≥18 years of age
2. Participant has a current diagnosis of PPD, as confirmed by the investigator
3. Participant agrees not to be the primary caregiver of any dependents during the infusion and must be accompanied by another adult (other than the home healthcare provider) during interactions with their child(ren)
4. Participant has no history of sleep apnea or any clinically significant respiratory conditions
5. Participant agrees to refrain from the use of central nervous system depressants, such as opioids, benzodiazepines, sleep aids and from drinking alcohol during the infusion
6. Participant is suitable for administration of ZULRESSO in a home setting, as per the judgement of the investigator
7. Participant's home is suitable and has necessary provisions for administration of ZULRESSO and meets the following criteria:
   - safe environment for the home infusion provider staff
   - access to a working telephone
   - electricity and grounded electrical outlets
   - running water
   - access to back-up emergency services (911 service or ambulance availability)
   - sanitary environment
8. Participant agrees to stay at home until the end-of-study visit has been completed, except for a medical emergency
9. Participant must have a negative pregnancy test at screening and on Day 1 prior to the start of the ZULRESSO infusion

8.2. Participant Exclusion Criteria

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

1. Participant has end stage renal failure
2. Participant has known allergy to progesterone or allopregnanolone or any excipients in the brexanolone injection
3. Participant is currently at risk of suicide, as judged by the investigator, or has attempted suicide associated with the current episode of PPD

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 serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number.

8.4. Investigational Product Discontinuation and Early Termination from the Study

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

The 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 electronic case report form (eCRF).

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 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 eCRF.

8.4.2. Early Termination from the Study

At the time of study withdrawal/stopping study participation, if possible, the assessments listed for the post-infusion 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.

8.4.3. Loss to Follow up

Not applicable

9. TREATMENT OF PARTICIPANTS

9.1. Description of Investigational Product

Brexanolone (ZULRESSO) is a sterile, clear, colorless solution that must be diluted prior to administration as an IV infusion. ZULRESSO 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 Investigator's Brochure.

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

9.2.1. Prior and Concomitant Medications and/or Supplements

Participants may receive standard of care for patients diagnosed with PPD, including psychosocial interventions. Any concomitant medication determined medically necessary for the welfare of the participant may be given at the discretion of the investigator at any time during the study.

All medications taken from signing of informed consent through the final study visit (including start and end dates, route, dose/units, frequency, and indication) will be recorded on the appropriate eCRF.

9.2.2. Prohibited Medications

Concomitant use of opioids, central nervous system depressants, such as benzodiazepines, or other drugs interacting with the $GABA_A$ receptor are prohibited in this study as these drugs may increase the risk for sedation-like AEs if administered concomitantly with ZULRESSO.

9.2.3. Other Restrictions

The participant should not engage in potentially hazardous activities requiring mental alertness and should not drive a car until after completion of the ZULRESSO infusion and until any feelings of sedation have dissipated. The participant must not leave her house for the duration of the infusion except in the case of a medical emergency. The participant must be accompanied during interactions with her child(ren) by at least 1 adult (other than the home healthcare provider) for the duration of the infusion.

Alcohol consumption while receiving ZULRESSO is prohibited.

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

9.3. Intervention after the End of the Study

Not applicable

9.4. Treatment Adherence

IP will be administered to participants by home healthcare provider staff, as described in Section 10.5. The 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 an open-label study in which all participants will receive ZULRESSO.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

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

10.2. Investigational Product Packaging and Labeling

IP will be provided to the home infusion provider.

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.

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

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

10.3. Investigational Product Storage

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.

Once the admixture in IV bags is dispensed to the participant's home, the IV bags should be stored under refrigerated conditions. IV bags may be stored refrigerated for up to 96 hours after they are admixed.

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

10.4. Investigational Product Preparation

The home infusion provider pharmacist or qualified designee will be responsible for preparing IP for dosing.

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, by a home healthcare provider in the participant's home. The prepared admixture will be administered at room temperature.

The specific infusion dose of IP will be calculated based on weight (obtained at screening and verified on Day 1 prior to the start of the infusion) for each participant and will be administered according to the dose regimen in Table 5.

Table 5: Infusion Rate

Time point	Day 1 0 to 4 hours	Day 1 4 to 24 hours	Day 2 to 3 24 to 52 hours	Day 3 52 to 56 hours	Day 3 56 to 60 hours
Dose	30 mcg/kg/h	60 mcg/kg/h	90 mcg/kg/h	60 mcg/kg/h	30 mcg/kg/h

The dose regimen will be preprogrammed into the infusion pump by the pharmacist or qualified designee. If necessary, the home healthcare provider may reprogram the pump in consultation with the home infusion provider pharmacy staff for any issues unrelated to safety. If the pump must be reprogrammed during the infusion due to safety, the home healthcare provider must consult the investigator and if necessary, the pharmacist or qualified designee.

Dosing should begin in the morning (on Day 1) to allow for recognition of excessive sedation during planned nonsleep periods when the dose increases to 60 mcg/kg/hour and subsequently to 90 mcg/kg/hour.

Dose adjustments are permitted as described in Section 7.4.

Administration of prepared IV bags at room temperature should not exceed 12 hours (ie, IV bags should be changed at least every 12 hours).

Refer to the pharmacy manual for complete details on preparation and administration.

10.6. Investigational Product Accountability, Handling, and Disposal

Upon receipt of IP (vials), the responsible pharmacist or qualified 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 pharmacist or qualified designee will ship the prepared infusion bags and ancillary supplies (see Section 10.8) to the participant's home. Participants will be instructed not to open shipments. Upon arrival at the participant's home on Day 1, the home healthcare provider will be responsible for opening and assessing the shipped supplies.

The home healthcare provider should check the prepared infusion bags and ancillary supplies and verify proper identity, quantity, integrity, and temperature conditions, and report any deviations, dispensing errors, or discrepancies to the sponsor, the investigator, and the home infusion provider immediately.

The home healthcare provider will access the telemedicine platform upon arrival to the participant's home prior to initiation of the IP infusion. Via the telemedicine platform, the home healthcare provider will provide the necessary participant-identifying information, including the participant identification number assigned at screening, and obtain the medication identification number for the IP to be dispensed and the weight-based dosing information for that participant. The medication ID number that was received at the participant's home must be recorded.

The IP provided is for use only as directed in this protocol. The investigator, pharmacist or qualified designee, and other home infusion provider staff involved in dispensing and administering the IP infusion must keep a record of all IP and ancillary supplies (see Section 10.8) received, used, and returned/discarded.

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, and other home infusion provider staff are responsible for IP and ancillary supply accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

At the end of the infusion for each participant, all used and unused IV bags will be returned to the home infusion provider for destruction per the home infusion provider's procedures; disposition of IP will be documented. IP may not be destroyed until accountability and reconciliation procedures have been completed.

10.7. Product Complaints

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

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

10.8. Ancillary Supplies

The home infusion provider will provide PVC, non-DEHP, nonlatex infusion sets and a programmable peristaltic infusion pump with alarm for each participant. The pharmacist or qualified designee will ship the infusion sets and preprogrammed infusion pump to the participant's home prior to Day 1. At the end of the infusion for each participant, the infusion set(s) and pump will be returned to the home infusion provider per the home infusion provider's procedures; disposition of ancillary supplies will be documented.

11. EFFICACY AND CLINICAL PHARMACOLOGY ASSESSMENTS

11.1. Efficacy Assessments

Not applicable

11.2. Clinical Pharmacology Assessments

Not applicable

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

All assessments will be recorded at the time points summarized in the Schedule of Assessments (Table 3).

12.1.1. Demography and Medical History

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

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

12.1.2. Weight and Height

After the participant provides informed consent, a body weight scale will be delivered to the participant's home. The participant will weigh herself on the scale approximately 7 days prior to Day 1 and report her body weight to study personnel. Body weight at screening/baseline is used to calculate ZULRESSO dose and is to be confirmed by the home healthcare provider on Day 1 prior to dosing to determine whether any change to ZULRESSO dose is required.

12.1.3. Vital Signs

Vital signs include blood pressure, respiratory rate, heart rate, and oxygen saturation. Blood pressure should be collected in the supine position at all scheduled time points. Respiratory rate, heart rate, and oxygen saturation will be monitored continuously through a wearable device. The wearable device may also track additional patient parameters such as body temperature and step count that will not be collected in the telemedicine platform or study database.

Additionally, vital signs should be collected 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 in the eCRF. Collection of vital signs should occur per local clinical practice, at a minimum until the participant is considered to have recovered from the event.

12.1.4. Oxygen Saturation

Participants will be monitored for hypoxia using continuous pulse oximetry equipped with an alarm. Oxygen saturation will only be recorded in the event of excessive sedation, loss of consciousness, hypoxia, or AESI. The infusion will be immediately stopped if pulse oximetry reveals hypoxia. After an episode of hypoxia, the infusion should not be resumed.

For any potentially serious adverse reaction, the home healthcare provider must assess the participant and administer oxygen in case of hypoxia and should contact local emergency services and the investigator, if warranted.

12.1.5. Remote Monitoring of Oxygen Saturation and Vital Signs

In addition to local monitoring in the home, oxygen saturation and vital signs will also be remotely monitored continuously throughout the duration of the infusion using a wireless,

[redacted]

12.1.6. Monitoring for Excessive Sedation

For the duration of the infusion, participants must be assessed for excessive sedation by a healthcare provider every 2 hours during planned nonsleep periods. If excessive sedation occurs at any time during the infusion, the infusion will be stopped until the symptoms resolve. The infusion may be resumed at the same or lower dose as clinically appropriate (see Section 7.4), and an AESI is to be reported (see Section 12.2.3).

For any potentially serious adverse reaction, the home healthcare provider must assess the participant and should contact local emergency services and the investigator, if warranted.

12.1.7. Suicidal Thoughts and Behaviors

Participants should be counseled before the start of the ZULRESSO infusion to pay close attention to any changes related to suicidal thoughts or behaviors, especially sudden changes in mood, behavior, thoughts, or feelings; participants should tell the healthcare provider right away if she has any new or sudden changes in mood, behavior, thoughts, or feelings.

The investigator should consider changing the therapeutic regimen, including discontinuing ZULRESSO, in participants whose depression becomes worse or who experience emergent suicidal thoughts and behaviors.

12.1.8. Pregnancy Screen

A urine pregnancy test will be conducted for all participants at screening; a urine pregnancy test will be conducted on Day 1 prior to the start of the infusion.

12.1.9. Nonadherence with the Safe-use Conditions for Administration of ZULRESSO

A secondary endpoint of this study is incidence of nonadherence with the safe-use conditions for administration of ZULRESSO. Nonadherence with safe-use conditions for administration of ZULRESSO in the home setting is defined by any of the following:

- Failure of the home infusion provider to train all pharmacy and home healthcare provider staff involved in dispensing and administration of ZULRESSO on risk of excessive sedation and loss of consciousness
- Failure of home healthcare providers to counsel participants on risk of excessive sedation and loss of consciousness
- Failure of home infusion provider to deliver ZULRESSO as per protocol requirements
- Failure to provide preprogrammed peristaltic pump with alarm
- Failure by the home healthcare provider to assess for excessive sedation every 2 hours during planned nonsleep periods

- Failure to have at least one home healthcare provider continuously available on site in the participant's home for the duration of the ZULRESSO infusion
- Failure to have fall protocol in place
- Failure to continuously monitor participants with pulse oximeter with alarm
- Failure to stop infusion when participant is primary caregiver of dependents
- Failure by the home healthcare provider to change the infusion bag according to the protocol
- Failure to stop the infusion upon identification of excessive sedation, loss of consciousness, or hypoxic episode
- Infusion resumed after an episode of hypoxia
- Failure to caution participants post-infusion against engaging in potentially hazardous activities requiring mental alertness, such as driving, until any sedative effects have dissipated
- Failure to complete the AESI/SAE form(s), as applicable

12.1.10. Daily and/or End-of-Shift Checklist/Journal

Throughout the duration of the infusion, home healthcare provider staff will complete checklists and/or journals at the end of each day and/or shift to document any use-related issues, including how the issues were addressed and followed-up. Any use-related issues determined to be critical in nature will be followed up immediately by a remote HF team member so that the information is recent and can be reported adequately and analyzed for root causes. This also includes nonadherence issues in relation to safe-use conditions for administration of ZULRESSO as described in Section 12.1.9.

12.1.11. Post-infusion Interview of Home Healthcare Providers

An HF team member will conduct a post-infusion remote interview (no more than 3 days after completion of the infusion) with the home healthcare provider to assess their comprehension of and compliance to processes and procedures and to identify potential procedural changes specifically for ZULRESSO administration in a home setting. Situations such as difficulties performing the tasks required to administer the infusion, procedural challenges, and unforeseen circumstances (eg, childcare issues, participant attempts to drive) will be documented.

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12.2. Adverse and Serious Adverse Events

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 study.

Laboratory abnormalities and changes from baseline in vital signs, and ECGs are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the investigator considers them to be clinically significant. Any abnormalities that meet the criteria for a serious adverse event (SAE) should be reported in an expedited manner (see Section 12.2.6). Laboratory abnormalities and changes from baseline in vital signs and ECGs that are clearly attributable to another AE do not require discrete reporting (eg, electrolyte disturbances in the context of dehydration, chemistry and hematologic disturbances in the context of sepsis).

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

Participants who discontinue the IP due to an AE, regardless of investigator-determined causality, should be followed until the event is resolved, considered stable, or the investigator determines the event is no longer clinically significant. Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF (which includes the telemedicine platform). The sponsor or its representative retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.2. Serious Adverse Event Definition

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

- Results in death
- Places the participant at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient 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 one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

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

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

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

12.2.3. Definition of Adverse Events of Special Interest

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

The following events are considered AESIs and should be reported on the SAE/AESI form within 72 hours.

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

If the AESI also qualifies as an SAE, the SAE/AESI form should be submitted per the guidelines per Section 12.2.6. At the end of the ZULRESSO infusion, the home healthcare provider must ensure the SAE/AESI form(s), if applicable, have been submitted prior to leaving the participant's home.

12.2.4. Relationship to Investigational Product

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

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

12.2.5. Recording Adverse Events

Adverse events spontaneously reported by the participant and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, outcome and seriousness (if applicable), and whether the AE

resulted in IP dose reduction or interruption, discontinuation of the IP, or withdrawal from the study.

Intensity will be assessed according to the following scale:

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

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

12.2.6. Reporting Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE(s), the investigator 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 report form, verify the accuracy of the information recorded on the SAE report form with the corresponding source documents, and send a copy to Sage 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 report form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

Serious adverse events occurring after the designated follow-up time for the study, should be reported to Sage 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 in participants who are under his or her oversight. Investigators will also be notified of all suspected unexpected serious adverse reactions (SUSARs) that occur during the clinical study. IRBs/IECs will be notified of SAEs and/or SUSARs as required by local law.

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

12.3. Pregnancy

Based on findings from animal studies of other drugs that enhance GABAergic inhibition, ZULRESSO may cause fetal harm. If a participant becomes pregnant after the first administration of IP, pregnancy information must be collected and recorded on the Pregnancy Form and submitted to 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

Overdoses in the absence of clinical signs and symptoms should not be recorded as a separate AE on the eCRF; 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. If an overdose results in an AE, the AE must be recorded.

12.5. Medication Error

Medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. All medication errors must be recorded and sent to Sage or designee within 24 hours of the site becoming aware of the medication error. The medication error must be reported to Sage or designee even if the medication error does not result in an AE. If a medication error results in an AE, the AE must be recorded and reported as described in Section 12.2.

13. STATISTICS

Detailed description of the analyses to be performed in the study will be provided in the statistical analysis plan (SAP). The SAP will be finalized and approved prior to database lock. 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 Safety Set will include all participants administered ZULRESSO.

13.2. Handling of Missing Data

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

13.3. General Considerations

For the purpose of all primary and secondary analyses where applicable, baseline is defined as the last measurement prior to initiation of the ZULRESSO 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 (eg, weight), will be summarized using the Safety Set.

Pregnancy test results will be listed but not summarized.

Medical history will be listed by participant.

13.5. Efficacy Analysis

Not applicable

13.6. Safety Analyses

Safety data collected in this study (ie, AEs, concomitant medication usage, changes from baseline in vital signs, nonadherence with safe-use conditions with administration of ZULRESSO, and [redacted]) will be listed by participant and summarized. All safety summaries will be performed on the Safety Set using treatment received.

13.6.1. Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or higher. A 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 (SOC) and preferred term. In addition, summaries will be provided by intensity (mild, moderate, severe) and by causality (related, not related) to IP.

Any TEAEs leading to IP discontinuation, dose reduction or interruption, 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. 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. Vital sign results will be listed by participant and timing of collection.

13.6.3. Oxygen Saturation

Oxygen saturation results at baseline and results recorded for any event of excessive sedation, loss of consciousness, hypoxia or AESI, if applicable, will be summarized. Oxygen saturation results, if applicable, will be listed by participant and timing of collection.

[redacted]

13.6.5. Nonadherence with Safe-use Administration of ZULRESSO

The incidence of nonadherence with safe-use administration of ZULRESSO will be summarized.

13.6.6. Use-related Issues Related to the Home Administration of ZULRESSO

Use-related issues of ZULRESSO will be summarized.

13.6.7. Medication Error

The incidence of medication error will be summarized.

[redacted]

13.6.9. Prior and Concomitant Medications

Medications will be recorded throughout the duration of 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.

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

13.6.10. Other Safety Analysis

Analysis of use-related issues and home healthcare provider comprehension of and compliance to processes and procedures will be described in the SAP.

13.7. Clinical Pharmacology Analyses

Not applicable.

13.8. Sample Size and Power

The sample size is based on assuming a 7% incidence rate of TEAEs leading to IP discontinuation or interruption, which is the rate observed in the post-marketing setting. With 50 participants who receive ZULRESSO, the probability is 0.87 for observing at least 2 events; 0.69 for observing at least 3 events, and 0.47 for observing at least 4 events.

13.8.1. Interim and Data Monitoring Committee Analyses

Not applicable.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of Sage Therapeutics will remotely assess the investigational study site per Sage SOPs to determine suitability of the investigator to oversee the clinical study and 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 the investigational team is adhering to the protocol, and that data are being accurately recorded
- Remotely review electronic source data collected through the telemedicine platform and review any participant medical records, 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 and SAEs have been properly documented in the telemedicine platform and confirm any AESIs or SAEs have been forwarded to Sage Therapeutics and those SAEs that met criteria for reporting have been forwarded to the IRB or IEC.

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). 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 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 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 study-related duties and functions conducted during the study. When the investigator retains the services of any individual or party to perform study-related duties and functions, the investigator must ensure the individual or party is qualified to perform study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed, and any data generated.

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

16. ETHICS

16.1. Ethics Review

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

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

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

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

16.2. Ethical Conduct of the Study

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

16.3. Informed Consent Process

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

When the participant decides to participate in the study, the participant (or the participant's legally authorized representative) must give informed consent by providing their handwritten signature executed to an electronic record. The electronic record must also capture and record the date that the participant (or the participant's legally authorized representative) provides informed consent. If any or all of the consent process takes place remotely and is not personally witnessed by study personnel, the electronic system must include a method to ensure that the person electronically signing the informed consent is the participant who will be participating in the study or is the participants' legally authorized representative. The electronic 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 electronic, signed Informed Consent Form. A copy of the electronic, signed Informed Consent Form must be given to the participant or to the participant's legally authorized representative.

Throughout the study participants should be informed of any changes made to the study and as new safety and or risk information becomes known. The provision of this information will be documented in the participant's source records, and when applicable, an updated ICF will be provided.

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. 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 investigational product. Sage is responsible to inform the investigator/institution as to when study documents no longer need to be retained.

18. PUBLICATION POLICY

All information concerning ZULRESSO 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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Protocol 547-PPD-404, Amendment 1

Date of Amendment: 23 June 2021

Assessment of Safe-Use Conditions for Administration of ZULRESSO in a Home Setting

Rationale for Protocol Amendment

The primary purpose for this protocol amendment is to address FDA comments regarding the recommendation to document ZULRESSO home infusion use-related issues. Associated changes to the amendment have been incorporated, including:

- Addition of incidence of use-related issues related to the home administration of ZULRESSO as a secondary endpoint.
- Clarification on documenting situations such as difficulties performing the tasks required to administer the infusion, procedural challenges, and unforeseen circumstances (eg, childcare issues, participant attempts to drive, etc.).

Other changes incorporated with this amendment include the following:

- Correction to the synopsis stating that the SAE/AESI form must be completed and submitted to the investigator (instead of the post infusion/loss of consciousness form) to align with the protocol body.
- Clarification on the schedule of the vital signs collection (in Table 3, Schedule of Assessments footnotes).
- Clarification on vital signs remote monitoring and reporting.
- Clarification on medication error definition and reporting.
- Clarification on documenting information regarding diagnosis, isolation, and/or hospitalization due to COVID-19 as part of medical history (in Table 3, Schedule of Assessments footnotes).
- Clarification on the schedule of AEs and prior/concomitant medication/procedure collection (in Table 3, Schedule of Assessments footnotes).
- Minor textual changes have been made throughout the protocol to increase clarity of the study procedures.
- Minor corrections to typographical errors, punctuation, grammar, abbreviations, and formatting have been made.

Confidential Information