

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211371Orig1s000

OTHER REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation I
DIVISION OF PSYCHIATRY PRODUCTS

NDA/BLA #s: NDA 211371
Products: Zulresso (brexanolone injection) 5 mg/ml for intravenous use
APPLICANT: SAGE THERAPEUTICS INC
FROM: Marc Stone, M.D., Deputy Director for Safety
DATE: *see DARRTS date stamp*

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use (ETASU) is necessary for Zulresso to ensure that the benefits of the drug outweigh the risks of serious harm resulting from excessive sedation and sudden loss of consciousness during Zulresso infusion. In reaching this determination, we considered the following:

- A. Estimates of Postpartum depression (PPD) prevalence in the United States vary by state from 8.0% to 20.1% with an overall average of 11.5%. This estimate is based on: Ko JY, Rockhill KM, Tong VT, Morrow B, Farr SL. Trends in postpartum depressive symptoms – 27 states, 2004, 2008, and 2012. *MMWR Morb Mortal Wkly Rep.* 2017;66(6):153–8.
- B. Postpartum depression is a serious condition that is characterized by a major depressive episode temporally and pathophysiologically related to pregnancy. Postpartum depression is a common complication of childbirth, is potentially life-threatening due to risk of suicide, and confers enormous suffering for mothers, children, and families.
- C. Clinical evidence from studies of Zulresso as a treatment for PPD demonstrates a substantial and clinically meaningful improvement compared to currently available therapies (for the

treatment of major depressive disorder which have not been demonstrated to have adequate efficacy for PPD) while potentially avoiding prolonged exposure to side effects associated with available therapies.

- D. It is expected that patients will use Zulresso as a one-time treatment of PPD.
- E. Zulresso poses serious risks involving excessive sedation and sudden loss of consciousness. During premarketing clinical studies of Zulresso, sedation and somnolence that required dose interruption or reduction, was reported in 7% of Zulresso-treated patients compared to 0% of placebo-treated patients. Some patients were also reported to have loss of consciousness or altered state of consciousness during the Zulresso infusion (4% of the ZULRESSO-treated patients compared with 0% of the placebo-treated patients).
- F. Zulresso contains brexanolone, which is a new molecular entity.

The elements of the REMS will be ETASU B (healthcare settings and pharmacies that dispense Zulresso are specially certified), ETASU C (Zulresso is only dispensed to patients in a certified medically supervised healthcare setting), ETASU D (Zulresso is dispensed to patients with evidence or other documentation of safe-use conditions), ETASU E (each patient using Zulresso is subject to certain monitoring), and ETASU F (each patient using Zulresso is enrolled in a registry), an implementation system, and a timetable for submission of assessments.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERMIAS ZERISLASSIE
03/18/2019 11:01:06 AM

MARC B STONE
03/18/2019 12:22:53 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: March 14, 2019
Requesting Office or Division: Division of Psychiatry Products (DPP)
Application Type and Number: NDA 211371
Product Name and Strength: Zulresso (brexanolone) injection
100 mg/20 mL (5 mg/mL)
Applicant/Sponsor Name: Sage Therapeutics, Inc.
FDA Received Date: March 11, 2019 (via email)
OSE RCM #: 2018-850-1
DMEPA Safety Evaluator: Loretta Holmes, BSN, PharmD
DMEPA Team Leader: Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Psychiatry Products (DPP) requested that we review the revised container label and carton labeling for Zulresso (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review^a as well as other recommendations from the Agency.

2 CONCLUSION

Our recommendations were implemented and we find the revised container label and carton labeling acceptable from a medication error perspective. We have no further recommendations at this time.

^a Holmes, L. Label and Labeling Review for Zulresso (NDA 211371). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Sep 18. RCM No.: 2018-850.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LORETTA HOLMES
03/14/2019 02:39:21 PM

LOLITA G WHITE
03/14/2019 03:45:23 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

*****Pre-decisional Agency Information*****

Memorandum

Date: February 8, 2019

To: Latrice Wilson, Regulatory Project Manager
Division of Psychiatry Products (DPP)

Kimberly Updegraff, Associate Director of Labeling, DPP

From: Christine Bradshaw, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZULRESSO™ (brexanolone) injection, for intravenous use, [controlled substance schedule pending]

NDA: 211371/O-1

In response to DPP's consult request dated May 1, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide and carton and container labeling for the original NDA submission for ZULRESSO™ (brexanolone) injection, for intravenous use, [controlled substance schedule pending](Zulresso).

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPP (Kimberly Updegraff) on February 8, 2019, and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on January 30, 2019.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DPP (Latrice Wilson) on January 22, 2019, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Christine Bradshaw at (301) 796-6796 or Christine.Bradshaw@fda.hhs.gov.

19 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTINE J BRADSHAW
02/08/2019 03:51:31 PM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: January 30, 2019

To: Mitchell Mathis, MD
Director
Division of Psychiatry Products (DPP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Christine Bradshaw, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): ZULRESSO (brexanolone)

Dosage Form and Route: Injection, for intravenous use, (b) (4)

Application Type/Number: NDA 211371

Applicant: Sage Therapeutics

1 INTRODUCTION

On April 19, 2018, Sage Therapeutics, submitted for the Agency's review an original New Drug Application (NDA) for ZULRESSO (brexanolone) Injection, for intravenous use, (b) (4), for the proposed indication of use for the treatment of postpartum depression.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry Products (DPP) on May 1, 2018 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ZULRESSO (brexanolone) Injection, for intravenous use, (b) (4)

2 MATERIAL REVIEWED

- Draft ZULRESSO (brexanolone) MG received on April 19, 2018 and received by DMPP and OPDP on January 22, 2019.
- Draft ZULRESSO (brexanolone) Prescribing Information (PI) received on April 19, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 22, 2019.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

5 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHAWNA L HUTCHINS
01/30/2019 12:13:04 PM

CHRISTINE J BRADSHAW
01/30/2019 12:42:58 PM

LASHAWN M GRIFFITHS
01/30/2019 12:56:33 PM

MEMORANDUM

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research**



Date: January 15, 2019

To: Mitchell Mathis, M.D., Director
Division of Psychiatry Products

Through: Dominic Chiapperino, Ph.D., Director
Silvia Calderon, Ph.D., Senior Pharmacologist
Martin Rusinowitz, M.D., Senior Medical Officer
Controlled Substance Staff

From: Shalini Bansil, M.D., Medical Officer
Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: **Product name** Brexanolone (allopregnanolone) Injection
NDA Number: 211,371 (**IND Number:** 122,279)
Trade Name, dosages, formulations, routes: Zulresso 5 mg/mL solution provided in a 20-mL single-use vial, diluted prior to use, and administered intravenously (IV) as a 60-hour continuous infusion targeting a maximum therapeutic dose of 90 µg/kg/h.
Indication: Treatment of postpartum depression (PPD)
Sponsor: Sage Therapeutics
PDUFA Goal Date: March 19, 2018

Materials Reviewed:

All abuse-related data in Original NDA submission dated April 19, 2018, and subsequent amendments.

Table of Contents

I.	SUMMARY	2
1.	Background	2
2.	Conclusions	3
3.	Recommendations	3

II. DISCUSSION	4
1. Chemistry	4
1.1 Substance Information	4
2. Nonclinical Pharmacology	5
2.1 Receptor Binding and Functional Assays	5
2.2 Animal Behavioral Studies	5
2.3 Physical Dependence Studies in Animals	8
3. Clinical Pharmacology	10
4. Clinical Studies	10
4.1 Human Abuse Potential Study	10
4.2 Adverse Event Profile Through all Phases of Development	18
4.3 Safety Profile	22
4.4 Evidence of Abuse, Misuse and Diversion in Clinical Trials	23
4.5 Physical Dependence Studies in Humans	23
5. Regulatory Issues and Assessment	24
6. Other Relevant Information	24
III. REFERENCES	25

I. SUMMARY

1. Background

This memorandum responds to a consult request dated May 17, 2018, by the Division of Psychiatry Products (DPP). They request the Controlled Substance Staff (CSS) evaluate abuse-related preclinical and clinical data submitted by Sage Therapeutics in NDA 211,371 (IND 122,279) for Zulresso (Brexanolone [Allopregnanolone], previously known as SAGE-547), a 5 mg/mL solution administered intravenously (IV) as a 60-hour continuous infusion targeting a maximum therapeutic dose of 90 µg/kg/h. The drug product is indicated for the treatment of postpartum depression (PPD). Zulresso received Breakthrough Therapy Designation for the indication of PPD on August 23, 2016.

Postpartum depression is a serious illness which is characterized by a major depressive episode temporally related to parturition that results in significant functional impairment for the mother. It may be life-threatening due to suicidal ideation with potentially morbid consequences for mothers, children, and their families. There are no approved therapies for the treatment of PPD. Current therapies include antidepressants approved for major depressive disorder, which require many weeks to have an onset of effect, during which time the mother is at risk of worsening depressive symptoms. It is postulated that PPD may result from changes in endogenous neurosteroid concentrations such as allopregnanolone and γ-aminobutyric acid receptor function during pregnancy and postpartum, which are capable of provoking affective dysregulation.

SAGE-547 Injection (brexanolone) is a proprietary formulation of allopregnanolone, an endogenous metabolite of progesterone. Brexanolone is a positive allosteric modulator of synaptic and extrasynaptic GABA-A receptors, which makes the drug an endogenous, naturally-occurring neuroactive steroid. The proposed dosing is intended to achieve plasma concentrations that approximate endogenous levels of allopregnanolone associated with the third trimester of pregnancy.

Brexanolone is chemically related to alfaxalone, a Schedule IV substance under the Controlled Substances Act (CSA) that is approved as an anesthetic for veterinary use. However, the Sponsor asserted that the abuse potential and physical dependence potential of brexanolone is low. Thus, they proposed that brexanolone should not be scheduled as a controlled substance.

2. Conclusions

- **Preclinical studies:** Drug discrimination studies in animals demonstrate that brexanolone produces interoceptive cues that are similar to those of midazolam, a Schedule IV sedative. This is not unexpected, since both drugs act through GABA agonism.
- **Human abuse potential (HAP) study:** The results indicate that brexanolone, in supratherapeutic doses, produces drug liking similar to alprazolam, a Schedule IV sedative.
- **Adverse events in clinical trials:** In double-blind studies in PPD, euphoria was not reported. However, sedation, an abuse related AE, was reported in 4-30% (mean 5.7%) subjects on SAGE-547 and 0-2% (mean 0.9%) subjects on placebo.
- **Physical dependence:** An animal study evaluating physical dependence was not valid because the positive control (alprazolam) did not produce expected sedative effects during drug administration or expected withdrawal symptoms upon drug discontinuation. In humans, headache occurred more frequently during brexanolone discontinuation. However, dependence could not be adequately evaluated because the drug was not abruptly discontinued, but instead was gradually tapered off.
- In summary, preclinical and clinical data indicate that the abuse potential of brexanolone is similar to that of other Schedule IV depressants such as benzodiazepines.

3. Recommendations

Drug Scheduling: Based on the findings of the non-clinical and HAP studies, and the incidence of abuse-related AEs in clinical trials, we recommend that brexanolone be placed in Schedule IV of the CSA.

Drug label: CSS recommends the following changes to the Sponsor's label, where additions are indicated in bold underlined text and deletions have been stricken through:

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

(b) (4) [This section cannot be completed until DEA finalizes a scheduling action.]

9.2 Abuse

In a human abuse potential study, (b) (4) 90 mcg/kg (b) (4) 180 mcg/kg and 270 mcg/kg (b) (4) ZULRESSO (b) (4) were compared to (b) (4) oral alprazolam (w) (u) (1.5 mg and 3 mg). (w) (u) On positive subjective (b) (4) measures of "drug liking," "overall drug liking," "high," and "good drug effects," (b) (4) 90 mcg/kg (b) (4) produced scores that were similar to placebo. (b) (4) Scores on these positive subjective measures for both doses of ZULRESSO 90 mcg/kg and 180 mcg/kg were lower than both alprazolam doses. However, the scores on the positive subjective measures for ZULRESSO 270 mcg/kg were similar to those produced by both doses of alprazolam. In this study, 3% of subjects administered ZULRESSO 90 mcg/kg reported euphoric mood and 12.5% administered ZULRESSO 270 mcg/kg (over one hour) reported euphoric mood compared to none administered placebo.

9.3 Dependence

(b) (4)
In all clinical studies conducted with ZULRESSO, drug discontinuation occurred through tapering. Thus, it is not possible to assess whether abrupt discontinuation of ZULRESSO produces withdrawal symptoms indicative of physical dependence. It is recommended ZULRESSO should be tapered according to the schedule in the Dosing and Administration section (Section 2).

II. DISCUSSION

1. Chemistry

1.1 Substance Information

Brexanolone (USAN name) is a new molecular entity identified by CAS registry number: 516-54-1. It is the proprietary name of allopregnanolone, chemically known as 5 α -pregnan-3 α -ol-20-one. It has a molecular formula of C₂₁H₃₄O₂ and a molecular weight of 318.5. It is a white to off-white crystalline powder with a melting point of 178.6°C. It is insoluble in water, very slightly soluble in *n*-heptane, sparingly soluble in ethyl acetate, slightly soluble in methanol, soluble in 2-methyl-tetrahydrofuran, and freely soluble in tetrahydrofuran.

The drug product is a sterile, clear, colorless solution intended for dilution followed by IV infusion. The drug product contains brexanolone, Betadex Sulfobutyl Ether Sodium USP/NF (Captisol®) as a solubilizer, citric acid and sodium citrate as (b) (4), and water for injection. (b) (4) (b) (4) is adjusted to a pH (b) (4) using either sodium hydroxide or hydrochloric acid.

2. Nonclinical Pharmacology

2.1 Receptor Binding and Functional Assays

a. Receptor binding studies (Study# SGE-00102-09-A, SSN-404; SSN-1158-SGE-00102; SSN-01096)

In receptor binding studies with brexanolone, testing was done with 70 receptors, 14 ion channels, 4 transporters, 6 transient receptor potential ion channels, and 2 enzymes. There was significant affinity (>50% binding) to GABA-chloride channel (97%), androgen (87%), progesterone (82%), GABA-benzodiazepine (80%), and sigma (59%) sites. None of the binding data were converted to K_i or K_d values. The ability of brexanolone (allopregnanolone) to bind to steroid receptors is expected since this compound is found during endogenous androgen and progesterone synthesis. The ability of brexanolone to bind to GABA-related sites is also expected, since progesterone-related compounds (such as alfaxalone) are known to act at these sites.

There was also no significant affinity for the following sites associated with abuse potential: opioids (μ , κ , δ), dopamine (D1 and D2), serotonin (1a, 1b, 2a, 3, 5a, 6, and 7), cannabinoid, NMDA/glutamate, channels (calcium, potassium, and sodium), or monoamine transporters (dopamine, serotonin, or norepinephrine).

Three major metabolites of brexanolone were identified: M133 (SGE-03211), M136 (SGE-03212), and M137 (SGE-03227). None of these compounds have activity at GABA sites or chloride channels, or at any other abuse-related binding site.

b. Functional Studies (Study #SSN-401; SSN-402; SSN-01097-SGE-00102)

An assessment of functional activity of brexanolone at GABA receptors was conducted with electrophysiological recordings of GABA-evoked currents in cell cultures. Whole-cell patch electrophysiology showed that brexanolone enhanced the currents evoked by GABA with an EC_{50} of 60 nM using human $\alpha 1\beta 2\gamma 2$ GABA-A receptors. Similarly, when brexanolone was tested in Chinese hamster ovary (CHO) cells expressing either human $\alpha 4\beta 3\delta$ or human $\alpha 6\beta 3\delta$ GABA-A receptors, it produced an enhancement of GABA-evoked currents with an EC_{50} of 80 nM and 155 nM, respectively.

These data show that brexanolone increases GABA activity in nerve cells, as would be expected from a GABA agonist.

2.2 Animal Behavioral Studies

a. General behavioral observations (Study #SSN-600; SSN-419; SSN-599; SSN-601; SSN-605; SSN-01272; SSN-602; SSN-606; SSN-01273)

Acute and chronic administration of brexanolone to male and female rats and dogs produced dose-dependent behaviors indicative of sedation and muscle relaxation, including reduced locomotion, reduced rearing, increase in prostration, difficulty moving limbs, loss of righting reflex, reduced respiration and inability to arouse an animal. These behaviors are consistent with the GABA modulatory mechanism of action of brexanolone.

The Sponsor states that sedative-like effects in rats and dogs were not observed as long as animal plasma levels of brexanolone were ≤ 370 ng/mL, which is ~ 3.7 -fold greater than the highest mean C_{max} value (99 ng/mL) from Phase 3 studies in which sedation was not reported.

b. Rat locomotor behavior (SSN-423; SSN-474)

Male mice (n = 10/group) were treated with brexanolone formulated in [REDACTED] (b) (4) [REDACTED] at acute 3, 10, and 30 mg/kg (i.p.) or 30, 50, and 75 mg/kg (i.p.) 30 minutes prior to being placed in an open cage for observation.

At doses of 3-30 mg/kg, brexanolone did not have an effect on locomotor activity. However, there was a significant reduction in total distance travelled in the first 15 minutes following administration of brexanolone at 50 and 75 mg/kg compared to vehicle. This decrease in locomotion was due to the onset of sedation. These behaviors are consistent with the GABA agonist mechanism of action of brexanolone.

The animal plasma concentrations of brexanolone at 50 mg/kg was ~ 3650 ng/mL, which the Sponsor states is at least 37-fold greater than the highest mean C_{max} value observed in any of the Phase 3 clinical studies in PPD (~ 100 ng/mL). Thus, the Sponsor concludes that at the proposed therapeutic doses, brexanolone will not produce sedation in humans.

c. Drug discrimination study (Study #SSN-01319)

Drug discrimination is an experimental method of determining whether a test drug produces physical and behavioral responses that are similar to a training drug with specific pharmacological effects. Any centrally-acting drug can serve as the training drug. When the training drug is a known drug of abuse, drug discrimination in animals serves as an important method for predicting whether the effects of a new drug will similarly have abuse potential. Drugs that produce a response similar to known drugs of abuse in animals are also likely to be abused by humans.

In drug discrimination, an animal learns to press one bar when it receives the training drug and another bar when it receives a placebo. Once responding to the training drug and placebo is stable, an animal is given a challenge session with the test drug. A test drug is said to have "full generalization" to the training drug when the test drug produces bar pressing $\geq 80\%$ on the bar associated with the training drug.

Male rats (n = 12) that had previously been trained to discriminate midazolam 1 mg/kg (i.p.) from vehicle using a fixed ratio (FR) 10 schedule of reinforcement were used in this study. Test sessions ended as soon as the animal had received 100 reinforcers or after 30 minutes, whichever occurred first. Animals had to maintain greater than 90% correct responding throughout the whole session and <18 lever presses to the first reinforcement (FRF) for at least two consecutive sessions.

Rats were then tested with a range of half-log doses of midazolam (0.1, 0.32, 1, and 3 mg/kg, i.p.) to confirm a dose-response to the training drug. Brexanolone was then tested at 0.3, 1, 5, 10, and 30 mg/kg (i.p.). The Sponsor states that these doses were selected based on prior pharmacokinetic,

pharmacological and toxicological studies such that the plasma levels would parallel those in humans after therapeutic doses, as well as suprathreshold doses. The intraperitoneal route was selected over the proposed therapeutic route of intravenous administration because it would produce a longer drug exposure to allow animals the chance to respond to the interoceptive cues produced by the drug. Rats were tested 20 minutes after brexanolone administration because that is the time point corresponding to C_{max}. These test sessions were performed once or twice weekly with at least two maintenance training sessions performed on the weekdays in between.

Results

Midazolam produced a dose-dependent generalization to the midazolam cue, such that the 0.1 mg/kg dose did not produce generalization, the 0.32 mg/kg dose produced partial generalization and the 1 and 3 mg/kg doses produced full generalization. However, the 3 mg/kg dose of midazolam produced a significant reduction in rate of responding, demonstrating that the drug produced sedative effects at this dose.

Brexanolone at the lower doses of 0.3, 1 and 5 mg/kg did not generalize to midazolam. When the dose was increased to 10 mg/kg, rats showed partial generalization to the midazolam cue (41%). The highest dose of brexanolone that was tested (30 mg/kg) produced full generalization to midazolam (>99%), along with a significant reduction in rate of responding.

A separate group of animals received brexanolone for pharmacokinetic analysis. The 10 and 30 mg/kg doses produced mean plasma concentrations of 219 ng/mL and 390 ng/mL at the 30-minute timepoint (equivalent to the timing of the behavioral testing). Animals that participated in the behavioral session were tested at the conclusion of the 30 mg/kg dose, which produced a C_{max} of 559 ng/mL. Since the Sponsor states that the human exposure to brexanolone in the Phase 3 studies was ~99 ng/mL, the doses tested in the rat drug discrimination study produced exposures that were 2.2-5.6-fold greater than human exposure.

Conclusions

These data demonstrate that brexanolone produces interoceptive cues that are similar to those of midazolam, a Schedule IV sedative. This is to be expected, since both drugs act through GABA agonism.

d. Self-administration studies

No self-administration studies with brexanolone were conducted by the Sponsor.

2.3 Physical Dependence Studies in Animals

Rat physical dependence study (Study #SSN-1193)

Methods

Male rats (n = 10/group) received vehicle, midazolam (Day 1 = 56 mg/kg (i.p.), Days 2-15 = 150 mg/kg (IV)), or brexanolone (Day 1 = 5, 10, or 30 mg/kg (i.p.), Days 2-15 = 10, 30, or 60 mg/kg (continuous IV infusion)). The initial i.p. administration was used to assess acute behavioral responses to the drugs. A separate group of male rats (n = 6/group) received brexanolone at 10, 30, and 60 mg/kg through continuous IV infusion for 15 days for pharmacokinetic evaluation.

These doses were selected on the outcome of a 14-day continuous IV infusion study in rats. Using an 18 mg/kg/day dose, the mean steady state plasma exposures was 121 ng/mL, which approximates the therapeutic clinical exposure. Thus, the Sponsor predicted that the selected doses of 10, 30, and 60 mg/kg/day would produce plasma exposures of 67, 202, and 403 ng/mL (respectively), equivalent to 1X, 3X, and 6X exposures relative to the clinically active exposure.

Animals were observed daily for behavioral changes and for changes in food consumption, body weight, and rectal temperature at baseline, after drug administration on Day 1 to assess acute behavioral responses, and on the first 5 days after drug discontinuation (Days 16, 17, 18, 19, and 20).

Behavioral evaluations included open-field evaluations to monitor behavioral activity and arousal, posture, rearing, bizarre behavior, clonic and tonic movements, gait, mobility, stereotypy, righting reflex, response to stimulus (approach, click, tail pinch, and touch), palpebral closure, pupil response, piloerection, exophthalmos, lacrimation, salivation, respiration, measures of defecation, and urination. Forelimb and hindlimb grip strength and locomotor activity were also measured, as was thermal pain responses. Body weight and temperature were also measured.

Results

Pharmacokinetics

Brexanolone at 10, 30, and 60 mg/kg produced C_{max} values at the end of the drug infusion on Day 8 (168 hours) of 55, 133, and 313 ng/mL. Thus, the tested doses represent 0.5X, 1.3X, and 3X exposure of the plasma levels of brexanolone produced following therapeutic human doses. This is approximately half of the exposure (1X, 3X, and 6X) that was estimated by the Sponsor prior to study initiation. The half-life of brexanolone was 5-6 hours.

Behavioral Responses

The study report does not provide tables with mean values and standard error values for each behavior in response to each drug treatment. Instead, the data are summarized solely by indicating a statistically significant difference in response to a drug treatment through the use of arrows with “size and direction of the differences inferred by size and direction of arrows”. Additionally, the tables do not provide any

information (symbolic or numeric) for most of the responses to the 10 mg/kg dose for Day 1 (acute) data. Thus, it is not possible to fully evaluate the data on a numerical basis.

However, the graphs provided for the data do not show meaningfully large changes (>1 point out of scales of 1-8 point) for most behaviors either during acute drug administration on Day 1 or during the drug discontinuation period for either the positive control drug, midazolam, or for brexanolone.

Conclusions

The validity of this study is questionable, given that a strong sedative response was not produced by midazolam upon acute drug administration, and that a strong withdrawal response was not produced upon midazolam discontinuation.

Thus, it is not possible to interpret a lack of strong response for brexanolone either upon acute drug administration or during the drug discontinuation period.

Dog Toxicity Study with Discontinuation Period

During toxicity testing with brexanolone in dogs, convulsions were observed during brexanolone discontinuation. According to Dr. Antonia Dow, pharmacology/toxicology reviewer in DPP (personal communication):

A convulsion was seen seven hours to four days after dose completion in a single dog in each of three repeat dose toxicity studies. Convulsions were seen:

- in the 5-day study at 30-times the exposure at the maximum recommended human dose (MRHD), but not at 28-times, following abrupt brexanolone discontinuation
- in the 14-day study at 7-times the exposure at the MRHD, but not at 2-times, following abrupt brexanolone discontinuation
- in the 28-day study at 3-times the exposure at the MRHD, but not at 1-time; the convulsion occurred 4 days after tapered brexanolone discontinuation over a 24-hour period

GABA agonists (such as benzodiazepines) are well-known to produce convulsions in animals and humans after long-term administration followed by abrupt discontinuation. These seizures are considered to be part of a withdrawal syndrome indicative of the development of physical dependence. Thus, the convulsions observed in the dog toxicity studies with brexanolone are consistent with the drug's mechanism of action and are similarly indicative that physical dependence can develop with prolonged administration of the drug.

However, given that the recommended duration of clinical brexanolone administration is limited to 52 hours before the start of an 8-hour drug tapering period, it is unlikely that convulsions would occur in humans receiving brexanolone according to label recommendations.

3. Clinical Pharmacology

Clinical studies with brexanolone evaluated IV doses ranging from 30 to 270 µg/kg/hr. Drug exposure with these doses appears dose-proportional. Since brexanolone is administered intravenously, absorption is complete immediately after drug administration. Brexanolone is metabolized into three major conjugated metabolites, M133, M136, and M137 (>10% of drug-related material circulating in plasma). Brexanolone and the three major plasma metabolites achieve C_{max} values at the end of the infusion, followed by a rapid initial drop in plasma levels. Brexanolone has a terminal half-life of 8-9 hours.

Intravenous infusion of ¹⁴C-labeled brexanolone for 4 hours led to recovery of radioactivity in feces (47.2%) and urine (41.8%). Negligible amounts of unchanged brexanolone were detected in the urine.

When the oral availability of 30 mg brexanolone was evaluated in humans, the overall oral bioavailability of the drug was shown to be very low (5%). This suggests that use of brexanolone for oral abuse purposes is unlikely.

4. Clinical Studies

The goal of the brexanolone PPD clinical program was to elicit a rapid response of significant magnitude and to examine the potential durability of response during a 4-week follow-up period. Clinical studies evaluated a 60-hour IV dose regimen targeting a maximum therapeutic dose of 90 µg/kg/h. The Sponsor conducted four studies in adult women with PPD: three randomized, double-blind, placebo-controlled clinical studies (Study PPD-202A, Study PPD-202B, Study PPD-202C) and one open-label clinical study (Study PPD-201). The clinical development program to support the approval of brexanolone for the treatment of PPD also includes seven clinical pharmacology (CLP) studies, a human abuse potential (HAP) study, and a Phase 2 study in subjects with essential tremor disorder (ETD). The Sponsor also evaluated brexanolone for the treatment of super-refractory status epilepticus (SRSE), an acute, life-threatening condition.

The incidence of treatment-emergent adverse events (TEAEs) in the brexanolone PPD clinical development program was summarized by MedDRA (Version 19.1) and classified by SOC, preferred term, and treatment group.

4.1 Human Abuse Potential Study

Title: A Randomized, Double-Blind, Active- and Placebo-Controlled, Double-Dummy, 6-Way Crossover Study to Determine the Abuse Potential of Intravenously Administered SAGE-547 in Healthy, Nondependent, Recreational Central Nervous System Depressant Users. 547-CLP-102

Primary objective: To assess the abuse potential of intravenously infused brexanolone relative to placebo and orally administered alprazolam (Schedule IV) in nondependent, recreational CNS depressant users.

Secondary objectives: To assess the pharmacokinetics (PK) of brexanolone in plasma when administered by IV infusion in nondependent, recreational CNS depressant users and to assess the safety

of intravenously infused brexanolone relative to placebo and orally administered alprazolam in nondependent, recreational CNS depressant users.

Sponsor's rationale for alprazolam as a positive control: "The profile of effects observed after brexanolone administration during exposures, most of which are documented in the literature, indicates pharmacologic effects potentially consistent with a drug with CNS depressant properties, with the most common physiologic effect being sedation. In addition, preclinical studies have indicated some CNS depressant effects consistent with those seen with other drugs known to cause CNS depression. Allopregnanolone is a potent positive allosteric modulator of GABAA receptor responses. As such, the appropriate pharmacologic class for a positive control in this study is the sedative (benzodiazepine) class, which 1) has known abuse potential, 2) has similar pharmacological effects (e.g., sedation), and 3) exerts its pharmacological effects through positive allosteric modulation of GABAA receptors. Alprazolam is a benzodiazepine sedative that is widely known to be abused and has been repeatedly demonstrated to show positive effects on common measures of abuse potential in clinical investigations."

Part A: Dose Selection Phase

Part A consisted of a Screening Visit, Dose Selection Visit, and Follow-Up Visit. The Dose Selection Phase employed an exploratory single-dose, randomized, double-blind, placebo-controlled study to evaluate the safety and tolerability of escalating doses of brexanolone given as an IV infusion over 1 hour. Each brexanolone dose level was tested in cohorts of eight new subjects, with subjects in each cohort randomized to receive a dose of either brexanolone (n = 6) or placebo (n = 2).

Within 30 days of screening, eligible subjects were admitted to the research clinic on Day -1 for their Dose Selection Visit and dosed on Day 1 with blinded study drug, either brexanolone or matching placebo, infused over 1 hour. Dose selection began with a brexanolone dose of 60 µg/kg administered via a 1-hour IV infusion, a dose approximating those that have been previously shown to be well tolerated in past studies in conscious subjects. After the completion of each cohort, available safety data were unblinded and reviewed by the Investigator, Sponsor, and designees. Following the review, dose escalation occurred if a higher dose could have been safely administered and if a maximum dose had not been identified. Subsequent cohorts were dosed with the next higher dose in 30-µg/kg increments, with a maximum of eight cohorts (60, 90, 120, 150, 180, 210, 240, and 270 µg/kg). The maximum dose (270 µg/kg) represented a three-fold increase in the maximum therapeutic dose planned for the PPD clinical development program (90 µg/kg).

Part B: Treatment Phase

The study included a Screening Visit, a 5-day (4-night) Qualification (Drug Discrimination) Phase, six 3-day (2-night) Treatment Periods, and a Follow-Up Visit. Subjects who continued in Part B must have had a washout period of at least 7 days between the last dose administered in the Dose Selection Phase (Part A) and the first dose administered in the Qualification Phase (Part B).

Within 30 days of screening, subjects entered a double-blind Qualification Phase during which they received alprazolam 2.0 mg and placebo in a randomized crossover manner to ensure they were able to

discriminate the positive effects of alprazolam. Doses in the Qualification Phase were separated by 48 hours.

Following a washout period of at least 6 days, eligible subjects entered the Treatment Phase. During the six treatment periods, subjects received doses of each of the following treatments in a randomized, double-blind, double-dummy fashion, with a washout period of at least 6 days between treatments:

- Treatment A: placebo solution (1-hour IV infusion) + two placebo encapsulated tablets;
- Treatment B: placebo solution (1-hour IV infusion) + alprazolam 1.5 mg (0.5-mg + 1.0-mg encapsulated tablets);
- Treatment C: placebo solution (1-hour IV infusion) + alprazolam 3.0 mg (1.0-mg + 2.0-mg encapsulated tablets);
- Treatment D: brexanolone 90 µg/kg solution (1-hour IV infusion) + two placebo encapsulated tablets;
- Treatment E: brexanolone 180 µg/kg solution (1-hour IV infusion) + two placebo encapsulated tablets;
- Treatment F: brexanolone 270 µg/kg solution (1-hour IV infusion) + two placebo encapsulated tablets.

Drug administration occurred on Day 1 of each treatment period followed by pharmacodynamic (PD), PK, and safety assessments for up to 24 hours post dose (i.e., following the end of infusion). Oral encapsulated tablets were administered at the start of the IV infusion. All oral dosing was to be completed within 5 minutes and occurred at the time of the start of IV infusion. Subjects were required to fast for at least 8 hours prior to dosing and for at least 4 hours post-dosing.

In Part B, a sufficient number of subjects were screened and enrolled into the Qualification Phase in order to randomize approximately 36 subjects into the Treatment Phase, with the intent of obtaining evaluable data from at least 24 subjects.

Inclusion Criteria: All Subjects

Subjects who met the following criteria were eligible to participate in the study (Parts A and B) if each one of the following inclusion criteria was satisfied at screening:

1. Healthy male or female subjects, 18 to 55 years of age, inclusive.
2. Current CNS depressant users who have used CNS depressants (e.g., benzodiazepines, barbiturates, zolpidem, eszopiclone, zopiclone, propofol/fospropofol, gamma-hydroxy-butyrate) for recreational, nontherapeutic reasons at least five times in the past year and at least once in the 8 weeks prior to screening.
3. Subjects who have used drugs for non-medical purposes by either the intranasal and/or IV route on at least three occasions in the past year.

Inclusion Criteria: Part B

Subjects must have passed the following qualification criteria to be eligible for entry into the Treatment Phase:

1. Peak score (Emax) in response to alprazolam 2.0 mg of ≥ 65 on the Drug Liking visual analog scale (VAS) and a peak VAS score at least 15 points greater than that reported during the placebo period.

2. Acceptable placebo response based on Drug Liking VAS (i.e., score between 40 and 60, inclusive).

Exclusion Criteria

1. Substance or alcohol dependence (excluding nicotine and caffeine) within the past 2 years, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM IV-TR), and/or subjects who had ever been in a substance or alcohol rehabilitation program to treat their substance or alcohol dependence
2. Smokers who were unable to abstain from smoking for at least 6 hours on a given day.
3. Current use of nicotine replacement therapy (any formulation) or use of varenicline therapy within 1 month prior to screening.

The primary endpoint analyses were based on Drug Liking VAS Emax and the following pairwise treatment comparisons were made:

- Each dose of alprazolam (1.5 mg, 3.0 mg) compared with placebo;
- Each dose of brexanolone (90 µg/kg, 180 µg/kg, 270 µg/kg) compared with each dose of alprazolam (1.5 mg, 3.0 mg); and
- Each dose of brexanolone (90 µg/kg, 180 µg/kg, 270 µg/kg) compared with placebo.

Results: Among the 40 randomized subjects in the Treatment Phase, 25 (62.5%) completed the study (Completer Population) and 15 (37.5%) discontinued the study. Reasons for discontinuation included: AE (n=2), study ended by Sponsor due to meeting target of 24 subjects (n=3), noncompliance (n=4), scheduling conflict (n=3), and withdrawal by subject (n=3). In the Treatment Phase, most subjects were male (72.5%), White (77.5%), and not Hispanic or Latino (95.0%). The mean (SD) age was 38.4 (8.62) years and ranged from 20 to 53 years.

Tables 1 and 2 display the abuse-related AEs in the Dose Selection Phase and the Treatment Phase respectively. All 40 randomized subjects (100%) were included in the Safety Populations in the Treatment Phase.

Table 1: Abuse related AEs in the Dose Selection Phase n (%) Study #547-CLP-102

	Placebo n=16	Brex 60 µg/kg n = 6	Brex 90 µg/kg n = 6	Brex 120 µg/kg n = 6	Brex 150 µg/kg n = 5	Brex 180 µg/kg n = 6	Brex 210 µg/kg n = 6	Brex 240 µg/kg n = 6	Brex 270 µg/kg n = 6
Somnolence	8 (50)	4 (66.7)	4 (66.7)	5 (83.3)	3 (60)	5 (83.3)	5 (83.3)	5 (83.3)	5 (83.3)
Euphoric mood	0	0	0	0	1 (20)	0	1 (16.7)	1 (16.7)	2 (33.3)
Feeling of relaxation	4 (25)	0	2 (33.3)	1 (16.7)	1 (20)	1 (16.7)	0	1 (16.7)	2 (33.3)
Disturbance in attention	0	0	0	0	0	0	0	0	1 (16.7)
Feeling abnormal	0	0	0	1(16.7)	0	0	0	0	0
Sluggishness	0	0	1 (16.7)	0	0	0	0	0	0

Brex = brexanolone

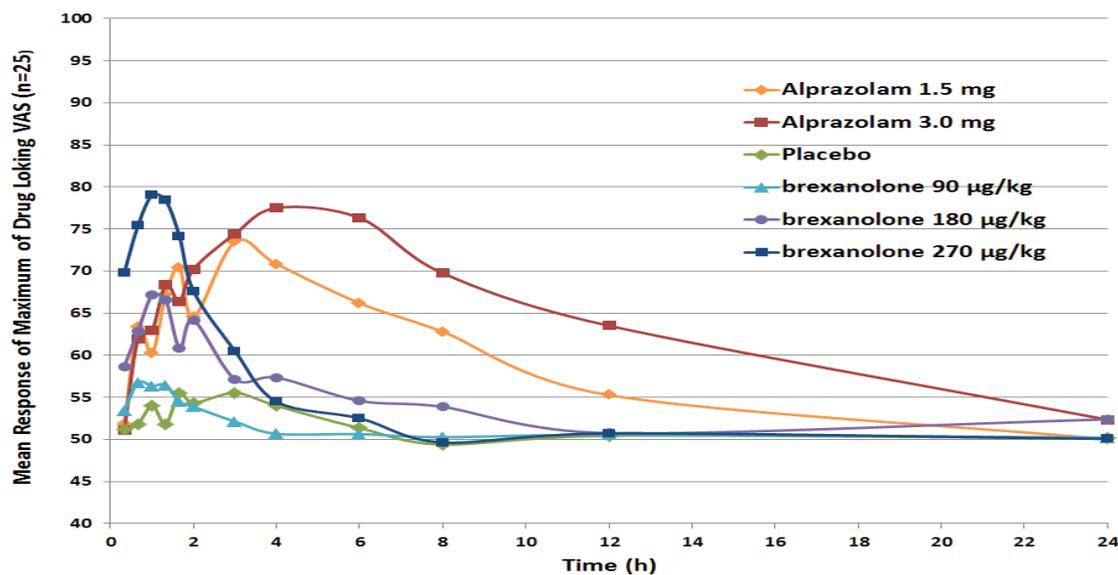
Table 2: Abuse related AEs in the Treatment Phase n (%) Study #547-CLP-102

	Placebo n=30	Alprazolam 1.5mg n=33	Alprazolam 3.0 mg n = 31	Brexanolone 90 µg/kg n = 32	Brexanolone 180 µg/kg n = 32	Brexanolone 270 µg/kg n = 32
Somnolence	10 (33.3)	32 (97)	31 (100)	20 (62.5)	28 (87.5)	30 (93.7)
Euphoric mood	0	1 (3)	6 (19.4)	1 (3.1)	3 (9.4)	4 (12.5)
Feeling of relaxation	3 (10)	3 (9.1)	2 (6.5)	1 (3.1)	0	3 (9.4)
Feeling abnormal	0	0	0	0	0	2 (6.3)
Psychomotor retardation	0	0	0	0	0	1 (3.1)
Disturbance in attention	0	1 (3)	0	0	1 (3.1)	0
Restlessness	0	0	0	0	1 (3.1)	0
Amnesia	0	0	3 (9.7)	0	0	0

During the Dose Selection Phase, euphoric mood was not noted in the placebo group but noted in brexanolone-treated subjects at doses greater than 150 µg/kg. During the Treatment Phase, euphoric mood was not noted in the placebo group, but occurred in a dose dependent manner in alprazolam group (3-19%) and in the brexanolone group (3-12.5%).

CSS obtained a statistics consult from the Division of Biometrics VI for this HAP study (Feng Zhou; DARRTS November 6, 2018). The following **Figure 1**, and **Tables 3-6** are referenced from their consult.

Figure 1: Mean Time Course Profiles for Drug Liking VAS (N=25)



As shown in the figure above, the peak Drug Liking occurs earlier for brexanolone 180 and 270 µg/kg (1 hour) than for both doses of alprazolam (3-4 hours). The duration of Liking is longer for alprazolam. Peak mean response of alprazolam 3mg is similar to brexanolone 270 µg/kg. There is a dose dependent increase in Drug Liking for brexanolone.

Figure 2. Mean plasma concentrations of brexanolone (ng/mL; Y axis) versus time (hours; X axis) (data derived from Sponsor’s table 14.2.1.1 Study 547-CLP-102)

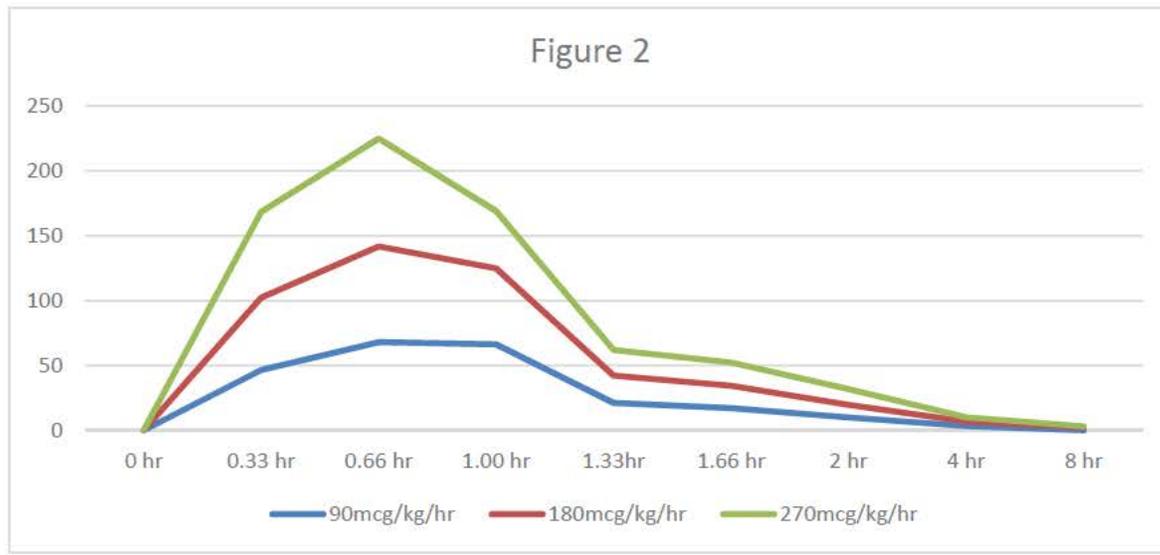


Figure 2 shows the mean plasma concentrations of brexanolone over time for all doses studied. As shown in the figure, C_{max} occurs at 0.66 hours which is around the time E_{max} for Drug Liking occurs (1 hour).

Table 1: Statistical Analysis Results for E_{max} of Drug Liking (Completer Population)

Statistic	Brex 90 µg/kg n=25	Brex 180 µg/kg n=25	Brex 270 µg/kg n=25	Alprazolam 1.5 mg n=25	Alprazolam 3.0 mg n=25	Placebo n=25
E_{max}						
Mean (STD)	62.8 (16.4)	75.7 (16.5)	86.92 (13.3)	82.1 (16.6)	89.5 (15.6)	59.8 (13.7)
Median	55	72	90	76	100	51
Q1, Q3	51, 69	67, 82	76, 100	71, 100	75, 100	50, 69
Min, Max	50, 100	50, 100	51, 100	51, 100	51, 100	50, 100
LS mean (SE)	62.3 (3.8)	75.8 (3.3)	86.9 (2.8)	81.9 (3.1)	89.7 (3.2)	59.80 (3.5)
Treatment Comparisons						
	LS Mean Difference (SE)		95% Confidence Interval		p-value	
Alprazolam 1.5 mg - Placebo	22.1 (3.3)		(15.3, 28.8)		<.0001	
Alprazolam 3.0 mg - Placebo	29.9 (3.4)		(23.0, 36.9)		<.0001	
Alprazolam 3.0 mg - Brexanolone 90 µg/kg	27.4 (3.7)		(19.9, 34.9)		<.0001	
Alprazolam 1.5 mg - Brexanolone 180 µg/kg	19.6 (3.6)		(12.3, 26.9)		<.0001	

Brexanolone 90 µg/kg Brexanolone 90 µg/kg - Placebo	2.5 (4.0)	(-5.6, 10.6)	0.2677
Alprazolam 3.0 mg - Brexanolone 180 µg/kg Alprazolam 1.5 mg - Brexanolone 180 µg/kg	13.9 (3.2)	(7.4, 20.4)	<.0001
Brexanolone 180 µg/kg - Placebo	6.1 (3.1)	(-0.29, 12.4)	0.0304
Alprazolam 3.0 mg - Brexanolone 270 µg/kg Alprazolam 1.5 mg - Brexanolone 270 µg/kg	16.0 (3.5)	(8.8, 23.2)	<.0001
Brexanolone 270 µg/kg - Placebo	2.8 (2.7)	(-2.8, 8.3)	0.1572
Alprazolam 3.0 mg - Brexanolone 270 µg/kg	-5.1 (2.5)	(-10.4, 0.2)	0.0291
Alprazolam 1.5 mg - Brexanolone 270 µg/kg - Placebo	27.1 (3.1)	(20.9, 33.4)	<.0001

Brex = brexanolone; 0: Strong disliking 50: Neither like nor dislike 100: Strong liking

Table 3 shows the results for the primary endpoint (Drug Liking VAS Emax). The HAP study is valid since the mean Emax for Drug Liking was significantly higher for alprazolam 1.5 mg and 3.0 mg compared to placebo. The low dose (90 µg/kg) of brexanolone was liked not significantly more than placebo, but the higher doses of brexanolone (180 µg/kg and 270 µg/kg) were liked significantly more than placebo. High dose brexanolone (270 µg/kg) had similar liking to high dose alprazolam

Table 4: Results for Emax of Overall Drug Liking VAS

	Brexanolone 90 µg/kg/IV n=25	Brexanolone 180 µg/kg/IV n=25	Brexanolone 270 µg/kg/IV n=25	Alprazolam 1.5 mg n=25	Alprazolam 3.0 mg n=25	Placebo n=25
Mean	59.6	73.0	78.4	84.0	91.6	58.7
Range	16-100	19-100	0-100	39-100	51-100	0-100

0: Strong disliking 50: Neither like nor dislike 100: Strong liking

Table 4 shows the results for Emax of Overall Drug Liking VAS. Similar to the Drug Liking VAS, the low dose of brexanolone did not differentiate from placebo, with Overall Drug Liking scores for the higher doses significantly higher than placebo. Likewise, the Overall Drug Liking scores for the 270 µg/kg dose of brexanolone were in the same range as those reported for the 3mg alprazolam dose (see also **Table 6**).

Table 5. Results for Emax of Take Drug Again VAS

	Brexanolone 90 µg/kg/IV n=25	Brexanolone180 µg/kg/IV n=25	Brexanolone 270 µg/kg/IV n=25	Alprazolam 1.5 mg n=25	Alprazolam 3.0 mg n=25	Placebo n=25
Mean	34.6	57.08	69.32	81.6	85.88	25.52
Range	0-100	0-100	0-100	0-100	0-100	0-100

0: Definitely not 100: Definitely so

Table 5 shows the results for Emax of Take Drug again VAS. All doses of brexanolone, including the 90 µg/kg, were associated with higher Take Drug Again scores than placebo. The Take Drug Again scores for the highest dose of brexanolone were similar to that of alprazolam 3mg (see also **Table 6**).

Table 6: Summary of the Results from Significance Tests for the Abuse Potential Measures Reviewed

Treatment Comparison	Drug Liking	Overall Drug Liking	High	Good Effects	Bad Effects	Take Drug Again
ALZ1.5 vs PBO	S (>)	S (>)	S (>)	S (>)	S (>)	S (>)
ALZ3.0 vs PBO	S (>)	S (>)	S (>)	S (>)	S (>)	S (>)
SAGE90 vs ALZ1.5	S (<)	S (<)	S (<)	S (<)	S (<)	S (<)
SAGE180 vs ALZ1.5	S (<)	S (<)	S (<)	S (<)	NS	S (<)
SAGE270 vs ALZ1.5	NS	NS	NS	NS	NS	NS
SAGE90 vs ALZ3.0	S (<)	S (<)	S (<)	S (<)	S (<)	S (<)
SAGE180 vs ALZ3.0	S (<)	S (<)	S (<)	S (<)	S (<)	S (<)
SAGE270 vs ALZ3.0	NS	NS	NS	NS	S (<)	NS
SAGE90 vs PBO	NS	NS	NS	NS	NS	S (>)
SAGE180 vs PBO	S (>)	S (>)	S (>)	S (>)	S (>)	S (>)
SAGE270 vs PBO	S (>)	S (>)	S (>)	S (>)	NS	S (>)

The sign (>) shows that on the average, A was greater than B. The (<) sign denotes that on the average, A was smaller than B. S and NS denote significant difference and nonsignificant difference, respectively

Table 6 summarizes the results from significance tests for the abuse potential measures. On all positive subjective measures (Drug Liking, Overall Drug Liking, High, Good effects, and Take Drug Again) brexanolone 270 µg/kg was similar to alprazolam 1.5 mg and 3mg. Brexanolone 270 µg/kg scores for Bad Effects were lower than those for 3mg of alprazolam.

The HAP study results provide evidence for brexanolone having similar abuse potential as alprazolam, a Schedule IV drug. The Sponsor asserts that brexanolone abuse potential is lower than that of alprazolam because only suprathereapeutic doses of brexanolone (270 µg/kg/hour) have similar drug liking as therapeutic doses of alprazolam (1.5mg and 3 mg). Single doses of alprazolam as high as 3mg are rarely prescribed, the more typical dose being 0.5 mg-1.5mg (Alprazolam PI). Additionally, in evaluating abuse potential, the effects of suprathereapeutic doses of a drug are considered because individuals are likely to abuse high doses. Brexanolone will be administered at a target dose of 90 µg/kg/hour for 28 hours (with lower dosing during the initial titration and tapering at the end of the infusion). The HAP

study demonstrated that 270 µg/kg over 1 hour was reinforcing. Thus, a single infusion will have several doses that could be abused. The Sponsor also states that there is a rapid offset of drug liking with brexanolone, however, the rapid onset of drug liking of brexanolone compared to alprazolam may increase its abuse potential even though it has a shorter duration of action.

Euphoric mood was reported by 10.6% (5/47) of subjects in the dose selection phase and 3-12% in the treatment phase in subjects on brexanolone. Euphoric mood was reported in 3-19% in alprazolam treated subjects.

Considering that fixed doses of brexanolone were administered in a one-hour period, during the HAP study, it is important to note that by increasing the infusion rate of a fixed dose of an active drug, the reinforcing effectiveness of the drug may increase. For example, Comer et al. demonstrated that a fixed dose of 40 mg of the opioid oxycodone served as a reinforcer only when it was delivered over 2 and 15 minutes, and not over 30, 60 or 90 minutes (Comer, Ashworth et al. 2009). Thus, it is likely that at a higher rate of infusion, the 90 µg/kg and 180 µg/kg doses brexanolone would have been associated with higher Drug Liking scores than those seen upon administration of the same doses at a one-hour infusion rate.

4.2 Adverse Event Profile Through all Phases of Development

Phase 1 Studies: Seven clinical pharmacology (CLP) were conducted in healthy subjects or those with renal or hepatic impairment. These included studies 547-CLP-101, 547-CLP-106, 547-CLP-108, 547-CLP-103, 547-CLP-104, 547-CLP-105, and 547-CLP-107. Somnolence was reported in 26 of 125 (20.8%) subjects receiving brexanolone and 2 of 27 (7.4%) receiving placebo. The occurrence of somnolence is consistent with the pharmacology of brexanolone. Euphoric mood was noted in one individual receiving placebo in these studies. One individual each reported agitation, apnea, chromatopsia, and abnormal dreams in the brexanolone-treated groups.

An Open-Label Proof-of-Concept Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of SAGE-547 Injection in the Treatment of Adult Female Patients with Severe Postpartum Depression. 547-PPD-201 Phase2a

The primary objective of this study was to evaluate the safety and tolerability of brexanolone injection when administered to adult female patients diagnosed with severe PPD. This was an open-label, proof-of-concept study. Following sentinel dosing and satisfactory safety and data review for the first two subjects, parallel dosing was performed for the remaining subjects. Each subject's involvement was up to 37 days, including up to a 3-day Screening Period, a 4-day (84-h) Active Treatment Period, and a 7-day AE Follow-up Period, plus an additional 23 days of SAE follow-up. The Active Treatment Period was the period of Day 1 of brexanolone IV infusion through completion of the infusion and taper on Day 3 and a 24 h follow-up on Day 4. Subjects were confined to the study center from the Screening Visit until after the 84-h assessments had been conducted on Day 4. On the morning of dosing (Day 1), subjects began the 12-h dose titration phase. Upon completion of titration, subjects began a maintenance infusion that continued for 36 h, targeting a plasma concentration of 150 nM. After constant dose therapy with brexanolone, the dose was tapered and discontinued over the course of 12 h. Total brexanolone dosing occurred over 60 h (12-h dose titration followed by a 36-h maintenance infusion followed by a 12-h taper). The maintenance infusion rate was 86 µg/kg/h.

Due to reasons unrelated to safety, the study was terminated early with only four subjects treated and contributing data for analysis. Sedation was reported in two (2) of 4 subjects, requiring dose adjustments.

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects with Severe Postpartum Depression. 547-PPD-202A Phase 2

The primary objective of this study was to determine if brexanolone Injection infused IV for 60 hours reduced depressive symptoms in subjects with PPD compared to placebo injection as assessed by the change from baseline in Hamilton Rating Scale for Depression (HAM-D) total score.

The study consisted of an up to 5-day Screening Period (Day -5 to -1), 3-day (72 hour) Treatment Period, and 30-day Follow-up Period. Subjects remained as inpatients during the study Treatment Period, which included the 60-hour infusion and the 72-hour assessments. The Treatment Period was the period of Day 1 of study drug (brexanolone or placebo) IV infusion through completion of the infusion on Day 3. On the morning of dosing (Day 1), subjects began a 4-hour dose titration period of 30 µg/kg/hour (0 to 4 hours), then 60 µg/kg/hour (4 to 24 hours), then 90 µg/kg/hour (24 to 52 hours); followed by a taper to 60 µg/kg/hour (52 to 56 hours), and 30 µg/kg/hour (56 to 60 hours). Total brexanolone Injection or placebo dosing occurred over 60 hours.

Twenty-one (21) subjects (10 brexanolone, 11 placebo) were enrolled, randomized, and treated. All 21 subjects completed the study. Three of 10 brexanolone subjects and 0/11 placebo subjects experienced sedation. Somnolence was reported in 2/10 brexanolone subjects and no placebo treated subjects. One subject who experienced somnolence was on clonazepam.

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects with Severe Postpartum Depression. 547-PPD-202B Phase 3

The primary objective of this study was to determine if brexanolone Injection infused IV up to 90 µg/kg/h for 60 hours reduces depressive symptoms in subjects with severe PPD compared to placebo injection as assessed by the change from baseline in Hamilton Rating HAM-D total score. This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the efficacy, safety, and PK of brexanolone in adult female subjects diagnosed with severe PPD.

The study consisted of an up to 7-day Screening Period (Day -7 to -1), 3-day (72-hour) Treatment Period during which study drug was infused for 60 hours, and a Follow-up Period to Study Day 30. Subjects remained as inpatients during the study Treatment Period, which included the 60-hour infusion and the 72-hour assessments. Subjects were randomized to achieve a 1:1:1 treatment ratio to brexanolone 60 µg/kg/h, brexanolone 90 µg/kg/h, or placebo. On the morning of dosing (Day 1), subjects began the 60-hour infusion according to the titration, maintenance and taper periods for each dose group. For the 60 µg/kg/h group, subjects began a 4-hour titration period of 30 µg/kg/h (0 to 4 hours), then 60 µg/kg/h (4 to 56 hours), followed by a taper to 30 µg/kg/h (56 to 60 hours). For the 90 µg/kg/h group, subjects began a 4-hour dose titration period of 30 µg/kg/h (0 to 4 hours), then 60 µg/kg/h (4 to 24 hours), then

90 µg/kg/h (24 to 52 hours), followed by a taper to 60 µg/kg/h (52 to 56 hours), and then 30 µg/kg/h (56 to 60 hours).

A total of 138 subjects were randomized and 122 subjects were dosed with study drug (43 placebo, 38 brexanolone 60 µg/kg/h, 41 brexanolone 90 µg/kg/h) as seen in Table 7. Sixteen subjects who were randomized withdrew from the study prior to dosing, most often due to withdrawal of consent or no longer meeting entry criteria.

Table 7: Abuse related AEs in Study 547-PPD-202B n (%)

	Placebo n=43	Brexanolone 60 µg/kg/hour n=38	Brexanolone 90 µg/kg/hour n=41
Somnolence	3 (7)	7 (18.4)	2 (4.9)
Sedation	1 (2.3)	1 (2.6)	2 (4.9)
Loss of consciousness	0	2 (5.3)	1 (2.4)
Syncope	0	0	1 (2.4)
Amnesia	0	1 (2.6)	0

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects with Moderate Postpartum Depression. 547-PPD-202C Phase 3

The primary objective of this study was to determine if brexanolone injection infused intravenously at up to 90 µg/kg/h for 60 hours reduces depressive symptoms in subjects with moderate PPD compared to placebo injection as assessed by the change from baseline in HAM-D total score.

This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the efficacy, safety, and PK of brexanolone in adult female subjects diagnosed with moderate PPD. The study consisted of an up to 7-day Screening Period (Day -7 to -1), 3-day (72-hour) Treatment Period during which study drug was infused for 60 hours, and a Follow-up Period to Study Day 30. Subjects remained as inpatients during the study Treatment Period, which included the 60-hour infusion and the 72-hour assessments. Subjects were randomized to one of two treatment groups (brexanolone or placebo) on a 1:1 basis and then confined to the study center for the Treatment Period. On the morning of dosing (Day 1), subjects began a four-hour dose titration period of 30 µg/kg/h (0 to 4 hours), then 60 µg/kg/h (4 to 24 hours), then 90 µg/kg/h (24 to 52 hours), followed by a taper to 60 µg/kg/h (52 to 56 hours), and 30 µg/kg/h (56 to 60 hours). A total of 108 subjects were randomized and 104 subjects were dosed with study drug (51 brexanolone and 53 placebo) as seen in Table 8.

Table 8: Abuse related AEs in Study 547-PPD-202C n (%)

	Placebo n=53	Brexanolone 90 µg/kg/hour, n=51
Feeling drunk	0	1 (2)
Somnolence	2 (3.8)	4 (7.8)
Sedation	0	2 (3.9)
Altered consciousness	0	1 (2)
Presyncope	0	1 (2)
Syncope	0	1 (2)

Studies of other potential indications for brexanoloneEssential Tremor Disorder (ETD)

Brexanolone was also evaluated in one double-blind, placebo-controlled study of 25 subjects with Essential Tremor Disorder (ETD) who were otherwise generally healthy.

Study 547-ETD-201

In Stage 1, double blind phase, mean increases in Stanford sleepiness scale (SSS) score were slightly greater for brexanolone versus placebo during the first 6 hours of treatment. During Stage 2 (open label phase with higher doses, up to 150 µg/kg/h) the mean increases in SSS score were larger than those seen in Stage 1, indicating higher levels of sleepiness at the higher dose. In Stage 1, one of 25 subjects in the brexanolone group reported somnolence but none did so in the placebo group. In Stage 2, one of 17 subjects noted sedation.

The Bond-Lader mood rating scale was designed to assess subjective mood. It is a self-administered visual analog scale that was administered in Stage 2 of the study. Increases in the mean Bond-Lader VAS scores were observed in Stage 2 subjects at 10 hours post-dose, indicating subjects were more drowsy and dreamy than at the pre-infusion.

Drug Effects Questionnaire (Stage 2 Only). A drug effects questionnaire (DEQ) was administered in Stage 2 of the study at the following time points: prior to the start of the infusion, and at 6 and 9 hours after the start of the infusion. The answers were recorded on a 100-mm VAS with the answer for each being “not at all” and “extremely” at the extremes. Overall, as seen in Table 9, subjects treated with brexanolone in Stage 2 experienced increases from pre-infusion levels in all drug effect parameters at 6 and 9 hours after infusion commenced, with increases higher at 6 versus 9 hours.

Table 9. Stage 2: Mean [SD] Changes from Baseline in Drug Effects Questionnaire Parameters (Safety Population) Sponsor's submission

Parameter Time point	SAGE-547 N=16	
	Dosage (µg/kg/h)	Mean [SD]
Total Score:		
Pre-infusion	0	0
6 hours	150	180.0 [77.9]
9 hours	150	149.1 [64.6]
Do You Feel A Drug Effect Right Now?		
Pre-infusion	0	0
6 hours	150	62.3 [28.8]
9 hours	150	52.3 [29.4]
Are You High Right Now?		
Pre-infusion	0	0
6 hours	150	35.8 [31.5]
9 hours	150	31.6 [25.7]
Do You Dislike Any Of The Effects You Are Feeling Right Now?		
Pre-infusion	0	0
6 hours	150	44.9 [32.8]
9 hours	150	37.5 [23.4]
Do You Like Any Of The Effects You Are Feeling Right Now?		
Pre-infusion	0	0
6 hours	150	17.1 [32.6]
9 hours	150	8.0 [35.3]
Would You Like More Of The Drug You Took, Right Now?		
Pre-infusion	0	0
6 hours	150	19.9 [30.9]
9 hours	150	19.6 [33.7]

Super-refractory status epilepticus (SRSE)

The Sponsor also evaluated brexanolone for the treatment of super-refractory status epilepticus (SRSE), an acute, life-threatening condition (Studies 547-SSE-201, 547-SSE-301, 547-SSE-302). ^{(b) (4)}

Within the limitations of a highly confounded, critically ill patient population, there were no abuse-related safety signals observed in this unconscious population receiving brexanolone, and no safety signals were detected in conscious subjects.

4.3 Safety Profile

Somnolence was reported by 15 of 140 (10.7%) subjects receiving brexanolone and 5 of 107 (4.7%) subjects on placebo in the double blind PPD studies. In these studies, sedation was reported by 8 of 140

(5.7%) subjects on brexanolone and 1 of 107 (0.9%) subjects on placebo. Euphoria was not reported. Thus, somnolence and sedation, which are indicative of abuse potential, were reported at a higher rate with brexanolone.

Feeling drunk was reported in only one (2%) subject on SAGE-547 in one study.

In the ETD study, there were no clear-cut abuse related AEs noted, however, this was a small study of 25 subjects.

4.4 Evidence of Abuse, Misuse and Diversion in Clinical Trials

In all clinical studies of brexanolone, there were no reports of misuse, abuse, diversion or dependence consistent with its administration in a controlled setting during the clinical development program. Since all administrations were conducted in a controlled setting by a healthcare practitioner, there were no subjects who discontinued participation without returning study drug.

4.5 Physical Dependence Studies in Humans

The potential for physical dependence in humans was evaluated based on all spontaneously reported AEs observed following discontinuation in clinical trials in which brexanolone was administered for a minimum of 24 hours and a comparison with on-treatment AEs was made.

Discontinuation-emergent AEs (DEAEs) were summarized by dose phase, as seen in the Sponsor's Table 10, as follows:

- Taper phase, defined as during the infusion of decreasing doses administered after the maximum titrated dose, or
- Acute follow-up phase, defined as after the study drug infusion until the start of the next study drug infusion, or until seven days after the end of study drug administration.

Table 10

Table 20: Number (%) of Subjects with Discontinuation-emergent Adverse Events Occurring in at Least Two Subjects

Preferred Term	All Studies Pool		Placebo-controlled Studies Pool			
	Taper Phase	Acute Follow-up	Taper Phase		Acute Follow-up	
	Brexanolone <100 µg/kg/h (N=182)	Brexanolone <100 µg/kg/h (N=182)	Placebo (N=107)	Brexanolone <100 µg/kg/h (N=140)	Placebo (N=107)	Brexanolone <100 µg/kg/h (N=140)
Headache	3 (1.6)	6 (3.3)	0	3 (2.1)	0	5 (3.6)
Dizziness	0	1 (0.5)	2 (1.9)	0	1 (0.9)	1 (0.7)
Rash	1 (0.5)	2 (1.1)	0	0	0	1 (0.7)

Headache occurred more frequently during withdrawal of brexanolone but there were no other consistent patterns of AEs that would indicate the emergence of a withdrawal syndrome following discontinuation. However, in all studies, the drug was tapered which would likely preclude the emergence of withdrawal symptoms.

5. Regulatory Issues and Assessment

The Sponsor states that allopregnanolone has been available as an uncontrolled substance for several decades and has not been subject to abuse. Brexanolone is a proprietary formulation of allopregnanolone, an endogenous major metabolite of progesterone, which is unscheduled. Since oral administration of brexanolone solution demonstrates poor bioavailability (< 5%) there would be little incentive to misuse or abuse brexanolone via the oral route of administration. Access to undiluted brexanolone will be limited to a controlled pharmacy setting. Once diluted, the admixture will be administered under the responsibility of a healthcare practitioner in a variety of clinical settings under a controlled chain of custody. Unlike benzodiazepines that are taken home and may be prescribed with refills, the potential risk for diversion with brexanolone, which will be prescribed once without potential for refills, is very low.

With respect to potential drug scheduling to address the abuse potential of brexanolone, the abuse-related data is summarized as follows:

Preclinical studies: These studies demonstrate that brexanolone produces interoceptive cues that are similar to those of midazolam, a Schedule IV sedative. This is to be expected, since both drugs act through GABA agonism.

HAP study: The results indicate that brexanolone, in supratherapeutic doses, produces drug liking effects similar to alprazolam, a Schedule IV drug.

Clinical trials: In double blind studies on PPD, euphoria was not reported, however, sedation, an abuse related AE, was reported in 4-30% (mean 5.7%) subjects on brexanolone and 0-2% (mean 0.9%) subjects on placebo.

In summary, the data indicate that brexanolone has the abuse potential of a Schedule IV drug.

Physical Dependence: Animal studies on physical dependence were not valid. In humans, headache occurred more frequently during withdrawal of brexanolone, however, dependence could not be evaluated because the drug was not abruptly discontinued but gradually tapered off.

CSS recommendations regarding the label are addressed in the Recommendations section.

6. Other Relevant Information

Sponsor's review: Brexanolone is not yet approved for marketing in any jurisdiction; therefore, there are no post-marketing data available. However, allopregnanolone has been available as a research compound. The Sponsor conducted a review of available data for allopregnanolone to identify potential cases of abuse, misuse, dependence, and diversion. The review included publicly available datasets (World Health Organization VigiBase®, FDA Adverse Event Reporting System [FAERS], poison center reports [National Poison Data System (NPDS)], emergency department [ED] reports from the Drug Abuse Warning Network [DAWN]), Internet searches of drug user forums, and a literature review. There were no reports for allopregnanolone in VigiBase or FAERS, which is expected, as allopregnanolone is not an approved medication. Therefore, for comparison purposes, a search of

Individual case safety reports (ICSRs) in Vigibase was conducted for alprazolam, a Schedule IV benzodiazepine, alphaxalone, a Schedule IV positive allosteric modulator of GABAA receptors indicated for veterinary use, and progesterone, an unscheduled drug that is the precursor to allopregnanolone. There were no reports of abuse, dependence, or withdrawal for alphaxalone. For alprazolam, the most common event was drug abuse (11.85% of events). There were $\leq 0.10\%$ of events related to drug abuse, dependence, and withdrawal for progesterone. A similar pattern of event rates was observed for alprazolam and progesterone in the FAERS database

There were no specific mentions of allopregnanolone in NPDS reports or ED visits in the DAWN datasets. There were no specific mentions of alphaxalone in these datasets either. Alprazolam was involved in 425,616 ED visits in 2011, and there were 74,050 reports to the NPDS in 2016. Progesterone was not mentioned in NPDS reports or ED visits in the DAWN datasets, though other hormones were reported.

CSS comments: Alphaxalone, which is chemically related to brexanolone, is a Schedule IV substance under the CSA. Due to the lack of easy availability of alphaxalone and allopregnanolone, their abuse may not be evident in datasets reviewed by the Sponsor. Comparison to the abuse of alprazolam, a very commonly prescribed drug, is therefore not relevant. Although brexanolone is to be prescribed in a monitored health care setting, and not easily available to the population, it would be accessible to health-care providers, who are susceptible to substance use disorders. The high incidence (about 12%)¹ of PPD, and the lack of availability of other treatments, may lead to common prescribing of brexanolone, thus increasing its availability for abuse.

III. REFERENCES

1. Shore S, Chee CYI, Ng ED et.al. Prevalence and incidence of postpartum depression among healthy mothers: A systematic review and meta-analysis. J Psychiatr Res 2018; Sep 235-248.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHALINI M BANSIL
01/15/2019 04:05:10 PM

KATHERINE R BONSON
01/15/2019 04:16:00 PM

MARTIN S RUSINOWITZ
01/15/2019 04:27:22 PM

SILVIA N CALDERON
01/15/2019 04:43:05 PM

DOMINIC CHIAPPERINO
01/15/2019 04:51:58 PM

Clinical Inspection Summary

Date	11/29/2018
From	Jenn Sellers, M.D., Ph.D., Medical Officer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Latrice Wilson, Pharm.D., Regulatory Project Manager Bernard Fischer, M.D., Clinical Reviewer Tiffany Farchione, M.D., Deputy Director Division of Psychiatric Products (DPP)
NDA #	211371
Applicant	Sage Therapeutics, Inc.
Drug	Zulresso (Brexanolone Injection)
NME	Yes
Therapeutic Classification	Neuroactive Steroid
Proposed Indication	Treatment of Post-Partum Depression
Consultation Request Date	05/29/2018
Summary Goal Date	12/05/2018
Original PDUFA Date	12/19/2018
Extended PDUFA Date	03/19/2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The sponsor Sage Therapeutics, Inc. and the clinical sites of Drs. Grainger, Harrison, and Johnson were inspected in support of this NDA. At Dr. Harrison's site, there was widespread poor record keeping with regard to the start times of the paper psychological assessments (including the primary efficacy measure, the HAM-D), making it very difficult to reconstruct how these assessments were administered. This raises questions regarding the quality of the psychological assessments for the affected subjects. That said, during the sponsor inspection, Sage described how, after the institution of protocol version 5, 14 subjects at site #017 had audio recordings of the HAM-D reviewed by a blinded central rater for Screening and Hour 60. The sponsor presented their analysis of queries for the HAM-D by the central rater, which they believe demonstrates good agreement between the sub-investigator at Dr. Harrison's site, who did all the HAM-D ratings, and the central rater (only 8% of HAM-D items queried). We therefore recommend that the review division conduct a sensitivity analysis to assess the effect of the widespread poor record keeping with regard to the start times of the paper psychological assessments at site #017 by excluding all but the 14 subjects (b) (6) for whom there was central review of the HAM-D at Screening and at Hour 60 in order to determine the robustness of the primary analysis.

The preliminary compliance classification of the inspections of the sponsor Sage and Dr. Grainger is No Action Indicated (NAI). The preliminary compliance classification of the inspection of Dr. Harrison is Official Action Indicated (OAI). The final compliance classification of the inspection of Dr. Johnson is Voluntary Action Indicated (VAI).

II. BACKGROUND

The applicant submitted this original NDA to support the use of brexanolone (SAGE-547)

injection for the treatment of post-partum depression (PPD). FDA granted the brexanolone PPD clinical program the Breakthrough Therapy designation. The following protocols were inspected in support of this application:

Protocol 547-PPD-202B, “A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects with Severe Postpartum Depression”

Protocol 547-PPD-202C, “A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-547 Injection in the Treatment of Adult Female Subjects with Moderate Postpartum Depression”

Study 547-PPD-202B took place at 32 sites in the United States, beginning August 01, 2016 and ending October 19, 2017. A total of 138 subjects were randomized.

Study 547-PPD-202C took place at 32 sites in the United States beginning July 25, 2016 and ending October 11, 2017. A total of 108 subjects were randomized.

These two studies shared the umbrella Protocol 547-PPD-202. At each site, subjects were screened for both studies and were enrolled into the appropriate study based on their HAM-D total score. Subjects with a HAM-D total score of ≥ 26 were assigned to participate in Study PPD-202B and subjects with a HAM-D total score of 20 to 25 were assigned to participate in Study PPD-202C.

The primary study objective of these two studies was to determine if SAGE-547 Injection infused intravenously at up to 90 $\mu\text{g}/\text{kg}/\text{h}$ for 60 hours reduced depressive symptoms in subjects with postpartum depression compared to placebo injection as assessed by the change from baseline in Hamilton Rating Scale for Depression (HAM-D) total score.

The primary efficacy assessment of these two studies was the change from baseline (Hour 0) in the HAM-D total score to the end of the infusion (Hour 60).

Rationale for Site Selection (and Sponsor Inspection)

Dr. Grainger’s site was selected because the data from his site impacted the overall efficacy results of the studies and because he has no prior inspection history.

Dr. Johnson’s site was selected due to high enrollment and no prior inspection history.

Dr. Harrison’s site was selected due to the following reasons:

- Complaint: OSI received a complaint on May 1, 2018 regarding (b) (4) a site management organization (SMO). Regarding Protocol 547-PPD-202, the complainant alleged that the (b) (4) for Protocol 547-PPD-202, had pre-signed psychological evaluations and assessments. Two other clinical investigators (CIs) at (b) (4) (not associated with this NDA) were also mentioned in the complaint. This PDUFA inspection was combined with the for-cause inspections for other two CIs.
- The data from this site impacted overall efficacy results of the studies
- High enrollment
- Several major protocol violations
- No prior inspection history

The study drug brexanolone injection is a new molecule entity. The sponsor Sage Therapeutics, Inc. was inspected to ensure that there are no data integrity concerns with the data submitted for this application. Sage does not have history of inspection.

RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects Enrolled	Inspection Dates	Classification
Site #005 David Grainger, M.D. 9300 E. 29 th Street North, Suite 104 Wichita, KS 67226	547-PPD-202B Subjects: 5	27-30 August 2018	NAI *
Site # 017 Heather Harrison, D.O. 1215 S. 1680 W. Orem, UT 84058	547-PPD-202B Subjects: 27 547-PPD-202C Subjects: 9	23-24, 27-31 August 2018; 5, 10-14, 17-19 September 2018	OAI *
Site # 039 David J. Johnson, M.D. 1200 Breckenridge Street Owensboro, KY 42303	547-PPD-202B Subjects: 24 547-PPD-202C Subjects: 27	09-13 July 2018	VAI
Sponsor Sage Therapeutics, Inc 215 First Street Cambridge, MA 02142	547-PPD-202B 547-PPD-202C	17-26 Sept. 2018	NAI *

Key to Compliance Classifications:

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations. Data unreliable

* = Preliminary classification based on information in 483 or preliminary communication with the field; the final EIR has not been received from the field and/or the complete review of final EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

General Comment on Inspections

To better understand the inspection findings, it should be noted that during the study there were three different ways of conducting and recording the HAM-D interview, which were instituted in the following order (as clarified by Sage during the sponsor inspection):

- **Paper and No Tablet**
 - Paper source
 - Start time and HAM-D item scores entered into electronic data capture system; no stop time entered so no duration calculable
 - Source data verification by monitor
 - Interview guide not mandated by Sage

- **Tablet and No Audio**
 - This was generally when they first started using the tablet, when there were still some technical difficulties
 - Paper source
 - Start time and HAM-D item scores entered into the tablet manually; no stop time entered so no duration calculable
 - Source data verification by monitor
 - SIGH-D interview guide mandated (this is an interview guide for the HAM-D)

- **Tablet and Audio Available**
 - Start time and stop time automatically date and time stamped by the tablet (duration of interview calculated)
 - HAM-D item scores entered into the tablet
 - SIGH-D interview guide mandated
 - Select audio recordings sent for central review

1. David Grainger, M.D.

At this site for Protocol 547-PPD-202B, 6 subjects were screened and 5 were enrolled, and of whom completed the study. A complete review of the records of all 6 screened subjects was conducted. These records included, but were not limited to, informed consent forms, drug accountability records, financial disclosures, training records, delegation of authority, study eligibility, adverse event reporting, the primary efficacy endpoint source documents, concomitant medications, and protocol deviations.

The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

2. Heather Harrison, D.O.

At this site for Protocol 547-PPD-202, 36 subjects were screened and 30 were enrolled (24 in Study 547-PPD-202B and 6 in Study 547-PPD-202C). All subjects completed the study, except for two in Study 547-PPD-202B who were discontinued. One subject (b) (6) withdrew consent prior to the first dose of the investigational product. The other subject (b) (6) withdrew consent during treatment.

A complete review of the records of 19 enrolled subjects was conducted. These records included, but were not limited to, informed consent forms, site staff CVs and training records, delegation of authority, IRB correspondence and approvals, correspondence between the investigator and sponsor, monitoring records, study eligibility, adverse event reporting, the primary efficacy endpoint source documents (and other psychological assessment records, including audio recordings), concomitant medications, drug accountability records, financial disclosures, and protocol deviations.

Two adverse events (headache for subject # (b) (6) and worsening depression for subject # (b) (6) were not reported. The primary efficacy endpoint data were verifiable.

A Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection. The findings included the following:

- Source records indicated that the primary efficacy endpoint interviews did not appear to be sufficient to allow for adequate assessment. Table 1 below provides the start times of the HAM-D and the start times of the next assessment. All assessments were performed by the same rater.

Table 1. HAMD and Next Assessment Start Time

Subject	Visit	HAM-D Start time	Next Assessment	Next Assessment Start time	Time to Complete HAM-D
(b) (6)	H: 12	22:40	CGI	22:42	2 min
	H: 4	11:23	CGI	11:25	3 min
	H: 72	8:26	C-SSRS	8:29	3 min
	H: 36	19:41	CGI	19:43	2 min
	D: 21	10:55	MADRS	10:57	2 min
	H: 0	07:05	C-SSRS	7:07	2 min
	H: 12	20:08	CGI	20:10	2 min

CI and sponsor response: The CI's response to this observation was not sufficiently detailed; the sponsor provided additional information. Together they argued that there is overlap between the HAM-D and the C-SSRS, CGI, and MADRS, which allows the instruments such as C-SSRS, CGI, and MADRS to be completed based on the HAM-D interview. Therefore, it is plausible that the times overlap for these assessments. In other words, the interviewer could have jumped between these assessments. In addition, since an interview guide was not mandated by Sage for paper/no tablet assessments, this jumping between assessments would have been permitted.

Reviewer's Comment: The sponsor/CI response is not adequate. First, it should be noted that it is poor practice to jump between psychological assessments when interviewing subjects in psychiatric trials. This is likely why a SIGH-D interview guide was mandated with introduction of the tablet. In addition, it is concerning that the sponsor and CI are hypothesizing what might have happened rather than the subinvestigator/rater (who is still at the site) making a definitive statement regarding how he conducted the assessments. On the whole, this observation is indicative of poor recording keeping, where it is very difficult to reconstruct how these assessments were administered. It raises questions regarding the quality of the psychological assessments for these subjects.

- The source records indicated that the documentation of the SIGH-D, the primary efficacy endpoint assessment [the SIGH-D is the interview guide for the HAM-D], was not completed contemporaneously with the subjects' responses. No hard copy paper-based evaluations were present in the subjects' files, nor were audio recordings available to support the assessment data collected by the rater. See Table 2 below for examples:

Table 2. Visit Date and SIGH-D Completed Date

Subject	Visit	Visit Date	SIGH-D Completed Date	Interim
(b) (6)	D: 30	07/17/2017	07/19/2017	2 days
	H: 72	06/23/2017	06/30/2017	7 days
	H: 12	06/27/2017	06/28/2017	1 day
	H: 24	06/28/2017	06/28/2017	2 hours
	H: 36	06/28/2017	06/29/2017	1 day
	H: 72	06/30/2017	06/30/2017	2 hours
	H: 36	08/23/2017	08/30/2017	7 days
	H: 48	08/24/2017	08/30/2017	6 days

CI's response: the "SIGH-D completed date" was the date that the SIGH-D was uploaded to the MedAvante portal (MedAvante was the vendor for the tablet), not the date the assessment was completed. Due to fire wall problems at that time, these assessments were completed using the option of the off-line mode on the tablet, called "paper only," so that the assessments could be finished within the window required by protocol. It was called "paper only" because it did not have an audio recording, but the source was still the tablet and not paper.

Reviewer's Comment: The CI's response is adequate because it was supported by exhibits, including emails between the site and MedAvante documenting the technical problems at that time. The actual visit dates of the subjects were also corroborated by the sponsor.

- Multiple assessments were being conducted and/or recorded by the same sub-investigator/rater between subjects at the same time.

On 06/20/2017, source records indicated subject # [REDACTED] (b) (6) had assessments completed by the same rater at the same time.

Subject # [REDACTED] (b) (6)	EPDS at 11:41 AM
	GAD-7 at 11:42 AM
	PHQ-9 at 11:42 AM
	BIMF at 11:45 AM
Subject # [REDACTED] (b) (6)	HAM-D at 11:40 AM
	CGI-S at 11:45 AM

On 12/11/2016, source records indicated subject # [REDACTED] (b) (4) had assessment completed by the same rater at the same time:

Subject # [REDACTED] (b) (6)	HAM-D at 12:40 PM
Subject # [REDACTED] (b) (6)	HAM-D at 12:36 PM
	SSS at 12: 41 PM
	CGI at 12: 42 PM

CI's response: At the site, subjects were provided with a packet of patient reported outcome (PRO) instruments at the beginning of the assessment period, which included the BIMF, EPDS, GAD-7, PHQ-9 and SF36. The rater usually provided the PRO package to two subjects at the same time, then administered the HAM-D to one subject while the other was completing the PRO package.

Reviewer's Comment: The CI's response is not adequate. It certainly does not explain why the HAM-D assessments for subjects [REDACTED] (b) (6) start 4 minutes apart. Even for subjects [REDACTED] (b) (6), if the rater was working with subject [REDACTED] (b) (6) while subject [REDACTED] (b) (6) was filling out the EPDS, GAD-7, PHQ-9 and BIMF (which are all patient reported outcome assessments), this does not explain why the sequential times for the patient reported outcome assessments for subject [REDACTED] (b) (6) are all in the sub-investigator/rater's handwriting. This observation is still indicative of poor record keeping, where it is very difficult to reconstruct how these assessments were administered. It raises questions regarding the quality of the psychological assessments for these subjects.

- Subject (b) (4): Progress notes dated 04/19/17 at 11:31 indicated that the subject was unhooked from the infusion from 09:21 to 10:58 (1 hour and 37 mins) due to complications with IV placement. However, the infusion log reflected continuous infusion during this time. Also, there was no indication in the infusion records that the subject received additional time at the prescribed flow rate. The EDC documents that this deviation was reported following a query on 06/5/17. An additional complication with IV placement was reported on the same day at 19:25, yet the infusion log again reflected continuous infusion. The total time period for which the infusion was stopped was not recorded, and records did not indicate whether additional time was added at the prescribed flow rate. This potential deviation of under dosing of investigational does not appear to have been reported.

CI's response: She understood that regardless of whether there were interruptions in the IV infusion, the infusion was to be terminated at the scheduled 60-hour time point. This understanding came from extensive training on the protocol, pharmacy manual, guidance documents, and additional communication from the sponsor. These documents stressed a 60-hour period and the importance of maintaining all assessments on schedule. None of the documents specifically addressed extending the infusion period beyond 60 hours in the event of interruptions. The research site did properly document the IV interruption. This information was made available to the sponsor at the monitoring visits, in the source records, and the EDC.

Reviewer's Comment: The CI's response is for the most part adequate. That said, this observation is another example of poor recordkeeping by the site, where the information in the infusion log contradicts that in the progress notes. Otherwise, IV infusion interruption was a protocol deviation, which was apparently reported to the FDA. However, as a result, this subject was likely under dosed, and this does not appear to have been reported to the FDA. The efficacy result of the study would not have been impacted by this likely under dosing of the investigational product, as the subject in question was in the placebo group.

- The Pharmacy Manual states if a subject was over 80 kg and was randomized to the 90 ug/kg dosing arm, a 4th infusion bag would need to be prepared and administered to accomplish dosing over a 60-hour period. Eleven (11) subjects were randomized into the 90 ug/kg treatment arm. A 4th infusion bag was not administered for any of these subjects

Reviewer's Comment: The CI did not respond to this observation in her letter dated October 5, 2018. Apparently, the Form FDA 483 was later updated with this observation, and the CI may have been using the original 483 in writing her response. However, this reviewer checked the dosing for these subjects against the source records and found that they had been dosed appropriately.

- There were two different versions of the Day 1-Hour 0 SIGH-D assessment in the source records for subject (b) (6), neither of which matched the data submitted by the sponsor.

CI's response: The reason there were two versions of the Day 1-Hour 0 SIGH-D assessment was that changes were made after a query issued by the (b) (4) central reviewer. Therefore, there were 2 versions: one was the original and the other had modified entries. The audit trail provided the history of the changes. The modified version matched the sponsor data.

Reviewer's Comment: The CI's response is adequate, especially as it is corroborated by the sponsor. According to the data submitted by the sponsor, there was an audio recording of the HAM-D assessments for subject (b) (6). The SIGH-D at Screening, H0, and H60 were all sent for central review. This reviewer confirmed that version 2 of the SIGH-D signed by the rater at the site matched the data submitted by the sponsor.

- The source paper record for the Day 1 Hour 0 SIGH-D for subject #017-418 does not match the sponsor data submitted for this timepoint

CI's response: The original source record was the (b) (4) electronic document for subjects (b) (6) as protocol version 4 was active at that time, which required data to be entered directly into the tablet. The electronic document of the Day 1 Hour 0 assessments of subject (b) (6) was printed out for FDA's review. Unfortunately, the printout was mistakenly labeled by hand as (b) (6) and placed in the binder of subject (b) (6).

Reviewer's Comment: The CI's response is adequate, as this reviewer examined the record for the Day 1 Hour 0 SIGH-D for subject (b) (6) that was submitted by the CI and confirmed that it matched the sponsor data.

- Investigational drug disposition records were not adequate with respect to dates, quantity and use by subjects. The findings regarding drug accountability were not detailed in this summary as these violations did not impact the efficacy results of the studies or the safety of subjects.

3. David J. Johnson, M.D.

At this site for Protocol 547-PPD-202, 37 subjects were screened, 23 were enrolled, and 21 subjects completed the study. One subject was a no show prior to receiving drug, and the other subject withdrew consent after receiving drug. A complete review of the records of the 22 enrolled subjects was conducted, which included, but were not limited to, informed consent forms, drug accountability records, financial disclosures, training records, delegation of authority, study eligibility, adverse event reporting, the primary efficacy endpoint source documents, concomitant medications, and protocol deviations.

The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

A Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection, including the following finding:

Two out of 22 treated subjects received overdoses of brexanolone:

1. Subject (b) (6) was supposed to be receiving 1.6 mL/hr of brexanolone solution. Approximately 100 mL was delivered to the subject over a period of approximately 90 minutes due to an infusion pump malfunction. This corresponds to a rate of 66.67 mL/hr.
2. Subject (b) (6) was supposed to be receiving 5.9 mL/hr of brexanolone solution. Approximately 13.1 mL was delivered to the subject over a period of approximately 23 minutes due to an infusion pump malfunction. This corresponds to a rate of 34.2 mL/hr.

Both cases of overdose due to infusion pump malfunction were reported to FDA.

Reviewer's Comment: Dr. Johnson responded adequately to the inspection findings in a letter dated July 24, 2018. He noted that he had implemented corrective actions to prevent the recurrence of the inspection findings. There is no evidence that either of the two subjects who had received an overdose were harmed.

4. Sage Therapeutics, Inc.

The FDA field investigator, together with the subject matter expert (SME) from CDER/OSI, reviewed the following for this sponsor inspection: selection and monitoring of clinical investigators; data collection, handling, and management; electronic data capture and data systems; quality control and auditing; safety and adverse event reporting; management of the vendors; manufacturing, packaging, and labeling of investigational product (IP); IV preparation, including the sterile procedure; the sponsor's oversight plan. No significant regulatory violations were noted.

During the inspection, the sponsor tried to address the problems discovered during our inspection of site #017 (Dr. Harrison). They described how, after the institution of protocol version 5, 14 subjects at site #017 had audio recordings of the HAM-D reviewed by central raters at Screening and Hour 60. The sponsor presented their analysis of queries for the HAM-D by the central rater, which they believe demonstrates good agreement between the sub-investigator at Dr. Harrison's site (who did all the HAM-D ratings) and the central rater. At our request, the sponsor officially submitted this information to the NDA on September 26, 2018.

Reviewer's Comment: Please see our recommendations in Section I of this clinical inspection summary.

{See appended electronic signature page}

Jenn W. Sellers, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm. NDA #211371
DPP /Project Manager/Latrice Wilson
DPP/Division Director/Mitch Mathis
DPP/Deputy Division Director/Tiffany Farchione
DPP/Medical Officer/Bernard Fischer
OSI /Office Director/David Burrow
OSI/DCCE/Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Jenn Sellers
OSI/GCP Program Analysts/Yolanda Patague

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENN W SELLERS
11/29/2018

PHILLIP D KRONSTEIN
11/29/2018

KASSA AYALEW
11/29/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: September 27, 2018
Requesting Office or Division: Division of Psychiatry Products (DPP)
Application Type and Number: NDA 211371
Product Name and Strength: Zulresso (brexanolone injection)
100 mg/20 mL (5 mg/mL)
Product Type: Single Ingredient Product
Rx or OTC: Prescription (Rx)
Applicant/Sponsor Name: Sage Therapeutics, Inc.
FDA Received Date: April 19, 2018
OSE RCM #: 2018-850
DMEPA Safety Evaluator: Loretta Holmes, BSN, PharmD
DMEPA Team Leader: Lolita White, PharmD

1 REASON FOR REVIEW

The Division of Psychiatry Products (DPP) consulted the Division of Medication Error Prevention and Analysis (DMEPA) to evaluate the container labels, carton labeling, Medication Guide and Prescribing Information (PI) labeling for NDA 211371, Zulresso (brexanolone injection), to determine if they are acceptable from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed container label, carton labeling, Medication Guide, and Prescribing Information (PI) to determine if there are any areas of needed improvement from a medication safety perspective. We identified the following:

Prescribing Information

(b) (4)

Container Label

(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LORETTA HOLMES
09/27/2018

LOLITA G WHITE
09/27/2018



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: 9/14/2018 **Date consulted:** 4/19/2018

From: Catherine Roca, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Psychiatry Products (DPP)

Drug: ZULRESSO (brexanolone)

NDA: 211371

Applicant: Sage Therapeutics

Subject: Pregnancy and Lactation Labeling

Indication: Treatment of postpartum depression

Materials

Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 211371
- DPMH consult request dated May 1, 2018, DARRTS Reference ID 4256757

Consult Question: "DPP would like to request input from DPMH regarding labeling."

INTRODUCTION AND BACKGROUND

On April 19, 2018, Sage Therapeutics, submitted an original NDA for ZULRESSO (brexanolone) NDA 211371, for the treatment of postpartum depression (PPD). ZULRESSO (brexanolone) received Breakthrough Therapy Designation on August 23, 2016. DPP consulted DPMH on May 1, 2018, to assist with the Pregnancy and Lactation subsections of labeling.

ZULRESSO (brexanolone) Drug Characteristics¹

Mechanism of action	(b) (4) The precise mechanism of action in the treatment of PPD is not fully understood. (b) (4)
Molecular weight	318.5 Daltons
Half-life	Terminal half-life is approximately 9 hours.
Protein binding	99%
Bioavailability	Low oral bioavailability (<5%)
	(b) (4)
Boxed Warning	The applicant has proposed adding (b) (4)

REVIEW

PREGNANCY

Major depression with peripartum-onset²

- The American Psychiatric Association’s Diagnostic and Statistical Manual, Fifth Edition does not use the term “postpartum depression,” but uses a qualifier of “with peripartum onset” for a diagnosis of major depression when the onset occurs either during pregnancy or in the four weeks following delivery.³
- Prevalence estimates of postpartum depression vary, in part due to the various definitions of postpartum depression, which may include major and minor depression with an onset

¹ ZULRESSO (brexanolone) proposed package insert

² While the applicant uses the term “Postpartum Depression” for the indication, in the applicant’s “Summary of Clinical Efficacy” the women enrolled in the clinical trials had their onset of depressive symptoms in the third trimester of pregnancy through four weeks after delivery, which would meet criteria for the DSM V definition of Major depression with peripartum-onset.

³ American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM V), American Psychiatric Association, Arlington, VA 2013.

up to 12 months postpartum.⁴ In the United States, a population-based survey using face-to-face interviews found a prevalence of unipolar major depression in approximately 9% of postpartum women.⁵

- Women diagnosed with MDD who discontinue their antidepressant medication before or during pregnancy are at a greater risk of relapse than those who continue their medication.⁶ Moreover, a pre-pregnancy mood disorder, such as MDD or bipolar disorder, is a strong risk factor for postpartum depression and re-hospitalization.⁷
- Unremitted depression is also risk factor for suicide, which remains one of the most common leading causes of maternal death during the year after delivery.^{8,9}
- Depression during pregnancy has been reported to be associated with poor obstetrical and neonatal outcomes.^{10,11,12} While these data are complicated by small sample sizes and confounding factors, a recent meta-analysis that included data from 25,663 women found significantly increased risk of both preterm birth (OR=1.56, 95% CI, 1.25-1.94) and low birth weight (OR=1.96, 95% CI, 1.24-3.11)¹³ in women with untreated depression during pregnancy.

Nonclinical Experience

The applicant reports in their Summary of Clinical Safety that administration of intravenous brexanolone to pregnant rabbits was associated with increased rates of abortion and numbers of late resorptions, fewer live fetuses and higher post-implantation loss. According to the study report,¹⁴ the fetotoxic effects were correlated with reduced maternal body weight.

Administration of intravenous brexanolone to female rates during gestation, parturition, and lactation was associated with fewer live pups/litter at birth that was thought to be related to lower maternal weights and decreased pup viability between postnatal day 0 and 4.

⁴ Banti S, et al. From the third month of pregnancy to 1 year postpartum. Prevalence, incidence, recurrence, and new onset of depression. Results from the Perinatal Depression-Research and Screening Unit Study. *Comprehensive Psychiatry*. 2011;52:343-352.

⁵ Vesga-Lopez O, et al. Psychiatric disorders in pregnant and postpartum women in the United States. *Arch Gen Psychiatry*. 2008;65(7):805-815.

⁶ Cohen L, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA*. 2006. 295(5):499-507.

⁷ Wisner KL, et al. Postpartum depression: a major public health problem. *JAMA* 2006. 296(21):2616-8.

⁸ Esscher A, et al. Suicides during pregnancy and the first year postpartum in Sweden, 1980-2007. *Br J Psychiatry*. 2016. 208(5):462-9.

⁹ Lindahl V, et al. Prevalence of suicidality during pregnancy and the postpartum. *Arch Women's Ment Health*. 2005. 8(2):77-87.

¹⁰ Venkatesh KK et al. Association of antenatal depression symptoms and antidepressant treatment with preterm birth. *Obstet and Gynecol*. 2016. 127(5):926-933.

¹¹ Straub H, et al. Antenatal depressive symptoms increase the likelihood of preterm birth. *Am J Obstet and Gynecol*. 2012. 207(4):329

¹² Yedid SM, et al. Is antenatal depression associated with adverse obstetric and perinatal outcomes? *J Maternal Fetal and Neonatal Medicine*. 2016. 29(6):863-867.

¹³ Jarde A, et al. Neonatal outcomes in women with untreated antenatal depression compared with women without depression: A systematic review and meta-analysis. *JAMA Psych*. 2016;73(8):826-837.

¹⁴ A continuous intravenous infusion embryo-fetal development study of SAGE-547 in rabbits. Sponsor Reference No. SSN-825, October 9, 2015.

The reader is referred to the full Pharmacology/Toxicology review by Antonia Dow, Ph.D. and Ikram Elayan, Ph.D.

Review of Pharmacovigilance Database

The applicant reported no spontaneous abortions, and one pregnancy (discussed below) during the clinical studies of brexanolone. Brexanolone has not been marketed in any country, so no postmarketing data are available.

- The patient had an estimated date of conception one day after the completion of the brexanolone infusion. She had no pregnancy complications and delivered a healthy infant by Cesarean section at 37 weeks gestation. No other details were reported.

Review of Literature

Applicant's Review of Literature

The applicant provided literature as part of the background for the application. This did not include papers on brexanolone use during pregnancy.

DPMH Review of Literature

DPMH performed a search of the literature using PubMed, Embase, Reprotox and Micromedex¹⁵ using the search terms, “brexanolone and pregnancy,” “brexanolone and birth defects,” “brexanolone and stillbirth,” “brexanolone and miscarriage,” and “brexanolone and fetal malformations.”

Brexanolone is not referenced in Micromedex or Reprotox. There are no descriptions of brexanolone exposure during pregnancy in the published literature.

Reviewer comment:

There is only one case of brexanolone exposure during pregnancy in the applicant's database and no cases in the published literature. Data from animal studies showed no adverse developmental effects, but did indicate reduced pup survival in the pre- and post-natal study. Data are insufficient to determine a drug-associated risk of birth defects and miscarriage related to brexanolone use during pregnancy.

LACTATION

Nonclinical Experience

The applicant's Summary of Clinical Safety does not comment on the presence of brexanolone in animal milk.

¹⁵ (b) (4), <http://www.micromedexsolutions.com/>. Accessed 7/2/2018

Applicant's Lactation Study¹⁶

The applicant performed an open-label lactation study of twelve women during a 60-hour dose regimen of intravenous administration of 90 mcg/kg/hr brexanolone.

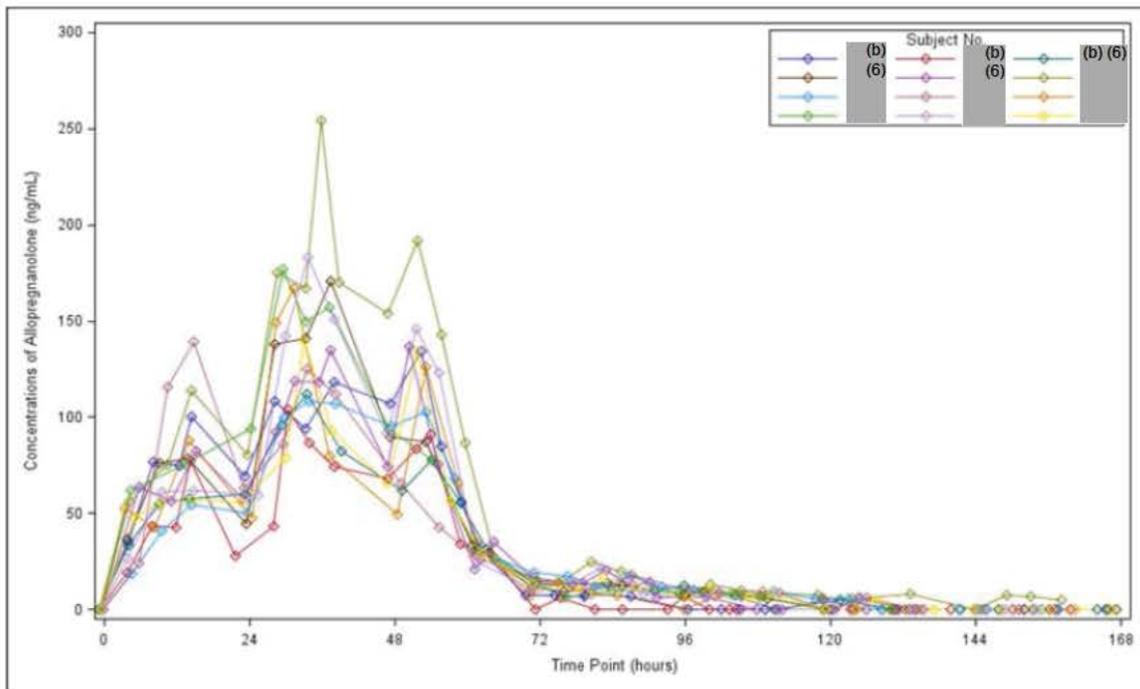
- Participants were less than 6 months postpartum and breastfeeding or maximally pumping seven days prior to pre-dose Day 1 and agreed to pump breastmilk through Day 7.
- Infants were not breastfed from Day 1 through Day 7.
- Participants were healthy and not on other medications other than vitamins, acetaminophen or oral contraceptives.
- The brexanolone infusion was administered as follows:

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 µg/kg/hr	60 µg/kg/hr	90 µg/kg/hr	60 µg/kg/hr	30 µg/kg/hr

- Maternal plasma samples were obtained at baseline, then at 12, 24, 36, 48, 56, 60, 61, 62, 64, and 72 hours after the start of the infusion, as well as Day 7.
- Breast milk samples were obtained at least every 12 hours between baseline and 72 hours after the start of the infusion, as well as on days 4, 5, 6, and 7.
- Study Results:
 - During the 60-hour infusion, the mean plasma concentrations of allopregnanolone increased during dose titration and decreased during dose taper. The concentrations of allopregnanolone in plasma were at the lowest quantifiable limit (1 ng/mL) by Day 3 and near or below the quantifiable limit by day 7 in all subjects. See figure 1.
 - Changes in allopregnanolone concentrations in breastmilk followed a similar pattern to plasma allopregnanolone concentrations.
 - There was no apparent accumulation of allopregnanolone in maternal plasma or breastmilk.
 - The milk: plasma ratio was 1.36.
 - The calculated maximum relative infant dose during the infusion was 1-2%.
 - There were no deaths or severe adverse events reported in the lactating women.

¹⁶ Applicant's report, "An open-label study evaluating concentrations of allopregnanolone following administration of SAGE-547 injection in the breast milk of lactating women," January 8, 2018.

Figure 1. Individual Concentration of Allopregnanolone in Breast Milk (Linear Scale)¹⁷



Note: The limit of quantification was 5ng/mL for breast milk

Reviewer comment:

The applicant concluded that the given the low RID, and low oral bioavailability of brexanolone, that the risk to a breastfed infant would be low. The applicant recommended that should

(b) (4)

This reviewer agrees with the applicant that the infant exposure to brexanolone through breastmilk appears to be low, and that benefits of breastfeeding outweigh the risks of exposure.

Review of Literature

Applicant's review

The applicant did not provide a review of the literature regarding brexanolone and lactation.

DPMH Review of Literature

DPMH conducted a search of *Medications in Mother's Milk*, the Drugs and Lactation Database (LactMed),¹⁸ and of the published literature in PubMed and Embase using the search terms "brexanolone and lactation," and "brexanolone and breast-feeding."

¹⁷ Applicant's report, "An open-label study evaluating concentrations of allopregnanolone following administration of SAGE-547 injection in the breast milk of lactating women," January 8, 2018.

No reports of brexanolone use during lactation were found.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Brexanolone administered via continuous intravenous infusion to male rats for 4 weeks prior to mating, through mating until termination at doses approximately 0.7, 2, and 3 times the maximum recommended human dose (MRHD) was associated with decreased mating and fertility indices, conception rate, lower prostate, seminal vesicle, and epididymis weight, as well as decreased sperm numbers at doses 2 and 3 times the MRHD.

Brexanolone administered via continuous intravenous infusion to female rats for 2 weeks prior to mating, through mating, and up to day 7 of gestation at doses approximately 0.7, 2, and 4 times the MHD was associated with decreased mating and fertility indices, and an increase in number of days to mating at 2 and 3 times the MRHD. Prolonged/irregular estrous cycles, as well as an increase in the number of days to mating, the number of early resorptions and post implantation loss were noted at 3 times the MRHD. Reversal of effects was observed following a 28-day recovery period.

The reader is referred to the full Pharmacology/Toxicology review by Antonia Dow, Ph.D. and Ikram Elayan, Ph.D.

Review of Pharmacovigilance Database

No data on infertility was described.

Review of Literature

Applicant's Review

The applicant did not provide a review of the literature on brexanolone and hormonal contraceptives or infertility.

DPMH Review of Literature

DPMH conducted a review of Micromedex, Embase, and PubMed using the terms, “brexanolone and fertility,” “brexanolone and contraception,” “brexanolone and oral contraceptives,” and “brexanolone and infertility.”

No reports were found in the published literature related to brexanolone and fertility or interactions with hormonal contraception.

Since the animal data indicated a possible effect on fertility, a search of the term “allopregnanolone” and “infertility” also was performed. No papers related to allopregnanolone as a cause of infertility were located. There was one paper describing a decrease in gonadotropins following administration of intravenous allopregnanolone.

¹⁸ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

- A study of ten women administered intravenous allopregnanolone and five women administered isoallopregnanolone (an isomer of allopregnanolone without GABA A receptor effects) demonstrated a reduction of serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) following administration of allopregnanolone- but not isoallopregnanolone.¹⁹

Reviewer comment:

The applicant did not include subsection 8.3 in the draft labeling. Data from animal studies using brexanolone indicate a possible effect on both male and female fertility. Allopregnanolone has been shown to be important in normal lordosis behavior in rats²⁰ and modulates LH serum concentrations, affecting ovulation in rats.²¹ It is unclear, however, if these effects on fertility are relevant to humans. Data from studies in humans have not established a link between allopregnanolone and infertility in humans. This reviewer agrees with not including subsection 8.3 in labeling and keeping the animal data in Section 13, Nonclinical Toxicology.

DISCUSSION AND CONCLUSIONS

Pregnancy

Brexanolone has not been marketed, so human data are limited to one first trimester pregnancy exposure during the clinical trials. The lack of available human data precludes a determination of drug-associated risk of birth defects and miscarriage during pregnancy. Animal data do not indicate a teratogenic effect of brexanolone on pregnant rats and rabbits. Data in pregnant rabbits indicated increased rates of abortion and late resorptions, and in rats, there was decreased pup survival in a pre- and post-natal study. However, both were associated with decreased maternal weights potentially indicating maternal toxicity. There is an established pregnancy registry for antidepressants. DPMH recommends that brexanolone participate in the existing pregnancy registry.

Lactation

There are no data on the effects on a breastfed infant or on milk production. The applicant provided a lactation study indicating a low maximum relative infant dose (1-2%); in addition, brexanolone has low oral bioavailability in adults so accumulation in a breastfed infant is expected to be low. The following statement will be included in Subsection 8.2, “The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ZULRESSO and any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition.”

Females and Males of Reproductive Potential

Data from animal studies indicate effects on male and female fertility in rats. Effects in female rats are reversible. There are no data on the effects of brexanolone on fertility in humans. While there is one study indicating an effect of allopregnanolone on gonadotropin release, it is a small study and a search of the literature did not locate studies linking allopregnanolone with

¹⁹ Timby E, et al. Allopregnanolone, a GABA A receptor agonist, decreases gonadotropin levels in women. A preliminary study. *Endocrinology*. 2011;27(12):1087-1093.

²⁰ McCarthy MM, et al. Infusions of diazepam and allopregnanolone into the midbrain central gray facilitate open-field behavior and sexual receptivity in female rats. *Horm Behav*. 1995;29:279-95.

²¹ Laconi MR, et al. Allopregnanolone alters the luteinizing hormone, prolactin, and progesterone serum levels interfering with the regression and apoptosis in rat corpus luteum. *Horm Metab Res*. 2012;44:1-17

infertility in humans. DPMH recommends that subsection 8.3 is not necessary and that the animal data remain in Section 13.1.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/>

Risk Summary

There are no available data on ZULRESSO use in pregnant women to determine a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, malformations were not seen in rats or rabbits at plasma levels up to 5 and 6 times the maximum recommended human dose (MRHD), respectively. Development and reproductive toxicities were seen in rats and rabbits at 5 and ≥ 3 times the plasma levels at the MRHD, respectively. These effects were not seen in rats and rabbits at 2 and 1.2 times the plasma levels at the MRHD. Brexanolone administered to pregnant rats during pregnancy and lactation resulted in lower pup survival at doses which are approximately ≥ 2 -times the plasma levels at the MRHD. These effects were not seen at 0.8 times the plasma levels at the MRHD (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In pregnant rats and rabbits, no malformations were seen when brexanolone was given during the period of organogenesis at continuous intravenous doses up to 60 and 30 mg/kg/day, respectively. These doses are 5 and 6 times the plasma levels at the maximum recommended human dose (MRHD) of 90 mcg/kg/h, in rats and rabbits, respectively. In rats, a decrease in fetal body weights was seen at 60 mg/kg/day (5 times the plasma level at the MRHD). In rabbits, increased numbers of late resorptions and a decrease in fetal body weights were seen at doses equal to and greater than 15 mg/kg/day (3 times the plasma levels at the MRHD) with

fewer live fetuses and a higher post implantation loss seen at 30 mg/kg/day (6 times the plasma levels at the MRHD) in the presence of maternal toxicity (decreased food consumption and decreased body weight gain and/or body weight loss). Effects in rats and rabbits were not seen at 2 and 1.2 times the plasma levels at the MRHD, respectively.

When brexanolone was administered to pregnant rats by continuous intravenous administration at 30 and 60 mg/kg/day (2 and 5 times plasma levels at the MRHD, respectively) during the period of organogenesis and throughout pregnancy and lactation, increased numbers of dead pups and fewer live pups at birth were seen. Decreased pup viability between postnatal day 0 and 4 in the presence of maternal toxicity (decreased body weight gain and food consumption during lactation) was seen at 5 times the plasma levels at the MRHD. These effects were not seen at 2 times the plasma levels at the MRHD.

8.2 Lactation

Risk Summary

Available data from a sponsor-conducted lactation study in 12 women indicate that ZULRESSO is transferred to breastmilk in nursing mothers. However, the relative infant dose (RID) is low, 1-2% of the maternal weight-adjusted dose (*see Data*). Also, ZULRESSO has low oral bioavailability (<5%) in adults; therefore, infant exposure is expected to be low.

There are no data on the effects of ZULRESSO on a breastfed infant or on milk production. There is a potential risk to the breastfed infant which may present as transient somnolence; however, the likelihood of this risk is low when considering the RID and expected low oral bioavailability.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZULRESSO and any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition.

Data

A study was conducted in twelve healthy adult lactating women treated with intravenous ZULRESSO according to the recommended 60-hour dose regimen (maximum 90 mcg/kg/h). Concentrations of ZULRESSO in breast milk were at low levels (<10 ng/mL) in >95% of women by 36 hours after the end of the infusion of ZULRESSO. The calculated maximum relative infant dose for ZULRESSO during the infusion is 1-2%.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise pregnant women to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy with ZULRESSO. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ZULRESSO during pregnancy [*see Use in Specific Populations (8.1)*].

APPENDIX A –Applicant’s Proposed Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

ZULRESSO contains brexanolone, a compound that is chemically identical to endogenous allopregnanolone. Allopregnanolone is produced in the placenta resulting in high plasma concentrations during pregnancy.

There are no available data on ZULRESSO use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. ZULRESSO may cross the placental barrier; therefore, ZULRESSO may be transmitted from the mother to the developing fetus.

In animal embryofetal development studies, no adverse developmental effects were seen when brexanolone was administered by continuous intravenous infusion to rats or rabbits during the period of organogenesis at doses ranging from approximately 1 to 2-times the maximum recommended human dose (MRHD) based on body surface area (mg/m^2 ; approximately 2.2 $\text{mg}/\text{kg}/\text{day}$, respectively, based on a human body weight of 60 kg). In an animal pre-and post-natal development study, administration of brexanolone to pregnant rats continuously during pregnancy, delivery, and lactation resulted in lower pup survival at doses that are approximately ≥ 2 -times the MRHD based on mg/m^2 [see Data]. The clinical significance is not known, therefore, advise patients of the potential risk of administration during pregnancy.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15- 20% of clinically recognized pregnancies.

Data

Animal Data

Brexanolone was not teratogenic in pregnant rats when administered during the period of organogenesis at continuous intravenous doses of 15, 30, and 60 $\text{mg}/\text{kg}/\text{day}$, approximately 1, 2, and 4 times the MRHD of 2.2 $\text{mg}/\text{kg}/\text{day}$ for PPD based on body surface area (mg/m^2). A decrease in fetal body weights (concurrent with decreased maternal body weight gain and food consumption) was observed at 60 $\text{mg}/\text{kg}/\text{day}$.

Brexanolone was not teratogenic in pregnant rabbits when administered during the period of organogenesis at continuous intravenous doses of 7.5, 15, and 30 $\text{mg}/\text{kg}/\text{day}$, approximately 1, 2, and 4 times the MRHD of 2.2 $\text{mg}/\text{kg}/\text{day}$ for PPD based on body surface area (mg/m^2). Increased numbers of late resorptions were observed at 15 and 30 $\text{mg}/\text{kg}/\text{day}$ with fewer live fetuses and a higher post implantation loss seen at 30 $\text{mg}/\text{kg}/\text{day}$. A decrease in fetal body weights (concurrent with decreased maternal body weight gain and food consumption) was observed at 15 and 30 $\text{mg}/\text{kg}/\text{day}$.

In a study in which pregnant rats were administered brexanolone by continuous intravenous administration at doses of 10, 30, and 60 $\text{mg}/\text{kg}/\text{day}$ (0.7, 2, and 4 times the MRHD) during the period of organogenesis and through lactation, increased numbers of dead pups and fewer live

pups at birth were observed at 2 and 4 times the MRHD. Decreased pup viability between postnatal day 0 and 4 (concurrent with decreased maternal body weight gain and food consumption during lactation) was observed at 4 times the MRHD. There were no effects on offspring growth, development, or reproduction.

8.2 Lactation

Risk Summary

In a study of healthy nursing mothers, ZULRESSO was detected in breast milk. The mean concentration of ZULRESSO in breastmilk is approximately 1.36 times the plasma concentration. Concentrations of ZULRESSO in breast milk were at low levels (<10 ng/mL) in >95% of women by 36 hours after the end of the infusion of ZULRESSO.

Relative infant dose (RID) is the dose of a drug to which an infant is exposed if breastfed during administration of the drug. This can be calculated as a percentage of the mother's dose. The calculated maximum RID for brexanolone during infusion is 1.3%. This RID is associated with low risk to the breast-fed infant. ZULRESSO is not absorbed systemically (<5%) following oral administration. Therefore, brexanolone in breastmilk is not expected to be orally bioavailable to the infant. The effects of ZULRESSO have not been assessed in the breastfed infant. There is a potential risk to the breastfed infant which may present as transient somnolence, however, the likelihood of this risk is low when considering the RID and expected low oral bioavailability.

No data are available to assess the effects of ZULRESSO on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZULRESSO and any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition.

Clinical Considerations

For women who prefer to interrupt breastfeeding while receiving ZULRESSO, it is recommended to pump and dispose of breast milk during the infusion and for up to 36 hours following the end of the infusion.

Data

In a study of twelve healthy adult lactating women in which breast milk was collected during administration of ZULRESSO according to the recommended 60-hour dose regimen (maximum 90 mcg/kg/h), the data demonstrated rapid equilibrium between milk and plasma at a 1.36-fold ratio of milk to plasma. The relationship between milk and plasma concentrations was linear, constant with time, and unaffected by the volume of milk expressed by the mother. Concentrations of ZULRESSO in breast milk were at low levels (<10 ng/mL) in >95% of women by 36 hours after the end of the infusion of ZULRESSO.

17 Patient Counseling Information

Pregnancy

Advise pregnant patients that the risk to a fetus is unknown [see *Use in Specific Populations (8.1)*].

Nursing Mothers

Discuss with patients the benefit/risk of continued breastfeeding versus temporary cessation of breastfeeding during the infusion of ZULRESSO [*see Use in Specific Populations (8.2)*].

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CATHERINE A ROCA
09/14/2018

MIRIAM C DINATALE
09/14/2018

LYNNE P YAO
09/19/2018

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	211,371
Brand Name	Zulresso
Generic Name	Brexanolone (SAGE-547)
Sponsor	Sage Therapeutics
Indication	Postpartum depression
Dosage Form	Solution for IV injection
Drug Class	A positive allosteric modulator of GABA _A receptors that is chemically identical to endogenous neurosteroid allopregnanolone
Therapeutic Dosing Regimen	The proposed treatment regimen is a continuous IV infusion over 60 hours (2.5 days). Hours 0 to 4: 30 µg/kg/h Hours 4 to 24: 60 µg/kg/h Hours 24 to 48: 90 µg/kg/h Hours 48 to 52: 90 µg/kg/h Hours 52 to 56: 60 µg/kg/h Hours 56 to 60: 30 µg/kg/h
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	Not determined
Submission Number and Date	Sequence 0001, 04/19/2018
Review Division	DPP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of brexanolone (SAGE-547) treatment (a 5-hour intravenous infusion starting at a rate of 60 µg/kg/h and increasing each hour to 90, 120, 150, and 180 µg/kg/h) was detected in TQT study 547-CLP-106. The largest upper bound of the 2-sided 90% CI for the mean difference between brexanolone treatment and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 1, indicating that assay sensitivity was established.

In this randomized, blinded, three-period crossover study, 30 healthy subjects were administered with brexanolone treatment (IV infusion as described above), matching IV placebo, and matching IV placebo co-administered with a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bound for brexanolone treatment and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Total N	Time (hour)	Mean $\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Brexanolone (a 5-hour IV infusion starting at a rate of 60 $\mu\text{g}/\text{kg}/\text{h}$ and increasing each hour to 90, 120, 150, and 180 $\mu\text{g}/\text{kg}/\text{h}$)	30	4	3.1	(0.5, 5.8)
Moxifloxacin 400 mg*	28	7	10.1	(7.5, 12.8)

*Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 6.4 ms.

The supratherapeutic dose of brexanolone (180 $\mu\text{g}/\text{kg}/\text{h}$ dose level that was administered for 1 h in the 5 h continuous IV infusion treatment with increasing doses) produces mean C_{max} values of 146.5 ng/mL. This exposure is 1.9-fold of the $C_{\text{max, ss}}$ of 78.9 ng/mL produced by highest therapeutic dose of 90 $\mu\text{g}/\text{kg}/\text{h}$ as observed in Phase 3. No intrinsic or extrinsic factors are anticipated to increase the C_{max} of the drug.

There was no statistically significant exposure-response (concentration-QTc) relationship for brexanolone.

2 PROPOSED LABEL

The Sponsor has not provided any QT-related labeling language in the proposed label.

The following is QT-IRT's proposed labeling language, which is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of brexanolone on the QTc interval was evaluated in a Phase 1 randomized, placebo and positive controlled, double-blind, three-period crossover thorough QTc study in 30 healthy adult subjects. At 1.9-fold of the therapeutic exposures for highest recommended clinical dose, brexanolone did not prolong the QTc interval to any clinically relevant extent.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Brexanolone (SAGE-547) is positive allosteric modulatory of GABA_A receptors that is chemically identical to the endogenous neurosteroid allopregnanolone. The Applicant is seeking an indication for the treatment of post-partum depression.

3.2 MARKET APPROVAL STATUS

Brexanolone is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

SAGE-547 showed minimal potential to inhibit the hERG channel at clinically relevant concentrations. In a GLP study, SAGE-547 was tested at concentrations of 0.8 to 6.6 μM (255 ng/mL to 2102 ng/mL). Minor inhibition was noted at concentrations of 0.8 μM (approximately 4%) and 6.6 μM (approximately 12%) as compared to vehicle control (approximately 2%) (SSN-634). Based on a plasma protein binding value of $\geq 99\%$, an unbound concentration of 6.6 μM (2102 ng/mL) represents a concentration of 210,203 ng/mL in the presence of plasma. This value is at least 2128-fold greater than the highest mean C_{max} and steady state concentrations of SAGE-547 in the plasma of PPD patients in the Phase 3 clinical studies (98.8 ng/mL and 75.3 ng/mL, respectively).

3.4 PREVIOUS CLINICAL EXPERIENCE

Brexanolone does not appear to increase the risk of cardiovascular events, respiratory depression, or cause clinically significant changes in vital signs at the recommended dose. A slight increase in flushing was noted, which may be related to brexanolone administration. An evaluation of cardiovascular and respiratory events, including vital sign data, showed that a few subjects in the total brexanolone group developed events of mild to moderate hypotension or tachycardia; however, aggregate analyses of the blood pressure and heart rate data showed variations in these measures but no clear relationship between changes in blood pressure or heart rate and brexanolone.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of brexanolone's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 122,279 (*see the QT-IRT memo dated 03/06/2017*). The sponsor submitted the study report 547-CLP-106 including descriptive statistics for the study with ECG assessments, electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Thorough QT (TQT) Study Evaluating the Effect of SAGE-547 Injection on Cardiac Repolarization in Healthy Male or Female Volunteers: A Randomized, Three Period Crossover Study

4.2.2 Protocol Number

547-CLP-106

4.2.3 Study Dates

Date of first informed consent: 04 January 2017

Date of final post-study observation: 02 March 2017

4.2.4 Objectives

Primary: To evaluate the effects of SAGE-547 on cardiac repolarization by assessment of QTc interval corrected (QTc) interval.

Secondary:

- To evaluate the pharmacokinetics (PK) of SAGE-547.
- To evaluate the effects of SAGE-547 Injection on other electrocardiograph (ECG) parameters heart rate [HR], QRS, and PR).
- To evaluate the safety and tolerability of SAGE-547 Injection.
- To demonstrate the study's ability to exclude small QTc effects (assay sensitivity) by evaluation of the QTc effect of moxifloxacin.
- To evaluate the effect of SAGE-547 on T-wave morphology.

4.2.5 Study Description

4.2.5.1 Design

This was a Phase 1, single-center, randomized, placebo-controlled, 3-period crossover thorough QT study in healthy subjects.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The positive (moxifloxacin) control was not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Subject randomized to one of six treatment sequences (ABC, ACB, BAC, BCA, CAB, or CBA).

- Treatment A: SAGE-547 Injection (a 5-hour IV infusion starting at a rate of 60 µg/kg/h and increasing each hour to 90, 120, 150, and 180 µg/kg/h);

- Treatment B: placebo (infusions at the same rates as SAGE-547 Injection); and
- Treatment C: placebo (infusions at the same rates as SAGE-547 Injection) plus moxifloxacin 400 mg given orally.

4.2.6.2 Sponsor's Justification for Doses

Supratherapeutic dosing in the TQT study 547-CLP-106 was selected based on dose-limiting side effects. The dose regimen utilized in TQT study 547-CLP-106 is titration up to a supratherapeutic dose of 180 µg/kg/h and it is double the maximum maintenance dose proposed in the submission under NDA 211,371 (0001).

Reviewer's Comment: Acceptable. The QT-IRT previously indicated that the selection of doses for the TQT study 547-CLP-106 was acceptable (see the QT-IRT memo for IND 122,279 dated 03/06/2017).

4.2.6.3 Instructions with Regard to Meals

Reviewer's Comment: Not applicable, as brexanolone is administered via IV infusion.

4.2.6.4 ECG and PK Assessments

PK sample times: At -60 minutes, 1, 3, 4, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 24 hours with respect to infusion onset. Infusion is 5-hours in duration

Holter ECG recording times: -45, -30, -15 minutes with respect to infusion onset. Starting at infusion onset, all ECG recordings were acquired at the same time as PK samples.

Reviewer's Comment: Acceptable. The maximum infusion rate of 180 µg/kg/h occurs from 4 to 5 hours post-infusion onset. The proposed PK and ECG sampling time of 5 hours is expected to be near T_{max} . The QT-IRT previously indicated that the ECG/PK assessments are able to capture and delayed effects over 24-hours in TQT study 547-CLP-106 (see the QT-IRT memo for IND 122,279 dated 03/06/2017).

4.2.6.5 Baseline

Baseline for each treatment period was defined as the average of the measured QTc intervals from the three ECG time points recorded before the start of infusion (-45, -30, and -15 minutes) on Day 1 in each treatment period.

4.2.7 ECG Collection

Electrocardiograms were obtained during all three treatment periods using a continuous 12-lead Holter ECG digital recorder system.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 30 subjects were randomized and 27 subjects (90.0%) completed the study. Reasons for discontinuation included clinically significant change in laboratory parameter(s), eligibility criteria not met, and lost to follow-up (1 subject each).

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The sponsor analyzed the QTc data using a linear mixed-effects model with fixed effects for treatment, time, period, sequence and time-by-treatment, and baseline QTcF as a covariate with a random effect of subject on the intercept. The largest upper bounds of 90% CI in $\Delta\Delta$ QTcF for mean differences between SAGE-547 and placebo were below 10 ms at all time points during and after the SAGE-547 Injection infusion.

Reviewer's Comments: Both sponsor's results and this reviewer's results concluded that there is no QT prolonging effect from SAGE-547 observed in this study. We provided our independent analysis in Section 5.2.

4.2.8.2.2 Assay Sensitivity

Sponsor used the same model as described in the primary analysis.

Reviewer's Comments: Both sponsor's results and this reviewer's results concluded assay sensitivity is demonstrated in this study. We provided our independent analysis in Section 5.2.

4.2.8.2.3 Categorical Analysis

There was no subject with QTcF >480 ms at any time point and no subject with QTc increase from baseline >30 ms during the SAGE-547 Injection treatment period.

Reviewer's Comments: We provided our independent analysis in Section 5.2. Our categorical analyses concurred with the sponsor's conclusion.

4.2.8.3 Safety Analysis

There were no deaths or other serious AEs were reported. One subject had the SAGE-547 Injection infusion discontinued due to a TEAE of apnoea (34 minutes post increase to 180 μ g/kg/h dose).

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results for brexanolone are presented in Table 2.

Table 2: Summary of Brexanolone PK During 5-hour IV Infusion Period up to Supratherapeutic Dose Level of 180 µg/kg/h in TQT Study 547-CLP-106

Parameter	All Data	Excluding Anomalous Data for Subject (b) (6)
	Mean (SD) N = 30	Mean (SD) N = 29
C _{max} (ng/mL)	146.5 (43.16)	145 (39)
t _{max} (hours)	5.0 ^a	5.0 ^a
AUC _{0-t} (ng.h/mL)	682.0 (446.97)	605 (100)
AUC _{0-∞} (ng.h/mL)	636.7 (114.52) ^b	637 (115)
t _{1/2} (h)	6.3 (0.79) ^b	6.31 (0.79)
CL (mL/min/kg)	15.6 (2.21) ^b	15.6 (2.2)
V _z (mL/kg)	8414.3 (1038.35) ^b	8410 (1040)

AUC_{0-∞} = area under the plasma concentration time curve extrapolated to infinite time; AUC_{0-t} = area under the plasma concentration time curve from zero to the time of the last quantifiable sample; CL = total body clearance; C_{max} = maximum plasma concentration; SD = standard deviation; t_{1/2} = terminal half-life; t_{max} = time at which C_{max} occurred; V_z = volume of distribution

^a Median

^b N = 7

Source: *sequence 0001, 547-clp-106-body.pdf, page 48 of 412*

4.2.8.4.2 Exposure-Response Analysis

The Applicant concluded that there is no significant relationship between brexanolone (SAGE-547) and $\Delta\Delta$ QTcF observed in the exposure-response analysis.

Reviewer's Comment: The reviewer's analysis concurs with the sponsor's analysis that there was no statistically significant positive slope for the concentration-QTc relationship (see Section 5.3).

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for their primary analysis, which is acceptable since no large changes in heart rate were observed, *i.e.*, mean changes ≤ 10 bpm (section 5.2.2). Therefore, no assessment of the QT/RR correction methodology is necessary.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for SAGE-547

The statistical reviewer used mixed model to analyze $\Delta\Delta$ QTcF effects and the results are presented in Table 3. The model includes treatment, time, period, sequence, time and treatment interaction as fixed effect, baseline values as a covariate and subjects as random effect. The largest upper bound of the 2-sided 90% CI for the mean difference in $\Delta\Delta$ QTcF between SAGE-547 and placebo is 5.8 ms.

Table 3: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for SAGE-547

			Treatment Group		
			SAGE-547		
			Δ QTcF	$\Delta\Delta$ QTcF	
Time (h)	N	LS Mean	LS Mean	LS Mean	90% CI
1	30	-1.0	-0.0	1.0	(-1.6, 3.7)
3	30	1.6	1.1	-0.6	(-3.2, 2.1)
4	30	0.6	3.7	3.1	(0.5, 5.8)
5	30	1.9	2.6	0.7	(-1.9, 3.4)
5.5	30	1.4	0.3	-1.1	(-3.7, 1.6)
6	30	1.9	-0.3	-2.1	(-4.7, 0.5)
6.5	30	2.6	-0.5	-3.1	(-5.7, -0.5)
7	30	1.7	-0.7	-2.5	(-5.1, 0.2)
8	30	1.7	-0.5	-2.2	(-4.8, 0.5)
10	29	3.9	3.4	-0.5	(-3.2, 2.2)
12	30	2.6	3.4	0.8	(-1.8, 3.5)
24	30	1.3	-0.5	-1.8	(-4.4, 0.8)

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data as was used to analyze QTc data. The results are presented in Table 4. The largest unadjusted 2-sided 90% lower confidence interval is 7.5 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 6.4 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin could be detected from the study.

Table 4: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Moxifloxacin 400 mg

			Treatment Group			
			Moxifloxacin			
			Δ QTcF	$\Delta\Delta$ QTcF		
Time (h)	N	LS Mean	LS Mean	LS Mean	90% CI	*Adj. 90% CI
1	28	-1.1	-0.2	0.9	(-1.8, 3.5)	(-2.9, 4.4)
3	27	1.6	0.7	-0.9	(-3.6, 1.8)	(-4.7, 2.7)

		Treatment Group				
		Placebo		Moxifloxacin		
		Δ QTcF		Δ QTcF	$\Delta\Delta$ QTcF	
Time (h)	N	LS Mean	LS Mean	LS Mean	90% CI	*Adj. 90% CI
4	28	0.6	0.5	-0.1	(-2.8, 2.6)	(-3.8, 3.5)
5	28	1.9	8.7	6.8	(4.2, 9.5)	(3.1, 10.4)
5.5	27	1.3	10.2	8.8	(6.2, 11.5)	(5.1, 12.4)
6	28	1.8	10.6	8.8	(6.1, 11.5)	(5.1, 12.4)
6.5	28	2.6	11.5	8.9	(6.3, 11.6)	(5.2, 12.5)
7	28	1.7	11.9	10.1	(7.5, 12.8)	(6.4, 13.7)
8	28	1.6	10.8	9.2	(6.5, 11.8)	(5.5, 12.8)
10	27	3.9	11.2	7.3	(4.6, 10.1)	(3.5, 11.0)
12	26	2.6	8.0	5.4	(2.7, 8.1)	(1.6, 9.0)
24	28	1.3	6.2	4.9	(2.2, 7.6)	(1.2, 8.5)

*: Bonferroni method was applied for multiple adjustments for 4 time points.

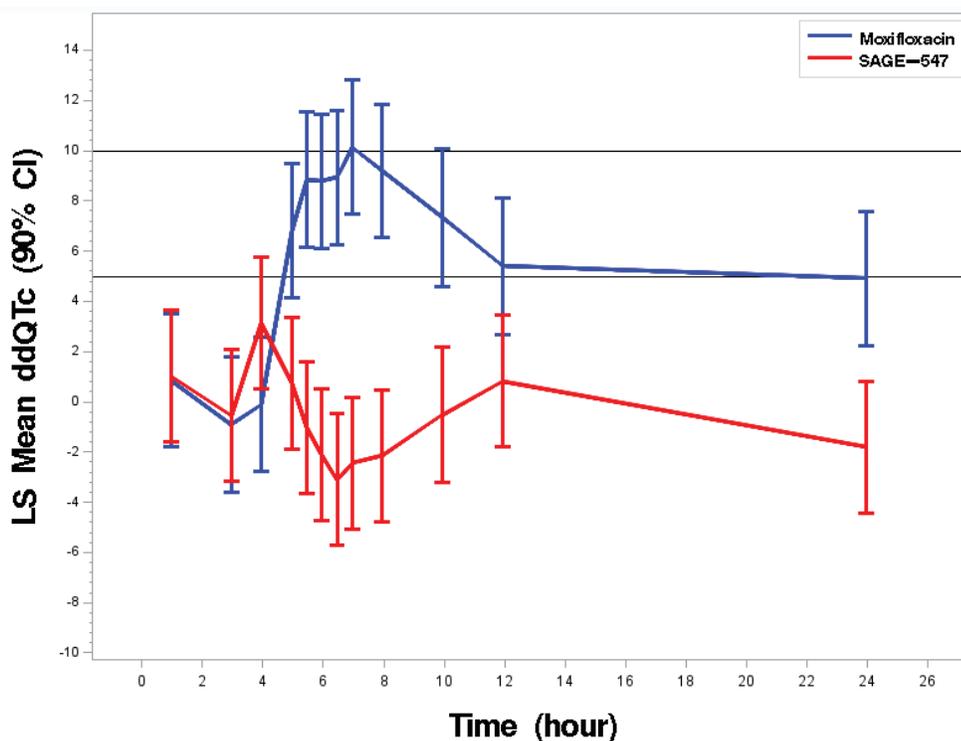
Reviewer's Comment: The largest increase in $\Delta\Delta$ QTcF was observed at 7 hours, which is different from peak usually observed at 2-4 hours for moxifloxacin. This could be due to moxifloxacin sampling time point selection in this study. There are ascending, peak, and descending phases for moxifloxacin profile in this study; in addition, the lower bounds crossed (both below and above) 5 ms. Overall, assay sensitivity was demonstrated.

5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

The following figure displays the time profile of $\Delta\Delta$ QTcF for different treatment groups.

APPEARS THIS WAY ON ORIGINAL

Figure 1: Mean and 90% CI Δ QTcF Time Profile



5.2.1.4 Categorical Analysis

Table 5 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms and between 450 ms and 480 ms. No subject’s QTcF in SAGE-547 group is above 480 ms.

Table 5: Categorical Analysis for QTcF

Treatment Group	Total N		Value ≤ 450 ms		450 ms < Value ≤ 480 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Moxifloxacin	28	331	26 (92.9%)	322 (97.3%)	2 (7.1%)	9 (2.7%)
Placebo	27	322	26 (96.3%)	319 (99.1%)	1 (3.7%)	3 (0.9%)
SAGE-547	30	359	30 (100%)	359 (100%)	0 (0.0%)	0 (0.0%)

Table 6 lists the number of subjects’ changes from baseline QTc ≤ 30 ms and between 30 and QTc 60 ms. No subject’s Δ QTcF in SAGE-547 group is above 30 ms.

Table 6: Categorical Analysis of $\Delta QTcF$

Treatment Group	Total N		Value \leq 30 ms		30 ms<Value \leq 60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Moxifloxacin	28	331	25 (89.3%)	323 (97.6%)	3 (10.7%)	8 (2.4%)
Placebo	27	322	27 (100%)	322 (100%)	0 (0.0%)	0 (0.0%)
SAGE-547	30	359	30 (100%)	359 (100%)	0 (0.0%)	0 (0.0%)

Reviewer's comments: The reviewer's analysis confirmed that no subject with $QTcF > 480$ ms at any time point and no subject with QTc increase from baseline > 30 ms during the SAGE-547 Injection treatment period.

5.2.2 HR Analysis

The point estimates and the 90% confidence intervals are presented in Table 7. The largest upper bound of the 2-sided 90% CI for the mean difference in $\Delta\Delta HR$ between SAGE-547 and placebo is 6.0 bpm. One subject experienced $HR > 100$ bpm in the SAGE-547 group.

Table 7: Analysis Results of ΔHR and $\Delta\Delta HR$ for SAGE-547

		Treatment Group			
		SAGE-547			
		ΔHR	ΔHR	$\Delta\Delta HR$	
Time (h)	N	LS Mean	LS Mean	LS Mean	90% CI
1	30	-1.8	-1.5	0.3	(-2.0, 2.7)
3	30	-1.4	-0.7	0.7	(-1.6, 3.0)
4	30	-2.1	1.2	3.3	(1.0, 5.7)
5	30	0.4	2.4	1.9	(-0.4, 4.2)
5.5	30	-1.6	2.0	3.6	(1.3, 5.9)
6	30	-1.7	2.0	3.7	(1.4, 6.0)
6.5	30	-0.5	0.3	0.8	(-1.5, 3.2)
7	30	-0.7	0.5	1.2	(-1.1, 3.6)
8	30	-0.7	0.8	1.5	(-0.9, 3.8)
10	29	10.6	12.6	2.1	(-0.3, 4.5)
12	30	10.4	11.1	0.6	(-1.7, 3.0)

		Treatment Group			
		SAGE-547			
		Δ HR		$\Delta\Delta$ HR	
Time (h)	N	LS Mean	LS Mean	LS Mean	90% CI
24	30	4.4	5.2	0.8	(-1.5, 3.1)

5.2.3 PR Analysis

The point estimates and the 90% confidence intervals are presented in Table 8. The largest upper bound of the 2-sided 90% CI for the mean differences in $\Delta\Delta$ PR between SAGE-547 and placebo is 4.5 ms. No subject's PR is above 200 ms.

Table 8: Analysis Results of Δ PR and $\Delta\Delta$ PR for SAGE-547

		Treatment Group			
		SAGE-547			
		Δ PR		$\Delta\Delta$ PR	
Time (h)	N	LS Mean	LS Mean	LS Mean	90% CI
1	30	1.2	1.0	-0.2	(-2.8, 2.3)
3	30	-0.6	1.3	1.9	(-0.6, 4.4)
4	30	-0.5	1.4	1.9	(-0.6, 4.5)
5	30	-1.0	0.1	1.1	(-1.4, 3.7)
5.5	30	-2.8	-1.2	1.6	(-0.9, 4.2)
6	30	-1.6	-1.7	-0.1	(-2.6, 2.4)
6.5	30	-2.0	-2.1	-0.1	(-2.6, 2.4)
7	30	-3.7	-2.7	1.0	(-1.6, 3.5)
8	30	-1.8	-3.5	-1.6	(-4.2, 0.9)
10	29	-6.7	-7.9	-1.2	(-3.7, 1.5)
12	30	-8.7	-9.0	-0.3	(-2.9, 2.2)
24	30	-2.5	-1.4	1.0	(-1.5, 3.6)

5.2.4 QRS Analysis

The point estimates and the 90% confidence intervals are presented in Table 9. The largest upper bound of the 2-sided 90% CI for the mean difference in $\Delta\Delta$ QRS between SAGE-547 placebo is 1.1 ms.

Table 9: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for SAGE-547

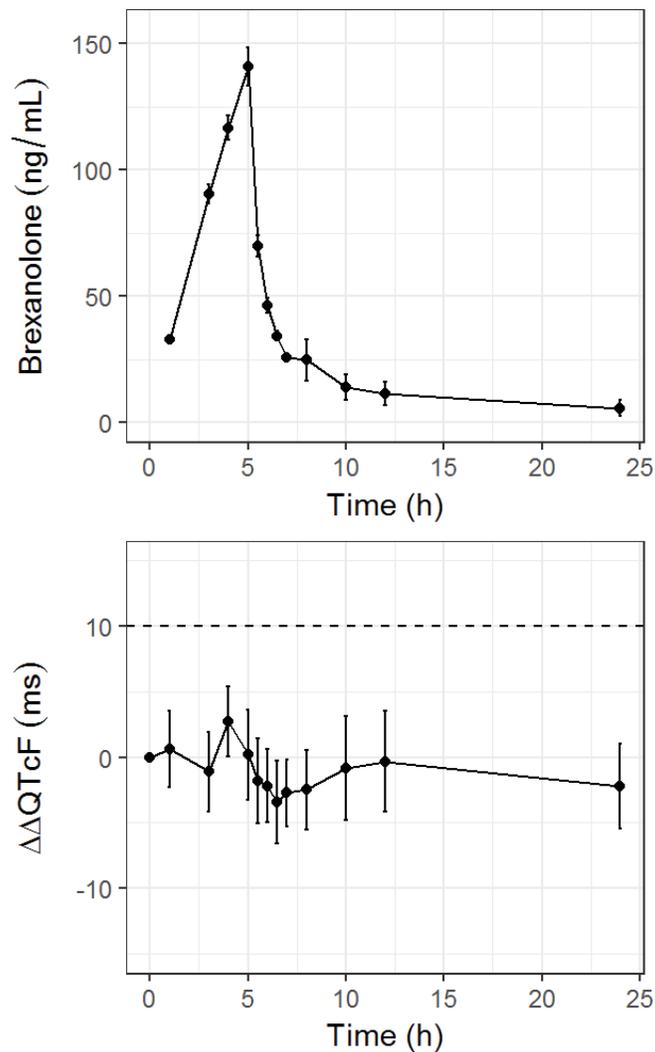
		Treatment Group			
		Placebo		SAGE-547	
		Δ QRS		$\Delta\Delta$ QRS	
Time (h)	N	LS Mean	LS Mean	LS Mean	90% CI
1	30	0.1	-0.1	-0.2	(-0.7, 0.4)
3	30	-0.1	-0.2	-0.1	(-0.6, 0.5)
4	30	-0.0	0.1	0.1	(-0.4, 0.7)
5	30	0.3	0.8	0.5	(-0.0, 1.1)
5.5	30	0.1	-0.0	-0.1	(-0.7, 0.5)
6	30	0.2	0.1	-0.2	(-0.7, 0.4)
6.5	30	0.2	-0.0	-0.3	(-0.8, 0.3)
7	30	0.1	-0.0	-0.1	(-0.7, 0.5)
8	30	0.4	0.1	-0.3	(-0.9, 0.3)
10	29	1.6	0.8	-0.8	(-1.3, -0.2)
12	30	0.1	0.5	0.4	(-0.2, 0.9)
24	30	0.4	-0.1	-0.5	(-1.1, 0.0)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The objective of the clinical pharmacology analysis is to assess the relationship between drug concentration and Δ QTcF.

Prior to evaluating the relationship using a linear model, the following key assumptions of the model were evaluated: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and Δ QTcF and 3) presence of non-linear relationship. There were no large changes in heart rate (>10 bpm) with treatment as described earlier in Section 5.2.2. An evaluation of the time-course of drug concentration and changes in $\Delta\Delta$ QTcF is shown in Figure 2, which do not show any hysteresis/delayed effects. Because there are no appreciable QTc effects, non-linearity in relationship was not relevant for evaluation.

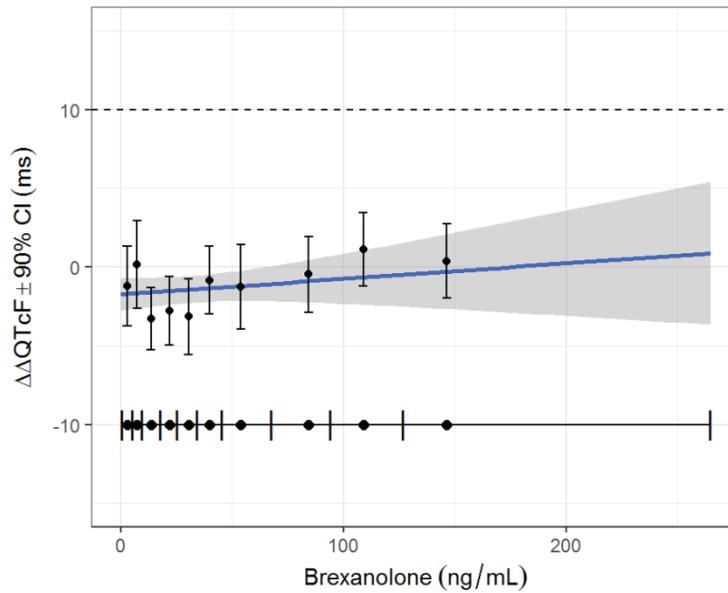
Figure 2: Time course of drug concentration (top), and QTcF effects (bottom) following a 5-hour IV infusion of brexanolone (starting at a rate of 60 $\mu\text{g}/\text{kg}/\text{h}$ and increasing each hour to 90, 120, 150, and 180 $\mu\text{g}/\text{kg}/\text{h}$)



Exposure-Response Relationship

The concentration-QTc relationship was assessed using the prespecified linear mixed-effects model. The slope for the relationship was not statistically significant (mean estimate = 0.00986 ms per ng/mL; $p = 0.4$). The relationship between $\Delta\Delta\text{QTcF}$ and brexanolone concentrations is visualized in Figure 3. At the C_{max} (141 ng/mL) for the suprathereapeutic dose (180 $\mu\text{g}/\text{kg}/\text{h}$), the mean predicted $\Delta\Delta\text{QTcF}$ is -0.34 ms with an upper bound of 90% CI of 1.94 ms. The upper bound is below the 10 ms regulatory threshold.

Figure 3: $\Delta\Delta\text{QTcF}$ vs. Brexanolone Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There were no clinically meaningful effects on the PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic Dose	<p>The recommended maximum dose for subjects with PPD, which was assessed for efficacy in PPD studies, is 90 mcg/kg/h.</p> <p>The dose regimen is administered as a continuous intravenous (IV) infusion over a total of 60 hours (2.5 days) as follows:</p> <ul style="list-style-type: none">• Initiate with a dose of 30 mcg/kg/h and infuse for 4 hours• Increase dose to 60 mcg/kg/h and infuse for 20 hours• Increase dose to 90 mcg/kg/h and infuse for 28 hours• Decrease dose to 60 mcg/kg/h and infuse for 4 hours• Decrease dose to 30 mcg/kg/h and infuse for 4 hours prior to completion of therapy
Maximum Tolerated Dose	<p>The maximum tolerated dose in conscious subjects has not been determined.</p> <p>In a human abuse liability study in subjects who were recreational drug abusers, a 1-hour infusion of up to 270 mcg/kg/h was tolerated (547-CLP-102).</p> <p>In healthy volunteers in the thorough QT study (547-CLP-106), the maximum dose of 180 mcg/kg/h for 1 hour following a 4-hour titration beginning at 60 mcg/kg/h with 30 mcg/kg/h increments was tolerated. One subject discontinued brexanolone infusion due to apnea (< 1 minute, associated with excessive sedation) which occurred 34 minutes post increase to 180 µg/kg/h dose.</p> <p>The maximum dose evaluated for an extended period of time in any study was 150 mcg/kg/h for 8 hours, after a two-step titration through 90 mcg/kg/h and 120 mcg/kg/h for an hour each which was tolerated in subjects with Essential Tremor Disorder (547-ETD-201). There was one report of moderate hypotension that resulted in early termination of the infusion while on the 120 mcg/kg/h titration step.</p>
Principal Adverse Events	<p>The principal adverse events in conscious subjects are related to the pharmacological action of brexanolone, notably somnolence, sedation, fatigue, dizziness, as well as headache. The adverse events leading to treatment discontinuation were sedation-related (loss of consciousness, vertigo, syncope, and presyncope) or infusion-site events (extravasation and infusion site pain). These adverse events are all monitorable, manageable and reversible.</p>

Maximum Dose Tested	The maximum doses tested in any awake subject was 270 mcg/kg/h (547-CLP-102) for one hour in subjects who were recreational drug users and 180 mcg/kg/h for 1 hour (with preceding titration) in healthy volunteers (547-CLP-106). The maximum dose tested for longer than one hour was 150 mcg/kg/h for 8 hours (with preceding titration) for 8 hours in subjects with Essential Tremor Disorder (547-ETD-201).	
Exposures Achieved at Maximum Tested Dose	<p>In Study 547-CLP-102, in which the maximum dose of 270 mcg/kg/h was administered for 1 hour, the brexanolone geometric mean [%CV] C_{max} was 227.6 [20.32%] ng/mL, and the AUC_{0-inf} was 309.4 [18.39%] ng·h/mL.</p> <p>In Study 547-CLP-106, in which the maximum dose of 180 mcg/kg/h was administered for 1 hour, the brexanolone mean [SD] C_{max} was 146.5 [43.16] ng/mL, and the AUC_{0-inf} was 636.7 [114.52] ng·h/mL.</p> <p>In Study 547-ETD-201, in which the maximum dose of 150 mcg/kg/h was administered for 8 hours, the brexanolone mean [SD] C_{max} was 152 [36] ng/mL, and the AUC_{0-inf} was 1380 [300] ng·h/mL.</p>	
Range of Linear PK	Over the dose range administered to subjects (30 mcg/kg/h to 270 mcg/kg/h), PK has been observed to be linear and dose proportional.	
Accumulation at Steady State	The degree of accumulation is consistent with the demonstrated characteristics of brexanolone.	
Metabolites	<p>Brexanolone is chemically identical to the endogenous metabolite of progesterone, allopregnanolone. Allopregnanolone is formed in the corpus luteum. During pregnancy, the majority of allopregnanolone is synthesized in the placenta.</p> <p>Brexanolone (ie allopregnanolone) is extensively metabolized in humans. Metabolites assumed to be present in plasma at >10% of drug-related material at steady-state are M136 (5α-pregnan-3α,20α-diol sulfate), M137 (5α-pregnan-3α,20α-diol glucuronide), and M133 (5β-pregnan-3α,20α-diol sulfate). These metabolites are not positive allosteric modulators of the GABA_A receptor and are not expected to contribute to the pharmacology of brexanolone. In addition, these metabolites were evaluated in a panel of drug metabolizing enzymes and transporters and are unlikely to alter the pharmacokinetics of concomitantly administered substrates. Brexanolone is eliminated as metabolites, with approximately equal amounts of drug-related radioactivity recovered in the feces and urine. Only very small amounts of brexanolone were detected in the urine and feces, indicating that brexanolone is cleared via biotransformation.</p>	
Absorption	Absolute/Relative Bioavailability	Not applicable for IV dosing; however, an experimental oral bioavailability study demonstrated low (<5%) bioavailability and no effect of a high fat meal on absorption.
	Tmax	Not applicable for constant-rate IV infusion

Distribution	Vd/F or Vd (L/kg) GeoMean (%CV)	Vss(L/Kg) 3 (55.8%)
	% unbound Geomean (%CV)	0.683 (16.4%)
Elimination	Route	Biotransformation
	Terminal t _{1/2} (h) Mean (%CV)	8.12 (55.4%)
	CL/F or CL GeoMean(%CV)	CL (L/hr) = 89.8 (21.1%)
Intrinsic Factors	Age	Not expected to impact the PK of brexanolone
	Sex	No sex-related differences in PK parameters
	Race	No evidence for PK-related differences
	Hepatic & Renal Impairment	<p>It is not necessary to adjust the dose in subjects with hepatic impairment.</p> <p>Systemic exposure to total brexanolone generally decreased with increasing degree of hepatic impairment, with geometric LS mean Dose-normalized (DN) C_{max} values 5.2%, 20.6%, and 42.4% lower and geometric LS mean DN AUC_∞ values 10.8%, 8.0%, and 24.1% lower in the mild, moderate, and severe hepatic impairment cohorts, respectively, when compared with the normal hepatic function cohort.</p> <p>Caution should be used in patients with severe renal impairment due to potential accumulation of the solubilizing agent, Captisol® (Betadex Sulfobutyl Ether Sodium USP/NF, also referred to as SBECD) and use is not advised in patients with end stage renal disease (ESRD) with eGFR of < 15 mL/min/1.73 m² unless an assessment of the benefit/risk to the patient justifies the use of brexanolone.</p> <p>Systemic exposure, based on C_{max} and dose-normalized (DN) AUC_∞ to total brexanolone was 34.2% and 29.6% lower, respectively, in the severe renal impairment cohort compared with the normal renal function cohort.</p> <p>Systemic exposure, based on C_{max} and DN AUC_{∞, ss}, to the excipient SBECD was 1.72- and 5.51-fold higher, respectively, in the severe renal impairment cohort compared with the normal renal function cohort.</p>

Extrinsic Factors	Drug Interactions	<p>Direct examination of extrinsic factors and their potential influence on brexanolone PK has not been conducted.</p> <p>Based on in vitro data, brexanolone has been identified as being a low probability victim of drug-drug interactions and as such no drug-drug interaction studies with brexanolone as a potential victim have been conducted.</p>
	Food Effects	<p>Not applicable for IV dosing</p> <p>Oral bioavailability of IV formulation of brexanolone, calculated from AUC_t values, was low when administered to fasted subjects and was similar when administered after a high-fat meal.</p>
Expected High Clinical Exposure Scenario	<p>Brexanolone is administered as a controlled continuous intravenous infusion using an infusion pump. The maximum dose is 90 mcg/kg/h maintained for 28 hours within a 60-hour dose regimen. Geometric mean exposures (% geometric CV) in Phase 3 subjects in the 90 mcg/kg/h treatment arm were AUC_{0-∞} 3820 ng.h/mL (23%) and C_{max} 78.9 ng/mL (21%). Brexanolone was administered as a 1-hour infusion at a suprathapeutic dose of up to 270 mcg/kg/h, 3-fold the recommended dose, without any new safety concerns. The intrinsic and extrinsic factors are not predicted to increase exposure to brexanolone.</p>	

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MOH JEE NG
07/26/2018

DALONG HUANG
07/26/2018

MOHAMMAD A RAHMAN
07/26/2018

MICHAEL A BEWERNITZ
07/26/2018

DHANANJAY D MARATHE
07/26/2018

MICHAEL Y LI
07/26/2018

CHRISTINE E GARNETT
07/26/2018