NDA Multi-Disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	NDA 211371/S-007
Priority or Standard	Priority
Submit Date(s)	12/20/21
Received Date(s)	12/20/21
PDUFA Goal Date	06/20/22
Division/Office	Division of Psychiatry / Office of Neuroscience
Review Completion Date	06/16/22
Established/Proper Name	Brexanolone
Trade Name	ZULRESSO
Pharmacologic Class	Neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator
Code name	SAGE-547, allopregnanolone
Applicant	Sage Therapeutics, Inc.
Dosage form	Injection for intravenous use
Applicant proposed Dosing Regimen	Administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows: • 0 to 4 hours: Initiate with a dosage of 30 µg/kg/hour • 4 to 24 hours: Increase dosage to 60 µg/kg/hour • 24 to 52 hours: Increase dosage to 90 µg/kg/hour (alternatively consider a dosage of 60 µg/kg/hour for those who do not tolerate 90 µg/kg/hour) • 52 to 56 hours: Decrease dosage to 60 µg/kg/hour • 56 to 60 hours: Decrease dosage to 30 µg/kg/hour
Applicant Proposed Indication(s)/Population(s)	Treatment of postpartum depression in patients ages 15 to 17 years
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	58703003 |Postpartum depression (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of postpartum depression in patients ages 15 to 17 years
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	58703003 |Postpartum depression (disorder)
Recommended Dosing Regimen	Administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows: • 0 to 4 hours: Initiate with a dosage of 30 µg/kg/hour

	• 4 to 24 hours: Increase dosage to 60 µg/kg/hour • 24 to 52 hours: Increase dosage to 90 µg/kg/hour (alternatively consider a dosage of 60 µg/kg/hour for those who do not tolerate 90 µg/kg/hour) • 52 to 56 hours: Decrease dosage to 60 µg/kg/hour 56 to 60 hours: Decrease dosage to 30 µg/kg/hour

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See archived signatory memos for each discipline.

APPEARS THIS WAY ON ORIGINAL

Glossary

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COA	clinical outcome assessment
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	diastolic blood pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	electrocardiogram
ECT	electroconvulsive therapy
FDA	Food and Drug Administration
GABA	γ-aminobutyric acid
HAM-D	Hamilton Depression Rating Scale
IV	intravenous
LOC	loss of consciousness
MDD	major depressive disorder
NDA	new drug application
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPD	postpartum depression
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SBP	systolic blood pressure
SI/B	suicidal ideation and behavior
WR	written request

1 Executive Summary

1.1. Product Introduction

The Applicant submitted a supplemental new drug application (sNDA) to support brexanolone (NDA 211371/S-07; also known as SAGE-547 and marketed as Zulresso) for the treatment of postpartum depression (PPD) in adolescents 15 to 17 years of age. In March 2019, the Agency approved brexanolone (Zulresso; NDA 211371) for the treatment of PPD in adults. Brexanolone, chemically identical to the endogenous allopregnanolone, is thought to exert its effects by acting as a positive allosteric modulator of the γ-aminobutyric acid type A (GABA-A) receptor. The Applicant had hypothesized that increasing allopregnanolone concentrations to levels observed during the third trimester of pregnancy could ameliorate symptoms of PPD. The proposed 72-hour intravenous (IV) infusion (recommended target dose of 90 µg/kg/hr) aims to return women to pre-delivery levels of allopregnanolone.

The Applicant plans to supply the drug product as a single-dose 20 mL (100 mg/20 mL) vial for IV administration. Prior to administration, the drug product requires dilution with sterile water for injection 0.9% sodium chloride to achieve a target concentration of 1 mg/mL. The proposed adolescent dose is identical to the product label-recommended dosing regimen for adults. Given the risk for excessive sedation and loss of consciousness (LOC), brexanolone is currently available only through the Zulresso Risk Evaluation and Mitigation Strategy (REMS) program. Patients can only receive brexanolone in a healthcare setting with a healthcare provider available to continuously monitor for sedative effects.

1.2. Conclusions on the Substantial Evidence of Effectiveness

During previous discussions with the Applicant regarding the postmarketing requirement (PMR 3535-1) for adolescent data for brexanolone, the Division acknowledged difficulties in conducting an adequate and well-controlled trial to evaluate the safety and effectiveness of brexanolone in adolescents with PPD. Although a confirmation of full extrapolation of efficacy from adult to pediatric patients has not yet been established for PPD, the Division recognized that, based on the literature and known clinical presentation of PPD in adolescents, PPD is likely clinically similar in both patient populations. The Division ultimately determined in this instance that partial extrapolation is feasible; and an adequate evaluation of brexanolone in adolescent PPD for labeling would require just one independent, open-label safety study (Study 547-PPD-304) containing an appropriate collection of efficacy and pharmacokinetic (PK) data.

A descriptive analysis of Study 547-PPD-304 suggests that brexanolone exhibits a nominally similar effect on PPD symptoms in adolescents relative to adults. Due to the similarity in disease, brexanolone exposures, and treatment effects between adults and adolescents, the Applicant has adequately demonstrated through partial extrapolation that brexanolone is effective for the treatment of PPD in adolescents 15 to 17 years of age.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Brexanolone (marketed as Zulresso) injection for intravenous (IV) use is a neuroactive steroid that is chemically identical to the endogenous human hormone, allopregnanolone. In March 2019, FDA approved brexanolone for the treatment of postpartum depression (PPD) in adults. Because of observed excessive sedation and loss of consciousness (LOC) events, brexanolone is currently available only through the Zulresso Risk Evaluation and Mitigation Strategy (REMS) program and patients can only receive brexanolone in a healthcare setting.

PPD is characterized as a major depressive episode with onset during pregnancy or within 4 weeks of delivery. Patients with PPD typically report similar symptoms to other types of depression, with the disease burden of PPD also including the risk of maternal suicide, child morbidity associated with impaired mother-infant bonding, and infant malnutrition. Standard of care for PPD includes chronically administered oral antidepressants and non-pharmacological interventions (i.e., electroconvulsive therapy, repetitive transcranial magnetic stimulation, and psychotherapy). Available antidepressants for the treatment of PPD often exhibit a delayed onset of effect (6 to 8 weeks). Prior adult studies used to support the approval of brexanolone in adults described a relatively shorter onset of effect (within 60 hours). Because PPD remains a condition of concern in adolescents with limited treatment options, FDA issued a Pediatric and Research Equality Act (PREA) postmarketing requirement (PMR 3535-1) to evaluate brexanolone in adolescents. Given the extremely low prevalence of PPD in early post-pubertal female adolescents, FDA agreed to require evaluation of brexanolone only in patients 15 to 17 years of age.

The Applicant initially designed Study 547-PPD-304 as a double-blind, randomized, placebo-controlled trial to evaluate brexanolone in adolescent females 15 to 17 years of age. However, the Applicant noted recruitment challenges related to low disease prevalence, the Zulresso REMS program requirements, and the relatively long 60-hour IV infusion. The Agency agreed to consider adolescent-onset and adult-onset PPD as clinically similar conditions given their comparable diagnostic criteria, phenomenology, and prognosis in current literature and studies to date. The Agency agreed with the Applicant's proposal, only for the condition of PPD, to leverage prior evidence of effectiveness in adults and revise Study 547-PPD-304 to an open-label safety, tolerability, and pharmacokinetic (PK) study. As brexanolone dosing is weight-based, the Applicant applied the same adult-recommended dose titration regimen to adolescents with acceptably similar PK exposure findings.

Although the interpretation of Study 547-PPD-304 is limited by its open-label study design and small sample size, adolescent subjects in the study displayed a nominally consistent pattern of initial response and sustained treatment effect relative to previous efficacy findings in adults. Regarding the prior adult brexanolone studies' major safety concerns of sudden LOC and excessive sedation during the infusion period, the observed incidence of these was similar between adults and adolescents. As before, no potential predictors were found to reliably detect excessive sedation or LOC before occurrence. Therefore, to mitigate these abrupt and unpredictable risks, brexanolone administration in

adolescents will also adhere to the Zulresso REMS program requirements.

Given the Agency's acceptance of partial extrapolation due to similarity of disease and expected response to intervention, and supportive evidence from an open-label study in adolescents that suggests a nominally comparable benefit-risk profile in adults and adolescents with PPD, brexanolone will be approved for the treatment of PPD in adolescents 15 to 17 years of age.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• PPD is a major depressive episode (identical diagnostic criteria) with onset during pregnancy or within 4 weeks of delivery • Adolescent-onset PPD share similar diagnostic criteria, phenomenology, and prognosis as compared to adult-onset PPD • Although the prevalence of adolescent pregnancies are low (approximately 6.3 births per 1000 among 15- to 17-year-olds and 0.2 births per 1000 among 10- to 14-year-olds) the prevalence of adolescent-onset PPD is two-folds higher than adult-onset PPD. • Risk factors for PPD in adolescents overlap with adult-onset PPD and include prior history of depression, anxiety, substance abuse, and psychological trauma • There is an extremely low prevalence of PPD in early post-pubertal female adolescents (250 annual cases for patients 10 to 14 years of age).	PPD is a serious and potentially life-threatening disease that is associated with a large societal burden. The current literature suggests similar presentation and prognosis between adult-onset and adolescent-onset PPD. Given the relatively higher prevalence of PPD among adolescent 15 to 17 years of age, an evaluation of brexanolone for this age group would be beneficial to public health (with a waiver for those under age 15).
Current Treatment Options	• Brexanolone is the only treatment available that is FDA-approved specifically for PPD in adults. There are no drugs approved for PPD in adolescents. • Healthcare providers commonly prescribe a combination of non-pharmacological interventions (e.g., psychotherapy) and oral antidepressants FDA-approved for major depressive disorder (MDD) as standard of care treatment for PPD; however, there are only two FDA-approved antidepressants for pediatric use (i.e., escitalopram	There is limited evidence available from clinical trials that suggest FDA-approved antidepressants are effective for PPD. Results from prior adult studies evaluating brexanolone indicate a shorter onset of effect relative to typical antidepressants, which is maintained during the course the PPD episode. Given that there are limited pharmacotherapeutic options available for

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and fluoxetine). • Pharmacological and non-pharmacologic interventions typically require 4 to 6 weeks to demonstrate an antidepressant effect.	adolescent-onset PPD, further treatment options that exhibit a shorter onset and maintained antidepressant effect are needed.
Benefit	• The Applicant noted several recruitment challenges that limited their ability to complete a randomized, double-blind, placebo-controlled study (547-PPD-304 in adolescents. Adolescent-onset and adult-onset PPD have comparable diagnostic criteria, phenomenology, and prognosis in current literature and studies to date. Accordingly, after discussion, the Division allowed the Applicant to revise Study 547-PPD-304 to an open-label safety, tolerability, and PK study (n=28). • The Applicant titrated the brexanolone dose according to the approved dosing regimen in adults (up to 90 µg/kg/hr). Because the range of body weights in the enrolled adolescent population was similar to a typical adult, the Applicant reported similar exposures in adolescents. • Although Study 547-PPD-304 was not adequately designed or statistically powered, a nominal comparison of the treatment effect on HAM-D total scores at Hour 60 (primary endpoint in adult trials) between adults and adolescents indicated a similar initial pattern of response (adolescents: -2.9; adults: -2.5 to -3.7). Analysis of treatment responders further suggested that the effect in adolescents was maintained through Day 30. • Analysis of other secondary and exploratory efficacy endpoints also described a nominally consistent pattern of response. • Given the small sample size and lack of placebo comparison in Study 547-PPD-304, analyses of subpopulations (e.g., race, disease severity, prior psychiatric history, concomitant antidepressant use) was not informative.	In general, full extrapolation of efficacy for a given indication requires a confirmation of disease similarity and similar exposure-response relationship between two populations. However, only one drug is approved for the treatment of PPD in adults, so an evaluation of exposure-response across multiple treatments was not feasible. Specifically for this case, the Division recognized the Applicant's recruitment challenges and the current unmet need for treatment in adolescents. The Division decided to recognize adult-onset and adolescent-onset PPD as clinically similar conditions. Because the response to brexanolone treatment was expected to be similar between the two populations, the Division was open to leveraging prior evidence of effectiveness in adults and utilizing partial extrapolation with supportive evidence from a single, open-label study to confirm brexanolone's effectiveness in adolescents 15 to 17 years of age. Due to nominally similar findings of efficacy at similar exposures relative to adults, the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		Applicant has adequately demonstrated that brexanolone is effective for the treatment of PPD in adolescents 15 to 17 years of age.
Risk and Risk Management	• The safety profile in adolescents was generally consistent with results from prior studies in adults. • No deaths occurred in the study. • Only one subject (5%) receiving brexanolone experienced moderate dizziness followed by LOC (with each issue recorded as the only two serious adverse events in the study). No subjects experienced excessive sedation or any adverse events (AE) leading to either treatment or study discontinuation. • The incidence of LOC in adults and adolescents was similar (5% versus 4%, respectively). Given the small sample size of adolescents, it is unclear whether the risk for excessive sedation or LOC is higher in adolescents. • Although all cases of excessive sedation and LOC in adults and adolescents were abrupt and unpredictable, all cases resolved within 60 minutes and required no intervention.	Based on safety data collected in adults, the Agency's major safety concern is the possibility of excessive sedation and LOC during the infusion period. Although the Applicant only reported one case in their adolescent study, the event of LOC was similar to those observed in the adult program—sudden and unpredictable. Therefore, to mitigate potential risks in the postmarketing setting, brexanolone administration in adolescents will also adhere to the Zulresso REMS program requirements.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	8.1.1, 8.1.2
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	8.1.1, 8.1.2
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	Patient experience data was not submitted as part of this application.			

2 Therapeutic Context

2.1. Analysis of Condition

Postpartum depression (PPD) involves a major depressive episode with onset during pregnancy or within 4 weeks of delivery. Symptoms of PPD may be indistinguishable from any other type of major depressive episode and typically include sadness and or anhedonia. Some patients may also experience symptoms of cognitive impairment, feelings of worthlessness and guilt, or suicidal ideation. Table 1 describes the Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria for a major depressive episode. Given the timing of PPD and accompanying financial and social changes, new mothers report difficulty connecting with their newborn with negative effects on the maternal-infant bond and infant development.

According to epidemiological studies, the annual prevalence of postpartum depression among new mothers ranges between 10% to 20%, which equates to approximately 1 in 7 women (Wang et al., 2021 and Shorey et al., 2018). The majority of mothers with PPD do not seek a mental healthcare provider, with the possible consequence that the most common cause of maternal death after childbirth is suicide (Oates, 2013). Risk factors for PPD include prior history of PPD, depression or anxiety, emergence of initial symptoms during pregnancy, and lack of access to healthcare (Norhayati et al., 2015).

Table 1: DSM-5 Diagnostic Criteria for a Major Depressive Episode

Depressive Symptoms	At least five symptoms for at least 2 weeks that are a change from previous function (one of which must include either depressed mood or anhedonia)	1. Depressed mood most of the day nearly every day 2. Anhedonia most of the day nearly every day 3. Significant weight loss or gain 4. Insomnia or hypersomnia 5. Psychomotor agitation or retardation 6. Fatigue or loss of energy 7. Feelings of worthlessness or excessive guilt 8. Diminished ability to think or concentrate, indecisiveness 9. Recurrent thoughts of death; suicidal ideation or attempt
Additional Required Criteria	Must meet all four criteria	Symptoms cause clinically significant distress or functional impairment
		Episode not attributable to physiological effects of a substance or another medical condition
		Episode not better explained by a psychotic disorder
		No history of manic or hypomanic episode

Source: Reviewer created table using DSM-5 criteria.

Although adolescent pregnancies have decreased over the past decade, the prevalence of depression in adolescent mothers ranges from 14% to 50% and is commonly described to be two-folds higher than in adult mothers (Dwinwiddie et al., 2018). Psychosocial challenges including isolation from peers, single motherhood, family conflict, low self-esteem, and body

dissatisfaction are known to contribute to the increased prevalence of PPD in adolescent mothers. Risk factors commonly associated with adolescent PPD generally overlap with adults and also include substance abuse and trauma history (Reid et al., 2007). Given the similarities in diagnostic criteria, phenomenology, and prognosis, adolescent-onset PPD can still be considered similar to adult-onset PPD.

Despite the increasing prevalence of PPD, the pathophysiology is not well characterized (Skalkidou et al., 2012). In a normal pregnancy, the body experiences numerous hormonal changes in preparation of childbirth and nursing. Current research indicates drastic changes in neuroendocrine hormones (i.e., estradiol and progesterone) during pregnancy could impact mental health (Maguire et al., 2019 and Schule et al. 2014). Allopregnanolone, an endogenous derivative of progesterone, reaches its peak concentration during the third trimester and is associated with a down-regulation of GABA-A receptors. After delivery, the sudden decline in allopregnanolone and up-regulation of GABA-A receptors back to baseline may give rise to PPD symptoms (McEvoy et al., 2018). However, previous studies also suggest that total allopregnanolone levels do not consistently correlate with PPD (Harris et al., 1996). The proposed neurohormonal hypothesis has subsequently led to the identification of several key targets for PPD treatments.

2.2. Analysis of Current Treatment Options

In March 2019, the Agency approved brexanolone (Zulresso; NDA 211371) for the treatment of PPD in adults. During drug development, the Applicant hypothesized that increasing allopregnanolone concentrations to levels observed during the third trimester would ameliorate symptoms of PPD. The proposed 72-hour intravenous (IV) infusion (recommended target dose of 90 µg/kg/hr) aimed to return women to pre-delivery levels of allopregnanolone; the initial titration and taper periods allowed patients to develop tolerance to sedation and prevent withdrawal symptoms, respectively. Placebo-controlled, randomized, clinical studies demonstrated that brexanolone decreased PPD symptoms within 60 hours and exhibited a sustained effect for 30 days. Given the risk for excessive sedation and loss of consciousness (LOC), brexanolone is currently available only through the Zulresso Risk Evaluation and Mitigation Strategy (REMS) program. Patients can only receive brexanolone in a healthcare setting with a healthcare provider available continuously in order to monitor for sedative effects (every 2 hours during planned, non-sleep periods) and to perform pulse oximetry assessments.

Current standard of care treatments in both adult and adolescent PPD also include the combination of oral antidepressants FDA-approved for the treatment of MDD (e.g., selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors) and nonpharmacological interventions (i.e., electroconvulsive therapy, repetitive transcranial magnetic stimulation, and psychotherapy). Relative to brexanolone, all available treatments can exhibit a delayed onset of effect (approximately 4 to 6 weeks) or require a longer duration of treatment.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

FDA initially approved brexanolone (trade name: Zulresso) in March 2019 for the treatment of PPD in adults. Currently, brexanolone is not approved for PPD in adolescents or for any other indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

Under current regulations (21 CFR 201.57(f)(9)(iv), a new indication in an adolescent population could be established by extrapolating the effectiveness results of adequate and well-controlled studies in adults, if it were believed that PPD is essentially the same disease in adults and adolescents. Although a confirmation of full extrapolation of efficacy from adults to pediatric patients has not yet been established for PPD, FDA ultimately determined that an adequate evaluation of brexanolone in adolescent PPD could require just one independent, open-label safety and tolerability study that also provides adequate pharmacokinetic (PK) data and collection of efficacy rating scales in the relevant pediatric age groups. The following list summarizes the rationale for this decision during the key milestone meetings for the development of brexanolone for the treatment of adolescent PPD under investigational new drug (IND) application 122279:

- October 20, 2017:
    - The Division communicated an Agreed Initial Pediatric Study Plan Letter which included a deferred plan to conduct a clinical study evaluating the efficacy, safety, and tolerability of brexanolone in adolescent females ages 15 to less than 18 years with PPD.
- March 20, 2018:
    - The Division submitted a Written Request (WR) to the Applicant that included a required, randomized, double-blind, placebo-controlled, parallel-group study and a PK study in adolescent females with PPD.
    - The Division reviewed protocol 547-PPD-304 (submitted on January 31, 2018) to satisfy the Pediatric Study Plan (PSP) and to fulfill the WR.
- March 19, 2019:
    - FDA approved brexanolone for the treatment of PPD in adults and included postmarketing requirement (PMR) 3535-1 to conduct a randomized, double-blind, placebo-controlled, parallel group study to evaluate efficacy and safety of brexanolone in adolescent females, 15 to less than 18 years of age, diagnosed with PPD.

- November 18, 2019: Type C Guidance Meeting to discuss the feasibility of Study 547-PPD-304 and the request to waive Pediatric Research Equity Act (PREA) PMR 3535-1

    - The Division acknowledged the Applicant's recruitment challenges for Study 547-PPD-304 due to the low incidence of PPD in adolescents, severity requirements, and general difficulties of recruiting adolescents for clinical trials.

    - Although the Division did not agree with a full waiver of PREA PMR 3535-1, the Division was open to an open-label safety study that included sparse PK sampling and collection of efficacy rating scales. The Division and the Applicant reached an agreement regarding the final study design and sample size (20 adolescent subjects).

    - The Applicant agreed to submit a request to amend the WR in order to address the modified study design.

    - On December 20, 2019, the Applicant submitted a protocol amendment (version #3) for Study 547-PPD-304 to reflect the agreement discussed during the Type C meeting.

- May 18, 2020:

    - The Division released the Sponsor from PMR 3535-1 but issued PMR 3535-5—conduct an open-label study evaluating safety, tolerability, and PK of brexanolone in adolescent females, 15 years to less than 18 years of age, diagnosed with postpartum depression—to reflect the agreement reached during the previous Type C meeting.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Given the relatively low sample size of subjects recruited across trial sites for Study 547-PPD-304, the Division did not consult OSI to conduct site inspections.

4.2. Product Quality

The Applicant did not submit any new product quality information. Refer to the original NDA for information on the drug product.

4.3. Clinical Microbiology

The Applicant did not submit any new clinical microbiology information. Refer to the original NDA for additional information.

4.4. Devices and Companion Diagnostic Issues

The Applicant did not submit any new information regarding companion devices. Refer to the original NDA for additional information.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant did not submit any new nonclinical pharmacology/toxicology information. Refer to the original NDA for additional information.

6 Clinical Pharmacology

6.1. Executive Summary

Brexanolone is an allosteric modulator of $GABA_A$ receptors and chemically identical to the endogenous metabolite of progesterone, allopregnanolone. The brexanolone drug product is a sterile, clear, colorless, 5 mg/mL solution formulated with [redacted] (b) (4) (betadex sulfobutyl ether sodium USP/NF). It is provided in a single use vial, diluted prior to use and administered intravenously as a 60-hour continuous infusion. The rapid clearance of brexanolone requires a continuous infusion to maintain therapeutic plasma concentrations. Brexanolone bioavailability is low (<5%) when administered orally.

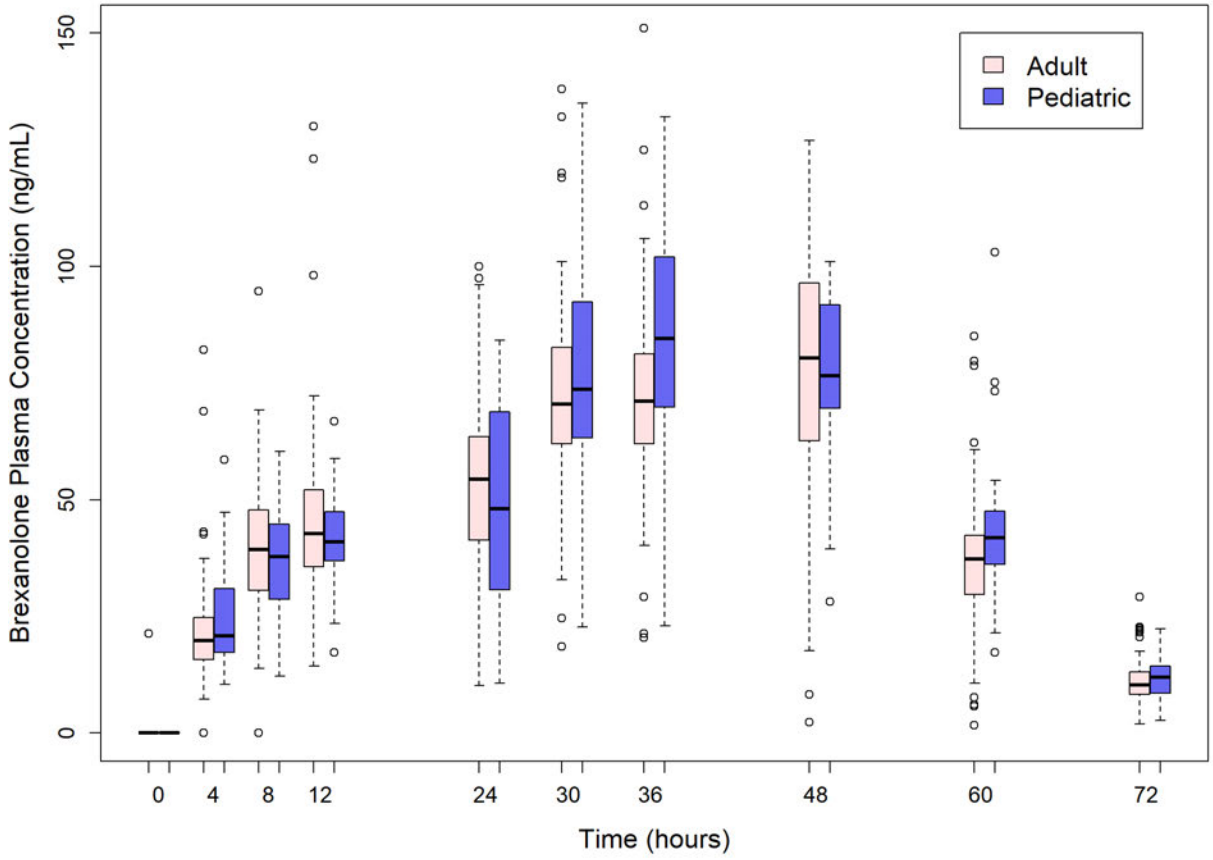
This supplement includes Study 547-PPD-304 to satisfy pediatric PMR 3535-5. The safety, PK, and efficacy results in adolescent PPD patients from Study 547-PPD-304 were compared to those in adult PPD patients (approved March 2019). Based on population PK model, the PK profile in the adolescent PPD population studied (15 to 17 years of age) was demonstrated to be similar to that in adult PPD population. At steady state, the geometric mean plasma C_{max} were estimated to be ~82 ng/mL in adolescent compared to ~79 ng/mL in adults. Similarly, the geometric mean plasma AUC were estimated to be ~4000 ng/mL in adolescent compared to ~3800 ng/mL in adults Therefore, the dosing strategy in adolescents (15 to 17 years) remains the same as that in adults (i.e., weight-based dosing), no dose-adjustment is needed. A validated bioanalytical method was used for the analysis of all PK samples.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Study 547-PPD-304 was a multicenter, open-label study evaluating the safety, tolerability, and pharmacokinetics of brexanolone in the treatment of adolescent female subjects (15 to 17 years of age) with PPD. A total of 20 participants received brexanolone during the study (8 during the Double-blind Phase and 12 during the Open-label Phase), and an additional 8 participants received placebo. Thus, the PK of brexanolone in adolescent female PPD patients was characterized using N=20. The PK of brexanolone in adolescent female PPD patients was comparable to the PK in adult female PPD patients. The geometric mean plasma C_{max} and $AUC_{0\text{-}inf}$ were estimated to be ~82 ng/mL and ~4000 ng*hr/mL, respectively, for adolescents. These were very similar to the C_{max} of ~ 79 ng/mL and $AUC_{0\text{-}inf}$ of ~3800 ng*hr/mL observed in adults. In addition, a side-by-side comparison of the time-profile for brexanolone plasma concentrations for pediatric PPD patients versus adult PPD patients show comparable PK throughout the course of brexanolone treatment.

Figure 1: Observed Brexanolone Plasma Concentration over Time by Age Group



The box plots represent the distribution of PK samples across the respective populations (adult or pediatric) at each nominal timepoint. The Adult group (light shade of red) consists of the pooled observed PK data from Studies 108 (Phase 1), 201 (Phase 2a), 202A (Phase 2), 202B (Phase 3), and 202C (Phase 3) from a total of n=118 subjects. The Pediatric group (dark shade of blue) is the observed PK data from n=20 subjects in Study 304. Both the Adult group as well as the Pediatric group in this figure received the following dosage regimen:

a) 0 to 4 hours: Initiate with a dosage of 30 µg/kg/hour
b) 4 to 24 hours: Increase dosage to 60 µg/kg/hour
c) 24 to 52 hours: Increase dosage to 90 µg/kg/hour
d) 52 to 56 hours: Decrease dosage to 60 µg/kg/hour
e) 56 to 60 hours: Decrease dosage to 30 µg/kg/hour

The detailed population PK analysis is presented in the Appendix (section 18).

6.2.2. General Dosing and Therapeutic Individualization

The PK were generally similar in adolescents compared to historical adult PK data. Therefore, the overall dosing strategy and therapeutic individualizations are identical in adolescents (females 15 to 17 years of age) and adult PPD patients.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant evaluated brexanolone in a single, open-label safety PK study (547-PPD-304) that included collection of efficacy rating scales in 20 female adolescents 15 to 17 years of age with moderate or severe PPD. The formulation and clinical dosing regimen utilized in Study 547-PPD-304 is identical to the dosing regimen approved for the treatment of PPD in adults; see Table 2 for additional trial information.

Table 2: **Listing of Clinical Trials Relevant to NDA 211371/S07**

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	Sample Size	Study Population	No. of Centers and Countries
547-PPD-304	NCT03665038	Open-label safety, tolerability, and PK study	60-hour IV infusion: Hours 0 to 4: 30 µg/kg/hr Hours 4 to 24: 60 µg/kg/hr Hours 24 to 52: 90 µg/kg/hr Hours 52 to 56: 60 µg/kg/hr Hours 56 to 60: 30 µg/kg/hr	Primary Endpoint: Incidence of AEs Exploratory Efficacy Endpoints: Change from baseline in HAM-D, MADRS, CDRS-R, HAM-A and EPDS total score at 60 hours and at 30 days	60-hour continuous IV infusion followed by safety and efficacy assessments occurring up to 30 days post-infusion	20	Adolescent females 15 to 17 years of age with moderate to severe PPD (HAM-D total score > 20)	8 sites in the United States

Source: Reviewer-created.
Abbreviations: AE = adverse event; CDRS-R = Children's Depression Rating Scale – Revised; EPDS = Edinburgh Postnatal Depression Scale; IV = intravenous; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale

7.2. Review Strategy

During a Type C Guidance meeting held in November 2019, the Agency acknowledged the Applicant's recruitment challenges due to the low incidence of PPD in adolescents, administration of a 60-hour infusion, and adherence to the Zulresso REMS program. Because adult-onset PPD shares similar disease characteristics with adolescent-onset PPD (Reid et al., 2007; Yozwiak, et al. 2010), and a similar range of brexanolone exposure is likely thought to elicit the same treatment response in adolescents, the Agency agreed to revising the proposed study design to an uncontrolled, open-label safety study. The clinical and clinical pharmacology teams reviewed the results of Study 547-PPD-304 to confirm whether the range of exposures, treatment response, and anticipated safety profile is consistent with the Applicant's previous findings in adults.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. 547-PPD-304: A Multicenter, Open-Label Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Brexanolone in the Treatment of Adolescent Female Subjects with Postpartum Depression

Trial Design

This was an open-label, multicenter study intended to evaluate the safety and tolerability of brexanolone in adolescent female subjects with PPD. Subjects received a single, 60-hour continuous IV infusion of brexanolone after undergoing a screening period. Due to the risk of excessive sedation and sudden LOC, investigators utilized continuous pulse oximetry to monitor for hypoxia every 2 hours during planned non-sleep periods. Participants remained confined through the completion of the brexanolone infusion and discharged, if medically appropriate, after completing the Hour 72 assessments. Subjects participated in follow-up visits on Day 7, Day 14, Day 21, and Day 30 after receiving the brexanolone infusion. Because the Applicant revised the study design from a randomized, double-blind, placebo-controlled study to an open-label study after study initiation, the Applicant also collected data among subjects randomized to receive placebo.

Study Eligibility Criteria

The target population consisted of adolescent females with PPD. The Applicant's comprehensive inclusion and exclusion criteria consisted of appropriate diagnostic and tolerability criteria, a list of prohibited and accepted concomitant medications, and acceptance thresholds for clinically significant abnormal laboratory values. Pertinent inclusion and exclusion criteria that could impact the evaluation of efficacy and safety are described below:

Key Inclusion Criteria:

- Diagnosis of a major depressive episode that began no earlier than the third trimester and no later than the first 4 weeks following delivery, according to the Structured Clinical Interview for DSM-5 (SCID-5)
- Hamilton Depression Rating Scale (HAM-D) total score ≥ 20 at screening and baseline
- ≤ 6 months postpartum at screening
- Stable dose of concomitant medications for the treatment of depression or anxiety from 30 days prior to dosing until the completion of the 72-hour assessment

Key Exclusion Criteria:

- Subject's most recent pregnancy resulted in miscarriage, still birth, or neonatal death; or subject terminated parental rights (e.g., child placed for adoption)
- Active psychosis
- Medical history of bipolar disorder, schizophrenia, or schizoaffective disorders
- Received electroconvulsive therapy (ECT) within 14 days prior to screening or planned to receive ECT before Day 7
- Attempted suicide during current episode of PPD
- Clinically significant and unstable medical illness in history or at screening.

Procedures and Schedule of Events

See Table 3 for the Applicant's schedule of procedures and study assessments during the infusion and follow-up periods. Because the coronavirus disease 2019 (COVID-19) global pandemic emerged during the study, the Applicant replaced onsite monitoring visits with remote visits, telephone contacts, and periodic all-site calls.

Patient Completion, Discontinuation, or Withdrawal

Investigators permitted subjects to withdraw from the study at any time for any reason without compromising their medical care. Withdrawn subjects completed an early termination visit, if possible, which included the assessments for the Day 14 visit. The Applicant did not replace any subjects who initiated the study drug infusion and subsequently withdrew for any reason.

Given the safety monitoring procedures outlined in the Zulresso REMS program, investigators could stop the treatment infusion at any time if subjects experienced excessive sedation or

LOC. Investigators were to immediately stop the treatment infusion and not resume it if pulse oximetry revealed hypoxia.

Prior and Concomitant Therapy

The Applicant permitted subjects to receive standard-of-care treatment (e.g., antidepressants, psychosocial therapy) for PPD during the trial. Subjects receiving opioids, central nervous system depressants (i.e., benzodiazepines), or other drugs interacting with the GABA-A receptors had to be on a stable recommended dose upon study initiation until completion of the 72-hour assessments. Based on clinical discretion, subjects could initiate any new medication for depression or anxiety after the 72-hour assessments.

Clinical Reviewer's Comment: Given the relative low prevalence of PPD in adolescents and the Applicant's previously stated recruitment challenges, the Division decided that the study design and target population of interest were acceptable to assess the stated objectives, although this design is less definitive than the originally planned randomized double-blind efficacy and safety study and is only being accepted due to the specific circumstances of this population and indication. The minimum HAM-D total score of 20 points (moderate to severe PPD) is consistent with the minimum severity score utilized in a prior adult study (547-PPD-202C) enrolling patients with moderate PPD (HAM-D total score between 20 to 25). Limiting disease severity to severe depression could create additional recruitment challenges; however, the planned enrollment of patients with moderate or severe depression is similar to the PPD severity range observed in prior adult studies and would allow for a reasonable evaluation of differences in efficacy measures between adults and adolescents. The proposed dosing regimen is also identical to the label-recommended dosing regimen in adults. Although the use of ECT is rare in adolescents, the restriction of ECT from 14 days prior to screening until after the Day 7 visit (same exclusion criteria for adult studies) is reasonable because ECT use could confound early efficacy assessments. Because the COVID-19 global pandemic emerged in early 2020 and resulted in travel restrictions and service disruptions (e.g., on-site study visits, laboratory assessments, access to site facilities), our team concluded that the Applicant's plan to include remote site and monitoring visits was acceptable and was unlikely to significantly affect trial results.

Table 3: **Schedule of Study Assessments (547-PPD-304)**

Study Procedure	Screening Period	Treatment Period/Inpatient Stay (Day 1 to Day 3)												Follow-up Period			
Visit Days	**14 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**2**	**3**	**3**	**3**	**7**	**14 or ET**	**21**	**30**
Hour		**0**	**2**	**4**	**8**	**12**	**24**	**30**	**36**	**48**	**54**	**60**	**72**				
Medical history	X																
Physical examination and laboratory assessments[a]	X												X		X		
Drug and alcohol test	X	X															
Pregnancy test	X	X													X		X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG	X	X											X		X		
C-SSRS	X	X											X	X	X	X	X
HAM-D	X	X				X	X		X	X		X		X	X	X	X
CGI-S	X	X															X
CGI-I														X	X	X	X
HAM-A		X										X		X	X	X	X
MADRS + CDRS-R		X					X			X		X		X	X	X	X
EPDS		X												X			X
Plasma PK		X		X	X	X	X	X	X	X		X	X				
Pulse oximetry + Monitoring for excessive sedation[b]		X---------->															

Source: Reviewer-created using CSR Table 1.
[a]Safety laboratory tests included hematology, serum chemistry, exploratory biochemistry, and hormone parameters. Investigators assessed coagulation only at screening.
[b]Continuous pulse oximetry occurred for the duration of the infusion. Investigators only recorded oxygen saturation in the event of hypoxia (also recorded as an AE). Investigators monitored for excessive sedation every 2 hours during planned non-sleep periods.
Abbreviations: CDRS-R = Children's Depression Rating Scale – Revised; CGI-I = Clinical Global Impression – Improvement Scale; CGI-S = Clinical Global Impression – Severity Scale; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EPDS = Edinburgh Depression Scale; ET = early termination; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery Asberg Depression Rating Scale; PK = pharmacokinetic

Study Endpoints

The primary endpoint was safety, as were several secondary endpoints: the incidence of AEs and changes in vital sign and laboratory assessments, physical examination, ECG parameters, pulse oximetry, and suicidal ideation and behavior (SI/B), respectively. There was no prespecified primary efficacy endpoint in this study.

The secondary efficacy endpoints include changes from baseline in the HAM-D, Montgomery-Åsberg Depression Rating Scale (MADRS), Children's Depression Rating Scale–Revised (CDRS-R), Clinical Global Impression–Severity and -Improvement (CGI-S and CGI-I), Hamilton Anxiety Rating Scale (HAM-A) and Edinburgh Postnatal Depression Scale (EPDS) total scores at time points specified in Table 3.

The Applicant estimated PK parameters using plasma concentrations of brexanolone, and when appropriate, metabolites of brexanolone.

Statistical Analysis Plan

Given that the final study design consisted of only single, open-label brexanolone treatment arm, the Applicant did not propose a formal statistical analysis plan.

Clinical Reviewer's Comment: The selection of the safety and efficacy variables are appropriate for this study. Of note, the CDR-R is traditionally used to evaluate changes in depressive symptoms in acute pediatric MDD trials and is listed in the FDA Clinical Outcomes Assessment (COA) compendium for depressive episodes associated with bipolar depression. Although the HAM-D and the MADRS instruments are not clinically validated in adolescent patients with PPD, the use of the HAM-D and MADRS total scores have been commonly used as secondary and exploratory efficacy measures in prior pediatric MDD studies to assess changes in depressive symptoms over time. The use of the HAM-D total score would also allow a reasonable comparison of treatment effects with prior adult studies.

Protocol Amendments

The Applicant submitted three amendments to the protocol. Important changes to the study protocol are highlighted below:

- Amendment 1 (September 2018; five subjects randomized prior to Amendment 1 and four subjects randomized after Amendment 1)
    - Assessment of brexanolone's effect on maternal behaviors was changed from a secondary to an exploratory objective
    - Inclusion criteria updated to include only subjects 15 to 17 years of age (as a result randomization was not stratified by age)

  - Exclusion criteria updated to exclude subjects who received ECT within 14 days prior to screening or planned to receive ECT before Day 7
  - Sample size calculation changed from 40 to 80 subjects
  - Concomitant medications to treat symptoms of depression or anxiety required at least 30 days of stable dosing prior to receiving study treatment

- Amendment 2 (June 2019; Seven subjects randomized after Amendment 2)
  - Safety monitoring updated to remain consistent with the FDA-approved prescribing information for Zulresso and the Zulresso REMS program
  - Included the use of a programmable peristaltic infusion pump to ensure accurate dosing
  - List of AEs of special interest (AESI) modified to exclude severe sedation-like events, syncope, and hypoxia and include excessive sedation
  - Required subjects to be accompanied during any interaction with their child(ren) during the infusion
  - Removed lactating or actively breastfeeding subjects as an exclusion criterion

- Amendment 3 (December 2019; 12 subjects enrolled after Amendment 3)
  - Study design changed from a double-blind, placebo-controlled study to an open-label study in which all subjects received brexanolone
  - Primary endpoint changed to the incidence of AEs
  - Target sample size decreased from 80 to 20 subjects, including those previously enrolled and randomized
  - Removed planned statistical analysis for the HAM-D total score
  - Changed the last follow-up visit from Day 90 to Day 30

The Applicant refers to Study 547-PPD-304 as having two phases, a double-blind and open-label phase. For the purpose of this review, study treatment administered to subjects before the implementation of Protocol Version 4 is referred to as "double-blind" and study treatment administered to subjects after the implementation of Protocol Version 4 is referred to as "open-label treatment."

Clinical Reviewer's Comment: *The review team previously determined that the incorporated*

protocol changes were reasonable. Because the Applicant initiated this study prior to revising the trial design from a double-blind, randomized study to an open-label study, this review will also include nominal comparisons of placebo and treatment response observed in the randomized population versus the open-label population and between adults and adolescents, although none of these comparisons are prespecified or statistically controlled.

8.1.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in accordance with the International Council for Harmonisation Good Clinical Practice Guidelines.

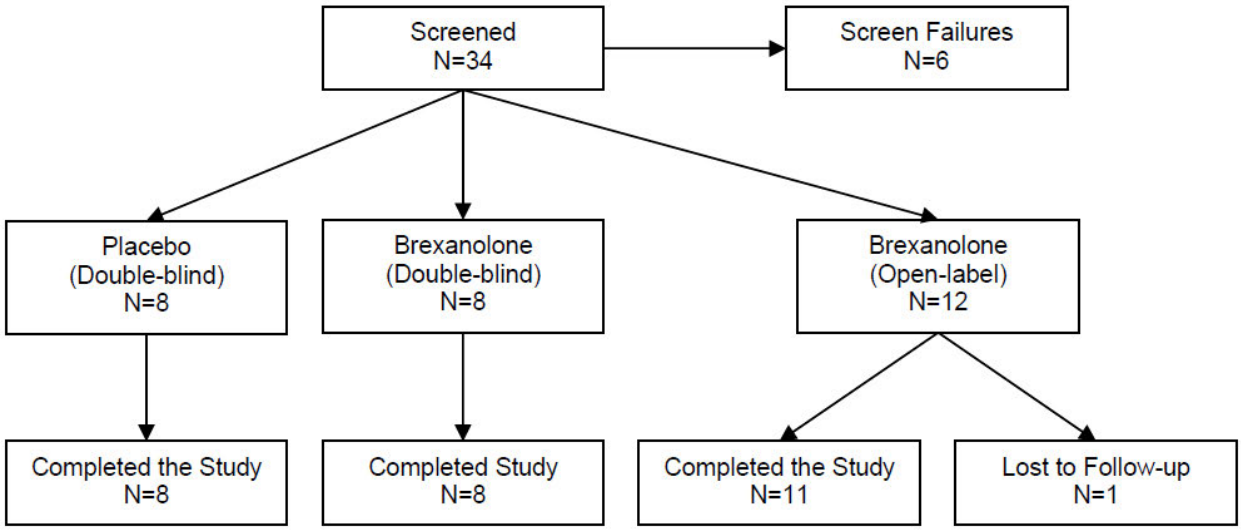
Financial Disclosure

Please refer to Section 15.2 of this review for detailed financial disclosure information. There are no disclosed financial interests or arrangements or missing disclosures that raise questions about the integrity of study data.

Patient Disposition

See Figure 1 for an overview of patient disposition. Overall, the Applicant screened 34 subjects based on study eligibility criteria and enrolled 28 subjects. Prior to the third protocol amendment, the Applicant randomized 16 subjects to receive either double-blind brexanolone or placebo. After the third protocol amendment, the Applicant enrolled 12 subjects to receive open-label brexanolone. Overall, a total of 20 subjects received brexanolone treatment during the course of the study. All subjects completed the entire 60-hr study treatment infusion; only one subject prematurely discontinued the study at Day 14.

Figure 2: Patient Disposition Information (547-PPD-304)



Source: Applicant's CSR, Figure 1.

Protocol Violations/Deviations

Table 3 describes the Applicant's listing of major protocol deviations during the study period. The Applicant indicated that 21 (72%) major protocol deviations were related to expired laboratory kits (no more than 30 days elapsed between expiration date and date of collection) that occurred across four study sites and involved six subjects. After the Applicant identified these deviations through clinical monitoring, the Applicant conducted a further investigation of their laboratory samples. Because the laboratory results obtained from the expired kits were consistent with the results obtained from other study visits, the Applicant determined that data integrity was not impacted. The Applicant reported three deviations related to lack of vital sign measurements for one subject during hospital transport due to loss of consciousness. Regarding study drug administration errors, one study site inadvertently utilized an earlier version of the pharmacy manual and, as a result, made three IV bag changes instead of the required five over the 3-day dosing period for one subject.

Clinical Reviewer's Comment: The described protocol violations do not substantially affect the interpretation of safety and efficacy results. A review of all deviations related to potentially expired sampling kits across six subjects was consistent with the Applicant's findings.

Table 4: Summary of Major Protocol Violations (547-PPD-304)

Protocol Deviations	Double-Blind Placebo (N=8)	Double-Blind Brexanolone (N=8)	Open-Label Brexanolone (N=12)
Major protocol deviations	3	2	6
Expired laboratory kits	1	0	20
Study drug administration	2	1	0
Laboratory Sample collection	0	1	1
Safety assessment	0	0	3

Source: Applicant's CSR, Listing 16.2.2.

Demographic and Baseline Characteristics

See Table 5 for a summary of demographic and baseline characteristics across treatment groups. The Applicant utilized seven clinical study sites across the United States to enroll their target population. Only two subjects (10%) that received brexanolone treatment were 15 years old.

Table 5: Demographic and Baseline Characteristics (547-PPD-304)

Demographic Characteristic	Double-Blind Placebo (N=8)	Double-Blind Brexanolone (N=8)	Open-Label Brexanolone (N=12)	Total Brexanolone (N=20)
Age (years)				
Mean (SD)	16.6 (0.5)	16.4 (0.5)	16.3 (0.8)	16.4 (0.7)
Median (Range)	17 (16 – 17)	16 (16 – 17)	16 (15 – 17)	16 (15 – 17)
Race, n (%)				
White	2 (25%)	2 (25%)	1 (8%)	3 (15%)
Black or African American	6 (75%)	6 (75%)	10 (83%)	16 (80%)
American Indian or Alaskan	0	0	1 (8%)	1 (5%)
Weight (kg), mean (SD)	77.8 (20)	64.9 (9)	70.6 (16)	68.3 (13)

Demographic Characteristic	Double-Blind Placebo (N=8)	Double-Blind Brexanolone (N=8)	Open-Label Brexanolone (N=12)	Total Brexanolone (N=20)
Height (cm), mean (SD)	163.3 (6)	162.8 (8)	164.1 (8)	163.6 (8)
BMI (kg/m^2), mean (SD)	28.9 (6)	24.5 (3)	26.1 (5)	25.4 (4)

Source: Applicant's CSR, Table 3.

Other Baseline Characteristics

See Table 6 for a summary of baseline psychiatric history, disease characteristics, and prior antidepressant treatment. All subjects entering the study were experiencing their first PPD episode. One subject receiving double-blind placebo and two subjects receiving double-blind brexanolone reported a previous pregnancy. Only one subject randomized to receive double-blind brexanolone also received prior antidepressant treatment for their current PPD episode.

Table 6: Disease and Psychiatric History (547-PPD-304)

Demographic Characteristic	Double-Blind Placebo (N=8)	Double-Blind Brexanolone (N=8)	Open-Label Brexanolone (N=12)	Total Brexanolone (N=20)
Onset of PPD, n (%)				
Third Trimester	4 (50%)	3 (38%)	2 (17%)	5 (25%)
Within 4 weeks of delivery	4 (50%)	5 (62%)	10 (83%)	15 (75%)
Co-morbid psychiatric disorders, n (%)	5 (63%)	6 (75%)	3 (25%)	9 (45%)
Major depressive disorder	0	1 (13%)	1 (8%)	2 (10%)
Generalized anxiety disorder	0	1 (13%)	1 (8%)	2 (10%)
Insomnia	5 (63%)	4 (50%)	0	4 (20%)
Other	0	1 (13%)	2 (16%)	3 (15%)
Prior antidepressant treatment, n (%)	0	1 (13%)	0	1 (5%)
Severity of Depression, mean (SD)				
HAM-D	26.5 (3.1)	25.8 (3.4)	26.8 (3.4)	26.4 (3.3)
MADRS	35.6 (5.2)	32.9 (4.7)	34.1 (4.1)	33.6 (4.3)
CDRS-R	64.2 (4.4)	62.8 (9.5)	63.3 (10.2)	63.1 (9.7)
EPDS	20.4 (3.8)	18.1 (4.2)	20.3 (4.3)	19.4 (4.3)
CGI-S, mean (SD)	4.9 (0.4)	4.8 (0.5)	5.0 (0.7)	4.9 (0.6)

Source: Applicant's CSR, Table 14.1.4, Listing 16.2.4.3, and Listing 16.2.4.4.
Abbreviations: CDRS-R = Children's Depression Rating Scale – Revised; CGI-S = Clinical Global Impression – Severity Scale; EPDS = Edinburgh Depression Scale; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery Asberg Depression Rating Scale

Reviewer's Comment: Overall assessment of baseline demographics, disease characteristics, psychiatric history, and prior psychiatric medication use indicates a low potential for confounding efficacy and safety results. Similar disease characteristics described in the current literature also suggest that an adolescent with psychiatric comorbidities that is experiencing a first pregnancy is at high risk for PPD (Dwinwiddie et al., 2018; Yozwiak et al. 2010). Evaluation of baseline depression severity based on various clinical outcome measures confirm that the Applicant enrolled subjects with moderate to severe PPD. Comparison between Study 547-PPD-304 and prior adult studies (547-PPD-202B and 547-PPD-202C) suggest similar onset of PPD (within 4 weeks of delivery) and incidence of co-morbid psychiatric conditions. In general, adult subjects exhibited a greater frequency of prior MDD episodes and antidepressant use than in the adolescent study. These differences are expected as adult patients are likely to have a longer MDD history.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant calculated treatment compliance using the following equation: (actual total dose (µg/kg)/planned total dose (µg/kg)) x 100. The Applicant determined that 19 subjects (95%) in the overall brexanolone group and seven subjects (87.5%) in the placebo group were at least 95% complaint with the full dosing regimen. One subject (12.5%) in the placebo group was in the 90 to 95% compliance category and one subject (5%) in the overall brexanolone group was <70% compliant. Reasons for not receiving the full dosing regimen included: AE, infusion line infiltration, loosening of infusion line, line occlusion, and subject showering.

Two subjects (25%) receiving double-blind placebo and three subjects (50%) receiving double-blind brexanolone also reported sertraline as a new concomitant antidepressant to treat symptoms of anxiety or depression. Subjects receiving open-label brexanolone treatment did not report any concomitant antidepressants or other psychotropic medications.

Reviewer's Comment: In general, the majority of patients exhibited adequate treatment compliance that would not lead to clinically meaningful differences in total drug exposure. The one subject that received <70% of the total brexanolone dose experienced loss of consciousness that required the infusion to be immediately stopped. All other reasons for treatment pauses were similarly reported in adult studies and in the postmarketing setting. Although the number of patients receiving concomitant antidepressants is low and similar to adult studies, antidepressants generally require several weeks to achieve steady state pharmacodynamic effects. Because it is unclear whether brexanolone's treatment effect was confounded among patients receiving sertraline, the impact of concomitant medications on brexanolone's treatment effect is summarized in the Efficacy Results subsection.

Efficacy Results–Primary Endpoint

The Applicant's primary endpoint is a safety one, the incidence of AEs. See Section 8.2.4 for a summary of the Applicant's safety results.

Data Quality and Integrity

Although OSI did not conduct a specific clinical site investigation, this review did not identify any substantial deficiencies in the quality and integrity of the efficacy data.

Efficacy Results – Secondary and other relevant endpoints

Because the Applicant did not provide a formal statistical analysis plan and did not specify any primary or key secondary endpoints, the analyses presented below are strictly qualitative and do not utilize formal statistical methods to compare between treatment groups. Any comparative interpretation of the data presented is limited accordingly.

HAMD-D

Mean change from baseline in the HAM-D total score during the 60-hour infusion and post-infusion follow-up period for each treatment group is displayed in Figure 3. Subjects receiving placebo and brexanolone treatment experienced a similar pattern of improvement to the adult trials in depressive symptoms during the 60-hour infusion that was maintained throughout the follow-up period. Because of the Applicant's revised study design (after Protocol Version 2.0 and 3.0), investigators did not collect efficacy assessments at Day 3, Day 60, and at Day 90 during the follow-up period. Table 7 describes the mean change from baseline in the HAM-D total score for each treatment group at the end of infusion and at Day 30. The average treatment effect observed at Hour 60 and Day 30 among randomized subjects was -2.9 points, and -1.4 points, respectively. The magnitude of separation between the double-blind placebo and brexanolone treatment groups appeared to decrease after Day 21 and dissipated at Day 60 and 90. The trajectory of treatment response among open-label and randomized subjects receiving double-blind brexanolone treatment was also similar during the infusion and up to Day 30.

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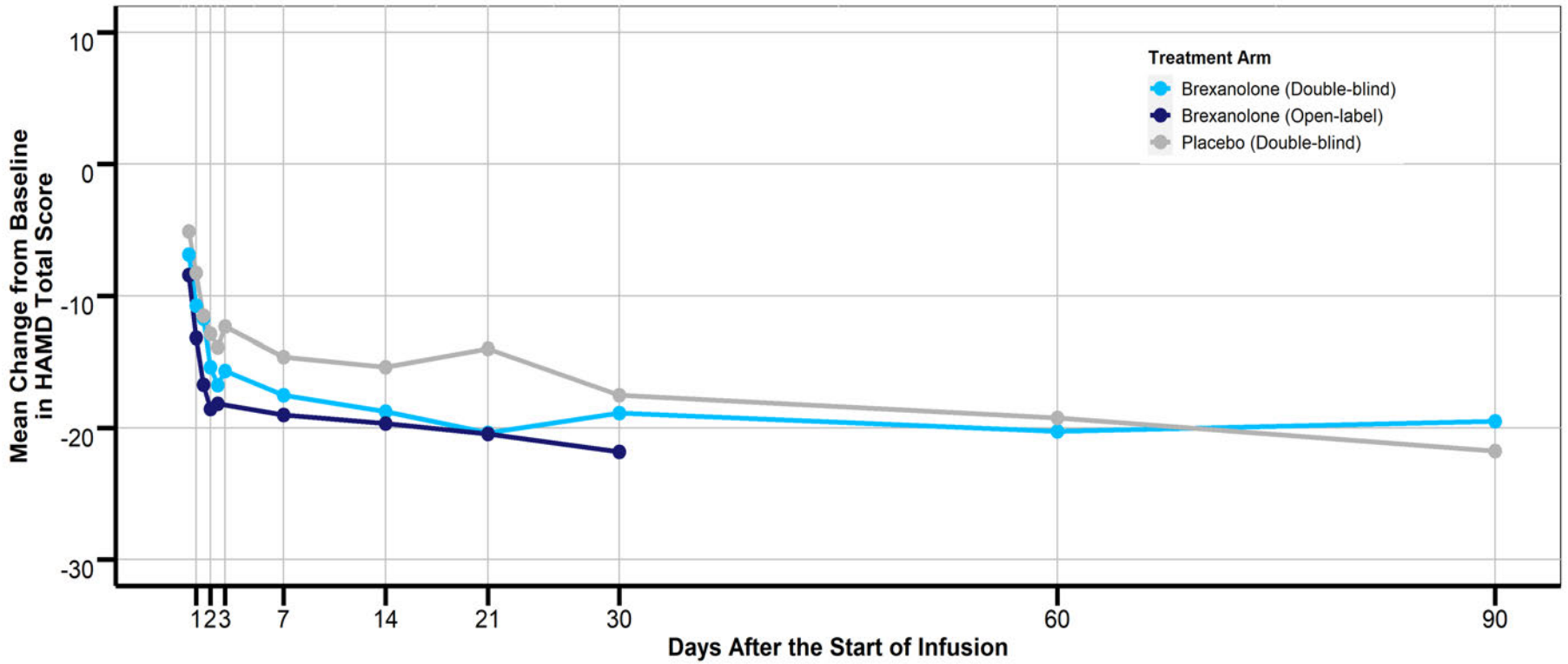
Figure 3: Mean Change from Baseline in HAM-D Total Score during the Double-Blind and Open-Label Phases (547-PPD-304)[1]



Source: Reviewer-created using the adqs.xpt dataset.
[1]After Protocol Version 2.0 and 3.0, the Applicant no longer required efficacy assessments Day 3, Day 60, and at Day 90 during the follow-up period.
Abbreviations: HAM-D = Hamilton Depression Rating Scale

Table 7: Mean Change from Baseline in HAM-D Total Score at Hour 60 and Day 30

	Double-Blind Placebo (N=8)	Double-Blind Brexanolone (N=8)	Open-Label Brexanolone (N=12)	Total Brexanolone (N=20)
Baseline, mean (SD)	26.5 (3.1)	25.8 (3.4)	26.8 (3.4)	26.4 (3.3)
Change at Hour 60, mean (SD)	-13.9 (8.1)	-16.8 (8.3)	-18.2 (6.4)	-17.6 (7.1)
Difference from placebo at Hour 60, mean	-	-2.9	-4.3	-3.7
Change at Day 30, mean (SD)	-17.5 (9.0)	-18.9 (7.2)	-21.8 (5.4)	-20.6 (6.2)
Difference from placebo at Day 30, mean	-	-1.4	-4.3	-3.1

Source: Reviewer-created using the adqs.xpt dataset.
Abbreviations: HAM-D = Hamilton Depression Rating Scale

In order to determine whether the change in HAM-D total score was potentially clinically meaningful, the Applicant further categorized subjects based on definitions for treatment response (defined as subjects with >50% change from baseline in the HAM-D total score) and treatment remission (defined as subjects with a HAM-D total score ≤7). Figure 4 and Figure 5 display the percentage of subjects that achieved treatment response and remission at each study visit. Approximately 75% and 50% of subjects receiving double-blind brexanolone and placebo exhibited treatment response per the Applicant definition at the end of infusion, respectively. At Day 90, the majority of subjects exhibited treatment response per the Applicant definition (88% versus 100%, respectively between drug and placebo arms). The percentage of treatment responders among subjects receiving open-label brexanolone treatment was also similar to the randomized brexanolone treatment arm. Approximately 75% and 38% of randomized subjects receiving double-blind brexanolone and placebo achieved treatment remission per the Applicant definition at the end of infusion, respectively. Although treatment remission among subjects receiving open-label brexanolone treatment was relatively low (50%) at the end of infusion, the percentage increased to 82% by Day 30. Similar to the percentage of treatment responders, the treatment remission at Day 90 was greater in the placebo treatment arm relative to double-blind brexanolone treatment.

An evaluation of subjects receiving concomitant antidepressants demonstrated that the average treatment effect (placebo-subtracted mean change from baseline on HAM-D total score) at Hour 60 and Day 30 was nominally greater relative to patients who did not receive any additional antidepressants (Hour 60: -4.66 versus -2.83; Day 30: -2.33 versus -0.67). Although the treatment effect appeared to decrease for subjects who did not receive concomitant therapy, the average treatment effect for subjects receiving concomitant antidepressant remained nominally similar at Day 60 and Day 90 versus earlier visits (Day 60: -1.3 versus -0.6; Day 90: -3.3 versus 4.9).

Reviewer's Comment: Although the presented analysis is markedly limited due to the low sample size across treatment arms, the lack of prespecified statistical comparison, and the inclusion of open-label subjects, the average change in the HAM-D total score during the infusion period and up to Day 30 is nominally greater among patients receiving brexanolone treatment versus placebo. However, changes in the HAM-D total score across all treatment groups plateaued after Day 30 and became nominally similar and was even higher in the double-blind placebo treatment arm. The plateauing effect and spontaneous resolution of symptoms is consistent with the average duration of PPD (approximately 3 to 6 months) and

length of treatment (Wisner et al., 2002). According to the DSM-5, the diagnosis of PPD should be based on symptoms that manifest within 4 weeks of delivery; therefore, worsening of symptoms after this 4-week period would be due to a new episode of MDD rather than a return of the PPD episode. Analysis of prior adult studies also indicated that the treatment effect on HAM-D total scores was larger among subjects with a higher baseline severity. Because only two subjects in the double-blind placebo group and three subjects in the double-blind brexanolone group had moderate PPD, the comparison of treatment effects between moderate versus severe PPD subjects was not reliable. Among subjects receiving concomitant antidepressant therapy, the consistent degree of separation during the follow-up period may suggest an additive effect.

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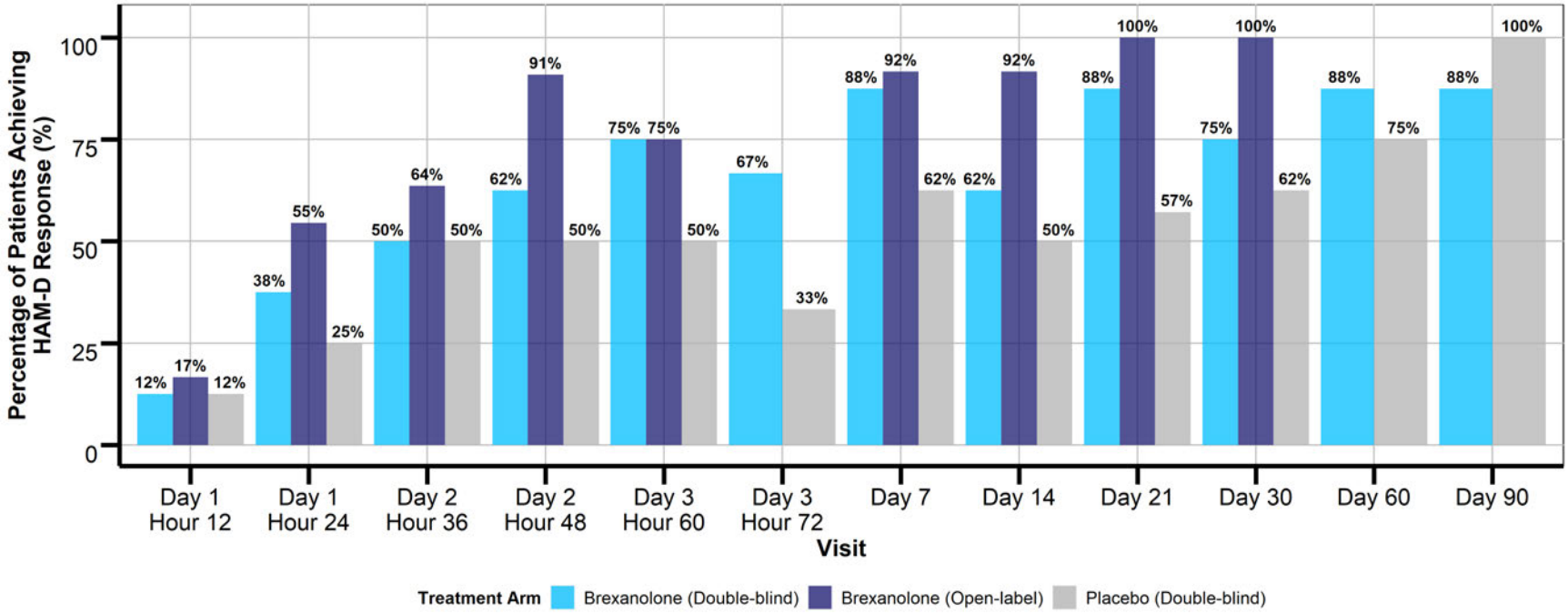
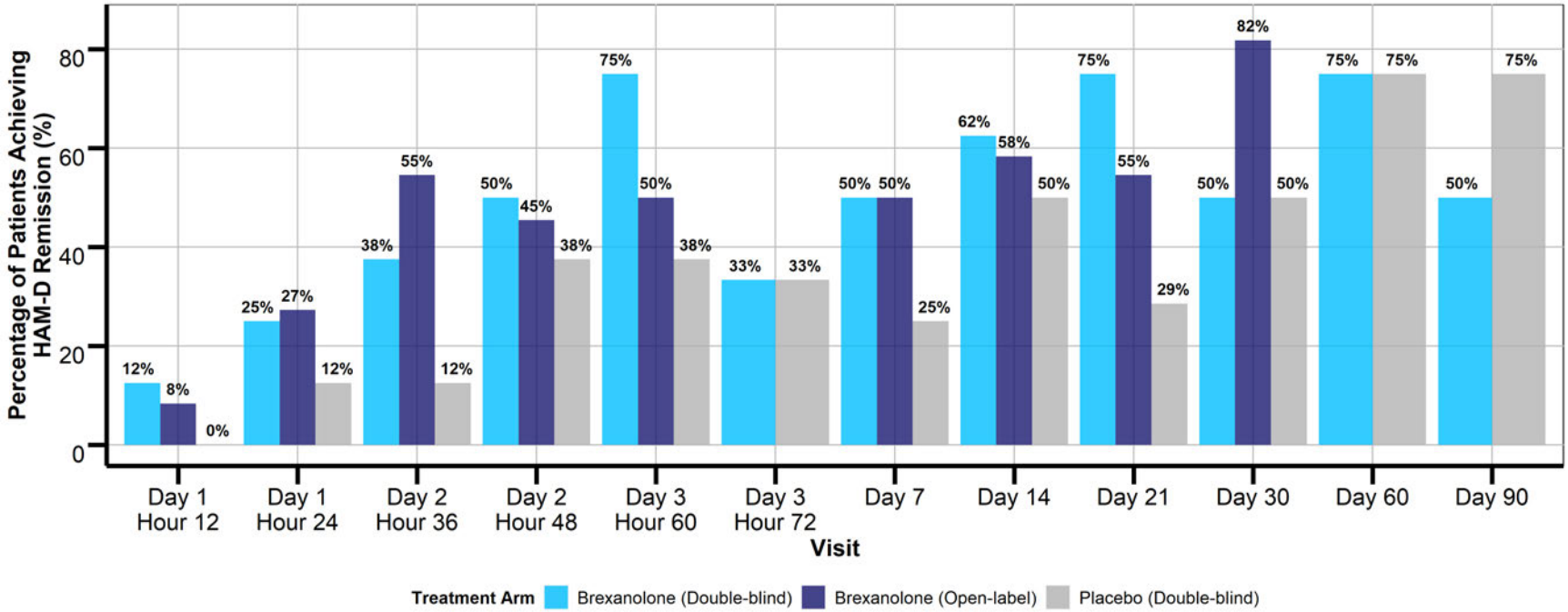
Figure 4: Percentage of Patients Achieving Treatment Response[a,b]



Source: Reviewer-created using the adqs.xpt dataset.
[a]After Protocol Version 2.0 and 3.0, the Applicant no longer required efficacy assessments Day 3, Day 60, and at Day 90 during the follow-up period.
[b]Applicant defined treatment response as > 50% change from baseline in the HAM-D total score
Abbreviations: HAM-D = Hamilton Depression Rating Scale

Figure 5: Percentage of Patients Achieving Treatment Remission[a,b]



Source: Reviewer-created using the adqs.xpt dataset.
[a]After Protocol Version 2.0 and 3.0, the Applicant no longer required efficacy assessments Day 3, Day 60, and at Day 90 during the follow-up period.
[b]Applicant defined treatment remission as a HAM-D total score ≤ 7
Abbreviations: HAM-D = Hamilton Depression Rating Scale

Similar to Study 547-PPD-304 in adolescents, adult Studies 547-PPD-202B and 547-PPD-202C also evaluated longitudinal changes in the HAM-D total score during infusion and follow-up periods. Please refer to the Agency's Multidisciplinary Review of the original NDA (Zulresso; NDA 211371) for additional information related to the study design, trial participant characteristics, and efficacy results for adult studies used to substantiate evidence of efficacy for Zulresso. Table 8 and Table 9 compares the mean change from baseline in the HAM-D total score, percentage of treatment responders, and percentage of subjects achieving treatment remission at Hour 60 and Day 30 between adults and adolescents. Overall, the average treatment effect (i.e., placebo subtracted difference) observed at Hour 60 and Day 30 in adolescents was consistent with that observed in adults.

Table 8: Comparison of Endpoints Based on HAM-D Total Score at Hour 60 between Adult and Adolescent Studies

Population	Sample Size	Endpoint at Hour 60 using HAM-D Total Score	Treatment		
			Placebo	Brexanolone[b]	Placebo Subtracted Difference
Adolescent Study 304[a] Moderate to Severe PPD (HAM-D > 20)	Placebo = 8 Brexanolone = 20	Mean Change from Baseline	-13.9	-16.8	-2.9
		Treatment Responders (%)	50%	75%	25%
		Treatment Remission (%)	38%	75%	37%
Adult Study 202B Severe PPD (HAM-D > 26)	Placebo = 43 Brexanolone = 41	Mean Change from Baseline[c]	-14.4	-17.7	-3.7
		Treatment Responders (%)	56%	72%	16%
		Treatment Remission (%)	16%	31%	15%
Adult Study 202C Moderate PPD (HAM-D 20 to 25)	Placebo = 53 Brexanolone = 51	Mean Change from Baseline[c]	-12.1	-14.6	-2.5
		Treatment Responders (%)	60%	76%	16%
		Treatment Remission (%)	39%	61%	22%

Source: Reviewer-created using the adqs.xpt dataset and NDA 211371 (Brexanolone) Multidisciplinary Review Figure 20, Figure 26, and Table 55.
[a]Evaluation of adolescent data based on subjects receiving double-blind treatment.
[b]Response to brexanolone therapy based on the 90 µg/kg/hr target brexanolone IV infusion rate
[c]Least-squares mean change from baseline
Abbreviations: HAM-D = Hamilton Depression Rating Scale

Table 9: Comparison of Endpoints Based on HAM-D Total Score at Day 30 between Adult and Adolescent Studies

Population	Sample Size	Endpoint at Day 30 using HAM-D Total Score	Treatment		
			Placebo	Brexanolone[b]	Placebo Subtracted Difference
Adolescent Study 304[a] Moderate to Severe PPD (HAM-D > 20)	Placebo = 8 Brexanolone = 20	Mean Change from Baseline	-17.5	-18.9	-1.4
		Treatment Responders (%)	62%	75%	13%
		Treatment Remission (%)	50%	50%	0%
Adult Study 202B Severe PPD (HAM-D > 26)	Placebo = 43 Brexanolone = 41	Mean Change from Baseline[c]	-13.8	-17.6	-3.8
		Treatment Responders (%)	50%	69%	19%
		Treatment Remission (%)	31%	39%	8%
Adult Study 202C Moderate PPD (HAM-D 20 to 25)	Placebo = 53 Brexanolone = 51	Mean Change from Baseline[c]	-15.2	-14.7	0.5
		Treatment Responders (%)	79%	71%	-8%
		Treatment Remission (%)	62%	48%	-14%

Source: Reviewer-created using the adqs.xpt dataset and NDA 211371 (Brexanolone) Multidisciplinary Review Figure 20, Figure 26, and Table 55.
[a]Evaluation of adolescent data based on subjects participating in the Double-Blind Phase.
[b]Response to brexanolone therapy based on the 90 µg/kg/hr target brexanolone IV infusion rate
[c]Least-squares mean change from baseline
Abbreviations: HAM-D = Hamilton Depression Rating Scale

Reviewer's Comment: The primary efficacy endpoint utilized in both referenced adult studies was the change from baseline in HAM-D total score at Hour 60. Prior to the Applicant's revision of the study design, they Agency expected brexanolone exposures and response to treatment for PPD should be similar between adults and adolescents. Due to the limited sample size of randomized adolescent subjects participating in Study 547-PPD-304 (n=8), a formal statistical comparison was not conducted to determine the significance of brexanolone's effect on PPD. However, nominal comparisons of the treatment effect for various endpoints based on the HAM-D total score indicated that the observed adolescent treatment effect at the end of infusion and Day 30 was within the expected adult range. In both populations, the initial response during the infusion was quick and sustained during the follow-up period.

Analyses of other secondary and exploratory endpoints are presented in Table 10. Across all variables, subjects experienced a robust response to brexanolone treatment during the infusion, which was sustained through the end of the follow-up period.

Table 10: Mean Change from Baseline in Secondary and Exploratory Efficacy Variables at Hour 60 and Day 30

Efficacy Variable	Time	Double-Blind Placebo (N=8)	Double-Blind Brexanolone (N=8)	Open-Label Brexanolone (N=12)	Total Brexanolone (N=20)
MADRS	Baseline, mean (SD)	35.6 (5.2)	32.9 (4.7)	34.1 (4.1)	33.6 (4.3)
	Change at Hour 60, mean (SD)	-19.5 (12.5)	-22.6 (9.6)	-25.4 (7.5)	-24.3 (8.3)
	Difference from placebo at Hour 60, mean	-	-3.1	-5.9	-4.8
	Change at Day 30, mean (SD)	-25.0 (12.3)	-24.5 (10.6)	-28.1 (7.0)	-26.6 (8.6)
	Difference from placebo at Day 30, mean	-	0.5	-3.1	-1.6
CDRS-R	Baseline, mean (SD)	64.2 (4.4)	62.8 (9.5)	63.3 (10.2)	63.1 (9.7)
	Change at Hour 60, mean (SD)	-23.3 (16.4)	-31.1 (16.6)	-36.2 (11.9)	-34.3 (13.6)
	Difference from placebo at Hour 60, mean	-	-7.8	-12.9	-11.0
	Change at Day 30, mean (SD)	-33.3 (20.0)	-34.3 (16.9)	-38.2 (11.1)	-36.5 (13.5)
	Difference from placebo at Day 30, mean	-	-1.0	-4.9	-3.2
EPDS[a]	Baseline, mean (SD)	20.4 (3.8)	18.1 (4.2)	20.3 (4.3)	19.4 (4.3)
	Change at Day 30, mean (SD)	-14.6 (7.1)	-15.8 (5.6)	-16.5 (6.3)	-16.2 (5.9)
	Difference from placebo at Day 30, mean	-	-1.2	-1.9	-1.6
CGI-S[a]	Baseline, mean (SD)	4.9 (0.4)	4.8 (0.5)	5.0 (0.7)	4.9 (0.6)
	Change at Day 30, mean (SD)	-	-	-3.2	-3.2
	Difference from placebo at Day 30, mean	-	-	-	-

Source: Reviewer-created using the adqs.xpt dataset.
[a]The Applicant did not collect data at the end of infusion (Hour 60)
Abbreviations: CDRS-R = Children's Depression Rating Scale – Revised; CGI-S = Clinical Global Impression – Severity Scale; EPDS = Edinburgh Depression Scale; MADRS = Montgomery Asberg Depression Rating Scale

Dose/Dose Response

The Applicant did not include different dosing regimens to characterize the dose-response relationship of brexanolone for PPD. During their adult program, the Applicant used a lower target dose in one arm of one phase 3 study (60 µg/kg/hr). They did not conduct further exploration of other potential dosing regimens (e.g., other target doses, shorter infusions, intermittent dosing). The original NDA approval letter describes the following postmarketing commitment (PMC): 3535-3 "Conduct a study to evaluate the efficacy of a lower dose of brexanolone." In September 2019, the Applicant subsequently submitted protocol (b) (4) to evaluate lower doses of brexanolone in adult women with PPD. The study has not yet been completed.

Durability of Response

To evaluate durability of response, the Applicant incorporated multiple efficacy assessments up to 90 days for subjects receiving double-blind treatment and up to 30 days for subjects receiving open-label treatment. Refer to Figure 3 for the change in HAM-D total score post-infusion and during the follow-up period. During the follow-up period, zero subjects receiving double-blind brexanolone and two subjects (25%) receiving double-blind placebo treatment experienced new depressive symptoms after completing the infusion (HAM-D total score > 16 after the Hour 60 HAM-D total score ≤ 16). Results, as described in Table 10, also suggest a consistent durability of response across other secondary and exploratory efficacy variables.

Reviewer's Comment: It is unclear why the Applicant collected efficacy measures beyond Day 30 (the duration of prior adult studies was 30 days). Although the treatment effect remains consistent between Hour 60 and Day 30, the treatment effect decreased between Day 30 and Day 90 and even appears to favor placebo by Day 90. As mentioned previously, worsening of depression after the initial 4-week period of symptoms would be, by DSM-5, a new episode of MDD rather than a relapse of the PPD episode. Therefore, the confirmation of durability of response was based on longitudinal data observed up to Day 30.

Persistence of Effect

The one-time infusion of brexanolone is not designed for persistence of treatment effect.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Refer to Table 10 for analyses of secondary and exploratory endpoints. There are no additional efficacy endpoints to discuss.

8.1.3. Integrated Assessment of Effectiveness

The Applicant submitted a single, open-label study (Study 547-PPD-304) to evaluate brexanolone for the treatment of PPD in adolescents. Study 547-PPD-304 was not adequately designed (i.e., randomized, double-blind, placebo-controlled) or statistically powered to detect a significant treatment effect on the HAM-D total score. However, because the Division acknowledged the similarity of PPD in adults versus adolescents and potential recruitment challenges associated with conducting an adequate and well-controlled study, the Division agreed to utilize partial extrapolation of efficacy based on prior adult studies and accepted a single, open-label safety and PK study to provide supportive scientific evidence of efficacy in adolescents in this instance. Even though the interpretation of Study 547-PPD-304 is limited by its open-label study design, sample size, and lack of prespecified, statistically controlled efficacy endpoints, the crude numerical similarity of the efficacy findings across multiple endpoints and with prior adult studies of similar design appear to generally show a similar pattern of initial response and sustained effect of brexanolone to treat PPD in adolescents.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety evaluation of this supplemental application is based on a single study primarily intended to evaluate the safety, tolerability, and PK of brexanolone in adolescents with PPD. Details regarding the study design and enrolled patient population for Study 547-PPD-304 are provided in Section 8.1.1 and Section 8.1.2 of this review.

In prior adult studies, adverse events of special interest (AESI) included oversedation and LOC. A thorough evaluation of brexanolone exposures, concurrent medications, medical history, and patient characteristics indicated that there was no apparent association with LOC or excessive sedation. Because of the abruptness and unpredictability of these events, the Agency did not believe that these risks could be mitigated solely through labeling. Therefore, the Agency approved brexanolone for administration under the Zulresso REMS program. Given the limited sample size of enrolled adolescents in Study 547-PPD-304, this review will assess whether the established safety profile, including the risk for excessive sedation and LOC, in adults is consistent with adolescents.

This safety analysis reviewed the following data:

- Adverse events
- Physical examinations and vital sign measurements
- Electrocardiogram (ECG) parameters
- Laboratory measurements
- Columbia Suicide Severity Rating Scale (C-SSRS).

8.2.2. Review of the Safety Database

Overall Exposure

Overall, subjects received either one, 60-hour IV infusion of double-blind brexanolone or placebo or open-label brexanolone (depending on their time of enrollment relative to the implementation of Protocol Version 4 (final version)). The dosing regimen utilized in Study 547-PPD-304 is identical to the FDA-recommended dosing regimen in adults. See the Treatment Compliance subsection under Section 8.1.2 for information regarding the proportion of subjects receiving the total brexanolone infusion. Among subjects receiving brexanolone treatment (both double-blind and open-label), only one subject (Subject ID: (b) (6)) had the infusion interrupted longer than 1 hour (infusion administered only for 30.5 hours) due to an AE.

Adequacy of the Safety Database

Given the limited sample size of subjects receiving placebo and brexanolone treatment, any comparisons of safety between treatment groups and across studies is purely descriptive.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

From a safety perspective, there are no issues regarding data integrity and submission quality.

Categorization of Adverse Events

The Applicant categorized AEs by system organ class and preferred terms using the Medical Dictionary for Regulatory Activities Version 23.0. The Applicant collected AEs as per the schedule of assessments provided in Table 3 in Section 8.1.1 of this review. The Applicant defined treatment-emergent adverse events (TEAEs) as AEs that occurred after the first administration of any study drug, regardless of causality. The Applicant considered laboratory abnormalities and changes in vital signs as AEs if they resulted in discontinuation or interruption of study treatment, required therapeutic medical intervention, or met protocol-specific criteria. The number and percentage of subjects with any AEs, drug-related AEs, AEs by severity (mild, moderate, and severe), serious AEs, AEs leading to discontinuation and AEs leading to death are summarized by treatment group.

Reviewer's Comment: The Applicant adequately described their AE monitoring approach, severity determinations, and mapping of verbatim-to-preferred terms. The Applicant's categorization of adverse events also aligns with their safety analysis of prior adult studies. Although the Applicant categorized excessive sedation and LOC as AESIs, this reviewer also included dizziness as an AESI due to high risk for evolving into sedation and LOC.
This reviewer grouped the following preferred terms into one combined term (infusion site reaction): infusion site pain, infusion site extravasation, infusion site inflammation, and infusion site swelling.

Routine Clinical Tests

The schedule of routine clinical tests is presented in Table 3 of this review. The scheduling of clinical tests appears adequate to support the review of clinical safety.

8.2.4. Safety Results

Deaths

The Applicant did not report any subjects that experienced an AE leading to death during the study period.

Serious Adverse Events

One subject (Subject ID: (b) (6)) who received open-label brexanolone experienced two serious AEs (SAEs), dizziness followed by a LOC, at approximately 24 hours after the start of the infusion. Approximately 1 hour prior to the event, the Applicant reported a nonspecified device infusion issue ("kink" in the infusion line), which was resolved without replacing the infusion

line. During and after the events, the Applicant did not report any abnormal oxygen saturation values based on pulse oximetry. Investigators interrupted the infusion immediately and restarted the infusion after the subject returned from the emergency room. The case narrative is summarized in Section 8.2.5.1. Given that the onset of both SAEs was proximal to an increase in the infusion rate (60 µg/kg/hr to 90 µg/kg/hr), causality assessments of the Applicant's case narratives suggests that the SAEs appeared to be related to the study medication.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant did not report any subjects that experienced an AE leading to either study drug discontinuation or study discontinuation.

Treatment Emergent Adverse Events and Adverse Reactions

A summary of the incidence of AEs occurring in subjects receiving double-blind brexanolone and placebo treatment and open-label brexanolone treatment is presented in Table 11. In general, the percentage of subjects reporting AEs was similar across all treatment groups. The most frequently observed AE (≥ 10%) in the total brexanolone group was dizziness (15%), infusion site reaction (15%), nausea (10%), and sedation (10%). Only one subject (Subject ID: (b) (6)) receiving open-label brexanolone experienced two moderate AEs of dizziness and LOC (see Section 8.2.5.1 for additional details). The Applicant described all sedation AEs as mild events. Evaluation of AESI onset suggest that all AESIs occurred within the first 48 hours after infusion initiation. Out of all subjects receiving concomitant antidepressant therapy, only one subject receiving concomitant sertraline experienced AEs of nausea and sedation.

Table 11: Incidence of Adverse Events among Subjects Receiving Double-blind and Open-label Treatment

Adverse Events[a,b]	Double-Blind Placebo (N=8)	Double-Blind Brexanolone (N=8)	Open-Label Brexanolone (N=12)	Total Brexanolone (N=20)
Subjects with one or more AEs	4 (50%)	3 (38%)	5 (42%)	8 (40%)
Dizziness	0	0	3 (25%)	3 (15%)
Infusion site reaction	2 (25%)	2 (25%)	1 (8%)	3 (15%)
Nausea	1 (13%)	1 (13%)	1 (8%)	2 (10%)
Sedation	0	1 (13%)	1 (8%)	2 (10%)
Headache	0	0	1 (8%)	1 (5%)
Migraine	0	0	1 (8%)	1 (5%)
Loss of consciousness	0	0	1 (8%)	1 (5%)
Upper respiratory tract infection	0	1 (13%)	0	1 (5%)
Localized infection	1 (13%)	0	0	0
Weight decreased	1 (13%)	0	0	0

Source: Reviewer-created using Applicant's adae.xpt dataset
[a]Subjects only counted once for any given event (classified by preferred term), regardless of the frequency of the event
[b]Infusion site reactions includes infusion site pain, infusion site extravasation, infusion site inflammation, and infusion site swelling

Reviewer's Comment: Overall, the incidence of AEs and AESI (i.e., dizziness (15%), sedation (10%), and loss of consciousness (5%)) and the timing of AESIs (during the infusion period) were consistent with previously reported safety findings in adults (dizziness (12%), sedation (15%), and loss of consciousness (4%)). Similar to adult subjects, all adolescent subjects that

experienced sedation and LOC recovered. The Applicant did not report any new AEs that were not previously observed in adult trials. Given that all subjects received the same target dose, a dose-response analysis for AEs was not feasible.

Laboratory Findings

The Applicant collected laboratory measures at screening, Hour 72, and at Day 14. No subjects experienced AEs related to serum chemistry or hematology results.

Potentially clinically significant values in serum chemistry included: one subject (5%) in the total brexanolone group with a post-baseline measurement of alkaline phosphatase (ALP) > 2 x the upper limit of normal at Hour 72, which decreased by Day 14; one subject (5%) in the total brexanolone group and one subject (13%) in the double-blind placebo group with low glucose (< 2.9 mmol/L); and one subject (5%) in the total brexanolone group with high phosphate (> 1.94 mmol/L). No subjects had liver function abnormalities that met the definition for Hy's Law.

Potentially clinically significant values in hematology parameters included: three subjects (15%) in the total brexanolone group and two subjects (25%) in the double-blind placebo group with low hematocrit (< 0.345); and two subjects (10%) in the total brexanolone group and one subject in the double-blind placebo group (13%) with low neutrophils (< 1.5 x 10^9/L).

Vital Signs

The Applicant collected vital sign assessments at baseline, throughout the infusion period, and at Hour 72, Day 7, and Day 14. No subjects experienced an AE related to changes in any vital sign measure. Potentially clinically significant changes in vital signs included: one subject in the total brexanolone group (5%) with increased systolic blood pressure (SBP > 10 mmHg) when moving from a supine to standing position; three subjects in the total brexanolone group (15%) with low heart rate (< 40 bpm) and SBP (< 90 mmHg); two subjects in the total brexanolone group (10%) and one subject in the double-blind placebo group (13%) with increased (> 20 mmHg) diastolic blood pressure (DBP) relative to baseline; and six subjects in the total brexanolone group (30%) and three subjects in the double blind placebo group (38%) with decreased (> 20 mmHg) DBP relative to baseline. More than 80% of potentially clinically significant changes in vital signs occurred within the 60-hour infusion period.

Electrocardiograms (ECGs)

The Applicant collected ECG data at baseline, Hour 72, and at Day 14. The Applicant did not report any clinically significant changes in any of the ECG parameters. Only one subject in the total brexanolone group (5%) had a potentially clinically significant QTcF with a maximum increase from baseline between > 30 and 60 msec.

Reviewer's Comment: Overall, changes in laboratory measures, vital signs, and ECG parameters associated with brexanolone treatment did not lead to any associated symptoms or adverse events. Analysis of pulse oximetry values and respiratory rate also suggested no consistent

pattern with AESIs. Results from study 547-PPD-304 do not suggest any new cardiovascular safety signals with brexanolone treatment in adolescents.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Loss of Consciousness

The Applicant only reported one subject that experienced moderate dizziness followed by LOC. A detailed summary of the case narrative is provided below:

Patient (b) (6) was a 16-year-old, African American female with a medical history of ongoing PPD. Prior and concomitant medications included medroxyprogesterone acetate for contraception (no antidepressant use reported).

On Study Day 2 (24 hours after the start of the infusion) and at the beginning of the 90 µg/kg/hour infusion, the subject had a heart rate of 92 bpm, blood pressure of 92/69 mmHg, and oxygen saturation of 98%. At 2 minutes after the start of the 90 µg/kg/h infusion rate, the subject experienced the event of dizziness of moderate severity. After 2 minutes (4 minutes since the start of the 90 µg/kg/hr infusion rate), the subject then experienced LOC of moderate severity. At the time of LOC, investigators immediately stopped the infusion, and called emergency medical services. The subject regained consciousness within 30 minutes from the onset of the event.

The Applicant described the event as having occurred following an unspecified device infusion issue (the infusion pump alarmed, was stopped and then restarted at approximately Hour 23). During and after the event, the Applicant did not report any abnormal oxygen saturation values. On Study Day 3, investigators restarted the study drug with the dose tapering schedule starting with 60 µg/kg/hour for 2:25 minutes and 30 µg/kg/hour for 4 hours. The Applicant did not report a recurrence of the AE or any additional AEs.

Reviewer's Comment: Given the occurrence of a single event, the relationship between LOC, the timing and exposure of brexanolone, and oxygen saturation was not characterized. Although the small sample size limits the interpretation of the true incidence of LOC in the adolescent population, the observed incidence (5%) is similar to the pooled incidence (4%) across all adult trials evaluating brexanolone. The reported time to full recovery (30 minutes) was also within the observed range in adults (15 to 60 minutes) experiencing LOC. Because the events are sudden, unpredictable, and require intervention (i.e., stopping the infusion), administration of brexanolone in adolescents will also require constant monitoring for the safety of the patient and her infant, as described in the Zulresso REMS program.

8.2.5.2. Suicidal Ideation and Behavior

At baseline, two subjects (10%) in the total brexanolone treatment group reported positive suicidal ideation that subsequently dissipated after treatment. No subjects experienced positive SI/B at any timepoint during the study period.

8.2.6. Safety Analyses by Demographic Subgroups

Given the limited sample size and the lack of demographic differences (e.g., age, race, region), the Applicant did not report (nor did the Division conduct) any subgroup safety analyses.

8.2.7. Specific Safety Studies/Clinical Trials

The Applicant did not submit any additional studies to substantiate the safety profile in adolescents.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The application did not include new human carcinogenicity studies.

Human Reproduction and Pregnancy

The application did not include new human reproduction or pregnancy data.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The application did not include any formal assessments related to drug abuse potential, withdrawal, and rebound.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

In March 2022, the Applicant submitted a Periodic Adverse Drug Experience Report (#12) and the Zulresso REMS: 3-year Assessment Report. The Applicant noted that a total of 545 patients received treatment with brexanolone since becoming commercially available in June 2019. Even though brexanolone is not authorized for marketing for the treatment of PPD in adolescents, the Applicant reported six subjects between 0 to 17 years of age that received brexanolone. The Applicant only specified the treatment indication for two subjects: status epilepticus (6-year-old) and treatment-resistant depression (15-year-old). Based on post-infusion forms collected during the 3-year postmarketing period, the Applicant described four cases (1.8%) of excessive sedation (adults only) and zero cases of LOC. A review of the Applicant's summary of individual case safety reports indicates that the most frequently reported AEs included dizziness, somnolence, infusion site reactions, drug ineffective, and product administration error.

Expectations on Safety in the Postmarket Setting

Healthcare providers will administer brexanolone to adolescents with PPD under the Zulresso REMS program. The Applicant did not submit any major REMS modifications (see separate Division of Risk Mitigation review). The Applicant's annual REMS assessment plan will include

program operation and performance data, summary of compliance, utilization data, REMS enrollment statistics, healthcare setting knowledge assessments, and safety surveillance (i.e., post-infusion forms documenting cases of sedation and LOC).

Reviewer's Comment: Safety data collected during the postmarketing period appears consistent with the Applicant's premarketing clinical trial data in adults and adolescents. Although the incidence of excessive sedation and LOC is rare, the administration of brexanolone under the Zulresso REMS program will ensure appropriate reporting of future cases.

8.2.10. Integrated Assessment of Safety

The Applicant only submitted a single study (547-PPD-304) to evaluate brexanolone's safety profile in adolescent. The observed safety profile in adolescents was generally consistent with adults. Based on safety data collected in adults, the Agency's major safety concern is the possibility of LOC during the infusion period. Although the observed incidence of LOC was similar between adults and adolescents (5% versus 4%, respectively), the small sample size of adolescent subjects receiving brexanolone limits the precision of this risk comparison. Evaluation of brexanolone exposures, onset of event relative to drug administration, use of concurrent medications, medical history, and patient characteristics across adult and adolescent studies suggest no potential predictors for excessive sedation or LOC. Therefore, to mitigate the risk of AEs associated with sedation and sudden LOC, brexanolone administration in adolescents will also adhere to the requirements in the Zulresso REMS program.

8.3. Statistical Issues

Given that the final study design consisted of only a single, open-label brexanolone treatment arm, the Applicant did not propose a formal statistical analysis plan. The results included in this review are strictly descriptive and limited due to the observed sample size.

8.4. Conclusions and Recommendations

Study 547-PPD-304 adequately fulfills PREA PMR 3535-5 to evaluate safety, tolerability, and PK data in adolescent females 15 to less than 18 years of age with PPD. The Division previously acknowledged the Applicant's reported difficulties in conducting an adequate and well-controlled trial to evaluate the safety and effectiveness of brexanolone in adolescents with PPD (i.e., enrollment challenges due to disease prevalence, disease severity criteria, and Zulresso REMS requirements). Although confirmation of full extrapolation of efficacy from adults to adolescents has not yet been established for PPD, the Division recognizes that PPD is clinically similar (i.e., similar diagnostic and monitoring criteria, phenomenology, prognosis, duration of illness, and potential treatment options) in both populations and accepts partial extrapolation of efficacy for PPD for adolescents 15 to 17 years of age. Therefore, in this instance, the Division only required one independent, open-label study (Study 547-PPD-304) to provide supportive evidence of efficacy, safety, and PK data for labeling in adolescents for comparison with adults.

A descriptive analysis of the study results suggests that brexanolone exhibits a nominally consistent effect on safety and efficacy in adolescents relative to adults. In addition to the Division's understanding that PPD is similar between adults and adolescents, the proposed adolescent dosing regimen achieved similar brexanolone exposures that also elicited a similar treatment effect and safety profile. Therefore, given the Agency's acceptance of partial extrapolation of efficacy based on clinical evidence of disease similarity and results from prior adult studies and the Applicant's supportive evidence from Study 547-PPD-304, brexanolone is safe and effective for the treatment of PPD in adolescents 15 to 17 years of age.

9 Advisory Committee Meeting and Other External Consultations

The Agency did not refer this marketing application to an advisory committee for review. This drug is not first in its class. The clinical trial designs are similar to those for the adult indication. Evaluation of the data did not raise significant, unexpected safety or efficacy issues. Therefore, the Agency concluded that outside expertise was not necessary.

10 Pediatrics

Study 547-PPD-304 fulfills PREA PMR 3535-1 and partially satisfies the amended pediatric WR. We continue to agree to a waiver for studying brexanolone in patients below 15 years of age due to impracticability of studying this population given the very limited prevalence of PPD in that age group.

11 Labeling Recommendations

The list below provides a summary of changes to the proposed product label:

- Section 1 (Indication and Usage): indication modified to patients 15 years of age and older
- Section 6.1 (Clinical Trials Experience): reporting of safety findings from Study 547-PPD-304
- Section 8.4 (Pediatric Use): described supportive evidence to establish pediatric use
- Section 12.3 (Pharmacokinetics): comparison of the PK profile in adolescent to adults with PPD

12 Risk Evaluation and Mitigation Strategies (REMS)

There is an approved REMS for Zulresso to mitigate the risk of serious harm resulting from excessive sedation and sudden loss of consciousness during Zulresso infusion. The most recently approved REMS (approved on December 13, 2019) for Zulresso includes elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. The REMS requirements will also apply to adolescent patients 15 to 17 years of age.

13 Postmarketing Requirements and Commitment

The Division will not issue any postmarketing requirements or commitments for this application. If concerning postmarket safety findings arise in adolescents with PPD, the Division will address them as warranted.

14 Signatory Comments

This review reflects my edits and feedback. I agree with the findings as described by the review team and concur with the approval decision.

15 Appendices

15.1. References

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15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 547-PPD-304

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 168		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

15.3.1. Population Pharmacokinetic Modeling

Report 547-ppd-304-poppk.pdf (submitted to sequence 0090, module 5335) is titled "Pharmacokinetic Analysis of Brexanolone in Adolescent PPD Subjects in Study 547-PPD-304" and describes the analyses of PK data collected from 20 subjects treated with Brexanolone in the phase 3 Study 547-PPD-304. The phase 3 study 547-PPD-304 (referred to hereafter as Study 304) is titled "A Multicenter, Open-Label Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Brexanolone in the Treatment of Adolescent Female Subjects with Postpartum Depression." In Study 304, 28 pediatric PPD subjects were randomized to receive placebo (n=8) or brexanolone (n=20). The subjects randomized to brexanolone received the following regimen, continuously, over the span of 3 days:

- 0 to 4 hours: 30 μg/kg/hour
- 4 to 24 hours: 60 μg/kg/hour
- 24 to 52 hours: 90 μg/kg/hour
- 52 to 56 hours: 60 μg/kg/hour
- 56 to 60 hours: 30 μg/kg/hour

Data Description

PK data were collected from all 20 subjects treated with brexanolone in Study 304. PK samples were acquired prior to treatment and at 4, 8, 12, 24, 30, 36, 48, 60, and 72 hours after infusion initiation. The dataset used for PK model includes 163 PK samples from 20 subjects (all of which are pediatric PPD subjects from Study 304; the PPK analyses did not include any adult patients). The analyses were performed using the NONMEM software version 7.4.3.

Analysis Description

The Applicant utilized the final model developed for adult PPD patients to predict the PK for the 20 pediatric PPD patients. In other words, the adult PPD PK model parameter estimates were included as the initial parameter estimates with MAXEVAL=0 and the POSTHOC option in the NONMEM control stream. The Applicant generated diagnostics plots and a visual predictive check to assess how well the adult PPD PK model described the pediatric PPD patient PK. The Applicant also used the adult PPK model to predict values of CL, Vss, AUCinf, and Cmax for the pediatric PPD population.

Details on the final adult PPD PK model can be found in section 22.4.2 of the Unireview for NDA 211371 archived on March 19, 2019. A summary of the final adult PPD PK model parameters that were applied in these analyses is shown below.

Model Description

Structural Model: The base structural model is a 2-compartment model. PK parameters include CL, V1, V2, and Q.
Allometric Scaling: CL, V1, Q, and V2 had allometric scaling applied using body weight normalized to 82.9 kg, the population median body weight in the adult PPD patient PK dataset.
Inter-individual variability: exponential
Residual variability: proportional error model
Covariates: No covariates were included in the final model.

The final model parameter estimates for the PK model in adult PPD patients are shown in Table 12.

Table 12: PK Parameter Estimates for Final PK Model (Run 1038) in Adult PPD Patients

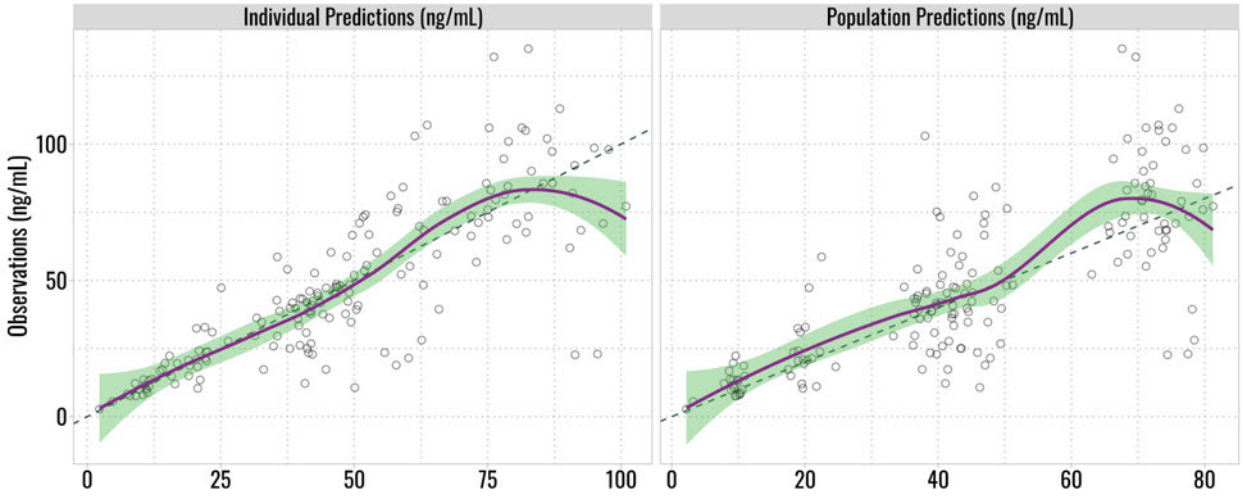
Parameter	Alias	Estimate	Relative SE (%)	95% CI
θ_1	CL ($L \cdot h^{-1}$)	89.8	1.8	(86.6 - 93.1)
θ_2	V_1(L)	117.	22.9	(64.6 - 170)
θ_3	Q ($L \cdot h^{-1}$)	37.9	7.7	(32.2 - 43.6)
θ_4	V_2 (L)	470.	5.9	(415 - 524)
θ_5	Proportional residual variability	0.272	4.1	(0.25 - 0.294)
$\omega_{1.1}$	ω^2_{CL}	0.0435	21.3	(0.0254 - 0.0617)
$\omega_{2.1}$	$\omega^2_{CL,V1}$	0.106	25.9	(0.0521 - 0.159)
$\omega_{2.2}$	ω^2_{V1}	1.15	28.1	(0.515 - 1.78)

Source: Sequence 0001, 547-pop-pk.pdf, page 37 of 151.

The IIV for Cl and V1 were estimated to be 21.1% CV and 147% CV, respectively, for the adult PPD model.

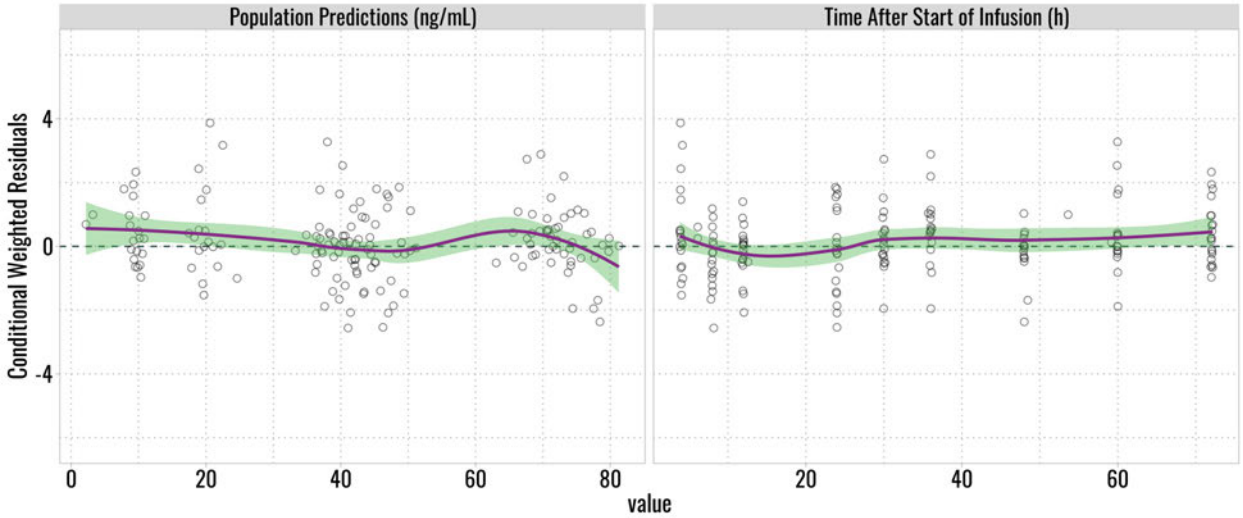
The final run for the pediatric PPD patients is run2 (run2-mod.txt in sequence 0094). Diagnostic plots for run2 are shown in Figure 6, Figure 7, and Figure 8.

Figure 6: Observed PK Values (DV) versus Individual Predicted PK Values (IPRED) for Model Run2 in Pediatric PPD Patients



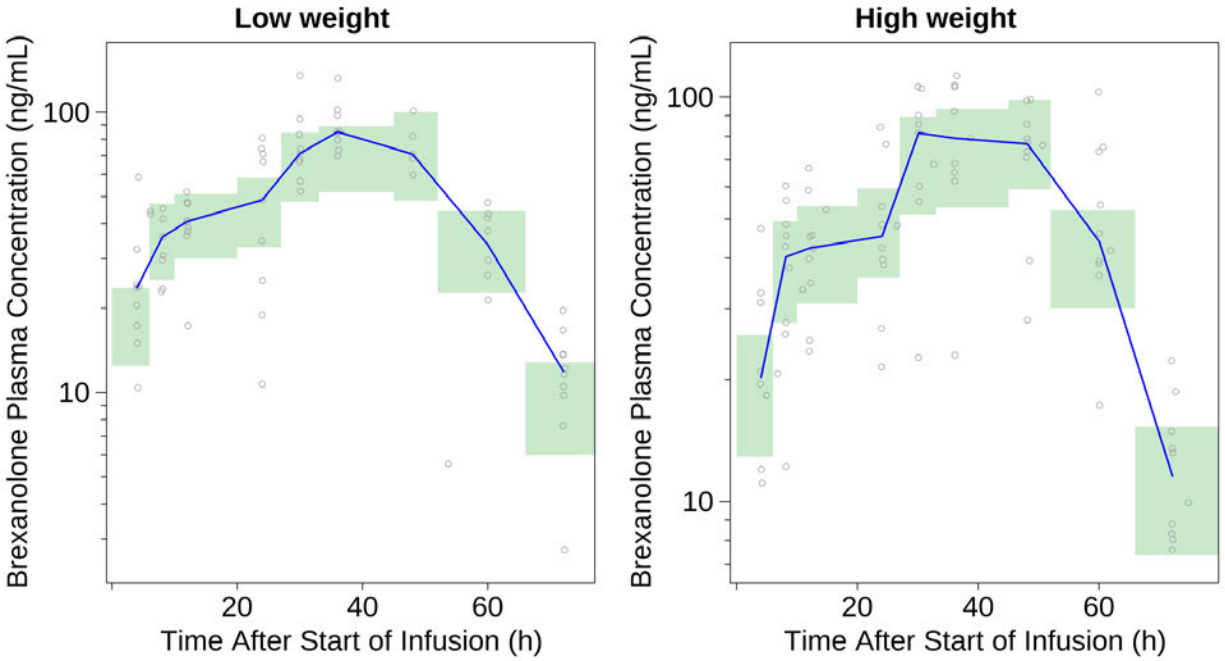
Source: Sequence 0090, 547-ppd-304-poppk.pdf, page 31 of 76.

Figure 7: Conditional Weighted Residuals (CWRES) versus Individual Predicted PK Values (IPRED) for Model Run2 in Pediatric PPD Patients



Source: Sequence 0090, 547-ppd-304-poppk.pdf, page 32 of 76.

Figure 8: Visual Predictive Check (VPC) for Pediatric Subjects in Study 304 by Weight



The weight range in the n=20 pediatric subjects that received Brexanolone in Study 304 is 43.9 to 92.6 kg, median value of 68.3 kg. The low weight group refers to 43.9 to 68.3 kg. The high weight group refers to weights > 68.3 kg to 92.6 kg.

Source: Sequence 0090, 547-ppd-304-poppk.pdf, page 32 of 76.

Reviewer comment: The VPC model does not indicate any worsening of performance of the model above 68.3 kg versus below 68.3 kg within the 20 pediatric PPD subjects.

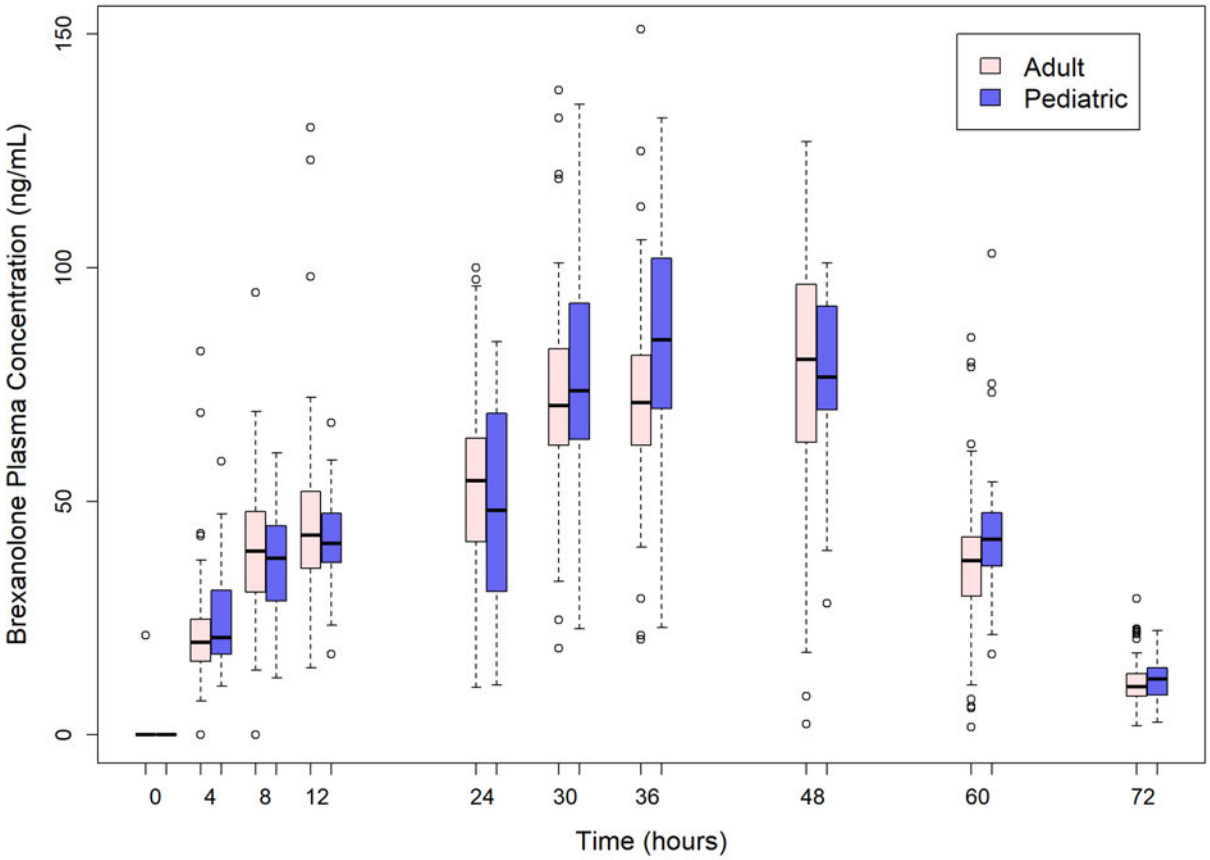
Using the model, the Applicant derived (predicted) geometric mean $AUC_{0\text{-}inf}$ of 4000 ng*h/mL (15% CV), geometric mean C_{max} of 82.4 ng/mL (14.7% CV), mean CL of 73.24 L/h (23.1% CV), and mean volume of distribution at steady-state (V_{dss}) of 529.4 L (30.8% CV) for the pediatric PPD patients. These derivations were made in run3 (run3-mod.txt, sequence 0094).
The Sponsor concludes that the PK of brexanolone in adolescent PPD patients is comparable to the PK in adult PPD patients. The Applicant cites these analyses as part of their overall conclusion that the PK, safety, and efficacy assessment in Study 547-PPD-304 are similar to the results from the studies that supported the initial Zulresso approval for the treatment of PPD. As such, the Applicant proposes to apply the same weight-based dosing in adolescent pediatric PPD patients as is approved for adult PPD patients.

Reviewer comment: The diagnostic plots do not demonstrate any obvious signs of bias with respect to individual predicted value or body weight. The Applicant's analyses do not reveal any obvious inconsistencies between the observed versus predicted PK data for pediatric PPD patients. The estimates of the mean CL and mean V_{dss} in pediatric patients (73.24 L/h and 529.4 L, respectively) are plausible in the context of the adult values (89.8 L/h and 117 L + 470 L = 587 L, respectively). The estimates of geometric mean C_{max} and AUC_{inf} in pediatric PPD patients (82.4

*ng/mL (14.7% CV) and 4000 ng*h/mL (15.5% CV), respectively) are comparable to adult PPD patients (78.9 ng/mL (21% CV) and 3820 ng*h/mL (23% CV), respectively; sequence 0001, module 5335, 547-pop-pk.pdf, page 46 of 151, Table 11).*

The Applicant collected PK in pediatric PPD patients from study 304 that received an identical weight-based dosing regimen as was administered in multiple studies of adult PPD patients. In addition, all the PK sampling times for the pediatric PPD patients were also applied to the adult PPD patients. As such, to provide a side-by-side PK comparison of adult PPD patients with pediatric PPK patients for the same weight-based dose regimen, the reviewer generated a plot showing a comparison of the distribution of observed PK from pediatric PPD patients with the distribution of observed PK from adult PPD (see Figure 9).

Figure 9: Observed Brexanolone Plasma Concentration over Time by Age Group



The box plots represent the distribution of PK samples across the respective populations (adult or pediatric) at each nominal timepoint. The Adult group (light shade of red) consists of the pooled observed PK data from Studies 108 (Phase 1; n=12), 201 (Phase 2a; n=4), 202A (Phase 2; n=10), 202B (Phase 3; n=41), and 202C (Phase 3; n=51) from a total of n=118 subjects. All subjects in the adult PK dataset were PPD patients except for Study 108 which enrolled healthy volunteers. The Pediatric group (dark shade of blue) is the observed PK data from n=20 subjects in Study 304. Both the Adult group as well as the Pediatric group in this figure received the following dosage regimen:

a) 0 to 4 hours: Initiate with a dosage of 30 µg/kg/hour
b) 4 to 24 hours: Increase dosage to 60 µg/kg/hour
c) 24 to 52 hours: Increase dosage to 90 µg/kg/hour
d) 52 to 56 hours: Decrease dosage to 60 µg/kg/hour

e) 56 to 60 hours: Decrease dosage to 30 µg/kg/hour

The approved dosing allows for a reduction rate during 24 to 52 hours from 90 µg/kg/hour to 60 µg/kg/hour in subjects who do not tolerate 90 µg/kg/hr. However, as all subjects in study 304 received 90 µg/kg/hr from 24 to 52 hours, then this plot included only subjects (adult or pediatric) that received the 90 µg/kg/hr dose level during this time frame. The data used to generate this figure originated from the input file for NONMEM analyses, nm_pk_all.xpt, submitted to → 0094\m5\datasets\547-ppd-304-poppk\analysis\legacy\datasets.

The results presented in Figure 9 suggest that there is no consistent difference between adult and pediatric patients. The timepoints with apparent differences between adult PK and pediatric PK (i.e., 24 hours and 36 hours) are not consistent in that they differ in sign (i.e., adult PK can be higher than pediatric PK at some times, and pediatric PK can be higher than adult PK at some times) and is likely due to random chance rather than a real difference between these two populations. Overall, based on the Applicant's analyses and the comparison of observed data in Figure 9, the PK in adult PPD patients is comparable to the PK in pediatric PPD patients down to 15 years of age.

At the time of this submission, the Brexanolone label recommends an infusion rate of 90 µg/kg/hr during the 24-to-52-hour time frame but allows reduction to 60 µg/kg/hr for subjects who do not tolerate 90 µg/kg/hr. No pediatric subjects received the 60 µg/kg/hr infusion rate during the 24-to-52-hour time frame in study 304. However, based on the Applicant's analyses as well as the reviewer's analyses, for the scenario of the 60 µg/kg/hr infusion rate from 24 to 52 hours, pediatric PPD patients down to 15 years of age are expected to present comparable PK to adult PPD patients. As such, the proposal to treat pediatric PPD patients down to age 15 years using the same dosing regimen as is approved for adults is acceptable from a PK perspective.

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