FDA Briefing Document

Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting

November 2, 2018

Topic: New Drug Application 211371/New Drug Application, brexanolone for the Treatment of Postpartum Depression

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought New Drug Application 211371, brexanolone for the treatment of postpartum depression, to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and, instead, is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1 DIVISION DIRECTOR MEMORANDUM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 4, 2018

FROM: Mitchell V. Mathis, M.D.
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Division of Psychiatry Products, HFD-130

TO: Members of the Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee

SUBJECT: November 2, 2018 Meeting of the PDAC

Introduction:

Brexanolone is a proprietary analogue of the endogenous human hormone allopregnanolone. It is a new molecular entity not currently marketed anywhere in the world for any indication. Brexanolone's proposed indication is treatment of postpartum depression (PPD). Its mechanism of action is unknown, but it appears to be a positive allosteric modulator of $GABA_A$ receptors with a binding site distinct from benzodiazepines. It has been administered as a 60-hour intravenous infusion including a titration to a target dose of 90 μg/kg/h and a taper. The Applicant also studied a 60-hour infusion with a target dose of 60 μg/kg/h in one study and showed effectiveness at that dose.

PPD is a major depressive episode with onset during pregnancy or within 4 weeks of delivery. As with other forms of depression, it is characterized by sadness and/or anhedonia and may present with symptoms such as cognitive impairment, feelings of worthlessness or guilt, or suicidal ideation. Because of the risk of suicide, PPD is considered a life-threatening condition. It also has profound negative effects on the maternal-infant bond and later infant development. Although there are approved antidepressant medications, none is specifically approved for PPD and there is little evidence of their efficacy for this condition.

Evidence of brexanolone's efficacy was derived from three studies: 547-PPD-202A, 202B, and 202C. The primary efficacy endpoint in these studies was change from baseline on the Hamilton Depression Scale at 60 hours after the start of the brexanolone infusion. In all three trials, brexanolone had a greater effect on the HAM-D than placebo.

The Agency's major safety concern is the observed loss of consciousness/pre-syncope (LOC) during the infusion (6 of 140 women exposed to brexanolone). After examining dose, timing of dose, blood level, concurrent medications, available medical history, and patient characteristics (e.g., age, body mass index) we observed no relationships of these variables to LOC events. Because LOC can be abrupt, and there is no way to predict the event, the Agency did not feel the risk could be mitigated solely through labeling. We therefore recommend implementing a risk evaluation and mitigation strategy (REMS) to improve the safety of the drug product. Aside from the risk of LOC, brexanolone appeared reasonably well-tolerated.

This PDAC meeting will focus on issues critical to the Center for Drug Evaluation and Research (CDER) assessment of whether brexanolone is safe and effective.

The following are points under consideration:

1. Has substantial evidence been presented by the Applicant to support a claim of effectiveness for brexanolone for the treatment of postpartum depression?

2. There is evidence that both a 60 μg/kg/h and a 90 μg/kg/h dose (after 24 hours) are effective. Which dose should be the recommended dose?
    - Start at 90 μg/kg/h with the option to decrease the dose to 60 μg/kg/h based on tolerability
    - Start at 60 μg/kg/h with the option to increase the dose to 90 μg/kg/h based on response

3. Has the applicant adequately characterized the safety profile of brexanolone for the treatment of postpartum depression? Do you believe the loss-of-consciousness events have been characterized sufficiently to enable safe use of brexanolone?

4. Given the efficacy as presented, when used in a certified facility by qualified staff and as outlined in the FDA's proposed REMS, do the benefits outweigh the risks of brexanolone for the treatment of PPD?

5. Discuss whether the FDA's proposed REMS will ensure safe use of brexanolone. If no, please provide what additional safeguards are needed.

6. What, if any, additional data are needed pre- or post-approval to support safe use of brexanolone at home and address outstanding issues? Please be clear whether you believe these data should be required prior to approval.

2 Objective of Meeting and Overview of Development Program

2.1. Purpose

The purpose of this Advisory Committee meeting is to obtain input from the committee on whether data provided by the applicant support a favorable benefit-risk profile of brexanolone that would support approval.

2.2. Postpartum Depression

Post- or peripartum depression (PPD) is a major depressive episode with onset during pregnancy or within 4 weeks of delivery. As with other forms of depression, it is characterized by sadness and/or anhedonia and may present with symptoms such as cognitive impairment, feelings of worthlessness or guilt, or suicidal ideation (see Table 1 for the diagnostic criteria for a major depressive episode). Indeed, the most common cause of maternal death after childbirth in the developed world is suicide.[1] A depressive episode at this time in a woman's life can not only deprive her of the enjoyment of a new infant, but can have serious effects on the maternal-infant bond and later infant development. Estimates place the prevalence of PPD in the United States at approximately 12% of births.[2]

Table 1. Diagnostic Criteria for a Major Depressive Episode.[3]

A	Five or more symptoms for 2 weeks (one of which must be 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
B	Symptoms cause clinically significant distress or functional impairment	
C	The episode is not attributable to the physiological effects of a substance or another medical condition	
D	The episode is not better explained by a psychotic illness	
E	There has never been a manic or hypomanic episode	

PPD is symptomatically indistinguishable from an episode of major depression. However, the timing of its onset has led to its recognition as a potentially unique illness.

There are no drugs specifically approved to treat PPD. Drugs approved for the treatment of major depression are used to treat PPD, but data on their effectiveness is limited. Non-drug treatments such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and psychotherapy are also used. All available depression treatments show a delayed effectiveness response. Antidepressant drugs take 4 to 6 weeks to demonstrate efficacy.

Similarly, a course of ECT is typically twice per week for 4 or 5 weeks, rTMS is given daily for 4 to 6 weeks, and psychotherapy usually involves 8 to 20 weekly sessions.

Many hormones are neuroactive. Because of the changes in hormone concentrations during pregnancy, they have been an attractive target for PPD investigations. The concentration of allopregnanolone, an endogenous derivative of progesterone, increases during pregnancy, reaches a peak during the third trimester, then abruptly falls after delivery. As recently reviewed by McEvoy and colleagues,[4] allopregnanolone is a potent GABA-ergic regulator. At low concentrations, it acts as a positive allosteric modulator at synaptic and extrasynaptic $GABA_A$ receptors—at high concentrations, it can directly stimulate them without GABA. Whereas benzodiazepines increase chloride channel opening frequency and barbiturates increase the duration of chloride channel opening, allopregnanolone does both.

As allopregnanolone levels rise during pregnancy, $GABA_A$ receptors are down-regulated. Nevertheless, animal models have shown that the receptors return to previous levels within 48 hours of delivery. Because total allopregnanolone levels have not consistently correlated with PPD, it is possible that the symptoms are more closely related to impairment in peripartum GABA receptor up- or down-regulation (or even changes in receptor subunits) and not necessarily to the abrupt decrease in allopregnanolone concentrations.

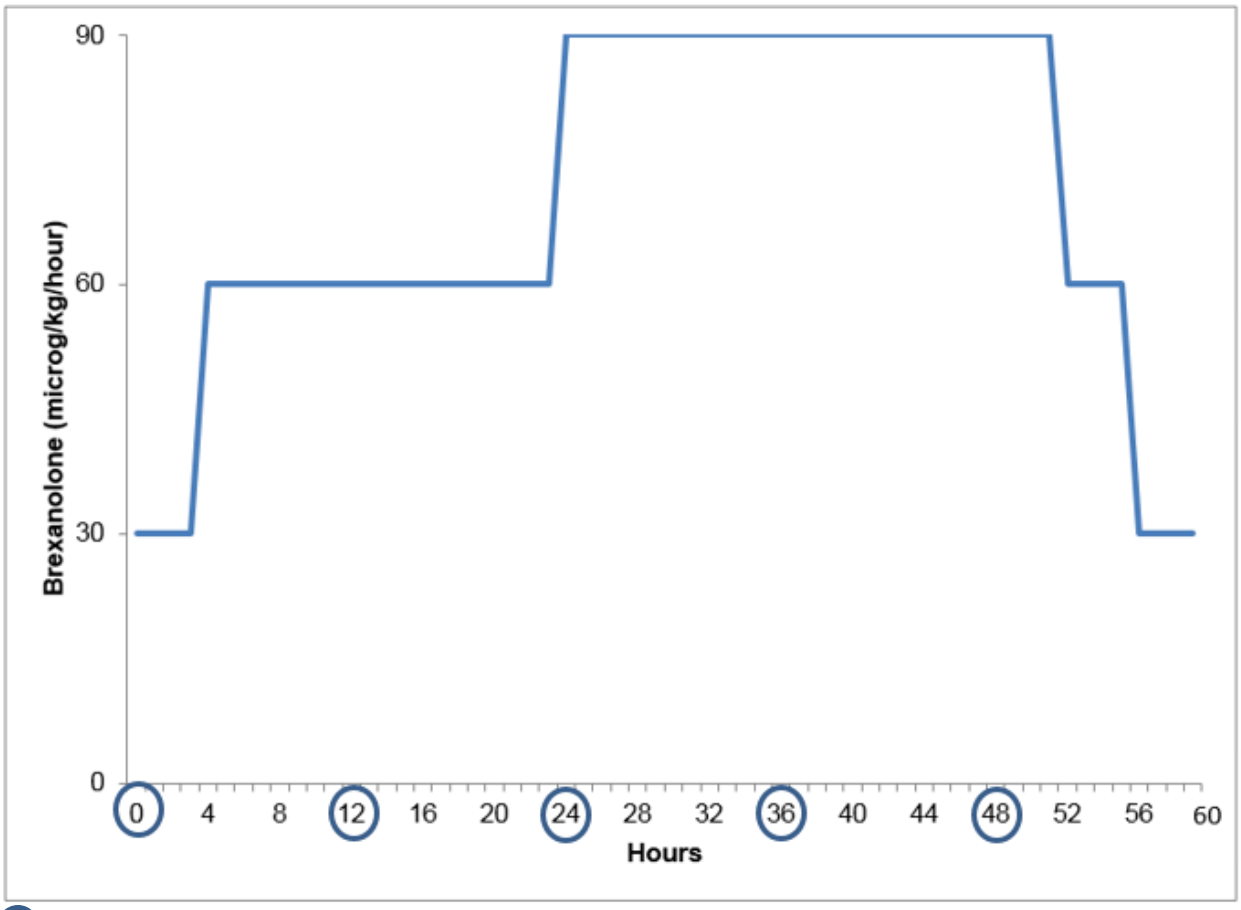
The Applicant hypothesized that, in women experiencing PPD, returning the allopregnanolone concentration to that of the third trimester would ameliorate symptoms. Brexanolone dosing was, therefore, based on returning women to pre-delivery levels of allopregnanolone. The initial titration was intended to allow women to develop tolerance to the associated sedation. The taper was meant to prevent withdrawal symptoms from a GABA-active agent. Because the Applicant believed the dose was well-tolerated, they did not try to determine the minimally effective dose. Because the dose was effective, they did not try to determine whether higher doses would be more effective.

2.3. **Product Under Review**

Brexanolone (Applicant code name SAGE-547) is a proprietary analogue of the endogenous human hormone allopregnanolone. It is a new molecular entity (NME) with the proposed indication of treatment of PPD (once per episode). Although its mechanism of action is unknown, it appears to be a positive allosteric modulator of $GABA_A$ receptors with a binding site distinct from benzodiazepines. Brexanolone is available as a 5mg/mL solution in sulfobutyl ether beta-cyclodextrin (Captisol), which is administered as an intravenous infusion over 60 hours. Once mixed, the infusion is only stable for 12 h at room temperature and 24 h refrigerated. The dose is weight- and time-based as follows (see also Figure 1):

- 4 hours at 30 μg/kg/hour
- 20 hours at 60 μg/kg/hour
- 28 hours at 90 μg/kg/hour
- 4 hours at 60 μg/kg/hour
- 4 hours at 30 μg/kg/hour

Figure 1. Dose and Timing for Brexanolone Administration.



◯=New infusion bag required.

2.4. Regulatory Background

Brexanolone has not been approved or marketed in the United States. On June 17, 2014, the Sponsor submitted Investigational New Drug (IND) application 122279 for brexanolone with the intention of providing documentation to support the initiation of a phase 2a study entitled, "An Open-Label Proof-of-Concept Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Sage-547 Injection in the Treatment of Adult Female Patients with Severe Postpartum Depression." The Division determined that the protocol was safe to proceed and sent the May Proceed letter on July 31, 2014.

Brexanolone was granted Breakthrough Therapy Designation on August 23, 2016, for the treatment of postpartum depression (PPD).

A meeting was held on November 2, 2016, with the Agency to discuss nonclinical and clinical development plans to support product approval.

On October 20, 2017, the Division communicated an Agreed Initial Pediatric Study Plan, which included plans to conduct a clinical study evaluating the efficacy, safety, tolerability, and

pharmacokinetics (PK) of brexanolone in adolescent females (age 15 to less than 18 years) with moderate to severe PPD.

On March 20, 2018, the Division communicated a Written Request to the Sponsor that included a required randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of brexanolone in adolescent females, 15 to less than 18 years of age, with PPD.

The Sponsor met with the Division on January 18, 2018, for a pre-NDA meeting to discuss the studies to be included in the NDA, content and format of the integrated summaries of safety and effectiveness, and content and search terms of the abuse liability package. The Sponsor then submitted the NDA on April 19, 2018.

In addition to PPD, brexanolone has also been studied as a potential treatment for essential tremor (IND 122280) and super-refractory status epilepticus (IND 117901).

Brexanolone has not been approved or marketed in any country.

2.5. Effectiveness of Brexanolone for Treatment of Postpartum Depression

2.5.1. 547-PPD-202 "Umbrella" Protocol

The Applicant used a central, "umbrella" protocol for a phase 2 study (202A) and two phase 3 studies (202B and 202C). These studies were randomized, double-blind, and placebo-controlled and were completed entirely in the United States (see Table 2). Brexanolone dosing was as previously described in Section 2.3. Infusions were administered in monitored settings (e.g., physician offices kept open overnight, overnight research centers); 15% received the infusion in a unit connected to a hospital. On-site health professionals varied from emergency medical technicians to nurses and physicians.

The primary efficacy endpoint for all three studies was the change from baseline on the Hamilton Depression Rating Scale (HAM-D) at Hour 60 (the end of the infusion). See Section 4: *Appendices* for the schedule of assessments for the 202 protocol.

Table 2. Studies Evaluated for Safety and Effectiveness.

Study 547-PPD-	Phase	NCT Number	Population Studied	Centers Enrolling Patients	N
202A	2	02614547	Severe PPD (baseline HAM-D ≥26)	4	21
202B	3	02942004	Severe PPD (baseline HAM-D ≥26)	32	138
202C	3	02942017	Moderate PPD (baseline HAM-D 20 to 25)	32	108

Important individual study differences were:

- Study 202B included an additional brexanolone arm (60 µg/kg/h).
- Studies 202A and 202B enrolled patients with severe PPD; Study 202C enrolled patients with moderate PPD.

Notable inclusion-exclusion criteria for all three studies were:

- 18 to 45 years
- Major Depressive Episode (MDE) starting during third trimester to as late as 4 weeks post-delivery
- Subjects enrolled within 6 months of delivery
- Excluded women with bipolar disorder, active psychosis, or a suicide attempt during index episode

Agency Comment: We encouraged the study of an additional dose arm and a study in PPD with moderate symptoms. The inclusion criteria differed slightly from the current DSM-5 PPD criteria (which allows the diagnosis of PPD if the depressive episode occurs at any time during pregnancy), but, considering brexanolone's initially proposed mechanism-of-action, this was appropriate.

2.5.2. **Study PPD-202A**

A summary of baseline demographic data is presented in Table 3.

Table 3. Demographic Characteristics, Study 202A.

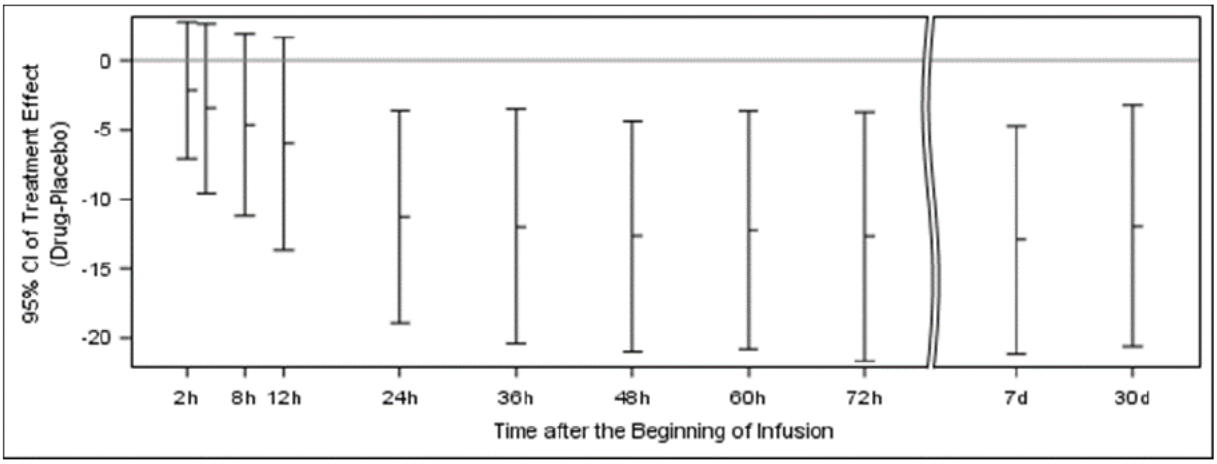
Characteristic	**Placebo** (n=11)	**Brexanolone 90 µg/kg/h** (n=10)
Age, years		
Mean (SD)	28.8 (4.6)	27.4 (5.3)
Median	28	27
Min, Max	22, 36	20, 40
Race, n (%)		
AA/Black	6 (55%)	7 (70%)
White	5 (45%)	3 (30%)
Ethnicity, n (%)		
Hispanic	0	0
Non-hispanic	11 (100%)	10 (100%)
Height, cm		
Mean (SD)	161.7 (6.7)	162 (7.1)
Median	162	164
Min, Max	151, 174	153, 175
Weight, kg		
Mean (SD)	77.0 (22.3)	86.7 (28.8)
Median	73.5	76.5
Min, Max	53.3, 122.6	49.7, 130.7
BMI, kg/m^2		
Mean (SD)	29.3 (7.8)	32.7 (9.9)
Median	28.2	30.5
Min, Max	21.0, 45.0	20.4, 47.1

The primary analysis result is summarized in Table 4. The time course of the treatment effect is graphically presented in Figure 2. Study 202A did not prespecify any secondary endpoints. Nevertheless, the placebo-adjusted least mean square change for the HAM-D at Day 30 was -11.9 (SE=4.1; $p<0.05$).

Table 4. Primary Efficacy Result, Study 202A.

	Placebo (n=11)	**Brexanolone 90 µg/kg/h** (n=10)
Mean score at Baseline (SD)	28.8 (1.99)	28.1 (1.29)
Mean Score at Hour 60 (SD)	19.7 (9.59)	7.5 (8.72)
LS Mean Change from Baseline (SE)	-8.8 (2.80)	-21.0 (2.94)
Placebo-subtracted Difference (95% CI)		-12.2 (-20.8, -3.7)
P-value		0.008

Figure 2. Least Square Mean Difference of Treatment Effect over Time.



Agency Comment: Although small, this study demonstrated a large brexanolone effect. Confidence intervals no longer overlapped baseline at 24 h and benefit appeared to continue at Day 30. Note that the full effect was present at 24 hours (at the 60 µg/kg/h dose).

2.5.3. **Study PPD-202B**

Study 202B included two brexanolone doses: 90 µg/kg/h and 60 µg/kg/h. Follow-up visits at Day 14 and 21 were added in an amendment. Therefore, earlier patients were not assessed at these time points and the sample sizes at these two visits are lower than the sample size at the other visits (Days 7, 30). The change from baseline in HAM-D total score at Day 30 was the prespecified secondary efficacy endpoint.

One-hundred-thirty-eight subjects were randomized into the study, 79 of whom received brexanolone and 43 of whom received placebo. Of the subjects who received study drug, nine discontinued the study early (one placebo, three brexanolone 60 µg/kg/h, five brexanolone 90 µg/kg/h). The intention-to-treat (ITT) population contains all 122 randomized subjects who

received brexanolone or placebo. Of the 122 subjects, 119 (97.5%) had a primary efficacy endpoint assessment (Hour 60) and 113 (92.6%) had the prespecified secondary endpoint assessment (Day 30). Baseline demographic data is presented in Table 5.

Table 5. Demographic Characteristics, Study 202B.

Characteristic	Placebo (n=43)	Brexanolone 60 µg/kg/h (n=38)	Brexanolone 90 µg/kg/h (n=41)
Age, years			
Mean (SD)	27.2 (6.1)	27.7 (6.5)	27.5 (6.1)
Median	27	27	27
Min, Max	18, 42	18, 42	19, 42
Race, n (%)			
AA/Black	15 (35%)	12 (32%)	8 (19%)
Am Indian/Alaskan Native	1 (2%)	0	0
Asian	0	0	1 (2%)
Native Hawaiian/Pacific Islander	0	0	1 (2%)
White	27 (63%)	25 (66%)	29 (70%)
Other	0	1 (3%)	2 (5%)
Ethnicity, n (%)			
Hispanic	7 (16%)	3 (8%)	7 (17%)
Non-hispanic	36 (84%)	35 (92%)	34 (83%)
Height, cm			
Mean (SD)	165.4 (8.0)	164.1 (6.5)	164.3 (6.7)
Median	164.4	165.0	163.0
Min, Max	145.0, 180.3	147.3, 178.5	149.8, 180.3
Weight, kg			
Mean (SD)	81.8 (23.4)	87.1 (20.8)	80.7 (20.5)
Median	74.9	85.5	82.7
Min, Max	48.1, 142.3	48.5, 134.7	52.2, 125.0
BMI, kg/m^2			
Mean (SD)	29.9 (8.2)	32.3 (7.4)	29.8 (7.1)
Median	28.6	31.7	29.3
Min, Max	17.9, 51.7	20.2, 48.0	19.0, 50.7

Agency Comment: The 2015 U.S. Census data reports that 77% of the population is white, 13% is African American/black, and 6% is Asian; Hispanics make-up 18% of the population. The demographics of included patients do not reflect the exact racial and ethnic make-up of the Country, but (for a study of its size) the Applicant did well; enrolling at least one Alaskan Native/American Indian and one Native Hawaiian/Pacific Islander. There were minor differences in proportions of patients of different races and ethnicities between arms, but we do not feel this represents a significant problem in interpreting the study's results. The mean/median ages appear to well-represent the population of interest (i.e., not skewed to younger or older mothers).

Differences in weight/BMI between arms could potentially affect the results because brexanolone dosing is weight-based. But the mean weights of the brexanolone 60 and 90 µg/kg/h arms were not statistically different (t-test 1.4; p=0.17).

A summary of statistical significance for the primary and prespecified secondary efficacy endpoint is presented in Table 6. Prespecified comparisons within the hierarchy were considered statistically significant based on the testing procedure. No sensitivity analysis was performed because of the negligible level of missing data.

Table 6. Primary and Secondary Efficacy Results, Study 202B.

Timepoint		**Placebo** (n=43)	**Brexanolone 60 µg/kg/h** (n=38)	**Brexanolone 90 µg/kg/h** (n=41)
Hour 60	Mean score at Baseline (SD)	28.6 (2.54)	29.0 (2.70)	28.4 (2.47)
	Mean Score at Hour 60 (SD)	14.6 (7.55)	9.2 (7.01)	10.7 (5.78)
	LS Mean Change from Baseline (SE)	-14.4 (1.15)	-19.5 (1.23)	-17.7 (1.19)
	Placebo-subtracted Difference (95% CI)		-5.5 (-8.8, -2.2)	-3.7 (-6.9, -0.5)
	P-value (unadjusted)		0.0013	0.0252
	Significance (MCP-adjusted)		Yes	Yes
Day 30	Mean Score at Baseline (SD)	28.6 (2.54)	29.0 (2.70)	28.4 (2.47)
	Mean Score at Day 30 (SD)	14.7 (9.46)	9.1 (7.97)	11.0 (8.34)
	LS Mean Change from Baseline (SE)	-13.8 (1.32)	-19.5 (1.44)	-17.6 (1.40)
	Placebo-subtracted Difference (95% CI)		-5.6 (-9.5, -1.8)	-3.8 (-7.6, -0.0)
	P-value (unadjusted)		0.0044	0.0481
	Significance (MCP-adjusted)		Yes	Yes

MCP=Multiple comparison procedures.

As shown in Figure 3, all treatment groups showed a decrease in HAM-D total score over the first 72 hours, with numerically greater change from baseline for both brexanolone groups at all time points starting at Hour 24. Compared with placebo, statistical significance was achieved for brexanolone at Hour 60 and Day 30.

Exploratory subgroup analyses on the primary endpoint were assessed by age group (18 to 24 vs. 25 to 45), race, baseline antidepressant use, baseline BMI, onset of PPD, and family history of PPD. Estimates in these smaller subgroups were subject to large sampling variation and the overall results do not indicate subset differences (analysis not shown).

Summary of 202B results:

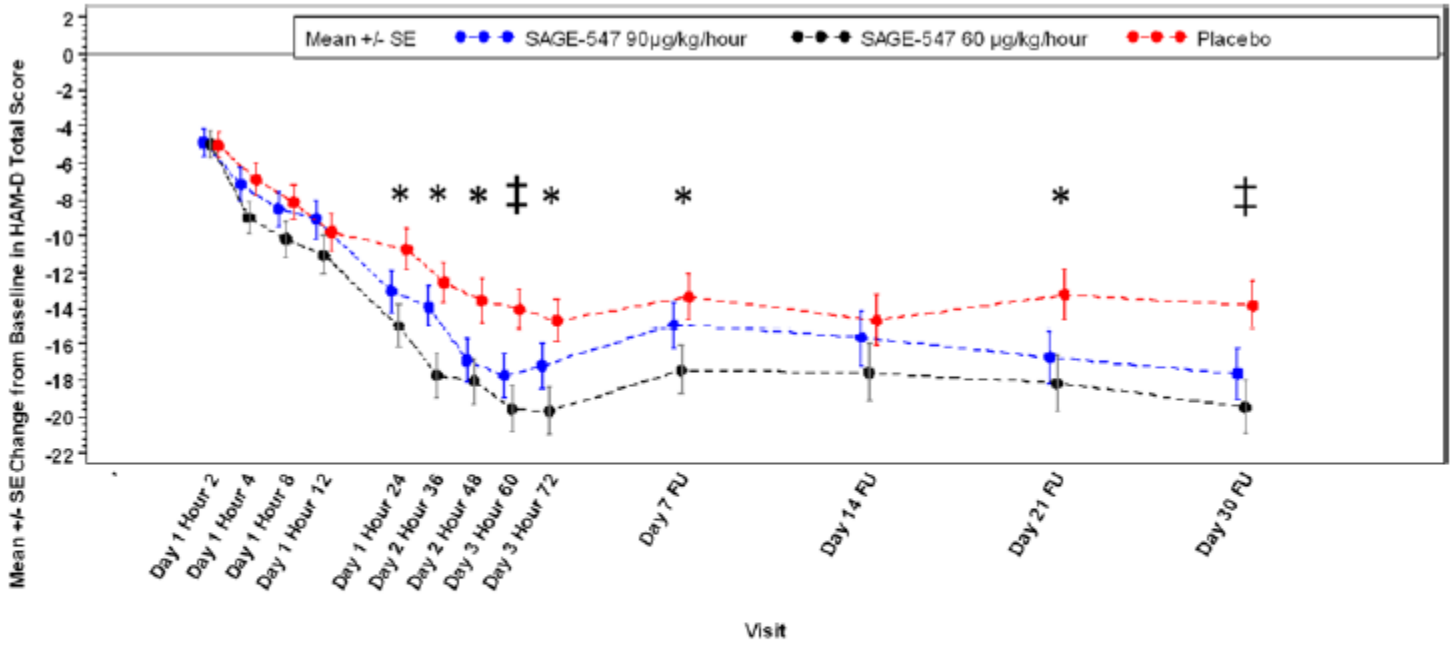
- **HAM-D: Brexanolone superior to placebo at 60 h (primary endpoint)**
  - 60 µg/kg/h, p = 0.001
  - 90 µg/kg/h, p = 0.03
- HAM-D: Brexanolone superior to placebo at 30 days (prespecified secondary endpoint)
  - 60 µg/kg/h, p = 0.004
  - 90 µg/kg/h, p = 0.048

- HAM-D: Separation from placebo began early in treatment
    - 60 μg/kg/h 24 h after start of infusion
    - 90 μg/kg/h 48 h after start of infusion
- HAM-D Response (>50% reduction in score): Brexanolone superior to placebo at 60 h and at 30 days
- HAM-D Remission (score ≤7): Brexanolone 60 μg/kg/h superior to placebo at 60 h

Agency Comment: Although Study 202B revealed a smaller effect than 202A, it was also larger and completed at more sites (introducing increased variability). It initially appears as though the 60 μg/kg/h dose is more effective than the 90 μg/kg/h dose. However, the doses begin to separate from each other during titration—when both groups were receiving the same dose—and, aside from Hour 36, have overlapping standard errors. The higher dose, however, showed no suggestion of a greater effect after 24 hours. The Agency would like input from the Committee on recommended dosing.

The placebo-subtracted difference in HAM-D scores for both the 60 and 90 μg/kg/h doses (-5.5 and -3.7, respectively) are consistent with the efficacy results of other, approved antidepressants.

Figure 3. Change over Time in HAM-D Total Score, Study 202B (Applicant Figure).



Abbreviations: HAM-D = Hamilton Rating Scale for Depression; FU = follow-up; LS = least squares; SE = standard error

Note: * indicates time points when statistically significant improvement was achieved for SAGE-547 60 µg/kg/h as compared with placebo. ‡ indicates time points when statistically significant improvement was achieved for both SAGE-547 groups as compared with placebo. Ns for Day 14 and Day 21 are lower than surrounding time points as these visits were added with Amendment 3. An unstructured covariance structure was used to model the within-subject errors.

Source: Clinical Study Report Figure 9.

2.5.4. **Study PPD-202C**

Study 202C included subjects with "moderate" PPD (HAM-D score of 20 to 25). As with Study 202B, follow-up visits at Day 14 and 21 were added in an amendment. Therefore, earlier patients were not assessed at these time points and the sample size at these two visits are lower than the sample size at the other visits (Days 7, 30). The change from baseline in HAM-D total score at Day 30 was the prespecified secondary efficacy endpoint in this study as well.

One-hundred-eight subjects were randomized into the study, 104 of whom received study treatment. Of the subjects who received study treatment, four discontinued the study early (three brexanolone and one placebo). Of the 104 subjects, 101 (97.1%) had a primary efficacy endpoint assessment (Hour 60) and 100 (96.1%) had the pre-specified secondary endpoint assessment (Day 30). Baseline demographic data is presented in Table 7.

Table 7. Demographic Characteristics, Study 202C.

Characteristic		Placebo (n=53)	Brexanolone 90 µg/kg/h (n=51)
Age, years			
	Mean (SD)	27.3 (5.9)	28.2 (6.1)
	Median	27	27
	Min, Max	18, 44	19, 42
Race, n (%)			
	AA/Black	19 (36%)	22 (43%)
	White	33 (62%)	29 (57%)
	Other	1 (2%)	0
Ethnicity, n (%)			
	Hispanic	14 (26%)	10 (20%)
	Non-hispanic	39 (74%)	41 (80%)
Height, cm			
	Mean (SD)	162.6 (8.4)	164.3 (6.2)
	Median	161.3	164.0
	Min, Max	142.0, 184.0	152.0, 181.0
Weight, kg			
	Mean (SD)	86.6 (24.5)	87.3 (24.8)
	Median	82.0	84.2
	Min, Max	50.8, 159.7	44.9, 150.2
BMI, kg/m^2			
	Mean (SD)	32.6 (8.2)	32.2 (8.5)
	Median	32.5	30.6
	Min, Max	21.5, 52.2	18.0, 52.0

Agency Comment: Study 202C was less racially diverse/representative of the U.S. population than 202B. Again, mean/median ages do not appear skewed.

A summary of statistical significance for the primary and prespecified secondary efficacy endpoints, according to the hierarchical testing procedure, is provided in Table 8. The primary efficacy endpoint was considered statistically significant, but the Day 30 data did not demonstrate an effect. No sensitivity analysis was performed because the negligible level of missing data.

Table 8. Primary and Secondary Efficacy Results, Study 202C.

Timepoint		**Placebo** (n=53)	**Brexanolone 90 µg/kg/h** (n=51)
Hour 60	Mean score at Baseline (SD)	22.7 (1.59)	22.6 (1.56)
	Mean Score at Hour 60 (SD)	10.7 (5.52)	8.5 (5.94)
	LS mean Change from Baseline (SE)	-12.1 (0.77)	-14.6 (0.78)
	Placebo -subtracted Difference (95% CI)		-2.5 (-4.5, -0.5)
	P-value (unadjusted)		0.0160
	Significance (MCP-adjusted)		Yes
Day 30	Mean score at Baseline (SD)	22.7 (1.59)	22.6 (1.56)
	Mean Score at Day 30 (SD)	7.6 (6.34)	8.4 (6.54)
	LS mean Change from Baseline (SE)	-15.2 (0.93)	-14.7 (0.96)
	Placebo -subtracted Difference (95% CI)		0.5 (-2.0, 3.1)
	P-value (unadjusted)		0.6710
	Significance (MCP-adjusted)		No

MCP=Multiple comparison procedures.

As shown in Figure 4, both treatment groups showed a decrease in HAM-D total score over the first 72 hours, with numerically greater change from baseline for the SAGE-547 group at all time points through Day 21.

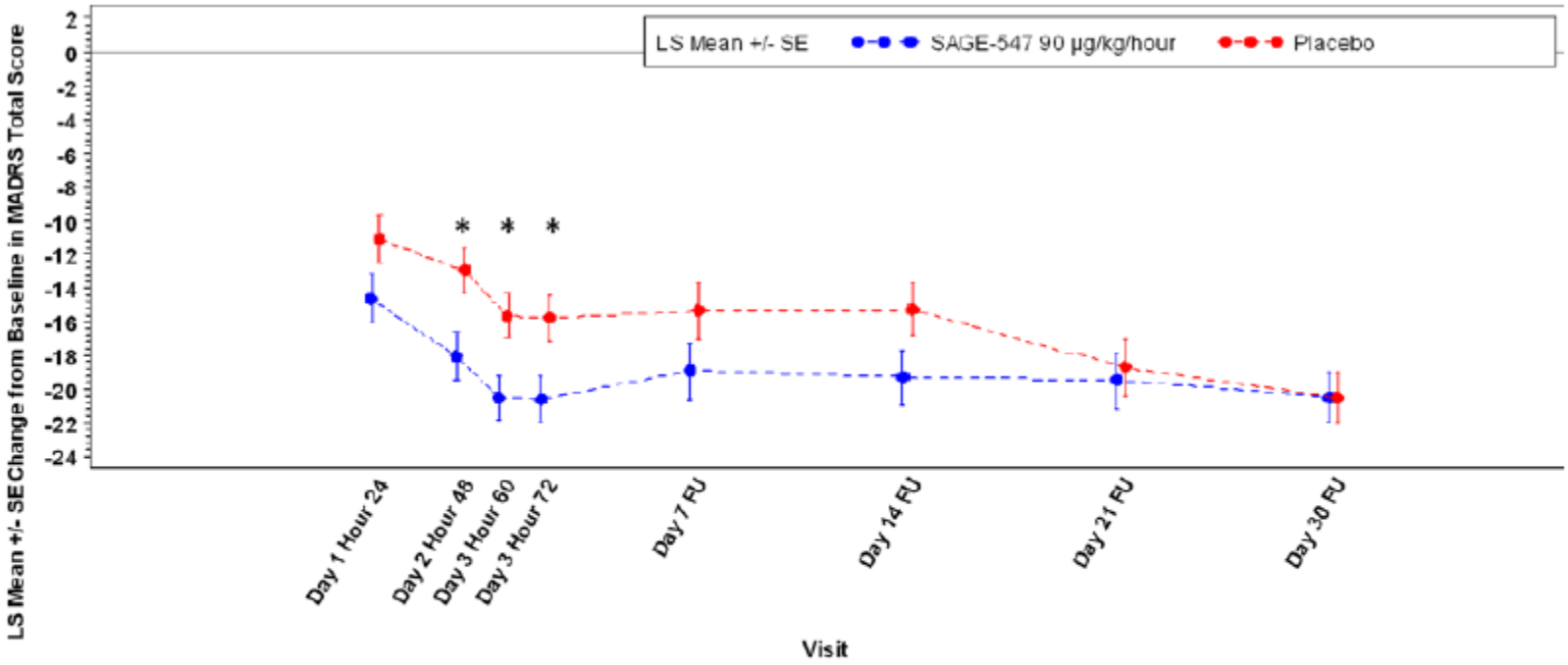
Exploratory subgroup analyses on the primary endpoint were assessed by age group (18 to 24 vs. 25 to 45), race, baseline antidepressant use, baseline BMI, onset of PPD, and family history of PPD. Results do not indicate subset differences (analysis not shown).

Summary of 202C results:

- **HAM-D: Brexanolone superior to placebo at 60 h, p = 0.02**
- HAM-D: Brexanolone no different from placebo at 30 days, p = 0.67
  - Brexanolone change from baseline at 30 days similar in magnitude to 60 h
- HAM-D: Separation from placebo began 48 h after start of infusion
- HAM-D Response (>50% reduction in score): Brexanolone superior to placebo at 60 h
- HAM-D Remission (score ≤7): Brexanolone superior to placebo at 60 h

Agency Comment: The placebo-subtracted difference in HAM-D score at Hour 60 (-2.5) is consistent with the efficacy results of other, approved antidepressants. Although the difference from placebo at Day 30 was not significant, it appears that the effect of brexanolone was maintained while the placebo group improved.

Figure 4. Change over Time in HAM-D Total Score, Study 202C (Applicant Figure).



Abbreviations: FU = follow-up; LS=least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; SE=standard error.

Note: * indicates time points when statistically significant improvement was achieved for SAGE-547 as compared with placebo. Ns for Day 14 and Day 21 are lower than surrounding time points as these visits were added with Amendment 3.

Source: Clinical Study Report Figure 2.

2.6. Safety of Brexanolone for Treatment of Postpartum Depression

2.6.1. Overarching Safety Issues

The Agency did not issue clinical holds for this development program. The review team identified loss of consciousness as the primary safety concern related to this product. We selected adverse events (AEs) for analysis that occurred during study drug infusion.

Randomization for 202B included two brexanolone arms. Therefore, the randomization ratio was 2 brexanolone:1 placebo for this study. Combining all brexanolone arms from 202B with the brexanolone arms from 202A and C (which had 1:1 randomization ratios) raises the possibility of Simpson's Paradox. Therefore, data are presented for 60 and 90 µg/kg/h doses separately as well as combined.

2.6.2. Deaths, Serious Adverse Events, and Adverse Events Leading to Premature Withdrawal from the Studies

There were no deaths in this development program.

There were two serious adverse events (SAEs) in this development program.

- Subject (b) (6), Study 202B, 60 µg/kg/h arm; 25-year-old white female: 2 days after completing the infusion, she reported suicidal ideation and intentional overdose on Percocet, Norco, and Flexaril. The patient informed her boyfriend of the overdose. Acetaminophen levels in the emergency department were inconsistent with the reported overdose amount (estimated fewer than five pills consumed). The emergency department noted the patient had a complex social situation (b) (6) and believed she was "attention seeking." The patient was not admitted.
- Subject (b) (6), Study 202C, 90 µg/kg/h arm; 25-year-old white female: syncope/altered state of consciousness (see Section 2.6.5: *Loss of Consciousness* for more details on this subject).

Agency Comment: The presentation of Subject (b) (6) is consistent with borderline personality disorder. While having borderline personality disorder does not preclude a concurrent diagnosis of PPD, we believe the suicidal ideation and intentional overdose are much more likely the result of a personality disorder than either the PPD or a drug effect.

Four patients discontinued study drug due to adverse events (AEs).

- Subject (b) (6), Study 202B, placebo arm; discontinued study drug after 59 hours of infusion due to infusion site extravasation.
- Subject (b) (6), Study 202B, brexanolone 60 µg/kg/h arm; discontinued study drug after 57 hours of infusion due to infusion site pain.
- Subjec (b) (6), Study 202C, brexanolone 90 µg/kg/h arm; discontinued study drug after 8 hours of infusion due to SAEs of syncope and altered state of consciousness.
- Subject (b) (6), Study 202C, brexanolone 90 µg/kg/h arm; discontinued study drug after 37 hours of infusion due to vertigo and presyncope.

Dose reduction and/or interruption was required in 10 brexanolone patients and 3 placebo patients as per Table 9.

Table 9. Dose Reductions/Interruptions.

Treatment	Adverse Event	n	Reduction or interruption
Placebo	Extremity pain/edema	1	Interrupted
	Infusion site pain	1	Interrupted
	Dizziness	1	Reduced
Brexanolone	Somnolence	2	Interrupted (1) Reduced (1)
	Syncope	3	Interrupted
	Infusion site pain/edema/itching	2	Interrupted
	Infusion site extravasation	1	Interrupted
	Fatigue	1	Reduced
	Hypotension	1	Reduced

Agency Comment: Aside from complications from the IV procedures (which effected the placebo arm as well)—and the loss-of-consciousness issue—brexanolone appears well-tolerated.

2.6.3. **Adverse Events**

Brexanolone adverse events greater than two percent and at least twice the rate of placebo are presented in Table 10. At 72 h, one placebo patient and two brexanolone 90 µg/kg/h patients had sedation; two brexanolone 90 µg/kg/h patients had dizziness/lightheadedness.

Agency Comment: In examining the distribution of AEs based on brexanolone dose at the time of the AE (see Table 11), there is no obvious dose effect. Indeed, sedation AEs are more common during the 30 µg/kg/h dose (as patients start the infusion) and none occurred at the highest dose. This lack of a dose-response for AEs indicates that lowering the dose of the infusion would not necessarily lead to better tolerability. This finding informs our decision on potential post-marketing commitments (PMCs; i.e., it would not be useful to patients to find a lower efficacious dose if it would not improve tolerability).

At 72 h, a patient may still not be safe to drive herself home from the infusion site.

Table 10. Adverse Events Greater than 2% and Twice the Rate of Placebo by Treatment Group in Studies 202A, B, and C; n(%).

Adverse Event	Placebo (n=107)	Any Brexanolone (n=140)	Brexanolone 60 µg/kg/h (n=38)	Brexanolone 90 µg/kg/h (n=102)
Sedation, somnolence	6 (6%)	21 (15%)	8 (21%)	13 (13%)
Dizziness, lightheadedness, presyncope, vertigo	7 (7%)	17 (12%)	5 (13%)	12 (12%)
Dry mouth, thirst	1 (1%)	7 (5%)	4 (11%)	3 (3%)
LOC, syncope	-	5 (4%)	2 (5%)	3 (3%)
Flushing, hot flash	-	4 (3%)	2 (5%)	2 (2%)
Diarrhea	1 (1%)	3 (2%)	1 (3%)	2 (2%)
Oropharyngeal pain	-	3 (2%)	1 (3%)	2 (2%)
Tachycardia	-	3 (2%)	0 (0%)	3 (3%)
Dyspepsia, indigestion	-	2 (1%)	0 (0%)	2 (2%)

Table 11. Adverse Events by Dose at the Time of the AE.[a]

Adverse Event	Brexanolone Dose		
	30 µg/kg/h (n=140)	60 µg/kg/h (n=140)	90 µg/kg/h (n=102)
Sedation, somnolence	16 (14%)	7 (5%)	-
Dizziness, lightheadedness, presyncope, vertigo	7 (5%)	9 (6%)	4 (4%)
Dry mouth, thirst	1 (1%)	5 (4%)	1 (1%)
LOC, syncope	1 (1%)	3 (2%)	1 (1%)
Flushing, hot flash	1 (1%)	3 (2%)	-
Diarrhea	1 (1%)	2 (1%)	-
Oropharyngeal pain	1 (1%)	1 (1%)	1 (1%)
Tachycardia	1 (1%)	1 (1%)	2 (2%)
Dyspepsia, indigestion	-	1 (1%)	1 (1%)

[a]Denominators assume all brexanolone patients (n=140) received 30 and 60 µg/kg/h doses (during titration). Patients experiencing the same AE at multiple doses are counted for each dose. Therefore, row totals from this Table may not match total brexanolone numbers in Table 10.

2.6.4. **Laboratory Studies, Electrocardiograms (EKGs), and Vital Signs**

There were no detected relationships between brexanolone and any abnormal laboratory value. There was one patient (Study 202B, brexanolone 90 μg/kg/h arm) who developed ALT and AST elevations approximately seven times the upper limit of normal. The subject's baseline ALT and AST were clinically unremarkable (58 and 43 U/L, respectively). However, on Day 3, the patient's ALT was 373 and AST was 234 U/L. By Day 7 the AST had decreased to 51 U/L, but the ALT remained elevated at 192 U/L. At Day 30, the ALT had decreased to 29. Throughout this time, the patient's bilirubin remained 8.6 to 14.3 μmol/L (within the normal range of 1.7 to 20.5 μmol/L). The patient's alkaline phosphatase ranged from 89 to 117 U/L (within the normal range of 30 to 140 U/L). This patient had no relevant medical history. In addition to brexanolone, she was taking sertraline. There were no other patients with transaminase elevations.

Agency Comment: The case of liver enzyme elevations did not meet criteria for Hy's Law (no elevation of bilirubin). The patient was also taking sertraline—which has been associated with rare instances of marked elevations in liver enzymes 2 to 24 weeks after starting the drug.[5] *Although there is no clear cause for this subject's transaminase elevations, we believe the sertraline is a more likely culprit than the brexanolone, which is an analogue of an endogenous hormone.*

There was no detected relationship between brexanolone and any EKG parameter. FDA's QT Interdisciplinary Review Team concluded:

> No significant QTc prolongation effect of brexanolone (SAGE-547) treatment (a 5-hour intravenous infusion starting at a rate of 60 μg/kg/h and increasing each hour to 90, 120, 150, and 180 μg/kg/h) was detected in TQT study 547-CLP-106. The largest upper bound of the 2-sided 90% CI for the mean difference between brexanolone treatment and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated…indicating that assay sensitivity was established (p. 1; QT IRT Review archived by Moh Jee Ng on July 26, 2018).

There was no detected relationship between brexanolone and pulse, blood pressure, or respiratory rate. Only one patient (Study 202C, brexanolone 90 μg/kg/h arm) was orthostatic by blood pressure criteria alone (standing heart rate was not measured). Other patients with postural dizziness were not orthostatic. Brexanolone was not associated with a pattern of respiratory distress (more respirations per minute than placebo) nor with respiratory depression (fewer respirations per minute than placebo) in either Study 202B (Figure 5) or 202C (Figure 6). Pulse oximetry was not recorded.

Figure 5. Minimum and Maximum Respirations per Minute by Drug Assignment, Study 202B.

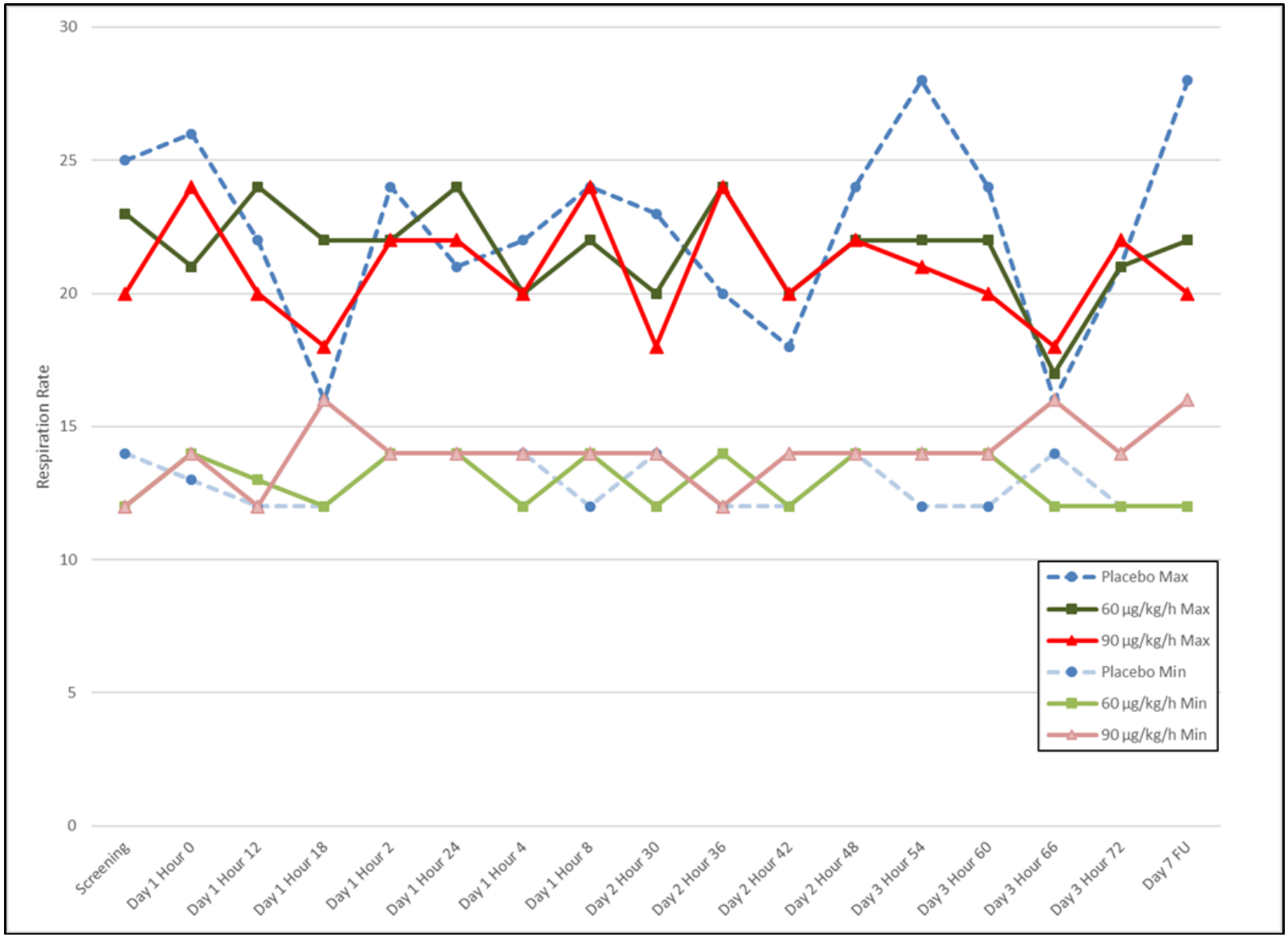
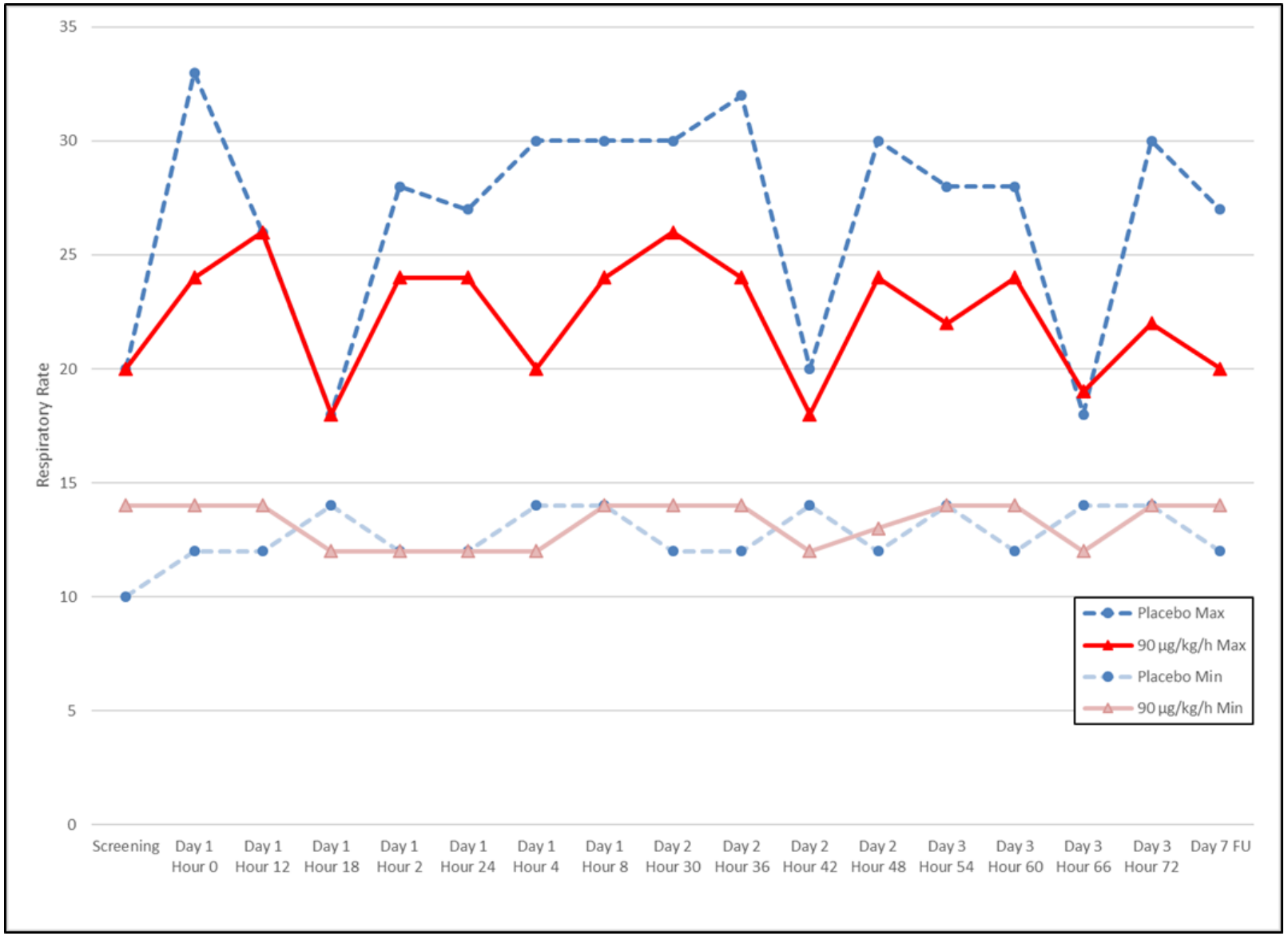


Figure 6. Minimum and Maximum Respirations per Minute by Drug Assignment, Study 202C.



2.6.5. **Loss of Consciousness (LOC) Events**

There were six patients with loss of consciousness, syncope, or presyncope in Studies 202A, B, and C (4% of total brexanolone exposures; see Table 12). Patient (b) (6) appeared to have a vasovagal reaction to a blood draw. Patien (b) (6) reported dizziness and vertigo that improved when she sat down (she never lost consciousness). The remaining four patients seemed to experience an abrupt onset of deep sleep.

All LOC events resolved within 15 to 60 minutes of infusion discontinuation. None required any intervention other than infusion discontinuation. There is no discernable pattern to the LOC events. Dosing, time elapsed since start of dose, blood levels, BMI, past medical history, and concurrent medication all varied.

Subject (b) (6) in Study CLP-106 (cardiac repolarization study) also lost consciousness. This subject was a 55-year-old man with no reported past medical history. He developed somnolence, confusion, and dizziness while receiving brexanolone 150 µg/kg. His blood level was 144 ng/mL. This subject had less than 1 min of apnea during the event. He was not obese.

Table 12. Cases of Loss of Consciousness, Syncope, Presyncope in Studies 202A, B, and C.

Subject ID (Study)	Demographics	Description of Event	Dose at time of LOC Event (µg/kg/h)	Timeline: Nearest PK to Event (ng/mL)
(b) (6) (202B)	31 yo, AA BMI 28.1 kg/m^2 78 days after delivery h/o MDD Medication -medroxyprogesterone	-Vasovagal syncope during venipuncture for PK sampling (reported fear of needles)	60	08/09/17 0800: Infusion start 08/10/17 0759: 64.6 0800: Syncope 1400: 64.0
(b) (6) (202B)	25 yo, W BMI 40 kg/m^2 40 days after delivery h/o anxiety Medication -labetalol -lansoprazole -promethazine -acetaminophen	-Infusion pump malfunction, dose unclear -BP lability before and during the event (71/48 to 140/101 mmHg) -LOC occurred 14 h after starting 90µg/kg/h (actual dose unclear) -LOC x 30 sec, "as if in deep, sound sleep" -Infusion stopped; felt well after 10 min	90[a]	06/16/17 0815: Infusion start 06/17/17 2005: 79.3 2238: LOC 06/18/17 0805: 102
(b) (6) (202B)	28 yo, W BMI 35 kg/m^2 82 days after delivery Medication -none	-Infusion pump malfunction, dose unclear -Asked if the drug made one sleepy, then fell forward "abruptly"; snoring -No change in vitals -Infusion stopped; recovered after 14 min	30[a]	09/08/17 0845: Infusion start 1016: LOC 1235: 29.5

Table 12. Continued.

Subject ID (Study)	Demographics	Description of Event	Dose at time of LOC Event (µg/kg/h)	Timeline: Nearest PK to Event (ng/mL)
(b) (6) (202B)	24 yo, W BMI 29 kg/m^2 185 days after delivery h/o anxiety, MDD Medication -ASA/acetaminophen/ caffeine	-Reported dizziness 20 h after starting 60 µg/kg/h -10 h later was extremely somnolent and unaware of surroundings -Infusion stopped; improved after 15 min, resolved after 45 min	60	08/04/17 1110: Infusion start 08/05/17 1102: 152 2200: LOC 2319: 103
(b) (6) (202C)	25 yo, W BMI 30 kg/m^2 189 days after delivery h/o anxiety, MDD Medication -sertraline (since 2016) -single dose ondansetron	-Reported dizziness 5 h after starting 60 µg/kg/h -Was eating Jell-O when abruptly dropped spoon and became unresponsive -Opened eyes to verbal stimuli after 10 min, but not responsive for 1 h -Sent to emergency department -No memory for event	60	08/07/17 0937: Infusion start 1741: 51.6 1815: Syncope
(b) (6) (202C)	36 yo, AA BMI 51 kg/m^2 115 days after delivery h/o HTN Medication -medroxyprogesterone -methadone (since 2012) -metoprolol -naproxen -lisinopril/HCTZ	-Reported dizziness and somnolence at 30 and 60 µg/kg/h -Presyncope/vertigo 13 h after starting 90 µg/kg/h -Sat down and presyncope resolved after 10 min, vertigo after 2 h	90	01/11/17 0800: Infusion start 01/12/17 0750: 82.1 1115: Presyncope 1400: 138

AA=African-American, ASA=aspirin, BMI=body mass index, BP=blood pressure, HCTZ=hydrochlorothiazide, HTN=hypertension, h/o=history of, LOC=loss of consciousness, MDD=major depressive disorder, W=white, yo=year old.
[a]Because of IV pump malfunction, actual dose unclear. PK samples from these patients do not indicate abnormally high doses.

Patient (b) (6) experienced dizziness 8.5 h after the start of the infusion. She then became unresponsive. Her vital signs were unremarkable (BP 125/89, HR 67, 98% on room air). Her infusion was stopped 3 min after she became unresponsive. After 10 minutes, she opened her eyes to verbal stimuli, but was not verbally responsive. She was verbally responsive after an additional 45 minutes. She was transferred to a local emergency room for further work-up. Her physical examination, EKG, complete blood count, and metabolic panel were unremarkable. She was amnestic for events from her LOC until she was in the emergency room.

Agency Comment: We have not determined predictors of LOC events. There were no recorded sedation- or dizziness-type AEs in patients (b) (6) *and* (b) (6) *prior to their losing consciousness. Patient* (b) (6) *asked if the drug made one sleepy, but then "abruptly" fell forward snoring. Both of these patients experienced IV pump malfunctions and their doses were unclear. However, PK samples from these patients are not consistent with abnormally high exposures (brexanolone $t_{1/2}$=approximately 9 h).*

In animal studies, there was no drug-effect on respiratory parameters at brexanolone exposures 6-times clinical exposure; however, some rats and dogs experienced respiratory changes in acute 14-day general toxicology studies. Given that allopregnanolone can act on GABA receptors in a manner similar to barbiturates, it is possible brexanolone could have respiratory effects in humans as well. Although we did not observe changes in respiration rates during the PPD-202 studies, the subject with apnea from the cardiac repolarization study illustrates the Agency's concern. In all LOC cases, the infusion was immediately halted and the patient required no other intervention for recovery. However, we have no data on the potential outcomes if an infusion was not halted after a patient lost consciousness. We do not know the exact nature of the LOC events and if it would be possible to "lose consciousness" while the patient is sleeping. Therefore, the Agency believes patients receiving the brexanolone infusion must be continuously monitored with pulse oximetry (which will alarm if oxygen saturation falls to an unacceptable level).

An abrupt loss of consciousness can be dangerous to the patient (e.g., falls, drowning) and to the infant (e.g., drops, smothering). Therefore, the Agency believes the patient must be continuously monitored and cannot function as her child(ren)'s primary care giver during the infusion.

Given the need for 24-hour monitoring during the infusion, the frequent need for dose/infusion bag changes, and the need to evaluate a situation and determine if the infusion needs to be stopped or additional help (emergency interventions) is required, we believe a health care professional must be the patient's monitor during infusions. We do not feel that use of a family member or friend would ensure the needed continuous monitoring.

If brexanolone were approved, it would be in the best interest of Public Health to have it widely available to the relevant patient population. We do not feel infusions must be done in an inpatient hospital setting. However, we do not feel it would be safe to allow home infusions at this time. Home infusions would require a healthcare professional on-site at all times. In this scenario, the responsibility for enforcing safe practices would shift from the setting (e.g., hospital, clinic) to the visiting professional. The Agency does not feel it is appropriate or possible for the visiting professional to police the infusion administration (e.g., to ensure the patient is not acting as the infant's primary care giver or not driving).

2.6.6. **Adverse Events by Concurrent Antidepressant and Benzodiazepine Use**

A greater percentage of patients on antidepressants at baseline reported sedation and dizziness AEs compared with patients not on antidepressants. Patients on benzodiazepines as well as antidepressants had an even greater percentage reporting sedation and dizziness AEs (see Table 13).

Table 13. Adverse Events by Antidepressant and Benzodiazepine Use at Baseline in Studies 202A, B, and C; n (%).

Adverse Event	Placebo			Any Brexanolone		
	AD Only (n=21)	AD+ Benzo (n=5)	Neither (n=80)	AD Only (n=23)	AD+ Benzo (n=11)	Neither (n=106)
Sedation, somnolence	1 (5%)	0	5 (6%)	4 (17%)	5 (45%)	12 (11%)
Dizziness, lightheadedness, presyncope, vertigo	2 (10%)	2 (40%)	3 (4%)	4 (17%)	3 (27%)	10 (9%)
Dry mouth, thirst	0	0	1 (1%)	1 (4%)	1 (9%)	5 (5%)
LOC, syncope	0	0	0	1 (4%)	0	4 (4%)
Flushing, hot flash	0	0	0	2 (9%)	0	2 (2%)
Diarrhea	1 (5%)	0	0	3 (13%)	0	0
Oropharyngeal pain	0	0	0	0	1 (9%)	2 (2%)
Tachycardia	0	0	0	0	0	3 (3%)
Dyspepsia, indigestion	0	0	0	0	1 (9%)	1 (1%)

AD=antidepressant, Benzo=benzodiazepine.

Agency Comment: There does appear to be additive sedation when using brexanolone and other, sedating drugs. We do not have data on how this might affect respiratory parameters or the risk for an LOC event.

3 Abuse Potential Assessment

Preclinical and clinical findings indicate that brexanolone has abuse potential similar to that of benzodiazepines.

The preclinical evaluation of the abuse potential of brexanolone includes receptor binding studies, functional studies, and animal behavioral studies, which demonstrate the following:

- Receptor binding studies indicate that brexanolone has significant affinity for GABA-chloride channels, androgen, progesterone, and GABA-benzodiazepine receptors.
- Functional studies indicate that brexanolone acts as an agonist at GABA receptor sites.
- In general animal behavioral studies, brexanolone produces dose-dependent depressant effects such as sedation and muscle relaxation in rats and dogs and decreased locomotion in mice.

- In a drug-discrimination study in rats, brexanolone produces full generalization to the benzodiazepine, midazolam (>99%). This suggests that brexanolone produces effects that are similar to a sedative with known abuse potential.
- A physical dependence study conducted in rats was not conclusive, as the positive control, midazolam, did not produce a strong withdrawal signal upon abrupt discontinuation.

Clinical studies with brexanolone further support that brexanolone produces subjective effects comparable to benzodiazepines, based on the following:

- A human abuse potential study produced dose-dependent subjective effects indicative of abuse potential. At the high dose tested (270 μg/kg/IV/1-hour infusion) brexanolone produced Drug Liking scores similar to those of alprazolam 3 mg.
- In phase2/3 double-blind studies, no events of euphoria were reported; however, sedation was reported in 4-30% (mean 5.7%) of subjects on brexanolone and 0-2% (mean 0.9%) of subjects on placebo. Somnolence, which may not necessarily be an abuse related adverse event (AE), was reported as an AE separate from sedation and occurred at higher rates in the active drug group compared to placebo.

4 References

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5 Appendices

5.1. Assessment Schedule for "Umbrella" 202 Protocol.

Assessments	Screening	Treatment													Follow-up						
	D -7 to -1	D1							D2				D3		D3		D7	D12[a]	D14[b]	D21[b]	D30
		H0	H2	H4	H8	H12	H18	H24	H30	H36	H42	H48	H54	H60	H66	H72					
History and Physical	X															X	X				
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
EKG	X											X					X				
Pulse Oximetry[a]		X	X	X	X	X	X	X	X	X	X	X	X	X							
Clinical Labs[c]	X															X	X				
Pregnancy Test[d]	X	X																			X
C-SSRS		X						X						X		X	X		X	X	X
HAM-D	X	X	X	X	X	X		X		X		X		X		X	X		X	X	X
CGI-S	X	X																			
CGI-I			X	X		X		X		X		X		X		X	X		X	X	X
MADRS	X	X						X				X		X		X	X		X	X	X
BIMF, SF-36[b]		X															X		X	X	X
EPDS, GAD-7, PHQ-9		X												X			X		X	X	X
HCRU	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SSS[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					

[a]Study 202A only (pulse oximetry not recorded on case report forms).
[b]Studies 202B and C only.
[c]Hematology, coagulation parameters, serum chemistries (including liver function tests), and thyroid stimulating hormone.
[d]Serum at screening; urine all other times.