INTRODUCTION

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Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting November 2, 2018

Objective

- The purpose of this joint 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.

Questions to the Committees

- Has substantial evidence been presented to support a claim of effectiveness for brexanolone for the treatment of postpartum depression?
- Has the Applicant adequately characterized the safety profile of brexanolone for the treatment of postpartum depression?
- Do the benefits outweigh the risks of brexanolone for the treatment of postpartum depression?

Questions to the Committees

- Discuss potential dosage recommendations
- Discuss risk mitigation strategies
- Consider what additional data would be needed to support safe use of brexanolone in alternative settings


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Brexanolone for Postpartum Depression: A Review of Effectiveness and Safety

CLINICAL OVERVIEW

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Outline

- Overview of Postpartum Depression (PPD)
- Overview of brexanolone
  - Regulatory history
- Effectiveness
- Safety
  - Key issues
  - Abuse potential

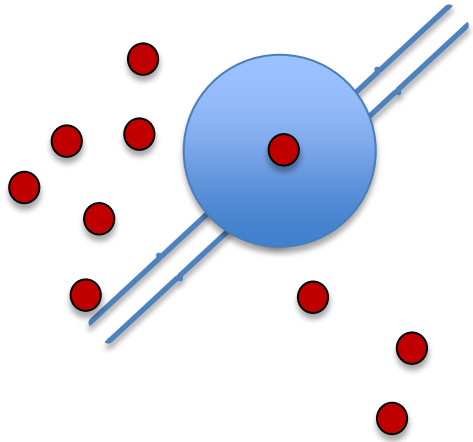
Postpartum Depression

- Major Depressive Episode
  - Onset during pregnancy or within 4 weeks of delivery
  - 7 to 12% pregnancies[1]
  - Risk of suicide[2]
  - Impacts mother-infant bonding
  - May impact later infant development

[1]Shorey S, et al. J Psychiatric Res 2018; 104:235-48.
[2]Oates M. Br J Psychiatry 2003; 183:279-81.

Postpartum Depression

- Symptoms identical to Major Depression
- Timing may indicate unique pathophysiology
  - Allopregnanolone
    - Increase during pregnancy
    - Abrupt fall after delivery
    - GABA-ergic regulator



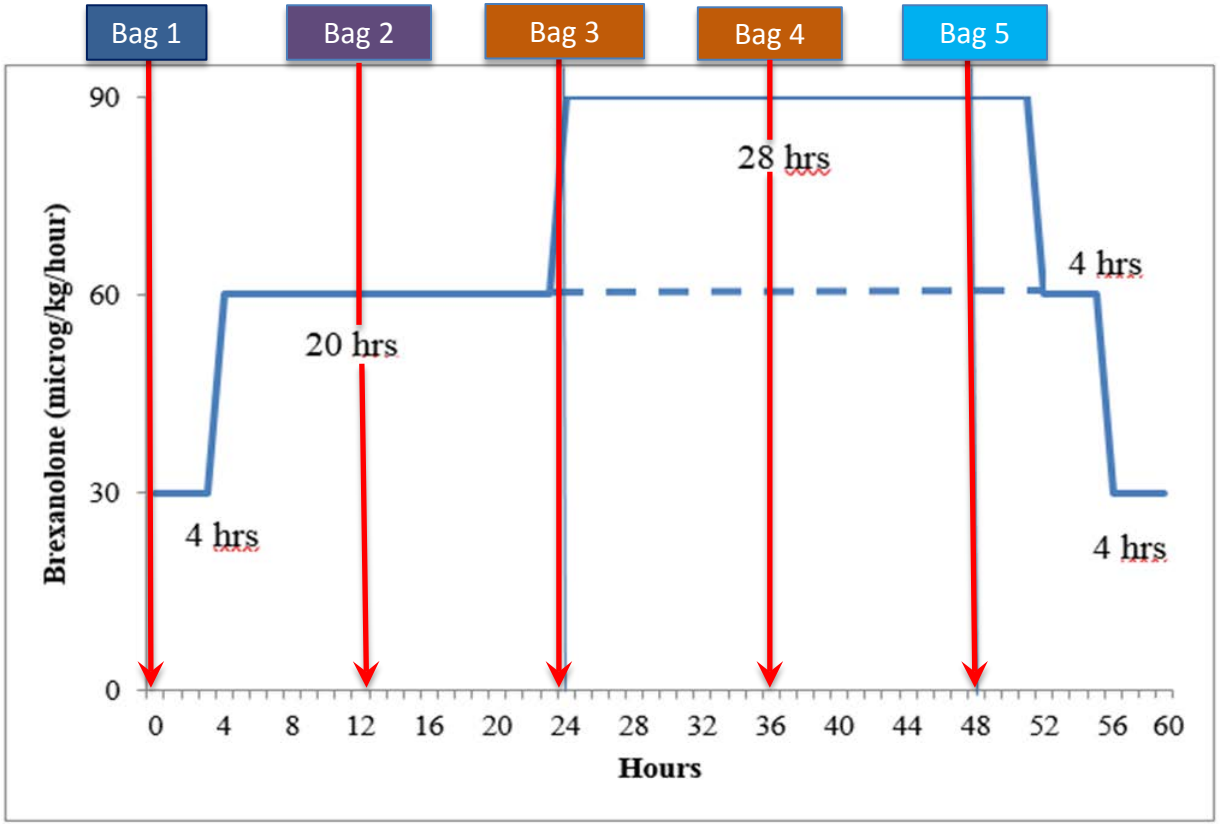
Postpartum Depression

- No drugs specific to PPD
  - Antidepressants commonly used
  - Limited efficacy data
- Psychotherapy
- Electroconvulsive therapy
- Transcranial magnetic stimulation

Brexanolone

- Chemically identical to allopregnanolone
- 5mg/mL solution
  - sulfobutyl ether beta-cyclodextrin
- Once mixed, stable
  - 12h Room temperature
  - 24h Refrigerated

Brexanolone Dosing



Regulatory History

- Not approved or marketed in any country
- Investigational New Drug (IND) June 2014
- Breakthrough Therapy August 2016
- New Drug Application (NDA) April 2018

Efficacy

- "Umbrella" protocol: PPD-202
  - 202A: Phase 2
  - 202B, 202C: Phase 3
  - Conducted entirely in the U.S.
  - Primary efficacy endpoint
    - Hamilton Depression Rating Scale (HAM-D) at Hour 60

Hamilton Depression Rating Scale (HAM-D)

- 17 items
  - Depressed mood
  - Guilt
  - Suicidal thoughts
  - Insomnia
  - Difficulty with activities
  - Weight
  - Slowed thoughts/activity
  - Agitation
  - Anxiety
  - Appetite
  - Libido
  - Preoccupation with physical symptoms
- Range 0-48
- Higher score=worse symptoms

Efficacy

Population

- 202A & 202B
  - Severe PPD
  - HAM-D ≥ **26**
- 202C
  - Moderate PPD
  - HAM-D **20-25**

Dosing

- 202A & 202C
  - 90 µg/kg/h
- 202B
  - 90 µg/kg/h
  - 60 µg/kg/h

Efficacy

- Enrolled population
  - PPD beginning 3rd trimester to 4 weeks post-delivery
  - Enrolled within 6 months of delivery
  - Excluded
    - Bipolar, active psychosis
    - Suicide attempt during index episode

Exposure in Efficacy Trials

Study	Placebo	Brexanolone 60 µg/kg/h	Brexanolone 90 µg/kg/h	Total Brexanolone	Total
202A	11	-	10	10	21
202B	43	38	41	79	122
202C	53	-	51	51	104
Total	107	38	102	140	247

202A Characteristics

Characteristic	Placebo (n=11)	Brexanolone 90 µg/kg/h (n=10)
Age, years		
Mean (SD)	28.8 (4.6)	27.4 (5.3)
Race, n(%)		
Non-white	6 (55%)	7 (70%)
White	5 (45%)	3 (30%)
BMI, kg/m^2		
Mean (SD)	29.3 (7.8)	32.7 (9.9)

202A HAM-D Results

	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

Placebo-subtracted difference in LS mean HAM-D Score on Day 30 was -11.9 (SE=4.1; $p<0.05$)

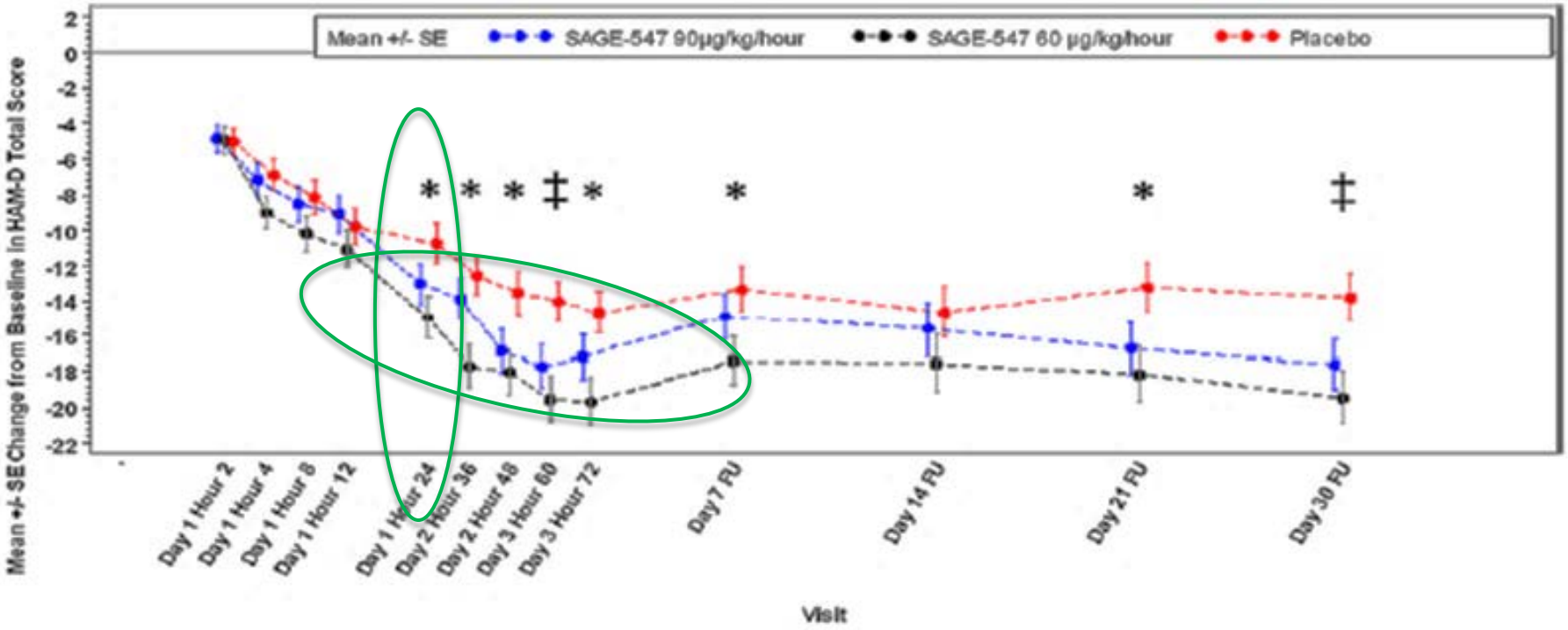
202B Characteristics

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)
Race, n(%)			
Non-white	16 (37%)	13 (34%)	12 (30%)
White	27 (63%)	25 (66%)	29 (70%)
BMI, kg/m^2			
Mean (SD)	29.9 (8.2)	32.3 (7.4)	29.8 (7.1)

202B HAM-D Results

		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
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

202B: Change in HAM-D Over Time



Source: Applicant, Clinical Study Report Figure 9

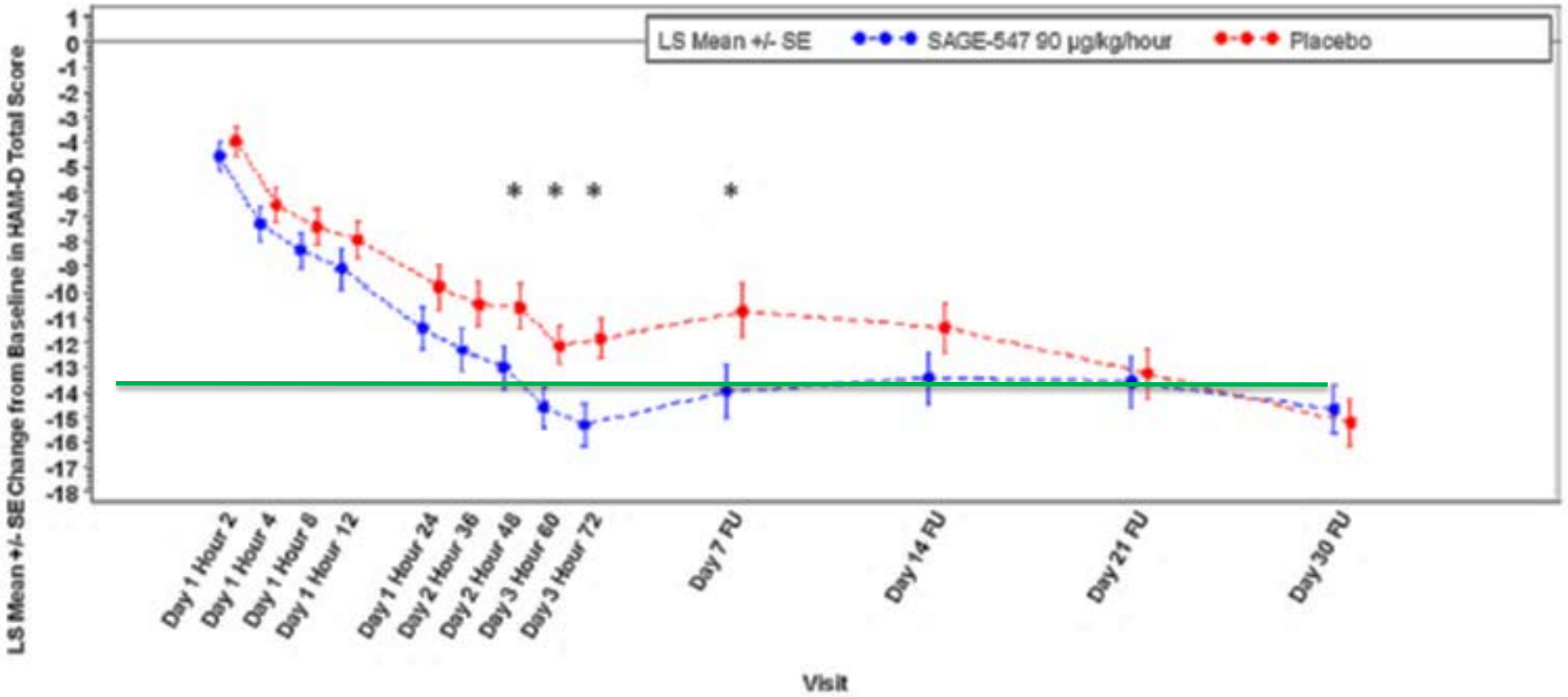
202C Characteristics

Characteristic	Placebo (n=53)	Brexanolone 90 µg/kg/h (n=51)
Age, years		
Mean (SD)	27.3 (5.9)	28.2 (6.1)
Race, n(%)		
Non-white	20 (38%)	22 (43%)
White	33 (62%)	29 (57%)
BMI, kg/m^2		
Mean (SD)	32.6 (8.2)	32.2 (8.5)

202C HAM-D Results

		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
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

202C HAM-D Results Over Time



Source: Applicant, Clinical Study Report Figure 2

Target Dosing

Target 60 µg/kg/h, increase to 90 as needed

- *Supporting*
  - 60 µg/kg/h performed better than 90
  - All patients were exposed to 60 µg/kg/h (during titration)
  - No need to expose to 90 µg/kg/h if respond to 60
- *Non-supporting*
  - 60 µg/kg/h starts separating from placebo at Hour 24 (both arms receiving 60 µg/kg/h)
  - More AEs in the 60 µg/kg/h arm (not safer than 90)
  - Some Patients who did not respond at 60 µg/kg/h responded at 90

Target 90 µg/kg/h, decrease to 60 as needed

- *Supporting*
  - 90 µg/kg/h was target in all three 202 studies (has most data)
  - Easier to recognize AE and decrease dose than recognize inefficacy and increase dose
  - Brexanolone group didn't separate from placebo until reached 90 µg/kg/h in 202C
- *Non-supporting*
  - The 60 µg/kg/h arm outperformed the 90 arm
  - With continued exposures, might expect 90 µg/kg/h dose to have more AEs

Safety: Deaths & Serious Adverse Events

- No deaths
- Two serious adverse events
  - 202B; 60 µg/kg/h arm: Suicidal ideation, 2 days after infusion
  - 202C; 90 µg/kg/h arm: Syncope/altered conciousness

Safety: Dose Interruptions & Reductions

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

Safety: Adverse Events by Assigned Arm

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%)
Loss of consciousness (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%)	-	3 (3%)
Dyspepsia, indigestion	-	2 (1%)	-	2 (2%)

Sedation-Related Adverse Events by Dosage

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%)
LOC, syncope	1 (1%)	3 (2%)	1 (1%)

Safety: LOC Events

- 6 subjects experienced LOC/syncope/presyncope during infusion (n=140)
  - All subjects received brexanolone
    - 1 fainted with blood draw (fear of needles)
    - 1 presyncope/vertigo standing, resolved after sitting
  - 4 appear to have suddenly fallen asleep
    - 25 yo, pump malfunction
    - 28 yo, pump malfunction, abrupt
    - 24 yo
    - 25 yo, abrupt (eating, dropped spoon)
- Resolved with dose interruption
  - Patient recovery in 10 to 60 minutes after loss of consciousness

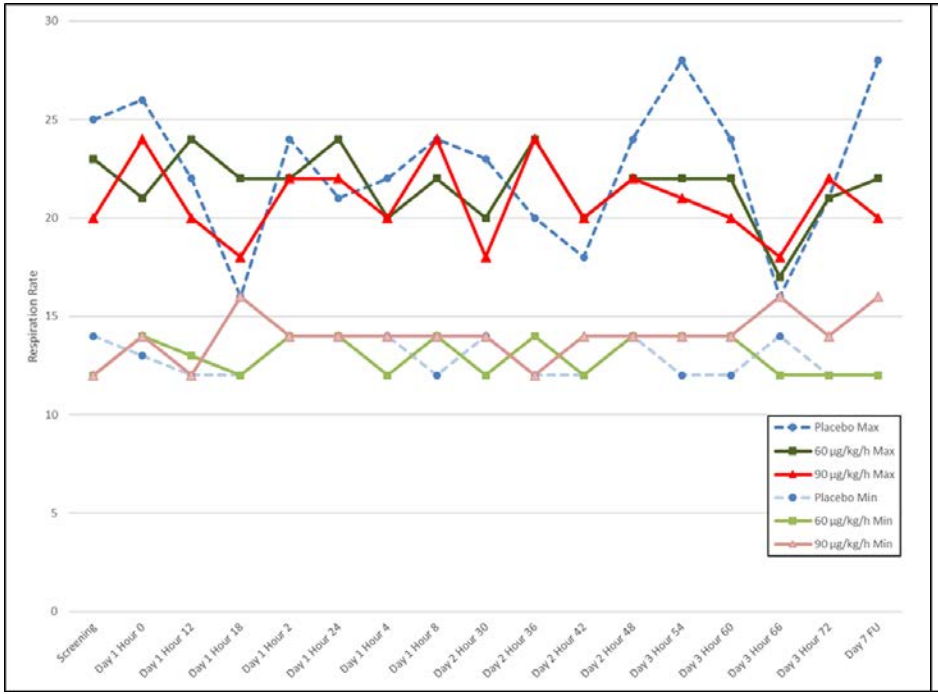
Safety: LOC Events

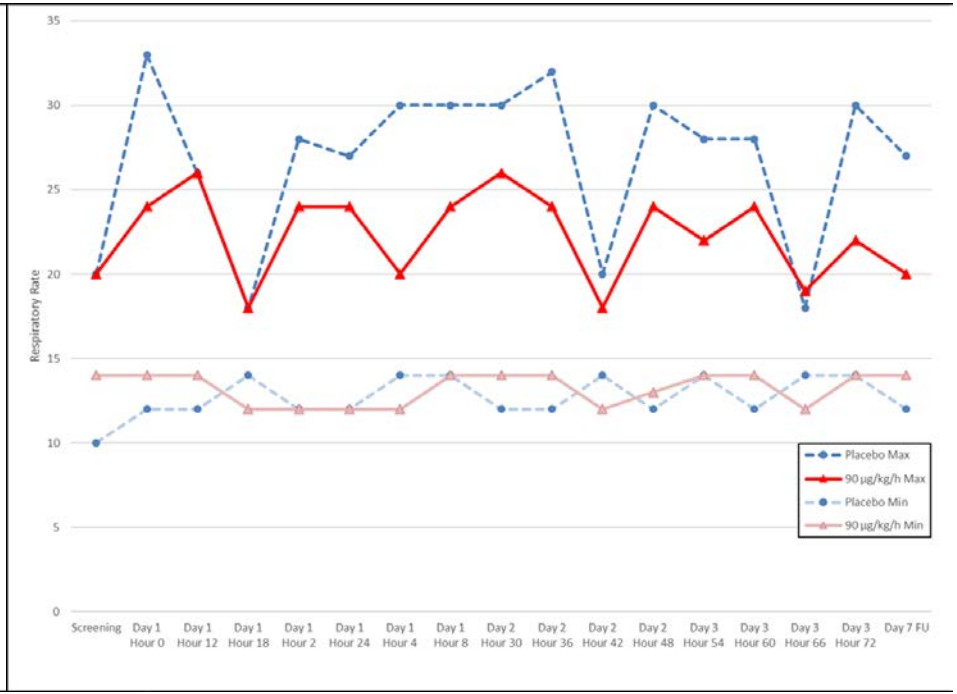
Interrupted/ Discontinued	Time Interrupted	Dose Re-started	Completed Study?
Interrupted	47 min	90 mcg/kg/h	Yes
Interrupted	88 min	90 mcg/kg/h	Yes
Interrupted	135 min	60 mcg/kg/h	Yes
Interrupted	60 min	30 mcg/kg/h x 9 h, 60 mcg/kg/h	Yes
Discontinued	-	-	No
Discontinued	-	-	Yes

Safety: LOC Events

- Possible apnea (<1 minute)
  - Cardiac repolarization study
  - 55-year-old male
  - No past medical history, not obese
  - Brexanolone dose: 180 µg/kg
  - Brexanolone blood level: 144 ng/mL

Safety: Respirations





Safety

No observed relationship between LOC and:

- Age
- BMI
- Vital signs
- Time since delivery
- Past medical history
- Brexanolone dose
- Brexanolone blood level
- Time on current brexanolone dose
- Concurrent medications

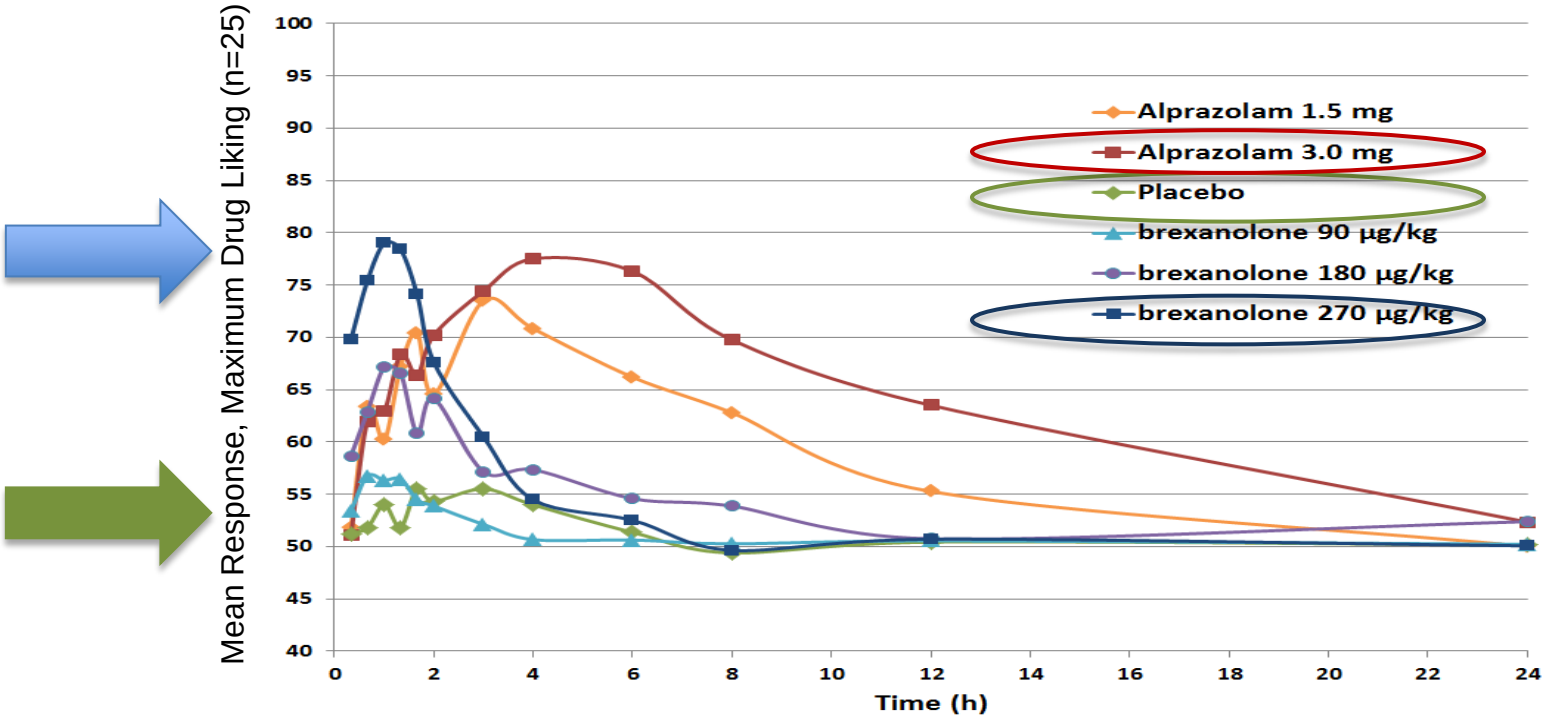
Safety: Loss of Consciousness

- LOC was abrupt in some cases
- No known way to predict risk
- Intervention is required
- Risks
  - To patient (e.g., falls)
  - To infant (e.g., drops, smothering)

Abuse Potential

- Significant affinity for GABA-benzodiazepine receptors
- In a drug discrimination study in rats:
  - Full generalization to midazolam
- In a human abuse potential study:
  - 270 µg/kg/h produced similar Drug Liking responses to alprazolam 3 mg

HAP Study, VAS Drug Liking Scores



HAP – Human Abuse Potential
VAS – Visual Analog Scale

Abuse Potential

- Brexanolone 270 mcg/kg also similar to Alprazolam 1.5 mg and 3 mg on these secondary VAS measures:
  - “Overall Drug Liking”
  - “High”
  - “Good effects”
  - “Take Drug Again”

Clinical Summary

- Evidence of effectiveness
  - Clinically meaningful change
  - Rapid improvement
- Evidence of safety
  - LOC events most concerning
  - Can monitor and intervene
- Abuse potential similar to benzodiazepines

PROPOSED RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

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Presentation Overview

- Risk Evaluation and Mitigation Strategies (REMS) overview
- Risk associated with brexanolone
- Risk management options:
  - Applicant proposal
  - FDA proposal

Risk Evaluation and Mitigation Strategies (REMS) Overview

A REMS is a drug safety program that FDA can require for certain drugs

- REMS are designed to achieve specific goals to mitigate risks associated with the use of a drug.
- REMS include strategies beyond labeling to ensure that the benefits of a drug outweigh the risks.
- The FDA Amendments Act (FDAAA) of 2007 authorized FDA to require applicants or application holders to develop and comply with REMS programs if determined necessary to ensure the benefits outweigh the risks.
- The FDA has authority to require a REMS pre-approval or post-approval.

A REMS can include a number of components

- Medication Guide or Patient Package Insert
- Communication plan for healthcare providers (HCPs)*
- Elements to assure safe use (ETASU)
- Implementation System
- Must include a timetable for submission of assessments*

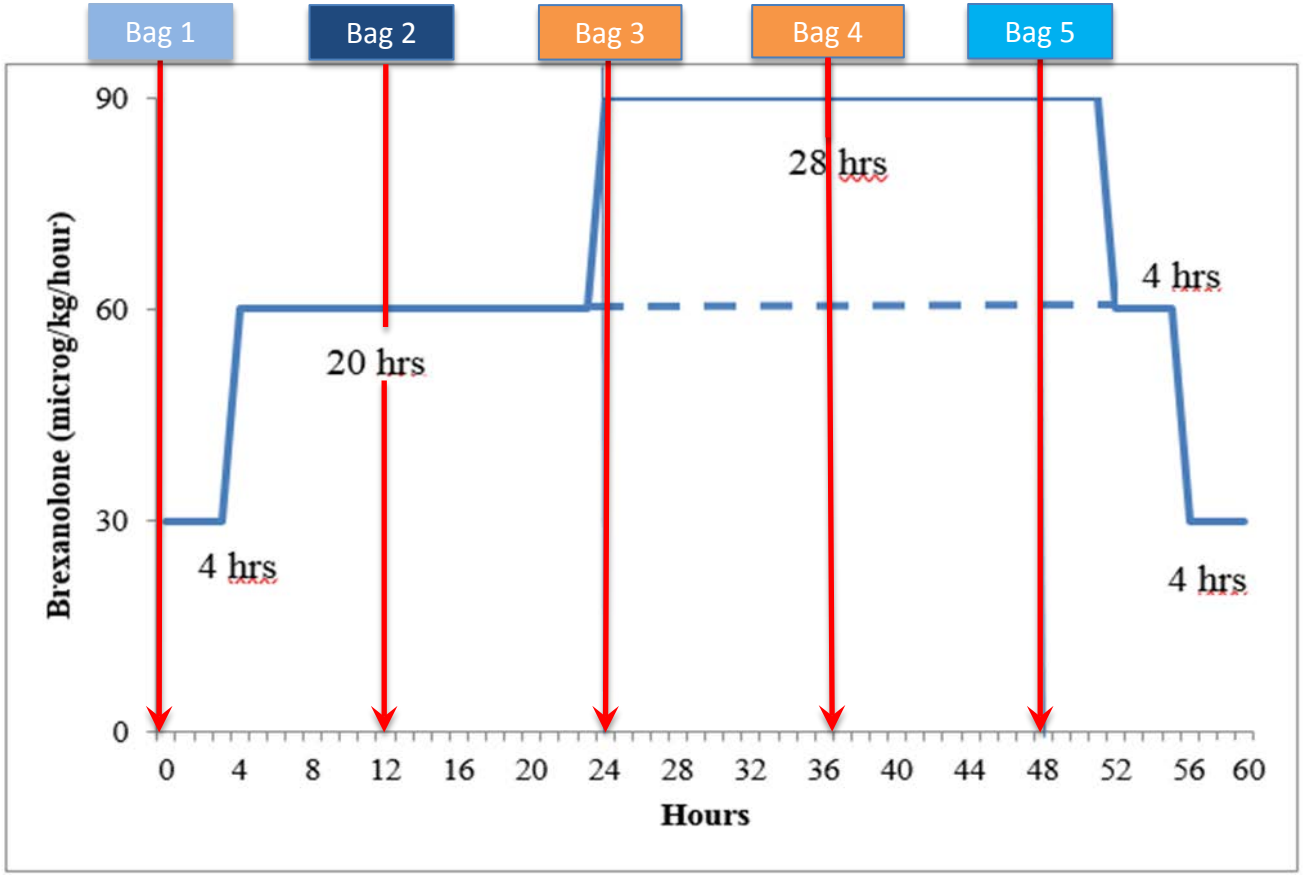
** This requirement only applies to NDAs and BLAs.*

A REMS can include any of the following ETASU if determined necessary

- Dispensing/administration of drug in limited settings, e.g., hospitals
- Certification and/or specialized training of HCPs who prescribe the drugs
- Each patient using the drug is subject to certain monitoring
- Enrollment of treated patients in a registry
- Certification of pharmacies or other dispensers of the drug
- Drug is dispensed/administered only with evidence of safe-use conditions, e.g., pregnancy test

Risk associated with brexanolone

Brexanolone Dosing



There are serious safety concerns associated with brexanolone if used outside of a medically-supervised setting

- 6 subjects experienced loss of consciousness (LOC)/syncope/presyncope during infusion (n=140)
- LOC could result in serious harm, accident, or injury to the mother and, potentially to the infant.
- Possible respiratory depression

Brexanolone administration in the clinical development program

- Settings required to have overnight capabilities for patients for approximately 72 hours, IV infusion capabilities, and a healthcare professional was required to be on site at all times.
  - Healthcare professional credentials varied
    - Emergency medical technicians, nurses and physicians
- 85% of subjects were dosed in a variety of non-hospital clinical research environments
  - 15% were dosed at units that were part of a hospital environment

Risk Management Options

Applicant's initial REMS proposal allowed for use in the home

- Goal: To inform patients, **competent companions**, and healthcare professionals on how to mitigate the risk of excessive sedation during brexanolone infusion
- ETASU
  - Certification of infusion providers
    - Could include delegated authorized representatives at hospital pharmacies, home infusion companies, or other infusion providers
  - **Competent companion** education and training, when applicable, (i.e. to supplement remote healthcare professional oversite) to recognize the symptoms of excessive sedation and respond appropriately

The FDA's proposed REMS is to mitigate the risk of loss of consciousness by ensuring:

Administration only in medically-supervised settings

Authorized Representative

- Establish policies and procedures to ensure that 1) all staff are trained on the risks and 2) the product is not dispensed for use outside the healthcare setting
- Patients must be continuously monitored, for the duration of the infusion and 12 hours after, by healthcare provider who can intervene if the patient experiences excessive sedation or loss of consciousness.

The FDA's proposed REMS includes a patient registry

Patients who are treated with brexanolone will be enrolled in a registry to better characterize the risk of LOC and management of the risk. A patient registry may capture data to allow for:

- An estimation of the risk of LOC associated with the use of brexanolone
- Identification of risk factors for LOC
- Other patient outcomes of interest

Summary

- If approved, brexanolone will require a REMS that ensures:
  - Administration in a medically-supervised setting settings that can ensure continuous patient monitoring by a HCP, and
  - Further characterization of the risk of LOC
- If approved, the Agency is considering what additional data is needed to support safe use of brexanolone in the home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