Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
November 2, 2018

Location: FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland

Topic: The committees discussed the efficacy, safety, and benefit-risk profile of new drug application (NDA) 211371, brexanolone 5 mg/mL intravenous injection, submitted by Sage Therapeutics, for the proposed indication of postpartum depression.

These summary minutes for the November 2, 2018 meeting of the Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration were approved on _____.

I certify that I attended the November 2, 2018 meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/S/
Kalyani Bhatt, BS, MS
Designated Federal Officer
Psychopharmacologic Drugs AC

/S/
Rajesh Narendran, MD
Chairperson
Psychopharmacologic Drugs AC

Summary Minutes meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
November 2, 2018

The meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met jointly on November 2, 2018, at the FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and Sage Therapeutics. The meeting was called to order by Rajesh Narendran, MD (Chairperson). The conflict of interest statement was read into the record by Kalyani Bhatt, BS, MS (Designated Federal Officer). There were approximately 150 people in attendance for the meeting. There were 14 Open Public Hearing speaker presentations.

Issue: The committees discussed the efficacy, safety, and benefit-risk profile of new drug application (NDA) 211371, brexanolone 5 mg/mL intravenous injection, submitted by Sage Therapeutics, for the proposed indication of postpartum depression.

Attendance:

Psychopharmacologic Drugs Advisory Committee Members Present (Voting): Walter S. Dunn, MD, PhD; Jess G. Fiedorowicz, MD, PhD; Satish Iyengar, PhD; Felipe A. Jain, MD Rajesh Narendran, MD (Chairperson); Erick Turner, MD; Kim O. Wictzak (Consumer Representative)

Psychopharmacologic Drugs Advisory Committee Members Not Present (Voting): Jessica J. Jeffrey, MD, MPH, MBA

Psychopharmacologic Drugs Advisory Committee Members Present (Non- Voting): Robert Russell Conley, MD (Industry Representative)

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Kelly Besco, PharmD, FISMP**,** CPPS; Marie R. Griffin, MD, MPH; Laurel A. Habel, MPH, PhD; Sonia Hernandez-Diaz, MD, MPH, DrPH; Martin Kulldorff, PhD; Steven B. Meisel, PharmD; Anne-Michelle Ruha, MD, FACMT; Anne-Michelle Ruha, MD, FACMT; Terri L. Warholak, PhD, RPh, CPHQ, FAPhA

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting): Denise M. Boudreau, PhD, RPh; Suzanne B. Robotti (Consumer Representative); Soko Setoguchi, MD, DrPh

Drug Safety and Risk Management Advisory Committee Members Not Present (Non-Voting): Linda Scarazzini, MD, RPh (Industry Representative)

Temporary Members (Voting): Gregory Burger, PharmD, CPPS, FASHP, NREMT; Sabrina Numann (Patient Representative); Tina Valbh, PharmD

FDA Participants (Non-Voting): Robert Temple, MD; Ellis Unger, MD; Mitchell Mathis, MD; Cynthia LaCivita, PharmD; Tiffany, Farchione, MD; Bernard Fischer, MD; Leah Hart, PharmD

Open Public Hearing Speakers: Varuna Srinivasan, MBBS MPH (National Center for Health Research); Tonya Fulwider **(**Mental Health America of Franklin County); Jabina Coleman, LSW, MSW, IBCLC (LIFE House Lactation & Perinatal Services and Perinatal Mental Health Alliance for Women of Color); Bassem Maximos, MD, MPH, FACOG (Texas Gulf Coast Maximos Ob/Gyn Bay Area Regional Medical Center); Nathaniel Z. Counts, JD (Mental Health America); Rebekah Long; Ann Smith, CNM P (Postpartum Support International); Steven D'Achille (The Alexis Joy D'Achille Foundation for Postpartum Depression); Stephanie Hathaway; Donna C. Kreuzer (video presented by Christine McNabb); Christine and Brandon McNabb CEO (This Mama Wines); Andrew Sperling (National Alliance on Mental Illness); Michael Pollock (The Depression and Bipolar Support Alliance); Kristina M. Deligiannidis, MD (Zucker School of Medicine at Hofstra/Northwell, and Zucker Hillside Hospital)

The Agenda was as follows:

Call to Order and Introduction of Committee	**Raj Narendran, MD** Chairperson, PDAC
Conflict of Interest Statement	**Kalyani Bhatt, BS, MS** Designated Federal Officer, PDAC
FDA Opening Remarks	**Tiffany Farchione, MD** Deputy Director Division of Psychiatry Products (DPP) Office of Drug Evaluation I (ODE I) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Sage Therapeutics, Inc.**
Brexanolone for Treatment of Postpartum Depression (PPD)	**Stephen J. Kanes, MD, PhD** Chief Medical Officer Sage Therapeutics, Inc .
Unmet Need for PPD Treatment	**Samantha Meltzer-Brody, MD** Ray M. Hayworth Distinguished Professor of Mood Disorders Associate Professor, Department of Psychiatry Director, Perinatal Psychiatry Program at Chapel Hill University of North Carolina Center for Women's Mood Disorders

Brexanolone Clinical Study Design and Efficacy	**Christopher Silber, MD** Senior Vice President, Clinical Development Sage Therapeutics, Inc.
Brexanolone Safety	**Helen Colquhoun, MD** Vice President, Medical Science Sage Therapeutics, Inc.
Clinical Perspective	**Samantha Meltzer-Brody, MD**
Clarifying Questions	
BREAK	
FDA PRESENTATIONS	
Clinical Overview	**Bernard Fischer, MD** Lead Medical Officer DPP, ODE I, OND, CDER, FDA
Safety Overview - Proposed Risk Evaluation and Mitigation Strategies	**Leah Hart, PharmD** Risk Management Analyst Division of Risk Management Office of Medication Error Prevention and Risk Management **Office of Surveillance and Epidemiology**, CDER, FDA
Clarifying Questions	
LUNCH	
OPEN PUBLIC HEARING	
Questions to the Committee/Committee Discussion	
BREAK	
Questions to the Committee/Committee Discussion (cont.)	
ADJOURNMENT	

Questions to the Committee:

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

Vote Result: **Yes: 18** **No: 0** **Abstain: 0**

Committee Discussion: *The committee unanimously agreed that substantial evidence has been presented by the Applicant to support a claim of effectiveness for brexanolone for the treatment of postpartum depression. Please see the transcript for details of the committee discussion.*

2. **VOTE:** 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?

   Vote Result: **Yes: 16** **No: 2** **Abstain: 0**

   Committee Discussion: *Most of the committee members agreed that the Applicant has adequately characterized the safety profile of brexanolone for the treatment of post-partum depression. These members agreed that the loss-of-consciousness events has been characterized sufficiently and can be addressed through a strong Risk Evaluation and Mitigation Strategy (REMS) program. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** There is evidence that both a 60 μg/kg/h and a 90 μg/kg/h dose (after 24 hours) are effective. Please discuss, if approved, 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

   Committee Discussion: *The panel members were conflicted on the dosing strategy. Some members noted that it may be easy to taper the dose down from 90 μg/kg/h to 60 μg/kg/h if the patient does not tolerate it well consistent with the clinical trial design. Some members noted "maybe more is not always better" and that the dose can be started at 60 μg/kg/h and then titrated up to 90 μg/kg/h based on inadequate response. One member noted perhaps starting and maintaining the dose at 60 μg/kg/h might simplify the administration of the drug and reduce medication errors. Please see the transcript for details of the committee discussion.*

4. **DISCUSSION**: Discuss whether the FDA's proposed REMS would ensure safe use of brexanolone. If no, please discuss what additional safeguards would be needed

   Committee Discussion: *Some members mentioned that the use of the drug should be restricted to the inpatient hospital settings. However, other members noted that the Agency should not dictate setting because it would be too restrictive and stifle innovation of clinics/providers to meet the recommended safety parameters outlined in the REMS for safe administration of the drug. Members agreed that the frequency of sedation monitoring should be outlined (for example every15 minutes). The panel members recommended the*

use/development of a structured sedation scale to monitor loss-of-consciousness. They recommended certification of all staff who would administer and monitor the infusion of the drug. Standardized order sets should be generated (by the Agency or Applicant) to reduce medication errors. The members recommended the clinical setting should have provisions for pulse oximetry and/or respiration monitoring and cardiopulmonary resuscitation (CPR availability). They also specified that the REMS should state that the mothers should not be allowed to handle their baby independently when receiving the infusion. Some members were in favor of a boxed warning for loss-of-consciousness in the label. Few members recommend that the duration of the stability and sterility be outlined for use in the REMS. Members also favored the Agency working with the Applicant to simplify the infusion paradigm (for example adopt standards such as one bag per concentration). They also mentioned that the REMS should caution against co-administration of brexanolone with GABAergic drugs (benzodiazepines, barbituates, anti-convulsant) and opioid drugs (methadone, buprenorphine) that may increase risk for sedation related adverse events. Please see the transcript for details of the committee discussion.

5. **VOTE**: Given the efficacy as presented, and 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 postpartum depression?

   Vote Result: **Yes: 17** **No: 1** **Abstain: 0**

   Committee Discussion: *The majority of the committee agreed that the efficacy as presented, and when used in a certified facility by qualified staff and as outlined in the FDA's proposed REMS, the benefits do outweigh the risks of brexanolone for the treatment of postpartum depression. Please see the transcript for details of the committee discussion.*

6. **DISCUSSION:** If approved, what additional data will be needed to support safe use of brexanolone at home and address outstanding issues?

   Committee Discussion: *The committee members were in favor of further examining: the efficacy of brexanolone in post-partum psychosis, bipolar disorder, and suicide; the efficacy at 30 micrograms vs. 60 micrograms vs. 90 micrograms/kg/hour; efficacy at 24 hours vs. 60 hours; the efficacy and safety in a large observational sample. They also recommended identifying sub-groups of patients that benefit the most from the medication and tolerate it the best. They also recommended the Applicant to pursue the efficacy and safety of a more patient-friendly intermittent dose administration strategy (such as daily infusions for 4 to 6 hours over 10 days). Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately *4:00 pm.*