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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE PSYCHOPHARMACOLOGIC DRUGS AND
DRUG AND RISK MANAGEMENT ADVISORY COMMITTEES
(PDAC and DSaRM)

Friday, November 2, 2018

8:00 a.m. to 4:04 p.m.

FDA White Oak Campus
Building 31, the Great Room
10903 New Hampshire Avenue
Silver Spring, Maryland

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6 Office of Executive Programs, CDER, FDA

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2 *(Consumer Representative)*

3 Co-Founder, Executive Director

4 Woodymatters

5 Minneapolis, Minnesota

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7 **PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEMBER**

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9 **Robert R. Conley, MD**

10 *(Industry Representative)*

11 Global Development Leader

12 Pain and Core Therapeutic

13 Team and Distinguished Scholar

14 Eli Lilly and Company

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13 Deputy Director for Clinical Science

14 CDER FDA

15 Deputy Director (Acting)

16 Office of Drug Evaluation I (ODE I)

17 Office of New Drugs (OND), CDER, FDA

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19 **Ellis Unger, MD**

20 Director

21 ODE I, OND, CDER, FDA

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Mitchell Mathis, MD

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1 P R O C E E D I N G S

2 (8:00 a.m.)

3 **Call to Order**

4 **Introduction of Committee**

5 DR. NARENDRAN: Good morning. I would first
6 like to remind everyone to please silence your cell
7 phones, smartphones, and any other devices if you
8 have not already done so. I would also like to
9 identify the FDA press contact, Sandy Walsh. If
10 you are present, please stand just right there.

11 My name is Raj Narendran. I'm the
12 chairperson for today's meeting. I will now call
13 the joint meeting of the Psychopharmacologic Drugs
14 Advisory Committee and the Drug Safety and Risk
15 Management Advisory committee to order. We'll
16 start by going around the table and introduce
17 ourselves.

18 We will start with the FDA to my left and go
19 around the table.

20 DR. UNGER: Good morning. My name is Ellis
21 Unger. I'm director of Office of Drug Evaluation I
22 in the Office of New Drugs, CDER.

1 DR. MATHIS: My name is Mitchell Mathis.
2 I'm the director of psychiatry products at the
3 Center for Drugs at CDER.

4 DR. FARCHIONE: Tiffany Farchione. I'm the
5 deputy director for psychiatry products.

6 DR. FISCHER: Bernie Fischer. I'm a
7 clinical reviewer in the Division of Psychiatry
8 Products.

9 DR. LaCIVITA: Good morning, Cynthia
10 LaCivita, director of the Division of Risk
11 Management and Office of Surveillance and
12 Epidemiology.

13 DR. WARHOLAK: Good morning. I'm Terri
14 Warholak and I'm a professor and assistant dean at
15 the University of Arizona College of Pharmacy.

16 DR. KULLDORFF: Good morning. My name is
17 Martin Kulldorff. I'm a biostatistician at Brigham
18 and Women's Hospital and Harvard Medical School.

19 DR. IYENGAR: I'm Satish Iyengar. I am in
20 the Departments of Statistics and Psychiatry at
21 University of Pittsburgh.

22 DR. DUNN: Good morning. I'm Walter Dunn.

1 I'm a psychiatrist at UCLA in the greater Los
2 Angeles V.A.

3 DR. TURNER: Good morning. I'm Erick
4 Turner. I'm at Oregon Health and Sciences
5 University and the V.A. Portland healthcare system.

6 DR. JAIN: Good morning. My name's Felipe
7 Jain. I'm a psychiatrist at Massachusetts General
8 Hospital and Harvard Medical School.

9 MS. BHATT: Good morning. My name is
10 Kalyani Bhatt. I'm the designated federal officer
11 for Psychopharmacologic Drugs Advisory Committee.

12 DR. NARENDRAN: Raj Narendran. I'm a
13 psychiatrist at UPMC in the University of
14 Pittsburgh.

15 DR. FIEDOROWICZ: Jess Fiedorowicz,
16 associate professor of psychiatry, epidemiology,
17 and internal medicine at the University of Iowa.

18 DR. WITCZAK: Good morning, Kim Witczak,
19 consumer representative.

20 DR. NUMANN: Good morning, Sabrina Numann,
21 patient representative out of Louisville.

22 DR. BESCO: Good morning, Kelly Besco. I'm

1 an inpatient pharmacist by background and,
2 currently, I serve as the medication safety officer
3 for Ohio Health, an 11-hospital health system in
4 Columbus, Ohio.

5 DR. GRIFFIN: Good morning, Marie Griffin.
6 I'm a general internist and pharmacoepidemiologist
7 at Vanderbilt University.

8 DR. MEISEL: Steve Meisel, director for
9 medication safety for Fairview Health Services in
10 Minneapolis.

11 DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz,
12 pharmacoepidemiologist, Harvard Center School for
13 Public Health in Boston.

14 DR. HABEL: Laurel Habel, epidemiologist,
15 Kaiser Permanente Northern California.

16 DR. RUHA: Hi, I'm Michelle Ruha. I'm a
17 medical toxicologist and professor at the
18 University of Arizona College of Medicine in
19 Phoenix.

20 DR. VALBH: Hi, I'm Tina Valbh. I'm a
21 clinical patient safety program development
22 pharmacist with Pharmaka Consulting.

1 DR. BURGER: Greg Burger. I am from
2 Stormont Vail Health in Topeka, Kansas, and the
3 medication safety coordinator, risk management.

4 DR. CONLEY: Good morning. I'm Rob Conley.
5 I'm the distinguished scholar for neuroscience for
6 Eli Lilly and an adjunct professor of psychiatry
7 and pharmacy science at the University of Maryland
8 and I'm here as the industry representative.

9 DR. NARENDRAN: Thank you. For topics such
10 as those being discussed at today's meeting, there
11 are often a variety of opinions, some of which are
12 quite strongly held.

13 Our goal is that today's meeting will be a
14 fair and open forum for discussion of these issues,
15 and that individuals can express their views
16 without interruption. Thus, as a gentle reminder,
17 individuals will be allowed to speak into the
18 record only if recognized by the Chairperson. We
19 look forward to a productive meeting.

20 In the spirit of the Federal Advisory
21 Committee Act and the Government in the Sunshine
22 Act, we ask that the advisory committee members

1 take care that their conversations about the topic
2 at hand take place in the open forum of this
3 meeting.

4 We are aware that members of the media are
5 anxious to speak with the FDA about these
6 proceedings. However, the FDA will refrain from
7 discussing the details of this meeting with the
8 media until its conclusion.

9 Also, the committee is reminded to please
10 refrain from discussing the meeting topic during
11 breaks or lunch. Thank you.

12 Now, I'll pass it to Kalyani Bhatt, who will
13 read the conflict of interest statement.

14 **Conflict of Interest Statement**

15 MS. BHATT: Good morning. The Food and Drug
16 Administration is convening today's joint meeting
17 of the Psychopharmacologic Drugs Advisory Committee
18 and the Drug Safety and Risk Management Advisory
19 Committee under the authority of the Federal
20 Advisory Committee Act, FACA, of 1972. With the
21 exception of the industry representative, all
22 members and temporary voting members of the

1 committees are special government employees and
2 regular federal employees from other agencies and
3 are subject to federal conflict of interest laws
4 and regulations.

5 The following information on the status of
6 this committee's compliance with federal ethics and
7 conflict of interest laws, covered by but not
8 limited to those found at 18 U.S.C., Section 208 is
9 being provided to participants in today's meeting
10 and to the public.

11 FDA has determined that members of these
12 committee are in compliance with the federal ethics
13 and conflict of interest laws.

14 Under 18 U.S.C., Section 208, Congress has
15 authorized FDA to grant waivers to special
16 government employees and regular federal employees
17 who have potential financial conflicts, when it is
18 determined that the agency's need for a special
19 government employee's services outweighs his or her
20 potential financial conflict of interest when the
21 interest of a regular federal employee is not so
22 substantial to be deemed likely to affect the

1 integrity of the service which the government may
2 expect from the employee.

3 Related to the discussion of today's
4 meeting, members and temporary members of these
5 committees have been screened for potential
6 financial conflicts of interest of their own, as
7 well as those imputed to them, including those of
8 their spouses or minor children, and for purposes
9 of 18 U.S.C. Section 208, their employers.

10 These interests may include investments,
11 consulting, expert witness testimony, contracts,
12 grants, CRADAs, teaching, speaking, writing,
13 patents and royalties, and primary employment.

14 Today's agenda involves discussion of the
15 efficacy, safety, and benefit-risk profile of new
16 drug application, NDA 211374, brexanolone,
17 intravenous injection submitted by Sage
18 Therapeutics for a proposed indication of
19 postpartum depression.

20 This is a particular matters meeting, during
21 which specific matters related to Sage
22 Therapeutics' NDA will be discussed. Based on the

1 agenda for today's meeting and all financial
2 reported by the committee members and temporary
3 voting members, no conflict of interest waivers
4 have been issued in connection with this meeting.

5 To ensure transparency, we encourage all
6 standing committee members and temporary members to
7 disclose any public statements that they have made
8 concerning the product at issue.

9 With respect to FDA's invited industry
10 representative, we would like to disclose that
11 Dr. Robert Conley is participating in this meeting
12 as a non-voting industry representative, acting on
13 behalf of regulated industry. Dr. Conley's role at
14 this meeting is to represent industry in general
15 and not any particular company. Dr. Conley is
16 employed by Eli Lilly.

17 We would like to remind members and
18 temporary members that, if the discussions involve
19 any other products or firms not already on the
20 agenda for which an FDA participant has a personal
21 or imputed financial interest, participants need to
22 exclude themselves from such involvement and their

1 exclusion will be noted for the record.

2 FDA encourages all participants to advise
3 the committee of any financial relationships that
4 they may have with the firm at issue. Thank you.

5 DR. NARENDRAN: Thank you. We will now
6 proceed with the FDA's introductory remarks,
7 presented by Dr. Tiffany Farchione, deputy
8 director.

9 **FDA Presentation - Tiffany Farchione**

10 DR. FARCHIONE: Hi, good morning, everyone.
11 Thank you for being here again so early in the
12 morning. And I want to particularly thank the
13 members of the committee who are here for their
14 second advisory committee date in a row.

15 I realize that, while it may be convenient
16 for travel planning and things to have you here for
17 two days in a row, that asking you to review two
18 background packages for two new molecular entities
19 is a heavy lift, so thank you for working so hard
20 and for reviewing these things so diligently. We
21 really appreciate it.

22 So today, we are here to talk about

1 brexanolone. So I think that, overall, having the
2 back-to-back advisory committee meetings, having
3 two novel antidepressants two days in a row is
4 exciting.

5 It has given me a lot of hope for the fact
6 that pharmaceutical companies are pursuing new
7 mechanisms of action and new treatments for mental
8 illness. There was a drought for a long time and
9 so, even though this is a lot of work for
10 everybody, it makes me really happy to have
11 everyone here and that we're talking about new
12 treatments for illnesses that affect a lot of
13 patients.

14 So today, what we have with brexanolone is a
15 new drug with a new mechanism of action and a new
16 route of administration for a new indication.

17 So again, we are talking about
18 antidepressant, but this is particularly for
19 postpartum depression and it would be the first
20 drug approved for that indication. So for today,
21 we're here to obtain input from the committee on
22 whether the data that was provided by the applicant

1 will support a favorable benefit-risk profile in
2 order to support approval for this new drug.

3 I do want to at least get you guys thinking
4 up front about the questions that we're going to
5 ask you towards the end of the day. As is usual,
6 we will ask you whether substantial evidence has
7 been presented to support the claim of
8 effectiveness for brexanolone for the treatment of
9 postpartum depression.

10 We will also ask whether the safety profile
11 has been adequately characterized and whether the
12 benefits outweigh the risks, so these are our usual
13 questions for the voting items.

14 But we'll also ask you to discuss a few
15 things that are pertinent to this particular
16 application.

17 So we're going to ask about the potential
18 dosing recommendations if this drug were to be
19 approved. We want to talk about risk mitigation
20 strategies because there are some unique safety
21 issues to discuss over the course of the day.

22 Then we want to talk about what additional

1 data would be needed to support the safe use of
2 brexanolone in alternative settings, so whether
3 inpatient, outpatient, home use, et cetera. What
4 would be the data that would be needed to support
5 those different settings?

6 So with that, I will pass it back over to
7 the committee. Thank you.

8 DR. NARENDRAN: Thank you. Both the FDA and
9 the public believe in a transparent process for
10 information gathering and decision making. To
11 ensure such transparency at the advisory committee
12 meeting, FDA believes that it is important to
13 understand the context of an individual's
14 presentation.

15 For this reason, FDA encourages all
16 participants, including the sponsor's non-employee
17 presenters, to advise the committee of any
18 financial relationships they may have with the firm
19 at issue, such as consulting fees, travel expenses,
20 honoraria, and interest in the sponsor, including
21 equity interests, and those based upon the outcome
22 of the meeting.

1 Likewise, FDA encourages you, at the
2 beginning of your presentation, to advise the
3 committee if you do not have any such financial
4 relationships.

5 If you choose not to address this issue of
6 financial relationships at the beginning of your
7 statement, it will not preclude you from speaking.

8 We will now proceed with Sage Therapeutics'
9 presentations.

10 **Applicant Presentation - Stephen Kanés**

11 DR. KANES: Good morning. Members of
12 today's advisory committee and members of the FDA,
13 my name is Steve Kanés. I'm a psychiatrist and the
14 chief medical officer of Sage Therapeutics. We're
15 here today to talk about postpartum depression and
16 brexanolone, a paradigm-changing treatment for this
17 important and debilitating condition.

18 Post-partum depression or PPD is a serious
19 condition and the most common medical complication
20 of childbirth. It affects 1 in 9 women who give
21 birth in the United States, which translates to
22 roughly 400,000 women and families affected every

1 year.

2 At a time in life when many women expect to
3 be happy and fulfilled, they're blindsided by the
4 onset of depression, causing enormous suffering for
5 both the mother and her family. Despite all this,
6 there are no approved treatment options
7 specifically for postpartum depression.

8 We've developed brexanolone based on
9 insights into the biology of PPD. Fluctuations in
10 pregnanolone levels in the peri-partum period have
11 been associated with symptoms of PPD.

12 These fluctuations also lead to changes in
13 GABA A receptor function in the brain. In
14 susceptible women, this process is disrupted,
15 leading to dynamic alterations in brain network
16 function.

17 PPD may occur when the brain fails to adapt
18 to these dynamic changes, resulting in depression.
19 Brexanolone is chemically identical to the
20 endogenous neuroactive steroid, allopregnanolone.
21 Unlike other GABA-positive allosteric modulators,
22 at therapeutic doses, brexanolone enhances both

1 synaptic and extra synaptic GABA-A receptor
2 function and increases the number of GABA-A
3 receptors.

4 These effects on the GABA system can produce
5 both rapid and sustained increases in brain network
6 inhibition. We know from imaging studies that
7 alterations in network connectivity are associated
8 with major depressive episodes and more recently
9 have been observed in PPD because GABA-A receptors
10 are powerful regulators of inhibition in neural
11 networks.

12 We hypothesize brexanolone is altering
13 symptoms of PPD by resetting dysregulated cortical
14 networks.

15 If you're familiar with antidepressants and
16 their mechanisms, you'll recognize that this is an
17 entirely different approach. The FDA designated
18 brexanolone as a breakthrough therapy for PPD.
19 This designation is granted for serious conditions
20 where preliminary clinical data indicate
21 substantial clinical improvement over currently
22 available therapy.

1 We've worked closely with the agency to
2 design and complete our clinical program and to
3 develop an approach for safe use. If approved,
4 this will be the first medication specifically
5 designed for postpartum depression. It's also the
6 largest prospective placebo-controlled set of data
7 ever collected for this condition.

8 Our proposed indication for brexanolone is
9 for the treatment of postpartum depression. The
10 DSM V defines PPD as a major depressive episode
11 with onset of symptoms during pregnancy or shortly
12 after delivery. However, brexanolone will only be
13 administered in the postpartum period.

14 In contrast to most antidepressant
15 therapies, which are taken orally over an extended
16 period of time, brexanolone is a single
17 administration of continuously infused over 60
18 hours.

19 Dosing is weight based. The recommended
20 maximum dosing regimen is 90 micrograms per
21 kilogram per hour, including both titration and
22 tapering steps. Our PPD clinical development

1 program includes 4 studies in adult women with PPD;
2 one open-label proof-of-concept study and 3
3 placebo-controlled randomized double-blind studies.

4 Our presentation today will focus on what we
5 call the key studies; 202A, 202B, and 202C. It is
6 noteworthy that every placebo-controlled
7 brexanolone study we've conducted has been
8 positive. To support the brexanolone PPD program,
9 we conducted a full suite of clinical pharmacology
10 studies as well an exploratory study in a different
11 indication. These studies characterize the
12 pharmacokinetics, pharmacodynamics, breast milk
13 concentration, and potential for abuse.

14 They show that brexanolone is rapidly
15 cleared. There's no need for dose adjustment in
16 patients with hepatic or renal impairment, nor is
17 it necessary to interrupt breast feeding during
18 infusion.

19 As you'll see, overall, our clinical program
20 consistently demonstrated that brexanolone provides
21 a reduction in depressive symptoms within 2.5 days,
22 which persists after treatment. In the context of

1 a new mom, this means being treated on a Friday and
2 feeling better by Sunday.

3 This is a unique profile for a drug used to
4 treat a psychiatric condition.

5 The safety profile of brexanolone is well
6 characterized and consistent with its GABA
7 mechanism of action. Brexanolone is well tolerated
8 in most women and we'll discuss the risk of
9 excessive sedation which was observed in some
10 patients. To mitigate this risk, we've taken a
11 number of steps which form the principles to ensure
12 safe administration. These incorporate and agree
13 with FDA's guidance.

14 In summary, brexanolone has the potential to
15 provide women suffering with postpartum depression
16 the rapid and sustained improvement we need to feel
17 well, care for themselves, and their families.

18 Let me review the agenda for the rest of our
19 presentation. Dr. Samantha Meltzer-Brody will
20 present the urgent unmet need for women suffering
21 from PPD. Dr. Christopher Silber will discuss the
22 design of our clinical trials and share the robust

1 and consistent efficacy results from our 3 studies.

2 Then Dr. Helen Colquhoun will present the
3 well-characterized safety profile for brexanolone
4 that reflects the primary pharmacology of the drug
5 and Dr. Meltzer-Brody will provide her clinical
6 perspective.

7 Finally, Dr. Schacterle will moderate any
8 questions the committee may have. We also have
9 additional experts with us today to answer
10 questions. All external experts have been
11 compensated for their time and travel. Thank you,
12 and I'll now turn the lectern to Dr. Meltzer-Brody.

13 **Applicant Presentation**

14 **Samantha Meltzer-Brody**

15 DR. MELTZER-BRODY: Thank you. I'm
16 Dr. Samantha Meltzer-Brody. I'm a practicing
17 psychiatrist at the University of North Carolina at
18 Chapel Hill and I direct the perinatal psychiatry
19 program at the UNC Center for Women's Mood
20 Disorders.

21 I'm also the president of the Marce Society
22 of North America, a perinatal depression research

1 society. I've been caring for mothers with
2 postpartum depression and their families for more
3 than 20 years and have been involved with
4 brexanolone development since Sage was a very small
5 start-up five years ago.

6 We began with an open-label study in women
7 with severe PPD. The results were impressive, so
8 we moved on to double-blind phase 2 and 3 trials.
9 I was the principal investigator in these trials.

10 Post-partum depression or PPD has often gone
11 undiagnosed, undertreated, and there is a great
12 unmet medical need. PPD is different than what we
13 call the baby blues, which are symptoms of feeling
14 sad or more tearful after having a baby.

15 The baby blues are a mild transient mood
16 lability that occurs in up to 80 percent of women
17 after giving birth. It is considered a normal,
18 emotional adjustment which causes no more than mild
19 dysfunction and generally resolves in 10 to 14
20 days.

21 But that's not the population we're talking
22 about today. While all moms with a newborn can

1 feel exhausted and vulnerable, the diagnosis of
2 postpartum depression is distinct and more severe.

3 Based on the Diagnostic of Statistical
4 Manual of Mental Disorders, the DSM V, PPD meets
5 the criteria for a major depressive episode, which
6 is the persistence of symptoms that cause
7 functional impairment most of the day, nearly every
8 day for at least 2 weeks. This is quite distinct
9 from the baby blues and warrants treatment.

10 Post-partum depression is usually considered
11 a type of major depression, more homogenous than
12 other forms of the disorder. It occurs in
13 reproductive-aged women at a discreet time point,
14 often in the third trimester of pregnancy or after
15 childbirth. It has a specific pathophysiology,
16 including sensitivity to hormonal fluctuations and
17 genetic contributions.

18 PPD is also more heritable than non-
19 perinatal depression. In the American Journal of
20 Psychiatry paper that I co-authored with a Swedish
21 group using their Twin Registry, we found that the
22 inheritability of PPD is 44 to 54 percent compared

1 to 32 percent of those with non-perinatal
2 depression.

3 Post-partum depression is debilitating and
4 women may have a broad range of clinical symptoms.
5 Patients in my clinical often describe symptoms of
6 low mood, decreased interest or pleasure in usual
7 activities, being unable to enjoy the baby, feeling
8 anxious, and having ruminating thoughts.

9 While it's normal for all mothers to
10 experience some increased vigilance after having a
11 baby, for moms with PPD, that vigilance can be
12 overwhelming and consuming. Commonly mothers with
13 PPD experience difficulty sleeping, even when the
14 baby is sleeping or being cared for by a partner.

15 Many of my patients report staying up all
16 night, watching their baby breathe. This quickly
17 becomes a family emergency. PPD symptoms may also
18 interfere with mother-baby bonding and attachment.
19 Some women even wish they didn't have the baby at
20 all.

21 In addition, there's a growing and robust
22 literature documenting that untreated PPD results

1 in significant adverse consequences for the child
2 and the overall family unit. There is a great need
3 for treatment options that can change this
4 trajectory.

5 Most unfortunately, women with PPD may
6 experience suicidal ideation and they have an
7 increased risk for suicides. Recent studies
8 suggest that 19 to 30 percent of women with PPD
9 experience suicidal ideation. And in developed
10 countries, suicide is the leading cause of maternal
11 death following childbirth.

12 In the most severe cases, women can have
13 intrusive thoughts about fear of harming the baby.
14 In 1 study, 41 percent of women with PPD reported
15 such intrusive thoughts compared with 7 percent in
16 a controlled population of mothers.

17 Because of the considerable stigma
18 associated with PPD, many women feel shame and
19 guilt about these symptoms, which prevents them
20 from reaching out for help.

21 Today, however, women with PPD are often not
22 treated or even diagnosed. One reason is that

1 screening for PPD is inconsistent. For example, at
2 UNC, we have universal screening and referral to
3 treatment. However, there are private practices
4 that do not screen at all.

5 Recently, we have seen a movement towards
6 improved national standardization of screening for
7 postpartum disorders. This year, the American
8 College of Obstetricians and Gynecologists released
9 fourth-trimester guidelines and California passed a
10 new bill both making screening a strong priority.

11 However, screening is only a first step. It
12 must be followed by referral and delivery of
13 effective treatment. But right now, there are no
14 pharmacologic therapies specifically approved to
15 treat postpartum depression.

16 The SSRI antidepressants approved for major
17 depressive disorder in general are the mainstay of
18 drug therapy for PPD, but studies have shown that
19 these antidepressants take weeks to months to have
20 an initial effect in women with PPD.

21 Many women do not ever achieve an adequate
22 response or symptom remission. I have to tell my

1 patients that it may take them weeks or longer to
2 get them feeling well. That can seem like an
3 interminable amount of time for a family in crisis
4 with a newborn and a sick mom.

5 Clearly, patients and their families need
6 new treatment options. In summary, giving the
7 lasting negative effects associated with untreated
8 or poorly treated PPD, there is a clear unmet need
9 for improved treatment options.

10 We need effective therapies with a rapid
11 onset of action. An effective and rapidly acting
12 medication would reduce the potential for
13 significant morbidity and mortality and allow
14 mothers to experience more positive interactions
15 with their babies and their families.

16 Thank you for your attention. I will now
17 turn the lectern over to Dr. Silber.

18 **Applicant Presentation - Christopher Silber**

19 DR. SILBER: Thank you, Dr. Meltzer-Brody.
20 I'm Chris Silber, senior vice president of clinical
21 development at Sage. I'll review the clinical
22 trial design of our three key studies that provide

1 evidence to support a positive benefit-risk
2 assessment for brexanolone.

3 The three key studies were separate studies;
4 study 202A, B, and C. These were conducted using
5 nearly identical study designs under what we're
6 referring to as an umbrella protocol.

7 Upon completion of study A, studies B and C
8 were designed in consultation with the FDA. They
9 each were placebo controlled to parallel group,
10 randomized trials, conducted in clinical research
11 sites in the United States.

12 Each study was self-contained in that it
13 enrolled its own placebo group. Patients were
14 randomized to a 60-hour infusion of brexanolone or
15 placebo. Each trial included the 90-microgram per-
16 kilo per-hour dose regimen.

17 Study 202B also included an arm to evaluate
18 a 60-microgram per-kilo-per-hour dose regimen.

19 The primary endpoint for each of these
20 studies was assessed at the end of the infusion at
21 hour 60, which is about 2.5 days. Following
22 completion of the infusion, patients remained at

1 the research site until hour 72 and then returned
2 home. They received no further study treatment and
3 were followed to day 30.

4 Each study included the same dosing regimen,
5 which is weight based, and was selected to optimize
6 tolerability by titrating up to the maximum dose
7 and then tapering down. Here, we will show the
8 dose along the Y axis and the 60-hour treatment
9 period along the X axis.

10 Brexanolone was administered as a continuous
11 IV infusion, starting with a 24-hour titration
12 phase followed by a 28-hour phase receiving the
13 maximum dose. And then the dose was tapered over 8
14 hours.

15 We also explored the brexanolone 60-dose
16 regimen in study 202B. It's important to note that
17 all brexanolone-treated patients received the same
18 dosing regimen for the first 24 hours.

19 Now, let's turn to the eligibility criteria
20 for these studies. In all three studies, women
21 were ages 18 to 45 and no more than 6 months
22 postpartum. Eligible patients met DSM criteria for

1 a major depressive episode, verified by the
2 structured clinical interview for DSM.

3 To enter in the trial, the onset of PPD
4 started either during the third trimester of
5 pregnancy or within 4 weeks following delivery.
6 Women had either ceased lactating or were willing
7 to temporarily cease breastfeeding.

8 The main difference in inclusion criteria
9 was the HAM-D total score prior to dosing. In
10 order to study a range of PPD severity, patients
11 were enrolled in studies 202A and 202B, with a
12 baseline score of 26 or greater typically
13 considered severe.

14 In study 202C, patients were enrolled with a
15 baseline score of 20 to 25 points, which is
16 considered more moderate depression. Turning to
17 the endpoints, primary endpoint in the 3 key
18 studies was a change from baseline in the 17-item
19 Hamilton Rating Scale for Depression, total score,
20 at the end of infusion or hour 60.

21 The HAM-D is recognized as a valid and
22 reliable scale used in clinical research to measure

1 the cardinal symptoms of major depression,
2 including those with PPD. It's a standard measure
3 used to quantify a drug effect for approval.

4 We consulted experts to adapt the HAM-D to
5 assess a rapid onset of action in the setting of
6 postpartum depression. The assessment was
7 standardized to minimize variability in collection
8 and scoring.

9 In studies 202B and 202C, the pre-specified
10 key secondary endpoint was the change from baseline
11 in HAM-D total score at day 30. We analyzed the
12 HAM-D in a variety of ways, by change over time,
13 individual item, subgroup by baseline
14 characteristic, HAM-D response, and HAM-D
15 remission.

16 An additional clinician-rated secondary
17 endpoint was the response on the Clinical Global
18 Impression Improvement or CGI-I.

19 Both data analyses were handled consistently
20 across the 3 studies. Each study had its own
21 prospective independent analysis plan. The full
22 analysis that was defined as all randomized

1 patients who were dosed. The primary and key
2 secondary endpoints were analyzed using a mixed
3 effects model for repeated measures or MMRM
4 analysis method.

5 According to the prospective SAPs, we will
6 show you the primary efficacy results independently
7 by study to demonstrate that efficacy is
8 reproducible across studies.

9 Let's look at the results. Few patients
10 discontinued in each individual studies and the
11 reasons were similar. Only one patient
12 discontinued the study due to an adverse event.
13 The low study discontinuation rate was similar
14 across the treatment groups.

15 Moving now to demographics, within each of
16 the key studies, demographics were balanced across
17 treatment groups. The mean age was about 28 years.
18 Patients were racially and ethnically diverse.

19 The mean weight was consistent with women in
20 the United States who have recently delivered a
21 baby. The baseline characteristics of the
22 population were also balanced across the treatment

1 groups within each key study. Approximately one-
2 quarter of patients were taking antidepressants at
3 baseline, so despite antidepressant treatment,
4 these women still met criteria for a major
5 depressive episode.

6 I'd like to point out that patients taking
7 antidepressants at baseline had to have been on a
8 stable dose for at least 14 days prior to
9 screening.

10 On average, women entered the study between
11 3 and 4 months postpartum. The majority of women
12 experienced PPD onset after delivery as opposed to
13 in the third trimester of pregnancy.

14 Now, we will look at the HAM-D results by
15 study. Each of the 3 key studies independently
16 demonstrated the efficacy of brexanolone. For each
17 of these, I'll show least squares mean change from
18 baseline in the total HAM-D score on the Y axis
19 with a 60-hour treatment period displayed on the X
20 axis.

21 First, let's look at study 202A.
22 Brexanolone met the primary efficacy endpoint with

1 a significantly greater reduction in baseline in
2 HAM-D total score compared to placebo at hour 60.

3 And this was maintained at day 30.

4 These results were replicated in study 202B
5 at hour 60 for both the 90 and 60 groups with a
6 significant difference maintained for both groups
7 at day 30.

8 In study 202C, where patients had lower HAM-
9 D scores due to enrollment criteria, the primary
10 endpoint was also met, although the difference from
11 placebo at day 30 was not significant. The effect
12 in the brexanolone group was maintained.

13 This finding is consistent with what you'll
14 see in the remission and response data at day 30
15 for 202C. Let me orient you to this forest plot of
16 the individual HAM-D items. Points to the left of
17 the zero line favor brexanolone and those to the
18 right favor placebo.

19 The individual item scores of the HAM-D
20 consistently favor brexanolone over placebo,
21 confirming an overall antidepressant effect of the
22 drug. Notably, for those items of particular

1 importance to women with PPD, namely depressed
2 mood, feelings of guilt, the suicide score, and
3 work, and activities, the brexanolone group had
4 significantly greater reductions than the placebo
5 group.

6 For completeness, here you see the
7 brexanolone 60 dose from study 202B, which shows
8 similar results. Brexanolone efficacy was also
9 consistent across subgroups. We examined a number
10 of subgroups to understand whether any baseline
11 characteristics influenced response.

12 As you can see from this forest plot, the
13 results across subgroups showed directional
14 consistency in favor of brexanolone over placebo.
15 Of particular interest, there was no difference in
16 effectiveness in those women taking and not taking
17 antidepressants.

18 Again, the brexanolone 60-dose results from
19 study 202B were similar. Turning to the results
20 for remission, response, and CGI-I, at hour 60, a
21 greater proportion of patients receiving
22 brexanolone achieved HAM-D remission.

1 Across studies, 50 percent of patients on
2 brexanolone ranging from 31 to 70 percent were in
3 remission at hour 60, with the results at day 30
4 for the 3 studies shown here.

5 Additionally, a greater proportion of
6 patients in the brexanolone group achieved HAM-D
7 response compared to placebo. 70 to 87 percent of
8 women receiving brexanolone were responders at hour
9 60.

10 Here are the results at day 30. For CGII, a
11 significantly greater percentage of patients in the
12 brexanolone group achieved CGI response compared to
13 placebo at hour 60. And here, we see the results
14 again at day 30. In general, results at day 30 for
15 HAM-D remission, HAM-D response, and CGII response
16 for brexanolone showed that patients who showed
17 improvement at hour 60 maintained improvement at
18 day 30.

19 In summary, the efficacy data from our key
20 studies demonstrate that brexanolone provides a
21 rapid and clinically meaningful improvement in PPD
22 symptoms with a single 2.5-day treatment. The

1 primary endpoint was met in 3 independent studies.
2 The efficacy results were consistent across
3 studies, severities of PPD, and across the primary
4 and secondary endpoints.

5 Brexanolone demonstrated a stable reduction
6 in depressive symptoms sustained through 4 weeks
7 after the end of the infusion. And both the 60 and
8 90 doses demonstrated efficacy.

9 I'll now turn the lectern to Dr. Helen
10 Colquhoun to present the safety results.

11 **Applicant Presentation - Helen Colquhoun**

12 DR. COLQUHOUN: Thank you. I'm Helen
13 Colquhoun, vice president of medical science at
14 Sage. I will be presenting the safety data from
15 our brexanolone clinical studies, starting with
16 safety exposures. In total, the PPD clinical
17 program includes data from 367 unique subjects
18 exposed to brexanolone, including 144 patients with
19 postpartum depression.

20 Today, we will focus on the safety data from
21 the 140 patients who were administered brexanolone
22 in our 3 key placebo-controlled studies, 202A, B,

1 and C.

2 I would like to explain our approach to the
3 data presentation in this safety section. As you
4 will see, the safety and tolerability profile of
5 brexanolone is well characterized and reflects the
6 primary pharmacology of the drug.

7 Most events related to the primary
8 pharmacology of brexanolone have onset in the first
9 24 hours of the infusion, when the brexanolone 60
10 and 90 dose groups were receiving the same dose.
11 After 24 hours, when the doses were different, the
12 frequency and type of adverse events were similar
13 for both groups.

14 Given the similar safety and tolerability
15 profiles of the brexanolone 90 and 60 dose groups,
16 we elected to combine them to compare to placebo.
17 The larger brexanolone dataset increases our
18 ability to detect and summarize less frequent
19 events.

20 For transparency, we will present the
21 combined total brexanolone group and the individual
22 dose groups alongside the pooled placebo data.

1 FDA and Sage agree that brexanolone, which
2 is chemically identical to endogenous
3 allopregnanolone, is unlikely to be associated with
4 off-target effects and generated no safety signals
5 in laboratory ECG or vital sign data at therapeutic
6 doses.

7 In this safety presentation, I'm therefore
8 going to present some data on our suicidality, then
9 data from our study in healthy, lactating women,
10 and then devote the rest of the presentation to
11 adverse events, particularly those that are related
12 to the primary pharmacology of brexanolone.

13 We carefully evaluated suicidality using the
14 Columbia Suicide Severity Rating Scale or C-SSRS.
15 There was no clinical worsening in patients on
16 brexanolone compared to placebo.

17 Two patients reported post-baseline suicidal
18 behavior. Both behaviors occurred after discharge
19 from the unit. One of these patients reported the
20 serious adverse events of suicidal ideation and an
21 intentional overdose of other medications.

22 The other patient reported non-suicidal

1 self-injurious behavior. Both patients had a
2 history of suicidal behavior prior to entry to the
3 study.

4 I will now review our recommendations around
5 breastfeeding. Our data support the continuation
6 of breastfeeding during the infusion of
7 brexanolone. The decision whether or not to
8 breastfeed during the infusion is one that will be
9 made by the mother and her doctor based on the
10 risk-benefit assessment of her situation.

11 In accordance with FDA guidance, we
12 conducted a study in 12 healthy lactating women who
13 were administered the 90 dose regimen. We measured
14 brexanolone concentrations in all the breast milk
15 collected over 7 days.

16 We used the data to calculate the relative
17 infant dose or RID, which was 1.3 percent at
18 maximum. Drugs with an RID of less than 10 percent
19 are considered to constitute low risk to the
20 breastfed infant of a mother taking that drug. In
21 addition, the oral bioavailability of brexanolone
22 is very low, less than 5 percent in adults.

1 Let's now turn to the presentation of
2 adverse events. In our key studies, the incidence
3 of adverse events on both brexanolone dose groups
4 and brexanolone overall was very similar to that on
5 placebo, about 50 percent in these dose groups.

6 One patient from each of the brexanolone-
7 alone dose groups experienced 2 serious adverse
8 events each and these were the only serious adverse
9 events reported in the PPD clinical program. 1
10 patient randomized to the 90-dose regimen who had a
11 serious adverse event terminated early from the
12 study and this was the only early discontinuation
13 in a key study due to an adverse event.

14 Study drug discontinuations were infrequent
15 in all groups. In the brexanolone group, 2
16 patients randomized to the 90 dose regimen
17 discontinued study drug due to sedation-related
18 events. 1 patient on placebo and one patient on
19 the 60 dose regimen discontinued study drug early
20 due to an infusion site-related event.

21 Dose interruption and reduction occurred in
22 10 patients in the brexanolone group, most commonly

1 due to reports of sedation-related events. 3
2 patients on placebo also experienced dose
3 interruption or reduction due to adverse events.
4 All these patients subsequently completed the study
5 and all adverse events resolved.

6 Approximately 2 percent of patients in each
7 group reported severe adverse events, including 1
8 patient on the 60 dose regimen and 2 patients on
9 the 90 dose regimen.

10 Most adverse events in the studies were
11 reported to be mild. There were no deaths in the
12 clinical PPD program.

13 Next, we will review the most commonly
14 reported adverse events. Brexanolone was tolerated
15 with a well-characterized adverse event profile.
16 Here, we present the adverse events that were
17 reported in at least 3 percent of patients in
18 either the combined brexanolone or placebo groups.
19 Adverse events such as headache, dizziness,
20 somnolence, and dry mouth were more common 60 than
21 90 and infusion site pain and nausea were more
22 common on the 90 dose.

1 You will note that several events were more
2 commonly reported on brexanolone overall than on
3 placebo such as dizziness, somnolence, sedation,
4 and fatigue. These are consistent with the primary
5 pharmacology of brexanolone, namely GABA-A
6 allosteric modulation.

7 To better summarize this type of event, we
8 grouped them together as sedation-related events.
9 Let me explain how we did this. As is typical in
10 clinical trials, we recorded all adverse events in
11 the database.

12 No standardized lexicon was utilized, so a
13 variety of different verbatim terms were used by
14 patients and investigators to describe sedative
15 effects. These verbatim terms were then coded to
16 the closest preferred term in an industry standard
17 coding dictionary.

18 Following coding, we grouped together those
19 terms that could have been related to the primary
20 pharmacology of brexanolone. This grouping was
21 called sedation-related events and allowed us to
22 better describe the incidents, time course, and

1 duration of these events. These are listed with
2 the percentage of patients on brexanolone who
3 reported each one.

4 The most common terms reported on
5 brexanolone were dizziness, somnolence, sedation,
6 and fatigue.

7 We further grouped together the terms that
8 indicate loss or near loss of consciousness, which
9 occurred in 4 percent of patients. These included
10 loss of consciousness, syncope, altered state of
11 consciousness, and presyncope.

12 I will now discuss the sedation-related
13 events and then describe the loss or near-loss of
14 consciousness events. Overall, sedation-related
15 events occurred in 27 percent of patients on
16 brexanolone, 34 percent on the 60 dose regimen, 26
17 percent on the 90 dose regimen, and 14 percent on
18 placebo.

19 We looked at factors that could predict
20 which patients were more likely to report sedation-
21 related events. We found that there was an
22 additive increase in the likelihood of reporting

1 these events in patients taking concomitant
2 antidepressant therapy. Sedation-related events
3 were also more likely to be reported by patients on
4 concomitant benzodiazepines.

5 We looked at the time of onset of sedation-
6 related events. This figure shows, on the Y axis,
7 the percentage of patients reporting sedation-
8 related events and, on the X axis, the time window
9 of onset of the event. The blue bar represents the
10 30, then 60 dose levels that everyone received for
11 the first 24 hours of the infusion.

12 For the rest of the infusion, the 60 dose
13 level is represented by the turquoise bar and the
14 90 dose level by the purple bars. Despite there
15 being a higher proportion of sedation-related
16 events reported on the 60, then the 90 dose
17 regimen, you can see that most sedation-related
18 events had onset in the first 24 hours of the
19 infusion, with all patients receiving the same
20 dose.

21 After 24 hours, the same proportion of
22 patients on the 60 and 90 doses reported sedation-

1 related events. Based on these group data, no
2 incremental risk was associated with titrating up
3 to the 90 dose level at hour 24.

4 Few sedation-related events were reported
5 after the end of the infusion and this was reported
6 by patients receiving both brexanolone and placebo.
7 This confirms that the risk of sedation-related
8 events is largely confined to when the infusion is
9 running.

10 The intervention of interrupting or
11 permanently discontinuing the infusion occurred in
12 5 patients who lost or nearly lost consciousness
13 while receiving the brexanolone infusion. In all
14 cases of loss of consciousness, there was a
15 preceding period of excessive sedation, during
16 which the patient was impaired by the sedative
17 effects of brexanolone.

18 During this time, each patient was able to
19 alert staff to the fact that they did not feel
20 well. In no case was their airway, respiratory, or
21 hemodynamic compromise. Nobody fell and there were
22 no sequelae.

1 We have identified that overdose effects on
2 brexanolone is a risk for loss of consciousness. 2
3 patients received higher than specified doses of
4 brexanolone due to infusion pump malfunctions. In
5 both cases, the infusion was interrupted and the
6 patients rapidly recovered.

7 After recovery, both resumed the infusion of
8 the protocol-specified dose and completed the
9 study. Neither patient had airway or respiratory
10 compromise. It is noteworthy that the estimated
11 bolus dose received by patient A was more than 700
12 micrograms per kilogram.

13 The estimated dose received by patient B was
14 more than 1,200 micrograms per kilogram per hour
15 over 90 minutes. For the other 3 cases which
16 occurred at protocol-specified doses, no consistent
17 predictive factors have been identified, but all 3
18 patients reported excessive sedation to staff prior
19 to losing consciousness.

20 The first patient was one of the serious
21 adverse events and she experienced an event
22 described as altered state of consciousness and

1 syncope. She had dizziness, sweating, and nausea,
2 and walked to the nurses' station to let them know
3 that she did not feel well.

4 She was given something to eat and drink and
5 returned to her bed, where she became unresponsive.
6 Staff turned off the infusion and, within 10
7 minutes, she opened her eyes to verbal stimuli.

8 Approximately 35 minutes later, she was
9 responsive but amnesic to the event. Her oxygen
10 saturation at the time of the event was 98 percent.

11 The next patient reported severe somnolence
12 on day 2 of the infusion. Shortly afterwards, she
13 sat down on the floor and then lost consciousness.
14 Her oxygen saturation at the time was 100 percent.
15 Staff paused the infusion immediately.

16 Within 15 minutes, she woke up and, within
17 45 minutes, the event had completely resolved. The
18 infusion was restarted initially at the lowest
19 dose, but then titrated up to the protocol-
20 specified dose and she continued without further
21 adverse events.

22 The last patient experienced moderate

1 vertigo and severe presyncope on day 2 of the
2 infusion. The infusion was permanently
3 discontinued within 10 minutes of the onset of
4 these symptoms of excessive sedation.

5 She did not lose consciousness and the
6 presyncope resolved within 10 minutes. It is
7 noteworthy that she had reported a self-limiting
8 episode to presyncope on day 2.

9 You have read in the briefing book about
10 another subject who was not in our key PPD studies.
11 This was a male participant in the TQT study, who
12 became severely somnolent with a brief episode of
13 apnea lasting less than a minute at the
14 supratherapeutic dose of 180 micrograms per
15 kilogram per hour.

16 In response to this excessive sedation, the
17 infusion was stopped and there was rapid recovery
18 with no loss of consciousness.

19 At the time of this event, his pulse
20 oximetry reading was 98 percent. Another male
21 participant, this time in the Essential Tremor
22 study, became overly sedated and hypotensive when

1 receiving 120 micrograms per kilogram per hour.
2 Again, the infusion was stopped and he recovered
3 without losing consciousness.

4 I will now explain why pausing the infusion
5 is an effective measure to manage excessive
6 sedation. The clearance of brexanolone is biphasic
7 and the initial phase has a half-life of just 40
8 minutes.

9 This results in rapid clearance of
10 brexanolone from plasma at the end of the infusion
11 or if the infusion is paused. There is also a
12 meaningful reduction in plasma concentrations of
13 brexanolone if the dose is reduced.

14 The rapid clearance of brexanolone from
15 plasma underpins the recommendations to pause the
16 infusion if there is successive sedation that is
17 progressing quickly, to reduce the dose if the
18 excessive sedation is progressing more slowly, and
19 to monitor the patient for the duration of the
20 infusion.

21 I will now present an overview of what we've
22 learned from our clinical trials that has informed

1 our approach to the safe administration of
2 brexanolone.

3 In our clinical trials, excessive sedation
4 was monitorable by healthcare professionals
5 supported by the patients being able to notify
6 staff that they felt overly sedated. Brexanolone
7 had no effect on oxygen saturation, even in those
8 patients when it was recorded at the time of
9 excessive sedation.

10 In the cases of loss of consciousness, the
11 infusion was immediately paused with rapid
12 recovery. Rapidly progressing excessive sedation
13 or somnolence was successfully managed by pausing
14 the infusion.

15 This strategy prevented loss of
16 consciousness in one of the three patients with PPD
17 that reported excessive sedation. Patients were
18 observed until they were fully awake.

19 Dose reduction was a successful strategy
20 employed in the clinical program to manage
21 excessive sedation or significant somnolence that
22 was evolving more slowly.

1 It is important to note that, in our
2 clinical trials, there were no sequelae to the
3 excessive sedation. There was no respiratory or
4 airway compromise. There was no hemodynamic
5 compromise. And there were no falls or injuries to
6 the patient or the baby.

7 After pausing the infusion, patients with
8 excessive sedation in our clinical trials were
9 observed until they were awake, which occurred
10 within 15 minutes. No other interventions were
11 necessary.

12 After recovery, consideration was then given
13 to restarting the infusion at the same or a lower
14 dose. 3 of the 5 patients with excessive sedation
15 due to brexanolone restarted the infusion, 2 at the
16 protocol dose and 1 at a lower dose.

17 We have taken all these learnings from our
18 clinical program to build the principles for safe
19 administration of brexanolone if approved.

20 These principles are oversight for the
21 entire duration of the infusion by a healthcare
22 professional qualified in each state to monitor

1 intravenous infusions.

2 Continuous pulse oximetry monitoring during
3 the infusion; this will particularly mitigate the
4 risk of adverse sequelae if the patient is overly
5 sedated during sleep. Communication of the risk of
6 excessive sedation and loss of consciousness to the
7 prescriber, healthcare professional, and patient
8 via the labeling and medication guide. I would
9 like to point out that the ability to review the
10 clinical trial data in aggregate improved our
11 ability to clearly convey the risks and mitigation
12 strategies for excessive sedation and loss of
13 consciousness.

14 In addition, the labeling will recommend
15 that the patient is not the primary caregiver of
16 the baby and that they should put the baby down, or
17 sit, or lie down if feeling dizzy or somnolent.

18 We have agreed with FDA that a REMS will be
19 implemented to support brexanolone after approval.
20 Let me outline the proposed REMS for you. The goal
21 of the REMS is to mitigate the loss of
22 consciousness that was observed with brexanolone.

1 The key components include enrolling all
2 prescribers in the REMS. The prescriber will then
3 enroll all patients into a registry which is
4 designed to collect information to further
5 characterize the risk of loss of consciousness
6 should this occur.

7 Distribution of brexanolone will be
8 restricted to certified healthcare settings. This
9 certification provides assurance that the infusion
10 will be overseen by an appropriately qualified
11 healthcare professional, that patients are enrolled
12 in the registry prior to receiving brexanolone,
13 that pulse oximetry will be employed for the
14 duration of the infusion, and that the patients and
15 healthcare professionals be trained on the risk and
16 mitigations for loss of consciousness.

17 Overall, the data support a positive
18 benefit-risk assessment for brexanolone as a
19 treatment for women with PPD. Efficacy was
20 demonstrated in 3 adequate well-controlled studies
21 and brexanolone has a well-characterized safety
22 profile with good tolerability.

1 The risk of loss of consciousness, which
2 occurred in 4 percent of patients in the key
3 studies, is mitigated by healthcare professional
4 oversight, continuous pulse oximetry monitoring,
5 the proposed labeling and medication guide, and the
6 REMS. The panel has been asked to comment on the
7 recommended dose. Sage looks forward to the
8 discussion and hearing the panel's views. We
9 recommend the 90 dose regimen for the following
10 reasons. Both dose regimens support efficacy and
11 tolerability. The efficacy of the 90 regimen has
12 been replicated in 3 studies.

13 It may be easier to operationalize titrating
14 down from 90 if there are tolerability issues
15 rather than assessing effectiveness at hour 24 and
16 titrating up only those who have not yet responded.
17 I will now return the lectern to Dr. Meltzer-Brody
18 to provide her clinical perspective.

19 **Applicant Presentation**

20 **Samantha Meltzer-Brody**

21 DR. MELTZER-BRODY: Thank you. I am pleased
22 to provide my clinical perspective on the data

1 presented today.

2 The goal of treatment for postpartum
3 depression is to reduce symptoms as quickly as
4 possible. Given that the postpartum period is such
5 a vulnerable time for women and their families, it
6 is critical to have a way to rapidly treat women
7 who suffer with PPD to improve depressive symptoms
8 and impairment in functioning.

9 In the brexanolone trials, the magnitude of
10 improvement of the HAM-D score from a 29 to a 9 in
11 60 hours is unlike anything we've seen before with
12 currently available treatments. Therefore,
13 brexanolone is a novel treatment that provides an
14 opportunity to urgently alleviate suffering from
15 PPD in women and their families.

16 When I prescribe an SSRI, in general it can
17 take weeks to months to see any kind of initial
18 treatment effect and many women don't fully
19 respond. In addition, many women that take SSRIs
20 experience troublesome side effects and treatment
21 for a major depressive episode, including PPD, is
22 usually recommended for 6 months to a year.

1 In contrast, because brexanolone is a 60-
2 hour infusion, I will know in 2.5 days if a patient
3 has responded. In our experience at UNC conducting
4 all phases of the clinical trials, we have been
5 able to safely manage sedation-related effects. In
6 my experience, reducing the dose was successful in
7 mitigating the risk of loss of consciousness.

8 However, it's also reassuring to me that the
9 sponsor is proposing, as part of their REMS, that a
10 licensed healthcare professional provide oversight
11 and monitoring of potential side effects throughout
12 the infusion period.

13 This closely matches the supervision that
14 occurred during the clinical trials. The data
15 indicate that brexanolone is a primary therapy for
16 PPD. The majority of patients who receive
17 brexanolone, 71 percent across all three clinical
18 trials, did not receive antidepressants before,
19 during, or in the 30-day follow-up period after the
20 infusion.

21 Efficacy was demonstrated regardless of
22 antidepressant use. Approximately 75 percent of

1 patients achieved a HAM-D response and nearly 50
2 percent of patients achieved HAM-D remission at
3 hour 60. These comparable rates demonstrated that
4 brexanolone is efficacious as a first-line
5 treatment.

6 Should a physician choose to use brexanolone
7 as an adjunct therapy, that can also be done. As a
8 clinician, what is most important to me is the HAM-
9 D remission data. What is clinically meaningful
10 about these data is that, before treatment with
11 brexanolone, a woman with PPD may be experiencing
12 symptoms of depression and anxiety, which may
13 impact all aspects of her life.

14 She is able to function in the way that she
15 wants and has positive interactions with her baby
16 and family. The ability to have a medication that
17 could quickly relieve suffering and offer at least
18 a 50 percent remission rate after 60 hours of
19 treatment would be a completely new and most
20 welcome tool for helping women who suffer with PPD.

21 In my experience with brexanolone, in all
22 phases of the clinical trials, I have been

1 impressed by the robust treatment effects that we
2 observed within the first 24 hours of treatment.
3 Before treatment, I observed women who presented
4 with depression, anxiety, social withdrawal,
5 complete loss of appetite.

6 After treatment, these women had a marked
7 brightening of their affect, returned to normal
8 eating behaviors, and marked improvement in their
9 ability to meaningfully interact both with their
10 baby and family.

11 This rapid improvement in symptoms was
12 striking. Thank you for the opportunity to discuss
13 this important public health issue. I'll now turn
14 the lectern to Dr. Schacterle.

15 DR. SCHACTERLE: Good morning. I'm Amy
16 Schacterle and I'm the senior vice president of
17 regulatory and quality at Sage and I'll be
18 moderating your questions today. Thank you.

19 **Clarifying Questions**

20 DR. NARENDRAN: Thank you. We appreciate
21 you finishing real fast. There's plenty of time
22 for extra questions. It's very impressive. So

1 panel members, if you have questions, we'll start
2 with Dr. Hernandez-Diaz?

3 DR. HERNANDEZ-DIAZ: Thank you very much.
4 Sonia-Hernandez-Diaz from Harvard School of Public
5 Health. I have two questions, actually. One is
6 about the dose that they are recommending and
7 another about the timing. For the time, I think
8 it's wonderful that you are approving the amount of
9 time that Mom can enjoy the baby and vice versa by
10 helping the person to get better faster. That's
11 wonderful.

12 But at the same time, that means that timing
13 is of the essence and having the mom removed from
14 the useful baby interactions for 2.5 days is an
15 incredibly long time. So I wonder if, based on the
16 results, some studies might suggest that, at 24 or
17 48 hours, there may be enough effect to explore
18 whether there may be a possibility, maybe post-
19 marketing, to try to reduce that time that Mom
20 needs to have the infusion and therefore be outside
21 her use at home. And I think that would be also
22 important, the timing, for healthcare burden and

1 access to this treatment for a larger proportion of
2 the population.

3 The second question is about the dose. I
4 was looking at the results and what I is that the
5 90 dose has the same efficacy, same adverse event
6 profile, but still you are recommending it versus
7 the 60 when we have heard that reducing the dose
8 might be able to control some somnolence and maybe
9 the lower dos can avoid some of the adverse
10 effects, but you are still recommending the 90, so
11 if you can please expand on that, that would be
12 great.

13 DR. SCHACTERLE: Thank you. First, I would
14 like to address your first question in terms of the
15 interaction with the baby. In fact, in all the
16 clinical trials, we allowed the mother to interact
17 with the baby as she wanted to throughout the
18 administration. Babies were welcome into the
19 clinical sites and we would envision that this
20 could be feasible in the post-approval settings.
21 It would not be necessary to separate the mother
22 from the baby.

1 Importantly, in all cases both during the
2 clinical studies and envisioning post-approval
3 settings, there would be a separate primary
4 caregiver. The mother would not be the primary
5 caregiver.

6 In terms of the timing, we have found that
7 the 60-hour duration of administration has been an
8 important time frame in terms of having full
9 response. We did do some analyses in which we
10 evaluated patients who are non-responders at 24
11 hours and saw that, as they continued on to the 60
12 hours, approximately two-thirds in both dose groups
13 went on to become responders. So that 60-hour time
14 frame does seem to be important.

15 Finally, your question around the dosing in
16 terms of the 90 versus 60; the 90 dose and the 60
17 dose, as you mentioned, are both effective and they
18 have similar safety profiles. We believe that the
19 90 dose or, actually, the data show that the 90
20 dose is effective in all 3 studies and has been
21 replicated across those studies.

22 As you heard our earlier presentations, this

1 is really a question of whether or not to go to 60
2 and then titrate up for lack of efficacy or go to
3 90 and titrate down for tolerability. Recall that
4 most patients did not have any adverse events and
5 approximately, excuse me, 70 percent of patients
6 did not experience any kind of sedation-related
7 adverse events, so 90 was very well tolerated.

8 So it is perhaps a simpler and more
9 straightforward activity to go to 90 and then turn
10 down for sedation or other tolerability events than
11 try to understand efficacy at 24 hours and trying
12 to turn that up. So that's why we favor the 90.

13 DR. NARENDRAN: Thank you. Next question?

14 DR. HABEL: Hi, this is Laurel Habel.

15 DR. NARENDRAN: Good.

16 DR. HABEL: I was just wondering, do you
17 have evidence that titrating up at, is it, the 24
18 hours actually improves response? I mean, if
19 they're not responding at 24 hours and you kept
20 them at the 60 dose, would you have a different
21 response than if they're not responding at 24 hours
22 or you increase it to 90? Do you see what I mean?

1 I'm wondering what kind of evidence you have that
2 up-titrating actually improves efficacy.

3 DR. MELTZER-BRODY: I have here an analysis
4 of the non-responders at hour 24 and their response
5 in the right-hand columns, whether yes or no, at
6 hour 60. If you follow the rows across, in fact,
7 for both the brexanolone 60 dose as well as the 90
8 dose, those that were not responders at 24 hours,
9 approximately two-thirds go on to become responders
10 in at hour 60.

11 So it's really more about the duration of
12 time than in particular about the dose at 24 hours.

13 DR. NARENDRAN: Thank you. Dr. Conley?

14 DR. CONLEY: Yes, just a clarifying question
15 on the sedation. On slide 55, where you look at
16 the no-incremental-sedation risk, those bars
17 altogether only add up to about 60 percent, not 100
18 percent. I'm sure that relates to something, but I
19 can't quite figure out what.

20 Just related to that, in slide 52, the
21 sedation is suggested to be about, like, twice as
22 much roughly on the sedation line with the 90

1 versus the 60, but back on that other slide, so
2 since people are really focusing on what's the
3 difference between the things, could you help the
4 committee understand that one better? I just
5 couldn't quite figure that one out.

6 DR. SCHACTERLE: Yes. I'd like
7 Dr. Colquhoun to address your question.

8 DR. COLQUHOUN: Helen Colquhoun. You can't
9 add up the percentages on this slide and have it
10 come to 27 percent because some patients have more
11 than 1 sedation-related event, so if they had one
12 onset at 3 hours and one with an onset at 33 hours,
13 they would actually be represented twice on this
14 graphic.

15 Then, if we put up the next slide, you're
16 correct that the incidence of somnolence is higher
17 on the 60 dose compared to the 90 dose.

18 However, because most of those events
19 occurred in the first 24 hours, we don't think that
20 is because they were randomized to the 60 dose,
21 because they were receiving the same dose as the 90
22 group in the first 24 hours. That's why we look at

1 the next, the other slide, which clearly shows
2 that, after 24 hours, when the doses are actually
3 different here, the incidence is the same.

4 So whether you were randomized to one dose
5 group or the other dose group, you receive the same
6 dose, 30 then 60, for the first 24 hours.

7 DR. CONLEY: That helps. Before you get
8 off, I just wanted to underline that. So when
9 they're being exposed to 90, they're not really
10 having more of a sedation experience. It's really
11 that, earlier, the people who happen to be going on
12 to 90 were contributing to that.

13 DR. COLQUHOUN: That's absolutely correct.

14 DR. SCHACTERLE: It might be helpful if
15 Dr. Meltzer-Brody also gave her clinical experience
16 around this subject.

17 DR. MELTZER-BRODY: I don't get the jazzy
18 height-enhancing stool over here. So in our
19 experience with all of the trials, beginning with
20 the open-label study, we were able to manage
21 sedation-related events by turning down the dose.
22 We did not have any events of loss of

1 consciousness.

2 The initial open-label trial was developed
3 with 90 being the target and, given that about a
4 third or a little bit less have sedation-related
5 effects, the rest do not, in my opinion, it makes
6 the most sense to optimize treatment and give every
7 patient that gets the drug the best opportunity to
8 have a treatment response.

9 So having someone experience sedation is
10 very obvious. People would report feeling more
11 sleepy and those that did; I think the dose is very
12 straightforward and, because it's an IV, the effect
13 is almost immediate in terms of reducing that side
14 effects.

15 That way, you're assuming anyone who's not
16 having the sedation-related effect is going to have
17 the best opportunity to have response and, because
18 we have the most data, in an all-trials, the 90, it
19 seems to me to make the most sense to be the best
20 opportunity to get well. So as a psychiatrist, my
21 motivation is to be able to treat people to
22 efficacy, into remission if possible while of

1 course monitoring side effects and maintaining
2 safety.

3 DR. MEISEL: Steve Meisel with Fairview,
4 several questions; I think they'll all be brief.
5 First of all, in terms of those pump failures, were
6 those actually pump failures or were they human
7 programming failures? Were they actual mechanical
8 malfunctions?

9 DR. SCHACTERLE: They were. Actually, in at
10 least 1 case, it was a motherboard that failed, so
11 they were pump failures.

12 DR. MEISEL: I find that 1.4 failure rate on
13 an IV pump seems extraordinarily high. I hope
14 that's been reported to FDA and they take that pump
15 off the market or something. Different division.

16 A couple of questions about subgroups; I
17 think I heard you say that the average enrollment
18 was about 3 or 4 months postpartum, but it ranged
19 from immediately postpartum to 6 months. Any
20 subgroup analysis done on at what stage they were
21 postpartum, when the diagnosis was made that might
22 have influenced the outcomes one way or another?

1 Then similarly, the question about baseline
2 SSRI or other antidepressant use; was there any
3 difference in outcomes on the basis of people who
4 were or were not on baseline antidepressants?

5 DR. SCHACTERLE: Yes. This is a slide from
6 the core presentation that illustrates the forest
7 plot, again, with brexanolone favoring the left
8 side and favoring placebo on the right side. The
9 bottom two rows, I think, address the first part of
10 your question, the duration from delivery to the
11 index treatment. Whether it was less than 3 months
12 postpartum versus greater than 3 months postpartum,
13 you can see that, for both doses, there was
14 improvement in similar efficacy.

15 Similarly, in terms of symptom onset, we
16 evaluated those that had onset of symptoms in the
17 third trimester as well as those within the 4 weeks
18 of delivery and, again, directionally, both favor
19 brexanolone with similar efficacy.

20 Then I think the last question that you had
21 was around antidepressant. Again, we evaluated
22 patients who were on concomitant antidepressants

1 compared with those patients who did not take
2 antidepressants and, again, no differences in
3 efficacy.

4 DR. MEISEL: Thank you. That helps. And
5 very briefly, two very brief questions; you talked
6 about the impact of breast milk or that very little
7 gets into the breast I'd like, if the baby did
8 swallow it, it would be absorbed. That's fine. Is
9 there any impact on breast milk production? Has
10 that been measured?

11 DR. SCHACTERLE: In the lactation study, we
12 did evaluate breast milk production and there did
13 not seem to be an impact.

14 DR. MEISEL: Then my last question; you had
15 a strong recommendation to use oximetry and I'm
16 struggling with why there was no impact on anything
17 where oximetry would make a difference one way or
18 another in terms of a person losing consciousness,
19 where the oximetry readings were normal. What's
20 the point?

21 DR. SCHACTERLE: Dr. Colquhoun?

22 DR. COLQUHOUN: You're correct that, in our

1 clinical trials, we had no airway or respiratory
2 compromise associated with any of the cases of
3 excessive sedation, but we are mindful that, if
4 approved, as brexanolone goes out into the real
5 world, that it would be prudent to mitigate against
6 any such occurrences post-approval. So the
7 objective for the pulse oximetry is to mitigate any
8 risk of adverse sequelae to excessive sedation even
9 though we have not seen that to date.

10 DR. NARENDRAN: Dr. Besco?

11 DR. BESCO: Yes, Kelly Besco, OhioHealth. I
12 have a question related to the sedation monitoring
13 and your protocol. So I'm wondering if there was
14 any required frequency specified in your protocol
15 for sedation monitoring to proactively monitor for
16 over-sedation and also interested if any sort of
17 sedation scale or assessment scale was integrated
18 in your study protocol to allow for an objective
19 determination for when to suspend the infusion or
20 when to initiate the next tier of the infusion
21 protocol.

22 DR. SCHACTERLE: Dr. Colquhoun?

1 DR. COLQUHOUN: So in the clinical trials,
2 the patients had vital sign and other measurements
3 done regularly during the trial, but the sites
4 where the infusions were administered were a
5 variety of different places, but if you imagine an
6 infusion center where there are beds and there are
7 nurses milling around, there was constant oversight
8 of the patients while they were receiving the
9 infusion. They were ambulant, so they could walk
10 around with their pumps, so again, they were never
11 really on their own in a room not being observed.

12 I can't recall your second question. Sorry.
13 Oh, scale. So we did, in the early study, in 202A,
14 employ the Stanford Sleepiness Scale and we found
15 it rather unhelpful, mostly because it was designed
16 to monitor patients coming out of anesthesia rather
17 than patients going into sleepiness and in
18 order -- because, if it's a subjective scale, if
19 somebody was sleepy, you actually had to wake them
20 up to ask them whether they were sleepy, so the
21 scores didn't match the adverse event reporting, so
22 in the end, we abandoned that and relied on the

1 adverse event reporting because we found that the
2 patients and their healthcare professionals were
3 very good at reporting the sedation-related events.

4 DR. BESCO: So just to follow up, then,
5 sedation monitoring and suspension, then, is based
6 purely on clinical judgment?

7 DR. SCHACTERLE: Yes.

8 DR. NARENDRAN: Dr. Griffin?

9 DR. GRIFFIN: Yes. I had another question
10 about dose. I mean, we don't see a dose response
11 for the sedation, but it may be that the studies
12 got more skilled at picking up sedation early and
13 lowered the dose. I'm just wondering. You said,
14 if somebody experienced sedation, you reduced the
15 dose. And then what are the instructions? Do the
16 patients still go on up to the 90 dose or do they
17 only get 60? Does everybody go on to the 90 dose?
18 And what would be the clinical instructions for
19 what to do in that situation?

20 DR. SCHACTERLE: I'd like Dr. Colquhoun to
21 address the dose reductions that occurred in the
22 trial.

1 DR. COLQUHOUN: So in the clinical trial,
2 there were 4 dose reductions in our key studies and
3 the decision to reduce the dose was made entirely
4 by the healthcare professional and the doctors at
5 the site.

6 So depending on the clinical picture in
7 front of them, how rapidly progressing the
8 somnolence was, they would make a decision to
9 reduce the dose and then decide whether or not to
10 titrate back up to the original dose or not. So
11 there were no pre-specified rules.

12 If I show you this slide, you'll see that,
13 in one case, the dose was reduced from 60 to 30
14 because of somnolence in someone who had
15 concomitant clonazepam, and then 2 other patients
16 were down-titrated from 90 to 60 and they completed
17 the infusion of those doses without any further
18 adverse events. There was 1 placebo patient who
19 was dizzy, who also had the dose reduced, their
20 infusion rate reduced.

21 DR. SCHACTERLE: You asked how we will
22 inform the prescribing population in the labeling.

1 So we do plan to include prominent warnings around
2 the risk of excessive sedation.

3 Those warnings will give directions around
4 allowing the patient to recover and then
5 consideration to either restarting or reducing the
6 dose after the dose has been paused.

7 DR. NARENDRAN: Ms. Witczak?

8 DR. WITCZAK: Kim Witczak, consumer rep.
9 Thanks for your presentation. Help me understand
10 just the general novel mechanism and in layperson
11 terms, just to help me understand, because I know
12 it's different, and we talked about antidepressant,
13 and that's one question.

14 Then did you guys follow these patients or
15 these mothers that, like, in 6 months or a
16 year -- I mean, can it be re-administered because
17 yesterday we heard a lot about difficult-to-treat
18 depression? And I know you guys start out with
19 major depressive disorder as part of this.

20 Then I guess a third part, and maybe it's
21 all one question; I know that you also did a
22 healthy men's study. And does this have the

1 potential for other future uses or is it only
2 because of the way it interacts with the woman's
3 brain because of being pregnant? And again,
4 layperson terms, please; thanks.

5 DR. SCHACTERLE: Sure. I'll answer your
6 later questions first and then I'll have one of my
7 colleagues address the mechanism of action.

8 To start, this is intended as one treatment
9 per postpartum depression episode. So we're not
10 envisioning retreatment. With the efficacy that we
11 observed, including the remission rates and the
12 response rates, we believe that's appropriate. In
13 terms of your question about men, this has
14 specifically been evaluated in postpartum
15 depression.

16 We did not evaluate it in major depressive
17 disorder, so we're here today to just talk about
18 the postpartum depression. And then I think I'll
19 turn it over to Dr. Doherty to address the
20 mechanism of action.

21 DR. DOUGHERTY: Jim Dougherty. So as you
22 heard earlier in the presentation, brexanolone acts

1 at therapeutic concentrations as a positive
2 allosteric modulator of GABA receptors. So the
3 GABA receptor system is a distinct system from what
4 you might think about for things like SSRIs that
5 are interacting with the serotonin system.

6 The GABA system is the primary inhibitory
7 system in the brain. It's a complex system. But
8 brexanolone acts as a modulator of that system.
9 What that means is, it doesn't directly activate
10 these receptors. That's a job for GABA.

11 But when it's present, it enhances the
12 function of those receptors so that they give a
13 larger response than they would in the absence of
14 brexanolone.

15 DR. WITCZAK: I was going to say that didn't
16 really feel really layperson, because I'm just
17 thinking about the average person that has to
18 understand. Is it like a steroid? Is it a
19 hormone? Is it just in those just -- and I know
20 you, a scientist, probably have way different
21 terms, but like, if you were a practitioner that
22 was going to tell a patient of this why it works

1 differently, and I think we've all heard about
2 antidepressants and the serotonin and it's
3 chemicals, and is it a chemical imbalance and all
4 of that, and I'm just trying to get real, like real
5 basic.

6 DR. DOUGHERTY: Sure, absolutely. In that
7 sense, it is a chemical and what it's doing is it's
8 just interacting with a different system in the
9 brain than from some of the other systems that you
10 might be thinking about.

11 It's endogenous. Right? So that does mean
12 that it's being produced in all of our bodies and
13 that system is there to do a job. And so
14 brexanolone is binding to that system and it
15 basically is helping to reduce activity in the
16 brain.

17 So in that sense, it still is interacting
18 with brain systems the way other antidepressants
19 do, but it's acting with a very different component
20 of the brain systems. Exactly.

21 DR. SCHACTERLE: Dr. Meltzer-Brody, would
22 you like to describe how you might talk to a

1 patient in terms of how it works.

2 DR. MELTZER-BRODY: We have such different
3 heights going on here. So why I was interested in
4 participating in the brexanolone studies was
5 because brexanolone is a proprietary formulation of
6 allopregnanolone. Allopregnanolone is a metabolite
7 of progesterone.

8 During pregnancy, estrogen and progesterone
9 go sky high in all women who birth. That's
10 considered normal physiology. And at the time of
11 delivery, they plummet. This is, again, normal
12 physiology. It's actually quite amazing.

13 We know we have estrogen and progesterone
14 receptors all over our brain; similarly,
15 allopregnanolone. Allo has been known to be what's
16 called a neuroactive steroid hormone, meaning that
17 it affects powerfully the brain and crosses the
18 blood-brain barrier.

19 So what's really interesting is that allo
20 has been of great interest in the field as being
21 involved in perhaps the etiology of postpartum
22 depression.

1 There's been studies looking at animal
2 models before pre-clinical models. It's been a
3 very finicky compound. So that's why it was really
4 exciting to have it developed in a way that could
5 be delivered to patients.

6 In the first open-label study, it was
7 unclear whether it was going to work or not, but it
8 is working by being, the fancy term, a positive
9 allosteric modulator of GABA, but it is working
10 directly on your brain with a major
11 neurotransmitter system that is unlike anything
12 that has been

13 DR. NARENDRAN: Dr. Ruha?

14 DR. RUHA: Thank you. Michelle Ruha. I'm
15 just curious about the remission and response rate
16 of 30 days. It seems that the most significant
17 difference is for the 60 dose and, in fact, I
18 think, with 202A, some of it's not even a
19 significant difference from placebo, and also with
20 202C. So I'm just curious. I'm not sure if there
21 was any follow-up data other than the 30 days. And
22 is it the natural course of disease for postpartum

1 depression to improve significantly in that short
2 amount of time?

3 Because it seems that maybe the placebo
4 group improved to meet the drug group. But I guess
5 my question is specifically the 60 dose seems to
6 fare as well, if not better, than the 90 dose and I
7 just was wondering if the sponsor had any comment
8 about that.

9 DR. SCHACTERLE: So you're correct. What
10 we're seeing over time is -- and we followed all
11 patients out to 30 days. We did not evaluate them
12 longer, and that's typical of antidepressants in
13 terms of evaluating efficacy for a treatment effect
14 and then following for a period of time; in this
15 case 4 weeks; to determine if that effect is
16 sustained.

17 So as you mentioned, we're seeing the effect
18 from the brexanolone group at 60 hours is sustained
19 through 30 days, even after treatment. And it's
20 the placebo group that is meeting the brexanolone
21 group. However, placebo in this trial is not
22 representative of the natural course of PPD and I'd

1 like Dr. Meltzer-Brody to speak further to that.

2 DR. MELTZER-BRODY: In all of the studies
3 you see, for those that responded at 60 hours, you
4 see maintenance of that response out to the 30
5 days. Depending on the trial, you see differences
6 in the placebo rate.

7 What was most interesting to me was in the
8 202A study. The placebo rate was much lower. And
9 then, when we got to the phase 3 studies, as is
10 common in depression clinical trials, you often see
11 a markedly increased placebo rate.

12 I will tell you that we had patients coming
13 in because they'd seen the first paper published
14 and heard about the study. And there was a lot of
15 expectation that they were going to perhaps get
16 active drug, coming in saying, "Here I am. Give me
17 my IV."

18 I really thought that was going to majorly
19 influence potentially the findings because the
20 expectation of treatment is very well known to
21 influence response rates and certainly a placebo
22 response.

1 DR. NARENDRAN: Thank you. Dr. Fiedorowicz?

2 DR. FIEDOROWICZ: Thanks for calling on me.

3 My question follows the last one, so I do want to
4 just comment, though, on the last question, of 60
5 micrograms per kilogram hour dose separates at 24
6 hours before it's actually a different dose.

7 While they're still receiving the titration,
8 I think that was mentioned in the materials from
9 the sponsor as well, so that's another explanation
10 for the difference at 30 days.

11 What I'd like to see is the safety data for
12 22B alone stratified by dose because half of the
13 participants receiving the 90 microgram per
14 kilogram per hour were actually in the moderate
15 depression group and certainly moderate to severe
16 depression could be a difference between dose.

17 So do you guys have the safety data for 22B
18 only, stratified by dose?

19 DR. SCHACTERLE: Here we go. This is the
20 pooled data.

21 DR. FIEDOROWICZ: This is the pooled.

22 DR. SCHACTERLE: Do we have 202B?

1 DR. FIEDOROWICZ: Yes. So the 60-milligram
2 dose here is all severe depression, where half of
3 the 90-milligram is moderate. And so it makes it
4 hard to compare some of the differences with
5 somnolence, for instance, when severe depression
6 can be associated with it.

7 DR. SCHACTERLE: We'll try to get you that
8 specific presentation after the break.

9 DR. FIEDOROWICZ: Thank you very much.

10 DR. NARENDRAN: Thank you. Dr. Jain?

11 DR. JAIN: Felipe Jain. A few questions.
12 One is, in the two patients who, after injection
13 experienced some suicidal ideation or behavior, how
14 did you determine that there was no clinical
15 worsening? Had they had that during the current
16 episode and, if so, how recently prior to the
17 injection had they had that suicidal behavior?

18 Then how rapidly following discharge did
19 they exhibit those symptoms again?

20 DR. SCHACTERLE: Dr. Colquhoun?

21 DR. COLQUHOUN: Helen Colquhoun. Both of
22 these patients had baseline reports of suicidal

1 behaviors. So one had a lifetime history. I'll
2 put these up. It's easier for me to read, too.

3 One had a lifetime history of suicidal
4 ideation and behavior and reported the self-
5 injurious behavior at day 7 and day 14. And 1 had
6 a lifetime history of prior suicide attempts and, 2
7 days after completing the infusion, she took an
8 overdose of non-study drugs, which the investigator
9 considered to be not related to brexanolone.

10 DR. JAIN: Got it. And do you have
11 information about whether any of those suicide
12 attempts occurred within the current episode or
13 were they within prior episodes?

14 DR. COLQUHOUN: They were all prior
15 episodes. It was an exclusion for the trial, any
16 suicide attempt with the current episode of PPD.
17 That was an exclusion.

18 DR. JAIN: So there are clear
19 pharmacodynamic effects of the medication on
20 sedation. Have you tested a slower initial
21 infusion period to determine whether that could
22 reduce the risk of excessive somnolence that seems

1 to emerge most prominently within the first 24
2 hours?

3 So for example, if the infusion were
4 extended to 72 hours, what would that look like in
5 terms of the rate of that adverse event?

6 DR. SCHACTERLE: So most of the adverse
7 events that are sedation related are occurring
8 within the first 24 hours. Our early study, our
9 201 study, actually evaluated a more rapid
10 titration and this dose regiment that we utilized
11 in these key studies is a slower regimen.

12 The 60-hour regimen has been replicated in
13 terms of efficacy and has a similar safety profile.
14 And then importantly, at the end of treatment, we
15 did evaluate whether or not there would be
16 continued efficacy.

17 By extrapolation, our model would not
18 progress to additional efficacy, so no need to
19 extend the treatment period. And there is a taper
20 at the end as well.

21 DR. JAIN: A question about that; is there
22 any theoretical or practical reason to believe

1 that, after achieving symptomatic response,
2 continued infusion is necessary or could patients
3 be tapered right at that moment?

4 DR. SCHACTERLE: We do not have any data
5 that evaluates treatment to response. Certainly,
6 the 60-hour infusion is already only 2.5 days to be
7 able to identify whether a patient gets well. And
8 2.5 days is a huge advancement forward for the
9 field.

10 DR. JAIN: In general, patients did not
11 relapse at 30 days. What proportion did? And what
12 plans does the company have regarding guidance on
13 ongoing or continued treatment?

14 DR. SCHACTERLE: I'll speak to the guidance
15 and then I'll ask Dr. Colquhoun to address the
16 data. In terms of the guidance, as I mentioned
17 before, it's considered recommended that this will
18 be administered one time per PPD episode. So the
19 guidance for patients who begin to have symptoms,
20 if they do at a later date, depending on how far
21 out, that could be a new onset of major depressive
22 disorder and so should be treated as such.

1 But certainly, this is a clinical decision
2 to be made by the prescriber along with the
3 patient.

4 DR. NARENDRAN: I do want to remind; one or
5 two questions, please; not a discussion. Dr. Dunn
6 is next. You can always come back and get back in
7 line if you have more questions.

8 DR. COLQUHOUN: Should I address the relapse
9 question?

10 DR. NARENDRAN: Quickly.

11 DR. COLQUHOUN: So the relapse rate at, say,
12 30 was 6 percent, so 6 percent relapsed, had
13 relapse at day 30.

14 DR. NARENDRAN: Thank you. Dr. Dunn next?

15 DR. DUNN: Walter Dunn, psychiatrist, UCLA.
16 As was mentioned before, this postpartum period is
17 very unique in a woman's life, in any family's
18 life. And given that antidepressant effect and
19 seeing that for 2.5 days is, of course, remarkable,
20 Friday to Sunday or Monday, right?

21 But I think, as any mother will tell you,
22 there is no longer weekdays and weekends. And so

1 this is a question that's a follow-up to my
2 colleagues about how long does this infusion really
3 have to be.

4 So I know Dr. Jain asked the question about,
5 is there a need to continue the infusion after
6 responses made? I know you don't have any data
7 specifically speaking to that, but what about data
8 separating patients who respond at 24 hours versus
9 patients who respond at 60 hours and the durability
10 or sustainability of the responses of those two
11 groups?

12 For those who took longer to reach remission
13 or response, at 60 hours, was there a rate of
14 sustainability less in those who achieved response
15 earlier?

16 Then the second question related to the
17 breastfeeding. At 60 hours, I know it looked like,
18 in the study, women were asked to suspend
19 breastfeeding, but were they still allowed to pump
20 during the 2.5-day infusion? And the question
21 specifically asks or points to, is there an
22 interaction or is there a theoretical interaction

1 between oxytocin levels and the antidepressant
2 effect?

3 So if women are still pumping, oxytocin
4 levels are still rising. Does it somehow
5 potentially blunt that or were women not even
6 allowed to pump during the trials?

7 DR. SCHACTERLE: During the trial, yes.
8 Women were allowed to pump; in the latter course of
9 the studies, were allowed to resume breastfeeding
10 after interrupting for 7 days. That was something
11 that was employed in the studies prior to having
12 the lactation data. I'd like Dr. Kanen to address
13 your other questions regarding oxytocin.

14 Just before he does that, your first
15 question around comparing our response at hour 60
16 versus sustained response at hour 4, we did not
17 have data for patients that did not go on to
18 treatment after hour 24. So I'm not sure how we
19 could conduct that analysis. Could you clarify
20 what you were asking for?

21 DR. DUNN: Yes, so perhaps patients who
22 achieve response at 24 hours as one group; the

1 other group, patients who need 60 hours to achieve
2 response; and then there are outcomes at 30 days

3 DR. SCHACTERLE: Thank you

4 DR. KANES: Steve Kanés. Specifically about
5 oxytocin, we didn't study oxytocin. What we know
6 is that there weren't changes overall in breast
7 milk overall in our breastfeeding study. And due
8 to the very short exposure, we wouldn't expect
9 there to be changes in that regard.

10 DR. DUNN: Sorry. Just to clarify, I think
11 before, someone asked if there were any changes in
12 breast milk production. You actually said there
13 was not.

14 DR. KANES: There were not.

15 DR. DUNN: Any sense of the percentage of
16 patients in the trials, how many were actually
17 pumping during the infusions?

18 DR. SCHACTERLE: Dr. Colquhoun?

19 DR. COLQUHOUN: We did not collect the data
20 on whether women were breastfeeding and suspended
21 breastfeeding for the trial. However, in the
22 follow-up period, we had no adverse events reported

1 of any difficulty resuming breastfeeding after the
2 7-day interruption.

3 DR. DUNN: But they had to suspend during
4 the trial. Right?

5 DR. SCHACTERLE: Yes.

6 DR. NARENDRAN: Thank you. Dr. Kulldorff?

7 DR. KULLDORFF: Thank you. Martin
8 Kulldorff, Harvard Medical School. I have two
9 questions. The first one; in tables 23 and 24,
10 your briefing materials, it shows that the risk of
11 sedation is twice as high in those patients that
12 have concomitant medication or antidepressant or
13 benzodiazepines. What are you thinking about in
14 concomitant administration of the study drug with
15 these two other things?

16 For example, if the study drug works so
17 well, is there any need actually for the women to
18 have the antidepressant during this time period or
19 should that be stopped before by getting the study
20 drug? Or what is your sort of general thinking
21 about the concomitant administration of these
22 drugs?

1 DR. SCHACTERLE: Because we were able to
2 demonstrate efficacy with or without administration
3 of an antidepressant, it's not necessary to stop
4 the antidepressant. The risk around sedation-
5 related events is one of an increased incidence.
6 In terms of severity, most of those adverse events
7 are mild, so it would not be necessary to stop
8 antidepressant administration if a patient was
9 already on it.

10 Certainly patients sometimes have difficulty
11 getting diagnosed and they may have difficulty
12 getting treatment. And so if patients had
13 progressed on antidepressant therapy, but still are
14 having symptoms that warrant treatment, then they
15 should be able to be eligible to have this
16 treatment.

17 I'm sorry; one other thing. The labeling
18 will include a warning in terms of the increased
19 risk of sedation-related events that may occur in
20 patients who are on concomitant antidepressants.

21 DR. KULLDORFF: The second question is, as a
22 non-clinician, my understanding of the biology here

1 is not complete, but the natural allopregnanolone
2 that's in the body; my understanding is that
3 steroids are replacing that. Before starting
4 treatment, did you try to measure the amount of
5 allopregnanolone of the body, of the woman, and
6 then to see whether the efficacy of the drug is
7 maybe higher in those who have very low amounts,
8 but may be less in those who have high amounts
9 because I assume that, yes, by chance maybe some of
10 the women who are depressed actually maybe would
11 have been depressed whether they had their
12 pregnancy or not. Therefore, maybe it's not because
13 of the lower amount of allopregnanolone in the
14 body.

15 So therefore, the study drug wouldn't work
16 for them, but it would work for those who had the
17 lower amount of the natural allopregnanolone. Did
18 you have a look into that to try to measure that to
19 see who would benefit from the study drug or not?

20 DR. SCHACTERLE: I'd like Dr. Colquhoun to
21 address your question around measurement.

22 DR. COLQUHOUN: So in the key studies, we

1 took full pharmacokinetic profiles and there was no
2 detectible allopregnanolone in the pre-dose samples
3 of any of the women. The limited quantification of
4 the assay is about 1 nanogram per mL. I think
5 there are theories about fluctuations in
6 allopregnanolone levels during pregnancy that may
7 be invoked in terms of the mechanistic basis for
8 PD, but the levels postpartum are not thought to
9 play a role. And as Dr. Doherty explained earlier,
10 we're not replacing levels that were there at the
11 end of pregnancy. This is a GABA-mediated
12 mechanism of action, something a little different.

13 DR. NARENDRAN: Thank you. When you're on
14 the concomitant meds and the mechanism -- I'll just
15 throw in my questions -- what percentage of your
16 people were on anticonvulsants? I know I saw that
17 sedation's increased with antidepressants and
18 benzodiazepines. Was there any significant
19 fraction who were on things like Depakote,
20 Lamictal, tiagabine for anti-seizures?

21 Because I would think that anything that
22 works with the GABA system would probably increase

1 sedation.

2 DR. SCHACTERLE: There was very few
3 patients, if any on anticonvulsants. However, we
4 did do a drug-drug interaction study with
5 phenytoin, which is of course an anticonvulsant.
6 And we did see pharmacodynamic increase in the
7 number of patients that reported adverse events.

8 The labeling will include the risk of
9 sedation or sedation-related events for all CNS
10 depressants. And so by that way, we get to the
11 whole class.

12 DR. NARENDRAN: A second thing I noticed
13 was, 2 of the subjects who had severe loss of
14 consciousness were on medroxyprogesterone. Given
15 that this is a derivative of progesterone, were
16 there more people on medroxyprogesterone? It did
17 okay or --

18 DR. SCHACTERLE: Yes.

19 DR. NARENDRAN: What percentage? How many
20 people were on progesterone derivatives?

21 DR. SCHACTERLE: Dr. Colquhoun?

22 DR. COLQUHOUN: Helen Colquhoun. I'm trying

1 to find it. I'll put the slide up. It's easier
2 when it's larger. So that shows the medications
3 reported by more than 5 percent of patients in any
4 of the treatment groups and, 10 rows from the top,
5 you'll see the MPA, so 6.5 percent on placebo, 8
6 percent on brexanolone, 65 percent on 90, 6 percent
7 in the total brexanolone group.

8 DR. NARENDRAN: That's 6 to 7 percent of the
9 total. You had 2 severe adverse events. I don't
10 know what that ratio would be, but we'll move to
11 the next question. Dr. Iyengar?

12 DR. IYENGAR: Satish Iyengar. Duration
13 seems to matter. Did you look at the 60-hour non-
14 responders to see if there was any sort of delayed
15 response? And did you consider longer
16 administration for any of them?

17 DR. SCHACTERLE: Could I have the
18 extrapolation beyond 60 hours? So in this slide,
19 we're showing the actual data from studies 202B and
20 202C for the HAM-D total score and evaluated the
21 progression through modeling. And this data show
22 that there's no real advantage in extending the

1 infusion beyond 60 hours.

2 Patients that had not responded by the 60-
3 hour treatment can certainly be considered for
4 treatment with other antidepressants. And that's
5 really what we would recommend.

6 DR. NARENDRAN: Next question, Dr. Turner?

7 DR. TURNER: Yes. So I appreciate the
8 patient-friendly explanation of the mechanism of
9 action in terms of progesterone being relatively
10 sky high during the third trimester and plummeting.
11 I think that was the word that was used.

12 So after birth, in that spirit, so if we
13 think of the cause being plummeting of progesterone
14 and its downstream metabolites such as
15 allopregnanolone, that I'm thinking about such a
16 replacing of an analog with allopregnanolone.

17 Then when it's taken away, we have a second
18 plummeting, which makes me think about the day 30
19 endpoint a bit more. And I realize that wasn't the
20 primary efficacy outcome. The focus was primarily
21 on the 60-hour time point, but still, I guess the
22 patients are going to be wondering about, am I

1 still going to be feeling fine for a couple of days
2 and then I'm going to go back? And I realize that
3 we did take a look at that to some degree, but if I
4 noticed correctly, the efficacy outcomes were at
5 least in the slides and were shown separately for
6 the 3 trials.

7 I don't know that I saw many pooled
8 analyses, at least not as many as there were for
9 the primary outcomes. And then in addition to the
10 efficacy outcomes, by the way, the efficacy
11 outcomes; by splitting them up by study, you've got
12 that very impressive first study, which amazingly
13 and despite that teeny-tiny end of only 10 or a
14 dozen patients in each group, you've got wonderful
15 p values, but unfortunately, that didn't replicate
16 in the subsequent 2 studies.

17 But anyway, aside from the efficacy, a
18 pooling of that data at the later time point
19 bolsters safety outcomes because, again, if we
20 think about the mechanism of action, it's mediated
21 through the GABA receptor, and I think in the FDA
22 packet, it was like how the actions were like in

1 the benzodiazepines in one respect and to
2 barbiturates in another response.

3 Again, if you're exposing a patient to this
4 60 hours and then you pull it away --

5 DR. NARENDRAN: Dr. Turner had a question.

6 DR. TURNER: Yes. Sorry. The question
7 is --

8 DR. NARENDRAN: I'm unclear myself what the
9 question is. I'm sorry. I'm unclear what the
10 question is.

11 DR. TURNER: So yes. Do we have a look at
12 the pooled safety measures rather than individual
13 adverse events like Hamilton, HAM-D, item number
14 three for suicide? Which look good on the slides
15 shown, but what about at day 30, other pooled
16 efficacy outcomes in safety, I mean, and anxiety,
17 insomnia, things that you might expect from
18 benzodiazepine of arbitrary withdrawal.

19 DR. SCHACTERLE: I'm going to start with the
20 pooled data out to 30 days. So this is the pooled
21 data 490 shown in the purple line compared to
22 placebo in the gray line. And then for

1 transparency, we're including brexanolone, 60 dose
2 regimen, in the blue line.

3 You can see that the data are maintained.
4 The efficacy is maintained from hour 60 out through
5 30 days, even in those pooled data. I also have
6 individual HAM-D items at day 30 that are also
7 pooled.

8 Again, this is a similar forest plot that I
9 showed before. It has the same profile that we saw
10 at hour 60 in terms of most of the results favoring
11 brexanolone for both the 90 and the 60 dose groups.

12 Then I think you also mentioned, around
13 202A, influencing the pool. We do have some data
14 around the pooling of 202B and C, and just one
15 moment.

16 DR. TURNER: Thanks for showing those. That
17 looks great. You had the suicide item. And
18 anxiety and insomnia are covered of course in there
19 as well? I didn't catch that.

20 DR. SCHACTERLE: Yes, they are. Let me show
21 the pooled. These are just studies B and C pooled.
22 And so you can see that the improvement in

1 sustainment in efficacy remains, even when we only
2 look at B and C. Now, I'll put the HAM-D items
3 back up.

4 You mentioned anxiety. That's sort of
5 midway, two-thirds of the way down. And insomnia
6 is about a third of the way down, again, both of
7 those favoring brexanolone.

8 So we see that across all of the symptoms,
9 but the important symptoms of mood, guilt, and
10 suicide, improvements across the board.

11 DR. NARENDRAN: Thank you. I'm going to
12 take two more questions from people that haven't
13 asked. Dr. Valbh?

14 DR. VALBH: Hi. Tina Valbh. My question
15 was details around the healthcare setting, where
16 patients were administered the medication. Did you
17 have criteria around what that healthcare setting
18 was? Was it inpatient? Was it a physician office
19 that stayed open 24 hours?

20 Also, did you have criteria around the type
21 of clinician that would be on staff to help monitor
22 the patient? And then the discharge criteria; was

1 there standardized discharge criteria applied to
2 all patients or was that based on physician
3 individual assessment?

4 DR. SCHACTERLE: So the healthcare settings;
5 we include a variety of healthcare settings. I
6 think I'll put this slide up so that you can see.
7 So the answer to your questions were, yes, and yes,
8 there were private research centers. There was a
9 hospital clinical research center; of course, a
10 perinatal psychiatry unit, urgent care facilities.

11 These are the types that were utilized in
12 the clinical trial, so most of them in fact were
13 not hospital-based settings. The healthcare
14 providers; the requirements were in concert with
15 GCP requirements, so there always had to be a
16 healthcare provider on sight. That was nursing
17 staff. There also was a physician attending to be
18 able to inform if there was an adverse event
19 occurring. And then certainly, there were
20 assessments across the time points. I'd like
21 Dr. Colquhoun to address discharge criteria.

22 DR. COLQUHOUN: Helen Colquhoun. Prior to

1 discharge at hour 72, there were a series of
2 assessments that were done, such as vital signs,
3 asking the patient if they felt well.

4 So if the patient was unwell in any way,
5 they were not discharged.

6 There were no formal discharge criteria.
7 But in general, the criteria was that the patient
8 had to be well, had to be alert and orientated.
9 And there had to be no abnormalities found on the
10 assessments done, such as an ECG or a vital sign
11 measurement.

12 DR. NARENDRAN: Thank you. Last question,
13 Dr. Burger?

14 DR. BURGER: Greg Burger, Stormont Vail
15 Health, Topeka, Kansas. I want to hear more about
16 study 201. And you said that you did more rapid
17 titration with that study and the adverse events
18 with that. Thank you.

19 DR. SCHACTERLE: Study 201 was an open-label
20 study. This was our initial study in postpartum
21 depressed patients. It enrolled 4 patients. I'd
22 like Dr. Colquhoun to discuss the titration

1 schedule.

2 DR. COLQUHOUN: Helen Colquhoun. At the
3 time we did the open-label study, we were using
4 slightly different doses, which we later rounded
5 for ease. So the dose regimen was 21.5 micrograms
6 per kilogram per hour, going up to 43, going up to
7 64.5, going up to 86, so somewhere below the 30 to
8 somewhere above the 30, then the 60, then the 90.

9 We did that over 12 hours. What that meant
10 was that we titrated everyone up to 90 just before
11 they all went to bed. And they were sleepy and
12 wanted to sleep. And we had one woman who did not
13 tolerate the up-titration and so was titrated back
14 down to 60 or the 64.5 overnight.

15 Another woman was difficult to rouse in the
16 morning. She was rousable, but she was very
17 sleepy. Clearly, she had not tolerated the 90 dose
18 titration overnight. So she had another down
19 titration of dose and successfully finished the
20 study.

21 Because of that, we decided that it would be
22 a much better idea to titrate up to the 90 in the

1 morning of day 2 rather than the evening of day 1,
2 hence the 30 to 60 dose regimen was born.

3 Then we maximized the amount of time within
4 the 60 hours on the highest dose, so we had a 28-
5 hour maximum dose period that we titrated down into
6 4-hour steps.

7 DR. NARENDRAN: Thank you. That was
8 excellent. I think we could take a 15-minute
9 break. It's 10:05, so we'll start at 10:20. Panel
10 members, please remember there should be no
11 discussion of the meeting topic during the break
12 amongst yourselves or with any other member of the
13 audience. 10:20, we'll meet back. Thanks.

14 (Whereupon, at 10:05 a.m., a recess was
15 taken.)

16 DR. NARENDRAN: We will now proceed with the
17 FDA presentations, starting with Bernard Fischer.

18 **FDA Presentation - Bernard Fischer**

19 DR. FISCHER: Good morning, everybody. I'm
20 Bernie Fischer, psychiatrist from the Division of
21 Psychiatry Products. I'm going to talk a little
22 bit about the clinical overview and focus on the

1 review aspects of the presentation.

2 So I'll talk a little bit about postpartum,
3 an overview of the compound, brexanolone, focusing
4 a little bit more on the regulatory history, then
5 discuss the effectiveness and safety, again
6 focusing on key issues, including loss of
7 consciousness events, and abuse potential for the
8 product.

9 So major depressive episode, onset within
10 pregnancy or within 4 weeks of delivery; that's how
11 we characterize postpartum depression. And it is,
12 as the applicant mentioned, a large percentage of
13 pregnancies in the U.S. And again, the risk of
14 suicide is quite high.

15 Again, in the developed world, it's the
16 leading cause of postpartum death. It definitely
17 impacts maternal-infant bonding and it may actually
18 have impact on later infant development, so a
19 serious condition.

20 The symptoms are identical to major
21 depression, but the timing, because it's
22 postpartum, may indicate a unique pathophysiology

1 for this disorder. Allopregnanolone, as we've
2 talked a little bit about this morning, does
3 increase during pregnancy. It reaches its peak in
4 the third trimester and then there's an abrupt fall
5 after delivery.

6 Now, allopregnanolone is an endogenous
7 neuroactive hormone and it's a GABA regulator, so
8 positive allosteric modulator. And the way that
9 GABA can affect the receptor, it can either make
10 the receptor open longer or it can increase the
11 amount of times it opens, the frequency of opening.

12 So benzodiazepines tend to make the receptor
13 open more frequently. And barbiturates tend to
14 make the receptor open longer. It appears that
15 allopregnanolone can do both. And this is
16 important as we go along in some of the agency's
17 thinking about the monitoring for this product.

18 So again, no drugs are specifically approved
19 for postpartum depression and the standard of care
20 is to use antidepressants that are approved for
21 major depressive disorder. However, there's
22 limited efficacy data that these are really

1 effective treatments.

2 There's also psychotherapy,
3 electroconvulsive therapy, and transcranial
4 magnetic stimulation. But one thing that all of
5 these tetramers have in common is that they take
6 weeks for an effect, so antidepressants take 4 to 6
7 weeks for an effect, even augmenting agents that
8 are approved as adjunctive use. They don't
9 decrease response time.

10 Psychotherapy is usually 8 to 20 weekly
11 sessions. Electroconvulsive therapy is usually 2
12 sessions a week for a number of weeks and the same
13 thing with TMS.

14 Brexanolone, again, is chemically identical
15 to allopregnanolone. Once it's mixed, we've found
16 that it's stable for 12 hours at room temperature
17 and 24 hours refrigerated.

18 This is an illustration of the dose. And as
19 you can see at the top, we can illustrate when the
20 bags would need to be changed out just based on the
21 stability of the product.

22 As far as the regulatory history, again,

1 it's not approved to be marketed in any country.
2 The IND was submitted, opened June 2, 2014.
3 Breakthrough therapy was granted August 2016 and
4 the NDA was submitted April of this year.

5 So again, as you've heard this morning, the
6 applicant had an umbrella protocol and they used
7 that umbrella protocol to run three separate
8 protocols, the PPD 202 studies. So there was 202A,
9 which was a phase 2 study, which was the smaller
10 sample size study, and then 202B and 202C, which
11 were the phase 3 studies.

12 The studies were conducted entirely in the
13 United States, so it's a population that does
14 reflect the U.S.

15 The primary efficacy endpoint, again, was
16 the Hamilton depression rating scale at hour 60, at
17 the end of the infusions.

18 Just a bit about the Hamilton for people who
19 are not familiar with it; it's 17 items and it
20 assesses a range of depression symptoms, both
21 physical symptoms like somatic complaints, but also
22 the more psychological symptoms like depressed

1 mood.

2 It ranges the score from 0 to 48 and a
3 higher score is equal to more symptoms.

4 In talking a little bit about the study
5 differences under the umbrella protocol, the
6 population was slightly different. In 202A and
7 202B, there was severe postpartum depression, which
8 the applicant defined as a HAM-D greater than or
9 equal to 26. The 202C was in moderate postpartum
10 depression, which the applicant defined as 20 to
11 25.

12 As far as dosing goes, all of the studies
13 that the applicant conducted contained a 90-
14 microgram per kilogram per hour arm. However, 202B
15 also included a 60-microgram per-kilogram arm. The
16 enrolled population; again, postpartum depression
17 had to have occurred beginning in the third
18 trimester, all the way up to 4 weeks' post-
19 delivery, and patients were enrolled in the studies
20 within 6 months of delivery.

21 People with bipolar disorder or active
22 psychosis were excluded as well as people who had a

1 suicide attempt during this index episode.

2 As far as exposures, you can see, for the
3 202 studies, the exposure, so a total of 140
4 exposed to brexanolone in these key studies.

5 Moving on to the individual studies, looking
6 at them as far as efficacy, the 202A studies, the
7 demographics, you see that the age range was around
8 27, 28, which is, as far as the Agency is
9 concerned, good. It wasn't weighted towards older
10 mothers or younger mothers. The mean tended to
11 reflect kind of an average range.

12 As far as non-white enrolled, it was
13 actually fairly good enrollment, diverse enrollment
14 for the study even though it was a small study, and
15 the BMI, which is important to look at since the
16 product has a dose based on weight, was very equal
17 in the groups. Looking at the results for this
18 small study, you can see that the placebo-
19 subtracted difference in this study was 12, and
20 this is something that gets the Agency to sit up
21 and take notice. Most antidepressants, after 4 to
22 6 to 8 weeks, would have a placebo-subtracted

1 difference of about 3.

2 We find that's clinically meaningful and
3 worthy of approval. And when we see this at 12,
4 this is something that is not only very meaningful,
5 but it also happened within 60 hours, not 6 weeks.

6 Although it wasn't a pre-specified endpoint,
7 in 202A, they did look at day 30. And again, there
8 was a significant difference which favored
9 brexanolone with a placebo-subtracted difference on
10 the order of 12.

11 Moving on to 202B, if you remember, this is
12 the study that enrolled severe postpartum
13 depression, but also included a 60 microgram arm.
14 So again, looking at the age, right around that 27,
15 where it doesn't seem weighted towards older or
16 younger women, a good enrollment, diversity of
17 enrollment; about 30 percent of the U.S. population
18 is non-white, so a fairly diverse enrollment; and
19 again, the BMI, not that different between the
20 arms.

21 Looking at the results, at hour 60, which is
22 the primary endpoint, we see that, for both the 60

1 and the 90 arms, there was a significant difference
2 from placebo. And again, this is on the order of
3 if not better than what we see with traditional
4 oral antidepressants. However, this is at 60 hours
5 and not at 6 weeks.

6 Looking at day 30, it looked like the
7 results that you see at day 60 are carried out and
8 reflect also the findings at day 30.

9 This is a graph from the applicant and, as
10 you can see, one of the questions that we have for
11 you is a discussion about dose. What dose should
12 we use for the product in labeling? So you can see
13 that, around hour 24, both groups start to separate
14 from placebo. And at hour 24, both groups are
15 still getting the 60 micrograms per hour infusion.

16 If you look at the first few visits here or
17 assessments, you can see, aside from hour 36, there
18 is overlapping error between the 60- and the 90-
19 microgram arm, indicating to a reviewer that,
20 although there may be differences from placebo, the
21 arms themselves aren't that different from each
22 other.

1 Since the separation started at hour 24 and
2 the arms don't seem very different from each other,
3 one interpretation would be that the 60 microgram
4 group is somehow different than the 90-microgram
5 group and it was maybe not a function of dose and
6 maybe just a function of the random enrollment
7 process.

8 Moving on to 202C; again, so this study, to
9 remind you, enrolled with women with moderate
10 postpartum depression. Again, you see that 27, 28
11 mean for the age. Again, you see fairly good
12 enrollment, diverse enrollment, and you see very
13 close BMIs, almost identical BMIs.

14 Looking at the differences here at hour 60,
15 you find, again, on the order of what we have seen
16 with traditional oral antidepressants as far as
17 placebo-subtracted difference. At day 30, you see
18 that the brexanolone group was not different from
19 placebo.

20 However, when we take a look at the
21 applicant's provided graph, we see the improvement
22 that the brexanolone group showed tends to continue

1 to day 30 and it really seems that the placebo
2 group is coming to meet them.

3 So there's not a significant difference
4 between the placebo and the brexanolone group, but
5 it's not because the brexanolone group is
6 relapsing. One interpretation that we have as
7 reviewers is looking at this in a different patient
8 population and we don't have very good natural
9 history of postpartum depression based on severity

10 It could be that women with moderate
11 postpartum depression just tend to get better
12 without much intervention over the course of a
13 month.

14 Now, as far as considering which dose would
15 be the most appropriate dose to use, one
16 possibility would be to target a 60-microgram dose
17 and increase to 90 micrograms as needed. And that
18 would probably be based on an assessment of
19 efficacy.

20 Supporting this type of dose regimen would
21 be the fact that the 60-microgram dose did perform
22 better than the 90-microgram dose in the 202B

1 study.

2 All the patients have experienced the 60-
3 microgram dose because even the ones randomized to
4 90 went through 60 on their way through the
5 titration.

6 There's just a general feeling among a lot
7 of clinicians. There's no need to expose somebody
8 to a higher dose if the lower dose will do the
9 trick.

10 Information that does not support this
11 dosing regimen; the 60-microgram dose does start to
12 separate from placebo at 24 hours when both groups
13 are receiving 60, so it may be a function the group
14 and not the dose. There's also more AEs that have
15 been seen in the 60-microgram arm, so at this
16 point, we can't say the data argues that it's safer
17 than the 90-microgram dose.

18 There were some patients who did not respond
19 at 24 hours when they were on the 60, but then
20 later responded. And we can't be sure whether it
21 was a duration effect or whether it was increasing
22 to the 90 micrograms that actually led to the

1 improvement.

2 So the other option would be to target a 90-
3 microgram dose, which is what the sponsor had
4 designed in their development program, and decrease
5 it to 60 as needed. And this would probably be for
6 adverse events.

7 So information that would support this
8 dosing regimen would be that the 90-microgram dose
9 was a target dose, at least for 1 arm in all of the
10 202 studies, but we have the most data about the
11 90-microgram dose. It's also, as the applicant
12 pointed out this morning, much easier to recognize
13 an AE and adjust the dose than it is to try and
14 assess efficacy.

15 The other supporting aspect of the dosing
16 regimen would be that the brexanolone group didn't
17 separate from placebo until it reached 90
18 micrograms in the 202C study, so it could be
19 there's a subset where 90 is really needed.

20 The information that would not support this
21 dosing regimen would be that the 60-microgram arm
22 did outperform the 90 in the 202B study. And when

1 we had continued exposures, this is, again, 140
2 people exposed to brexanolone in the key studies.
3 You might expect that maybe the 90-microgram dose
4 would have more AEs with continued exposure, more
5 AEs than the 60, but we don't know.

6 Moving on to talk about the safety from the
7 reviewer perspective, again, there were no deaths
8 in the development program. There were the two
9 serious adverse events in the 2 subjects, the
10 suicidal ideation 2 days after infusion and a
11 syncope-altered consciousness SAE, which we'll talk
12 more about when we get to loss of consciousness.

13 So these were dose interruptions and
14 reductions in the program, so you can see that 3
15 people in the placebo arms -- this is pooled data
16 from all three studies -- had their dose
17 interrupted or reduced. In the brexanolone group,
18 you can see there were patients who had their dose
19 interrupted or reduced.

20 Most of the interruptions or reductions were
21 related to infusion site difficulties or sedation,
22 dizziness AEs.

1 Now, this is the adverse events by assigned
2 arm and it's pooled data, so you have the
3 [indiscernible] brexanolone. So this was people in
4 the 90-microgram and the 60-microgram arms. And in
5 the 60-microgram arm, which was only in the 1
6 study, and then pooled the 90-microgram arms from
7 all 3 studies.

8 Now, looking at this table of AEs, these are
9 also AEs that were at least twice the rate in the
10 drug group as compared to the placebo group. So
11 this table differs a bit from the applicant's
12 table.

13 So most of the AEs, you could see here at
14 the bottom, are very low percentages and are not
15 very serious AEs; flushing, diarrhea, things like
16 that. However, the concerning one is the loss of
17 consciousness, so we're going to spend a little bit
18 of time discussing the agency's viewpoint on this.

19 So going back and looking at sedation-
20 related adverse events, by the dose that people
21 were receiving at the time they had the AE, so when
22 you have this dosing regimen where you have the

1 titration, you have a taper, not just looking at it
2 from what group people were assigned to, but
3 actually what dose were they getting when they
4 experienced their AE, so a few assumptions were
5 made for this table. One assumption is that
6 everybody received the 30- and the 60-microgram
7 doses on the way through their titration.

8 So figuring out the denominator, that would
9 be the 140 total exposed to brexanolone. Another
10 thing to note is that, if somebody experienced one
11 of these AEs during the 30-microgram dose and then
12 experienced it again during the 60-microgram dose,
13 I counted them twice, once for the 30 and once for
14 the 60, just to give them a more complete picture
15 of what people were experiencing as they went
16 through the titration.

17 As you can see, looking at the numbers,
18 there's really not a good dose response. A lot of
19 the sedation, somnolence occur when somebody first
20 starts the titration, when they're getting 30
21 micrograms.

22 When you look at the dizziness, light-

1 headedness, pre-syncope, vertigo, again, you don't
2 see a dose response, and the loss of consciousness,
3 again, is kind of spread throughout the dosing.

4 So about the loss of consciousness events,
5 there were 6 subjects who experienced a loss of
6 consciousness, syncope, pre-syncope during the
7 infusion.

8 One person had a vasovagal reaction when
9 they had a blood drawn. And I think that one was
10 probably not included in the applicant's table
11 because we did not feel that was drug related. She
12 had a known fear of needles and seemed to have this
13 vasovagal reaction.

14 There was another woman who appeared to have
15 pre-syncope vertigo when she was standing. And
16 once she sat down and then moved to the bed and
17 laid down, it resolved. And this did not seem to
18 fit the pattern that the other four women.

19 The pattern with the other four seems that
20 they, fairly abruptly, seem to have fallen asleep.
21 There are in the case reports how women started
22 snoring, how they seemed kind of unarousable. And

1 it really does seem like maybe they had fallen
2 asleep. You could see the ages and two of them did
3 have IV pump malfunctions. One thing that we have
4 looked at is the nearest PK blood level of
5 brexanolone near the loss-of-consciousness event,
6 and especially for these two ladies that had the
7 pump malfunction.

8 What it appears; we did not find abnormally
9 high brexanolone levels in the women who had the
10 pump malfunctions. So we would expect that, even
11 with a 40-minute half-life, that if somebody was
12 receiving an extraordinary rate of infusion, that a
13 blood level 2 hours later would show an increased
14 blood level of brexanolone compared to the other
15 women in the study, but we didn't find that.

16 There were 2 cases, one with the pump
17 malfunction and 1 with another woman in the study
18 that seemed fairly abrupt. There were 2 people in
19 the study who had lost consciousness who had not
20 reported a prior AE of dizziness, or somnolence, or
21 sedation.

22 All of the loss-of-consciousness events

1 resolved within 10 to 60 minutes after shutting off
2 the infusion. The reason our number goes out to 60
3 as opposed to 15 minutes; there was 1 woman who
4 aroused to verbal stimulation after 15 minutes, but
5 wasn't fully verbal herself and responsive for
6 another 45 minutes, so again, the only intervention
7 that was required was turning off the infusion, no
8 other support.

9 So looking at these 6 women, who had their
10 loss of consciousness or pre-syncope events, some
11 of them had their dose interrupted. Some of them
12 discontinued the study. One woman did not complete
13 the study. The other one who discontinued was very
14 close to the end of the study and just completed
15 the study without restarting. The other 4 women
16 who restarted the study titrated up to 90, 60
17 micrograms, and did not have a recurrence of the
18 loss of consciousness, so they were able to return
19 to a higher dose and not experience a recurrence.

20 You heard the case of the male subject who
21 was in the cardiac repolarization study, who had
22 less than 1 minute of apnea. Now, the man had no

1 past medical history. He was not obese. He did
2 have a higher blood level than the average that we
3 saw in the exposure with the women in the
4 postpartum depression studies.

5 Because the mechanism of action can be
6 consistent with barbiturates, we want to be mindful
7 of a possible respiratory risk and this case of,
8 even though it's less than 1 minute, this case of
9 possible apnea to give us a little pause, and
10 that's really what influenced us to think about
11 closer monitoring with maybe a pulse oximetry
12 monitoring.

13 These graphs; you don't need to see the
14 details. This is the respirations per minute, the
15 respiratory rate in the studies. And you can see
16 that the brexanolone groups did not have any faster
17 respiratory rate. They weren't in respiratory
18 distress. They didn't have any respiratory
19 depression.

20 The right-hand graph; the dotted blue line
21 at the top is actually the placebo group for the
22 maximum respiration.

1 So again, there wasn't a signal with
2 respiratory rate for any kind of depression. So
3 when it comes to safety, when it comes to these
4 loss of consciousness events, we did not see any
5 relationship and it's, again, based on the limited
6 data that we have. We did not see a relationship
7 between age, or BMI, or vital signs, time since
8 delivery and past medical history, the brexanolone
9 dose they were receiving, their blood level at the
10 time they were on their current dose.

11 One woman had a loss of consciousness event
12 13 hours after starting a 90-microgram infusion, so
13 it wasn't at the beginning of the start of the
14 dose.

15 We didn't see a relationship with concurrent
16 medications. The reason why this concerns us is
17 because the loss of consciousness could be abrupt
18 in some cases and we don't have a known way yet to
19 predict who is going to be at risk for the loss of
20 consciousness. Intervention is required in that
21 the infusion has to be stopped and we don't
22 actually know what would happen if the infusion was

1 not stopped, and somebody lost consciousness, and
2 the infusion continued.

3 We do worry, depending on the setting of the
4 administration of the infusion, risks to the
5 patient such as falls, and also risks to the infant
6 such as dropping the infant or maybe, during
7 breastfeeding, smothering the infant or something
8 if the woman were to abruptly lose consciousness
9 and there was nobody there to act.

10 As far as the abuse potential of
11 brexanolone, it does have a significant affinity
12 for the GABA receptor, as to benzodiazepines. In a
13 drug documentation in rats, there was a full
14 generalization to the benzodiazepine midazolam.
15 And in the human abuse study potential, a 270-
16 microgram per-kilogram per-hour dose produced a
17 similar drug liking response to alprazolam,
18 3 milligrams.

19 This is a graphical representation of the
20 drug liking, rated on a visual analog scale. And
21 you can see placebo in green at the bottom of the
22 graph. And you can see, at the top of the graph,

1 the brexanolone dose in blue and the alprazolam
2 dose in red.

3 Although there's a difference in time,
4 there's no difference in drug liking between the
5 two. So in summary, brexanolone, 270 micrograms
6 per kilogram, was similar to the alprazolam 1.3-
7 and 3-milligram doses on secondary measures during
8 the human abuse study such as overall drug liking,
9 high, drug effects, and that I would take this drug
10 again.

11 So the clinical summary; looking at it,
12 there is evidence of effectiveness. We think that
13 these are clinically meaningful changes. We think
14 that it's important the improvement is rapid.
15 Looking at the safety, the most concerning part is
16 the loss of consciousness, but we believe that this
17 can be monitored and intervention can be performed
18 to minimize risk with this. The abuse potential
19 does appear similar to benzodiazepines.

20 **FDA Presentation - Leah Hart**

21 DR. HART: Good morning. My name is Leah
22 Hart and I'm with the Division of Risk Management

1 and we will now discuss the proposed risk
2 evaluation and mitigation strategy for brexanolone.

3 During this presentation, I will give an
4 overview of risk evaluation and mitigation
5 significantly, referred to as REMS, including the
6 regulatory authority and components of a REMS when
7 the agency determines that a REMS is necessary. I
8 will briefly review the safety issues of
9 brexanolone, which you have heard about in detail
10 earlier.

11 Finally, I will discuss the applicant's
12 proposal for risk management and the FDA's
13 proposal. The participants who were part of
14 yesterday's meeting have heard this, so I will try
15 to be brief for those who were not present
16 yesterday.

17 REMS is a drug safety program that can be
18 acquired by the FDA for certain drugs. A REMS is
19 designed to mitigate risk associated with drug use
20 and includes strategies beyond labeling to ensure
21 the benefits outweigh the risks of the drug.

22 The FDA Amendments Act of 2007 gave the FDA

1 authorization to require applicants and application
2 holders to develop and comply with REMS programs if
3 determined necessary.

4 The FDA has the authority to require REMS
5 either pre- or post-approval. A REMS can include a
6 number of components such as a medication guide,
7 communication plan, elements to assure safe use,
8 and an implementation system, and a REMS must
9 include a time table for submission of assessments.

10 If determined as a necessary component of a
11 REMS, the elements to assure safe use can include
12 the following; certification and/or specialized
13 training of the healthcare providers that prescribe
14 the drug, certification of pharmacies or other
15 dispensers of the drug, limited settings for
16 dispensing or administering the drug, having each
17 patient using the drug subject to certain
18 monitoring.

19 The drug is dispensed and administered only
20 with evidence of safe use; for example a pregnancy
21 test or enrollment of treated patients in a
22 registry. Additionally, ETASU must align with the

1 specific serious risks listed in the labeling.
2 They cannot cause undue burden on patient access to
3 the drug, considering in particular patients with
4 serious or life-threatening diseases or conditions
5 in patients who have difficulty accessing
6 healthcare.

7 We will now discuss the risks associated
8 with brexanolone. To remind you of the complexity
9 of the administration, this is a 60-hour infusion
10 requiring titration and multiple bags with varying
11 concentrations. Note the colors depict the varying
12 concentrations of the infusion bags.

13 Of the 5 bags, there are 4 different
14 concentrations. The concentration depends on the
15 patient's wait. The agency has concerns associated
16 with brexanolone if used outside of a medically
17 supervised setting. Of the 140 subjects exposed to
18 brexanolone, 6 experienced a loss of consciousness,
19 syncope, or pre-syncope event, hereafter referred
20 to as LOC.

21 This could result in serious harm, accident,
22 or injury to the mother and potentially to the

1 infant. Also discussed in the clinical safety
2 portion of this AC, there is the possibility for
3 respiratory depression.

4 The clinical development program for
5 brexanolone utilized a wide range of sites of
6 administration. However, the minimum requirements
7 were overnight capabilities to house the subjects
8 for approximately 72 hours, IV infusion
9 capabilities, and most important, healthcare
10 professional to be on site at all times.

11 The credentials of healthcare professionals
12 ranged from emergency room medical technicians to
13 nurses or physicians depending on the site and
14 state regulations. 85 percent of subjects with
15 dosed in non-hospital clinical research
16 environments.

17 As heard before, these included sleep
18 centers, units used in the phase 1 trials, urgent
19 care facilities, a physician's outpatient office,
20 hospital clinical research centers, and a pediatric
21 wing of a private hospital.

22 Visits by the partner or spouse, family,

1 baby, and/or other children were permitted per the
2 rules of the site and clinical judgment of the
3 investigator. Some sites allow babies to stay
4 overnight. 15 percent were dosed in units that
5 were part of a hospital environment.

6 The applicants initially submitted an
7 outline of their proposed REMS with ETASU. The
8 initial proposal allowed for use in the home.
9 Their proposed goal was to inform patients,
10 competent companions, and healthcare professionals
11 on how to mitigate the risk of excessive sedation
12 during the brexanolone infusion.

13 Their proposal included certification of
14 infusion providers. These infusion providers could
15 be designated authorized representatives at
16 hospital pharmacies, home infusion companies, or
17 other infusion providers. You have heard the
18 applicants' most recent proposal earlier in the
19 presentation.

20 Now, I will discuss the agency's proposal.
21 The FDA's proposed REMS includes limiting
22 administration only in certified healthcare

1 settings, consistent with the settings that were
2 utilized in the clinical development program.

3 The authorized representative will be
4 responsible for establishing policies and
5 procedures to ensure that all staff are trained on
6 the risks and the product is not dispensed for use
7 outside of the healthcare setting.

8 In this certified healthcare setting, the
9 patient must be continuously monitored for the
10 duration of the infusion and for 12 hours after by
11 a healthcare provider who can intervene if the
12 patient experiences excessive sedation or loss of
13 consciousness.

14 The continuous monitoring includes pulse
15 oximetry and observation of the patient. The FDA's
16 proposed REMS also includes enrollment of patients
17 who are treated with brexanolone in a registry to
18 better characterize the risk of LOC and the
19 management of that risk.

20 A patient registry may capture data needed
21 for an estimation of the risk of LOC associated
22 with the use of brexanolone, identification of risk

1 factors for LOC, and patient outcomes of interest.

2 After further discussion, the agency and the
3 applicant have aligned on the need for a REMS with
4 ETASU that includes administration only in
5 medically supervised healthcare settings and the
6 inclusion of a patient registry.

7 Other elements proposed by the applicant are
8 still under consider. Although safe use in the
9 home has not been demonstrated, the agency is
10 considering what additional data is needed to
11 support the safe use of brexanolone at home.

12 **Clarifying Questions**

13 DR. NARENDRAN: Any clarifying questions for
14 the FDA? We'll start over here. Dr. Kulldorff?

15 DR. KULLDORFF: Thank you. Martin
16 Kulldorff, Harvard Medical School. I have a
17 question about the interpretation of question
18 number 2 that we are expected to vote on. So the
19 question says, has the applicant adequately
20 characterized the safety profile.

21 Does that mean on whether we should vote on
22 whether they have a good job to evaluate whether

1 the drug is safe or not safe irrespectively of
2 whether it is or not? Or does it mean that we vote
3 on whether they have shown that the drug is safe?
4 And if so, is it to show that the drug is
5 completely safe or reasonably safe.

6 DR. FARCHIONE: For that question, the main
7 issue here is -- and I know that, earlier, you were
8 also asking about the loss-of-consciousness
9 events -- we know no drug is completely safe, so
10 that is not the issue. The issue is whether you
11 think that they've done a good job of identifying
12 the adverse events, whether they've described them
13 adequately, and whether you think that those
14 adverse events can be labeled in such a way that
15 allows for appropriate prescribing, so do we
16 understand enough about the things that can go
17 wrong in order to instruct healthcare providers on
18 how to appropriate prescribe this medication? Does
19 that help?

20 DR. KULLDORFF: So we want to vote on
21 whether they have shown that it is reasonably safe?

22 DR. FARCHIONE: Not whether they've shown

1 whether it's reasonably safe, but whatever safety
2 they have, have they described it well enough?
3 Have they identified the risks? Yeah. It's
4 whether they've characterized it, not whether it's
5 safe.

6 DR. KULLDORFF: So suppose a hypothetical.
7 Suppose they had shown that there were 10 deaths in
8 the study. Well, then, they have characterized the
9 safety profile very well because they have shown
10 that there are deaths, but it's not a safe drug and
11 it shouldn't be approved.

12 DR. FARCHIONE: That's question 3, then,
13 because then that's the balance of benefit and
14 risk.

15 DR. KULLDORFF: So if that shows 10 deaths,
16 then we should vote yes on question 2 because they
17 characterized well?

18 DR. FARCHIONE: Yes. If 10 people died and
19 they said, yes, 10 people died and we figured out
20 what happened to them, because it's not just, did
21 something awful happen, but did you follow up on it
22 and find out why?

1 DR. KULLDORFF: Thank you. That clarifies
2 it. Thanks.

3 DR. NARENDRAN: Next question, Dr. Dunn?

4 DR. DUNN: Hi, Walter Dunn, two questions
5 related to safety. So it looks like, for all the
6 cases where there was an LOC, it was caught fairly
7 early, and then discontinuation of the infusion
8 resolved the problem. Once it gets out in the real
9 world, potentially the infusion keeps going. Do we
10 know if flumazenil can reverse the effects of this
11 medication?

12 DR. FISCHER: We actually don't know. It
13 has a different binding site than the
14 benzodiazepine, so it may not.

15 DR. DUNN: The second question; for those
16 patients where the infusion was abruptly
17 interrupted because of an AE, do we know -- did
18 they experience more pronounced withdrawal effects,
19 and then also for patients with perhaps an
20 underlying seizure disorder if we had to abruptly
21 discontinue, is the concern about seizure.

22 DR. FISCHER: The individuals who had an

1 abrupt discontinuation didn't appear to have a
2 withdrawal effect. I would assume, theoretically,
3 whenever you have, again, an agonist type of drug
4 that there is potentially an increased seizure
5 risk, but we haven't seen any of that in the
6 development program for this or the other
7 indications that the applicant had been developing
8 it for.

9 DR. NARENDRAN: Dr. Turner?

10 DR. TURNER: Yes, Erik Turner from Oregon
11 Health and Sciences University; two questions about
12 REMS. Could REMS be turned into essentially a
13 phase 4 study? And I wonder, because of the
14 ambiguity about the results, about whether to ramp
15 up the dose or not ramp up the dose, could that be
16 left up to the provider and they merely make that
17 as part of the registration of the REMS, and then
18 we collect more data and perhaps things will sort
19 of become clearer down the road, so that's one
20 question.

21 The second question about REMS is regarding
22 the so-called continuous monitoring, and

1 observation, and monitoring could be open to
2 interpretation in the clinical world and I'm
3 thinking, with that, I'm thinking of inpatient
4 psychiatry units where someone's in seclusion. I
5 believe that calls for a 15-minute documentation by
6 a nurse, but someone else might interpret it to
7 mean eyes on at all times. Someone else might
8 think checking on a patient once every hour or so.

9 I'm just wondering if that's going to be
10 fleshed out, operationalized.

11 DR. LaCIVITA: Cynthia LaCivita, Division of
12 Risk Management. Regarding the question about a
13 phase 4 trial in a REMS, a REMS drug that is
14 approved with a REMS is to mitigate the risk. The
15 registry, if it would be part of the REMS in this
16 case, would be to collect additional information
17 that's more than likely going to be event related.
18 Studies post-marketing would be a PMR, a post-
19 marketing requirement, to look at safety. So if
20 there are additional trials, I mean, there are REMS
21 assessments where you look at whether or not the
22 REMS is working the way it was intended, but for

1 additional post-marketing studies, if it's related
2 to safety, we can require studies post-marketing,
3 and then we also will negotiate post-marketing
4 commitments from an applicant if there are
5 additional studies that we would like to see with
6 regard to efficacy or things along those lines.

7 DR. FARCHIONE: But a REMS would not look at
8 a different change in dose and things like that.
9 They wouldn't collect that type of information.

10 DR. TURNER: I guess I wonder if it could be
11 left open and to provider discretion. And then it
12 could be collected as part of the --

13 DR. FARCHIONE: Not as part of the REMS, no.

14 DR. LaCIVITA: The REMS doesn't allow for a
15 lot of discretion.

16 DR. MATHIS: The REMS -- this is Mitch
17 Mathis -- is designed to use the drug as it's
18 labeled, and collect more data, and keep people
19 safe while doing it. Post-marketing commitments
20 and requirements are designed to have a new look
21 at, say, a different infusion regimen or other
22 questions that could be looked at in an environment

1 where you can actually tell the difference in what
2 you're doing and make some assessment besides just,
3 post-marketing, keeping patients safe.

4 DR. NARENDRAN: Dr. Jain?

5 DR. TURNER: There was a second question
6 because of what continuous observation means
7 exactly.

8 DR. LaCIVITA: Can you repeat the second
9 part of the question again? I'm sorry.

10 DR. TURNER: Yes. What is continuous
11 monitoring? Was one term used and observation was
12 also used? So what does that mean? Does that mean
13 every 15 minutes. I just would be concerned about
14 that being wide open to interpretation in the
15 clinical world and it could be anywhere from 5
16 minutes to continuous eyes on.

17 DR. FARCHIONE: Yes. We haven't got into
18 that degree of detail yet in our consideration of
19 the REMS, but I mean, that's an excellent question
20 and probably something that we'll need to discuss
21 as we move forward.

22 DR. FISCHER: One of the things that we were

1 thinking was the most concerning outcome of a
2 possible loss-of-consciousness event might be
3 respiratory depression and that was another reason
4 for the continuous pulse-ox monitoring, so even if
5 somebody wasn't eyes on, if they were at the
6 nurse's station, there would be an alarm or
7 something that would trigger some need for
8 intervention if there was a need for intervention.

9 DR. NARENDRAN: Dr. Jain?

10 DR. JAIN: Felipe Jain. I'd like to pose a
11 hypothetical. So let's say that the FDA approves
12 this medication. I'm trying to put myself in the
13 position of a woman who's struggling with
14 postpartum depression and has heard that the FDA
15 has approved a drug that is highly effective for
16 what she's going through. And then I'm trying to
17 weigh the risks and benefits for that individual of
18 potentially not having access to the treatment
19 because there are not certified centers or
20 healthcare settings in which she can receive it.

21 The potential frustration, the potential
22 negative outcomes for her not receiving treatment,

1 could you comment on? It seemed like the FDA's
2 concern was that it's a lot to expect from a
3 supervised healthcare monitor to be in the home
4 environment and to ensure that the brexanolone is
5 being administered in a safe fashion.

6 I'm wondering whether the FDA could consider
7 are there any heroic REMS, types of guidelines that
8 could be considered to make this accessible to
9 women in the home setting, so for example,
10 specifications between the number of feet between,
11 you know, the bed and the crib so that the woman is
12 not falling asleep with a baby and is potentially
13 rolling over on top of the baby or, you know, those
14 kinds of concerns.

15 DR. NARENDRAN: Before you answer,
16 Dr. Temple could introduce himself.

17 DR. TEMPLE: Bob Temple, deputy director,
18 ODE-1.

19 DR. NARENDRAN: You can answer.

20 DR. FISCHER: Hi, Bernie Fischer. This is
21 something that the agency has really struggled
22 with, with this product about access for women who

1 need it versus assuring safe use. And I think,
2 working with the applicant and designing some post-
3 marketing studies and collecting information from
4 the REMS when we have patients register and we can
5 look at adverse outcomes, I think we would all like
6 to have it more widely available. And so we're
7 really struggling with that balance.

8 The problem that we've run into is that a
9 REMS cannot really regulate someone's house like it
10 can an infusion center or a medical center.

11 DR. MATHIS: This is Mitch Mathis. So
12 should the drug be approved, we will collect data
13 in a registry. And we have 6 events and 140 here,
14 so we know how to use it safely in the way that
15 they've studied it, but we don't know much more
16 than that yet.

17 Over time, one could potentially learn more
18 and either through post-marketing commitments and
19 requirements or just exposure registries, learn
20 more, get a better number, more definition of
21 exactly how prevalent this problem is, if it's a
22 problem, how many of these cases ever go on to be

1 more than just what we've seen in the clinical
2 trials, for instance, or that never go on.

3 There's a lot to be learned, but we think it
4 should be done and in a logical way

5 DR. FARCHIONE: This is Tiffany Farchione.
6 So just to directly address your question about
7 potential heroics in a REMS, I mean, we obviously
8 thought about some of those things. We said, "What
9 could we possibly do to allow this drug to be
10 administered in a home setting?"

11 Because that would increase access if we
12 were to approve it. So the issue with the original
13 proposal of having a competent companion is that we
14 can't regulate a competent companion. There's no
15 statute or regulation that allows us to do that,
16 not even with a REMS. Like the idea of saying that
17 the bed had to be within a certain amount; we can't
18 do that.

19 And if we were to, you know, say that you
20 had to have a nurse in the home, there's nothing
21 that we can do to ensure that, if a nurse shows up
22 at the home, and hangs the bag, and then the

1 patient says, "I got things to do. I need you to
2 leave," there's nothing we can do about that,
3 either.

4 So a REMS can do a lot, but it can't do
5 everything.

6 DR. HART: Hi. This is Leah Hart. I had
7 just one more thing to add. One of our other
8 concerns about home infusion is, in all of the
9 clinical development programs, the mother was not
10 the primary caretaker of the child.

11 And so if a home health nurse comes into the
12 home, are they then required to police the mother
13 to not be the primary caretaker or is it their job
14 to say, "Well, you don't have another primary
15 caretaker because your significant other went to
16 the store. Now I have to stop the infusion." And
17 so we don't think that a home health nurse should
18 be responsible for either childcare or policing
19 whether or not the patient has another primary
20 caretaker for their children.

21 DR. NARENDRAN: That's good. I mean, just
22 to make a comment on that, it's always possible the

1 home health care worker is not going to be able to
2 say, "I'm going to have a shot of vodka," or, "I'm
3 going to have a glass of wine," which could also be
4 pro-benzodiazepine sort of sites that can increase
5 the sedation risk, so I think it seems reasonable
6 to start this way.

7 DR. MATHIS: This is Mitch Mathis. We are
8 also cognizant of the fact that these women have
9 just given birth and labored and need to sleep and
10 should be unconscious part of the time, that we
11 felt had to be monitored in some way that can keep
12 them safe while they're doing that and to do that
13 in a monitored healthcare environment seems a lot
14 more sensible to us, at least to start.

15 DR. NARENDRAN: Next question,
16 Dr. Fiedorowicz?

17 DR. FIEDOROWICZ: Yes. So there was the
18 patient who had vasovagal syncope and had a fear of
19 needles, and that was deemed unrelated. Did that
20 patient have any prior history of vasovagal
21 syncope?

22 DR. FISCHER: This is Bernie Fischer. I

1 actually don't know the answer to that.

2 DR. NARENDRAN: The sponsor maybe?

3 DR. SCHACTERLE: We can try and get you that
4 information at the break.

5 DR. NARENDRAN: Thank you. Do you have
6 other questions? Ms. Numann?

7 DR. NUMANN: Sabrina Numann, patient
8 representative. A quick labeling question; is the
9 label going to include anything on pregnancy? I
10 haven't heard any information on that.

11 DR. FISCHER: This is Bernie Fischer. Since
12 brexanolone wasn't studied in pregnant women, we
13 are going to say that it must be used postpartum,
14 that it would not be used during pregnancy.

15 DR. NUMANN: Right. But if they are
16 starting treatment approximately 4 months later,
17 they could potentially be pregnant again.

18 DR. FISCHER: True. Good point. We would
19 probably put in the label, "Get pregnancy test
20 before starting the medication."

21 DR. FISCHER: Thank you.

22 DR. NARENDRAN: Dr. Besco?

1 DR. BESCO: Kelly Besco, OhioHealth. One
2 thing I haven't heard discussed today that I think
3 might impact the potential treatment sites for this
4 therapy is potential hazardous drug implications .

5 So this is a metabolite of progesterone.
6 The National Institute for Occupational Safety,
7 NIOSH, or in health, NIOSH, requires that we have
8 handling precautions for preparation and
9 administration of progesterone, so I'm just
10 wondering if there are any similar properties of
11 this medication since it is a metabolite of
12 progesterone that would mandate that we align our
13 protocols with what we do for progesterone to
14 ensure that we have occupational safe-handling
15 precautions.

16 DR. FARCHIONE: That's probably a better
17 question for the applicant.

18 DR. NARENDRAN: Sponsor?

19 DR. KANES: We don't have any occupational
20 health specialists here with us today.

21 DR. BESCO: Yes. I just asked the question
22 because most of the treatment centers that were

1 specified wouldn't necessarily have 797-compliant
2 sterile clean rooms that would be able to provide
3 the level of safety necessary to provide those
4 administration precautions that would be necessary,
5 so that would have an impact on if those non-acute
6 treatment sites would remain eligible as a
7 treatment site.

8 DR. SCHACTERLE: So allopregnanolone does
9 not necessarily back-transform to progesterone.
10 I'd like Dr. Kanes to further address your
11 question.

12 DR. KANES: Yes, Steve Kanes. That's an
13 important point, so relative metabolite of
14 progesterone; it doesn't back-convert, nor does it
15 in its native state have demonstrable effects on
16 the nucleo [ph] receptors, so it'd likely be
17 handled in a very different way for the preparation
18 and so forth.

19 DR. BESCO: Just to clarify, it doesn't have
20 in animal studies any carcinogenic properties
21 similar to what progesterone showed in its studies?

22 DR. SCHACTERLE: Dr. Pawluik?

1 DR. PAWLUIK: Bob Pawluik. Based on the
2 short-term administration, there were no
3 carcinogenicity studies conducted with this
4 compound.

5 DR. SCHACTERLE: Can I ask the chair? There
6 was also a lot of questions around how this could
7 be administered in the home. Would it be helpful
8 if the sponsor gave some perspective around that?

9 DR. NARENDRAN: Sure.

10 DR. SCHACTERLE: Could I have slide PA-13
11 and then 14? So we, too, have been thinking about
12 how to have access be available to patients. And
13 when we think about access to the patient, we think
14 that the treatment options should be accessible,
15 comfortable, certainly family centric, supporting
16 the mother-baby bond, reducing stigma and
17 complexity, as we know is apparent with postpartum
18 depression.

19 There is risk of hospital-acquired or
20 community-acquired infection. So these are some of
21 the reasons why we think that there is an
22 importance to get to home infusion.

1 The next slide; so you were asking about the
2 REMS program. We think that this is more about the
3 oversight of patients as opposed to the setting of
4 care, so all the principles of the REMS could be
5 applied to the home healthcare setting.

6 Certainly, the healthcare professional's
7 supervision can be implemented for 24 hours at the
8 home for the duration of the infusion with access
9 to the prescribing physician and emergency medical
10 services.

11 Pulse oximetry; there are wearables on your
12 wrist now that are cleared pulse oximeters by CDRH.
13 The communications of the risk of sedation; there
14 certainly would be information for the patients
15 ahead of time as well as the healthcare providers
16 and prescribers.

17 Finally, certification on the healthcare
18 setting includes certification of the home infusion
19 provider and they would have to ensure that they
20 were operating in accordance with the REMS and that
21 they were enrolling patients in the registry.

22 The last piece was in terms of patient

1 selection. We were talking about how could the
2 home health care provider oversee the patient.

3 We have with us today an expert from a home
4 infusion company who can speak to patient
5 selection. This is not intended for all patients,
6 only those patients who would be compliant. So I'd
7 like to introduce --

8 DR. FARCHIONE: Hang on. I think that might
9 be appropriate for the --

10 DR. NARENDRAN: Yeah.

11 DR. SCHACTERLE: I'll stop. Thank you.

12 DR. NARENDRAN: Thank you. But for my own
13 clarification, I thought the agency and the sponsor
14 had agreed not to do home care infusion based on
15 the REMS that was presented? Is that not the case?

16 DR. SCHACTERLE: It is the case. We do
17 agree. We just wanted to give you information on
18 how this could be contemplated in the future.

19 DR. NARENDRAN: So down the line.

20 DR. KANES: Thinking ahead, yes.

21 DR. NARENDRAN: That's not current coming.

22 Thank you.

1 DR. FARCHIONE: Right. And this is not
2 information that we've actually seen at this point.

3 DR. NARENDRAN: Yes. I think it's less
4 useful for us to have that information at this
5 point because I feel like you guys have agreed on
6 the REMS to start in the healthcare setting.
7 Dr. Besco, was your question answered or do you
8 have more questions?

9 DR. BESCO: No. I'm good. Thank you.

10 DR. NARENDRAN: Dr. Griffin?

11 DR. GRIFFIN: Yes, Marie Griffin,
12 Vanderbilt. The way these episodes were described
13 sound very much like pre-syncope or syncope, but
14 the other 4, you described, Dr. Fischer, as "the
15 patient fell asleep." I mean, it almost sounds
16 more like narcolepsy or cataplexy, and they're not
17 the same thing. Do you think these are syncope or
18 is there a precedent for drugs causing narcolepsy?

19 DR. FISCHER: Hi, Bernie Fischer. We
20 actually have not come to a conclusion about
21 categorized them one way or another. It does
22 appear that they have fallen asleep. Either there

1 are instances where the women were snoring and it
2 seems like they were asleep from the descriptions
3 that we've seen, but we aren't sure what was
4 actually going on with them.

5 I'm not aware of drugs causing cataplexy
6 other than the orexin drugs that are used for
7 sleep.

8 DR. MATHIS: This is Mitch Mathis. And it
9 appeared that the patients were sedated. You turn
10 the infusion off and they get better with time, so
11 it looked like a sedation spectrum event. I don't
12 think we had characterized it as narcolepsy or
13 cataplexy, but rather sedation events and loss of
14 consciousness.

15 DR. NARENDRAN: Just to kind of add to that,
16 did the agency kind of look at other GABAergic
17 drugs like tiagabine, for example, which clearly
18 increases GABA, to see what's the worst that could
19 happen?

20 Because it sounds like there's a lot of
21 these things that loss of consciousness, delirium,
22 sudden onset of sedation, unarousable, it sounds

1 very GABA-ergic. It might be helpful to look at
2 those drugs besides the benzodiazepines. I mean,
3 personally, we did some studies with tiagabine and
4 flumazenil and we were giving them high doses of
5 tiagabine. It was under an IND.

6 We found a lot of people who did kind of
7 pass out, like, fall asleep and were very confused,
8 but with interruption or just giving it time, it
9 resolved.

10 See, having an IV route seems to be easier
11 to stop it so they can come back. It gives me more
12 reassurance, I think. I don't know. It might be
13 worth looking into the what's-the-worst-that-could-
14 happen. Next question, Dr. Meisel?

15 DR. MEISEL: Hi, Steve Meisel. I've got 3
16 questions. Yesterday, we were talking about 6
17 weeks as an endpoint in time for assessing
18 antidepressants. Today, we're talking about 30
19 days. There's a significant difference between 30
20 days and 6 weeks.

21 Is the agency satisfied that 30 days is long
22 enough for this assessment?

1 DR. FARCHIONE: For this condition and this
2 mechanism of action, basically what we're looking
3 at now; this is a new frontier when we're looking
4 at rapid-acting antidepressants. You have a
5 treatment separates from placebo within hours
6 rather than within weeks.

7 So the 30 days, I realize, is the primary
8 endpoint, but it's really designed to show the
9 durability of that effect. So also, with the
10 postpartum depression, you expect it to be episodic
11 as opposed to a chronic condition like major
12 depressive disorder, where it would continue well
13 beyond that period of time, so we think the 30 days
14 is fine.

15 DR. MEISEL: The second question is
16 something that I was not aware of at all until
17 Dr. Hart mentioned it. Four different
18 concentrations of drug; I'm not aware of any other
19 medication on the market that requires four
20 different concentrations.

21 Most organizations stick to one or two
22 because, otherwise, it's a major set-up for a

1 medication error and no IV pump is typically
2 configured to handle four different concentrations.
3 It could be, but they are typically not for error
4 purposes. Why? Why couldn't you just change the
5 infusion rate to match the dose as opposed to
6 changing concentrations to match the infusion rate?

7 DR. MATHIS: We too thought that this could
8 potentially lead to medication errors and have been
9 having those same discussions with the applicant
10 about how to simplify things and look at things in
11 the future, make them more simple.

12 When we reach the point in our discussions
13 of this where we agreed that, if this was to
14 happen, it would happen in a controlled
15 environment. I think we all decided we had time to
16 sort this out, but there probably are easier ways
17 to do these different regimens that might work that
18 would be more simple. And we just haven't laid
19 those out yet or thought about those to the point
20 of asking the sponsor to do them if it were to be a
21 condition of approval, should we get that far.

22 DR. MEISEL: Then my third question; the

1 agency keeps using the term "certified health
2 setting." I don't know what that means. Where do
3 we certify health settings? A setting that
4 requires X, Y, and Z in terms of monitoring is one
5 thing, but I think it's sort of dangerous to use a
6 term "certified health settings" because that's a
7 very, very vague term unless you guys have some
8 definitions that can go along with that.

9 DR. LaCIVITA: This is Cynthia LaCivita with
10 the Division of Risk Management. So the certified
11 healthcare settings are certified in the REMS
12 program that they would meet the requirements under
13 the REMS. So they would have to be able to monitor
14 the patient for the entire time that they're having
15 the infusion and have pulse ox available, so it
16 would be certification under the REMS. Where we
17 state the certification, that's what we're
18 referring to.

19 DR. MEISEL: So the requirements of the REMS
20 basically require a hospital. It's hard to dream
21 up a scenario or an environment where it isn't a
22 hospital, where we could do everything that's going

1 to be asked for in that REMS.

2 So it would be easier to stay in a hospital
3 unless you can dream up some sort of a waiver.

4 DR. LaCIVITA: Well, 85 percent of the
5 patients that received the therapy were not in a
6 hospital setting, but they were in a place where
7 they are observed overnight. So the internal
8 discussions that we had is there may be creative
9 ways to do this and we didn't really want to limit
10 that. It could be a sleep center that provides
11 that type of care. I mean, we just didn't want to
12 be so specific.

13 But if they could meet the requirements of
14 certification, that certainly would be a way to
15 make if the product was approved and it would be
16 available.

17 DR. MEISEL: So then could you then define a
18 healthcare provider because a sleep center's not
19 going to have an RN that can manage an IV pump in
20 the middle of the night? Nobody at home; and we're
21 not talking at a home, but no home care agency's
22 going to provide an R.N. that can manage an IV pump

1 in the middle of the night or 24/7.

2 So if we're not going to define "certified
3 healthcare setting," can we define a "certified
4 healthcare provider" or what type of healthcare
5 provider that is available?

6 DR. LaCIVITA: I think, in our internal
7 discussions, we called it a license provider.

8 DR. MEISEL: Licensed what? I mean, in some
9 states, a physical therapist can be licensed.

10 DR. LaCIVITA: I think that's still up for
11 discussion with us and we'd like to hear your
12 thoughts, too. I think these are some of the
13 questions that we're asking the panel later, so
14 that would be helpful.

15 DR. MATHIS: This is Mitch Mathis. I would
16 like to point out, though, that the conversation
17 has gone here as it did with us from, can't you
18 just do this at home to, shouldn't it be done in
19 the hospital. And then it seems that what they did
20 in the clinical trials is where we have our data.

21 So to have it more restrictive than that to
22 start with, if the goal is indeed to get it in the

1 home someday, it seems like perhaps taking a step
2 backwards unless there's a safety reason to do
3 that, that we don't understand.

4 DR. NARENDRAN: Next question,
5 Dr. Hernandez-Diaz?

6 DR. HERNANDEZ-DIAZ: I have questions for
7 Dr. Fischer and they relate to the 60 dose versus
8 90. Can we put the slides up. We have the slide
9 27. And to a highlighted point you made and for me
10 to have some interpretation of this data, since
11 submitted, there may be some depletion of
12 susceptibles going on here. Right?

13 Because everybody started with 30, 60, and
14 then some went to 90. So to compare the two
15 columns of 90 to 30, we are looking at different
16 patients where the ones that are getting to 90
17 already went through being able to survive the 30
18 dose and 60 dose.

19 But having said that, we cannot say that
20 there are very few with 90 because only those that
21 didn't react to 30 and 60 went there. Since
22 clinically we are proposing to go from 60 to 90, it

1 doesn't seem to me here that those that didn't have
2 events with 30 or 60, a significant proportion of
3 them went up to have them at 90.

4 Would it be a good interpretation like most
5 of the patients that are going to have an issue
6 with 90 seem to be having it with 30 or 60, at
7 least for sedation? And so maybe with syncope, we
8 still have one event, but what is your reading of
9 this regarding the decision about the dose?

10 DR. FISCHER: Bernie Fischer. Thank you.
11 Excellent point. People who are randomized to the
12 90 arm may have had the tolerability AEs; sedation,
13 somnolence; at lower doses.

14 So the way I view this is, like you had
15 said, if people make it through without the AEs,
16 they get to the 90, there's not a dose response
17 where, if you didn't see it at 30, you didn't see
18 it at 60, you still might see it at 90.

19 So the way I viewed it was that, whether we
20 choose the 60 or the 90, we're not going to see
21 much more AEs if we make 90 the dose.

22 DR. HERNANDEZ-DIAZ: I have a related

1 question if you can go to your slide 23. I love
2 this slide. Can you populate it? Yes. This
3 itself is helpful. I found this really helpful.
4 Thank you very much for putting it together. And
5 can you keep populating it? Because there is one
6 of the arguments that I kind of want to argue at
7 the very end, non-supported, with the very last
8 line on the right column with continued exposure,
9 might expect 90 dose to have -- no, sorry; for the
10 supporting, I cannot find it.

11 There is one argument that says that, with
12 increasing the dose, there were some patients that
13 benefitted, the last one on the left column. Some
14 patients who did not respond at 60 responded at 90.

15 But in this study group, we can compare
16 them. Some patients that have not responded at 60
17 respond at 60 also at the same rate when they
18 continue. So it seems to me that it was more the
19 time than the dose in that sense.

20 That was the only argument that I was not
21 clear with.

22 DR. FISCHER: Hi, Bernie Fischer. I agree

1 it's not clear whether it was just a longer
2 exposure to 60 or if it was the increase to 90.
3 It's not clear whether it's a duration effect or a
4 dose effect.

5 DR. HERNANDEZ-DIAZ: But the duration effect
6 was there for 60. I thought that it seemed that
7 the data supported that it was the duration and not
8 the dose that --

9 DR. FISCHER: Bernie Fischer. Since we have
10 a limited number of people in the target 60 arm,
11 we're not sure, based on the smaller sample size,
12 whether it was really the duration at 60 versus the
13 actual increase at 90.

14 The people who were at 60 who responded with
15 longer exposures; there were some, but again, we
16 don't have a lot of data to really say, "It was
17 definitely duration and it wasn't going up to 90."

18 DR. HERNANDEZ-DIAZ: Thank you.

19 DR. NARENDRAN: You guys can go to
20 Dr. Temple next.

21 DR. TEMPLE: Bernie, I wanted to ask you
22 about that. You say specifically that some people

1 who didn't respond to 60 responded to 90 because
2 they all got 60 up to 24 hours, but that happened
3 in both the 60-microgram group and the 90-microgram
4 group.

5 So there was no evidence of a dose response
6 in this at all, I would say.

7 DR. FISCHER: Bernie Fischer. I agree that
8 there's no evidence that it was a higher dose that
9 led to response as opposed to a duration.

10 DR. TEMPLE: Right.

11 DR. FISCHER: But I don't think it was
12 conclusive that it was the duration, either.

13 DR. MATHIS: This is Mitch Mathis and what
14 we don't have is more adverse events at the higher
15 dose than the lower dose. Is that right?

16 DR. FISCHER: Right.

17 DR. NARENDRAN: That clarifies it. Next
18 question, Dr. Ruha?

19 DR. RUHA: Hi, Michelle Ruha. So first, you
20 had mentioned what's, like, the worst with a GABA
21 agonist. I assume the loss of consciousness, from
22 what we know, is based on increased GABA, tone. We

1 do have other GABA-ergic drugs like phenobarbital,
2 tomady [ph], propofol, and you can have severe coma
3 and respiratory depression and die.

4 So I do think, in the clinical trials, when
5 somebody lost consciousness, they instantly had the
6 infusion shut off, so they were able to get better,
7 but I have to assume that, if it didn't get shut
8 off or if there was a large overdose, they could
9 potentially have a life-threatening effect.

10 That brings me to what my kind of
11 comment/question was. This administration of this
12 continuous infusion with dose changes and weight-
13 based programming in the dose and it changing
14 multiple times is guaranteed for medical errors.

15 Even in an intensive care unit with
16 experienced ICU nurses who do it all the time, we
17 still see errors with these types of thing. It's
18 difficult. So I think it needs to be made as
19 simple as it can be. I mean, we maybe can't
20 completely simplify it, but I'm wondering, it
21 sounded to me like we didn't see any withdrawal
22 with people coming off of it. Do we even need the

1 taper? Has that been shown, that a taper is
2 necessary?

3 It might be one thing that could be
4 eliminated.

5 DR. FARCHIONE: This is Tiffany Farchione,
6 so completely hypothetical, right, but we talked
7 about how, for possibly the etiology of postpartum
8 depression, it's that sudden drop in
9 allopregnanolone, so I personally would worried
10 that, if we had a sudden drop of this medication
11 without the taper, maybe we would sort of recreate
12 that.

13 Again, it is a little bit of a conundrum
14 because we don't have data with other more
15 simplified dosing regimens to look at and we would
16 probably want to ask for that data.

17 So if this were to be approved in its
18 current iteration, we would probably ask for data
19 to say can you look at this in some other way to
20 see if we still see efficacy with a different
21 dosing regimen that might be easier or less prone
22 to potential error, et cetera.

1 DR. MATHIS: Mitch Mathis. It might help if
2 we give you some pre-clinical evidence of what
3 happens when you turn the drug off quickly.

4 DR. DOW: Hi, this is Antonia Dow. I'm the
5 pharm tox reviewer. And one thing to keep in mind
6 is that this is a GABA-ergic drug and, in studies
7 longer than 5 days, there was an animal in each
8 study in dog that had a convulsion after dosing
9 stopped.

10 So even though we haven't seen it with
11 shorter duration in humans or in acute studies in
12 animals, it is a theoretical possibility. Also, in
13 animals in acute studies, the sponsor originally
14 looked at anesthetic doses and it is very
15 unpredictable.

16 In those studies, they did supplement rats
17 with oxygen and dogs also had very unpredictable
18 dosing, whether they could stay sedated and had
19 other toxicity findings.

20 DR. MATHIS: Mitch Mathis. Toni, the
21 animals are a lot like the humans. You can't
22 predict which ones are going to remain

1 anesthetized. Is that what you mean?

2 DR. DOW: Yes, that's correct.

3 DR. NARENDRAN: What's the blood-brain
4 barrier penetration of the drug? Is that known?
5 Is there, like, a substrate for any PGP or some
6 sort of active transport mechanism. And some
7 people are having this reaction and some are not.

8 DR. DOW: It's unclear, I think, how it's
9 getting in, but it is very rapid in animals. It's
10 within 15 minutes.

11 DR. NARENDRAN: In the brain?

12 DR. DOW: Into the brain, yes.

13 DR. NARENDRAN: So it passes quickly.

14 DR. DOW: Right.

15 DR. NARENDRAN: Dr. Burger, do you have a
16 question? No.

17 DR. BURGER: No. I think it was addressed
18 earlier about the four bags. I see, with three
19 bags of acetadote in the hospital setting, we get
20 the bags mixed up all the time.

21 DR. NARENDRAN: Dr. Besco?

22 DR. BESCO: Actually, I was going to comment

1 more on the bag issue as well. I had wondered if
2 being the proposed treatment types being non-acute
3 care settings, are there any stipulations within
4 the REMS on where the bag would be prepared?

5 Would it be prepared on site by potentially
6 someone who's not familiar with pharmaceutical
7 calculations? Or would it be required that it come
8 from an outpatient infusion pharmacy, where
9 pharmacists would be reviewing the appropriateness
10 of the calculations based on the patients' weight.

11 DR. HART: Hi, this is Leah Hart. So our
12 assumption is that, if we limit the setting to
13 certified healthcare settings, that it would be a
14 pharmacy and a pharmacist that would make the dose
15 797 compliant. I think that one of the
16 reasons -- and we've talked about it with the
17 applicant for the varying concentrations -- was for
18 ease of the infusion.

19 So it would constantly be, the patient would
20 first start at 3 milliliters an hour, then 6
21 milliliters an hour, and then 9 milliliters an
22 hour. So independent of their weight, because it

1 is a weight-based dose, so instead of programming
2 in 60 micrograms per kilo per hour, instead, if you
3 make the bags, the concentration based on weight,
4 you then have a constant infusion rate that is
5 applicable to all patients.

6 DR. BESCO: We do that similarly, I think,
7 for rituximab with a 90-minute infusion at our
8 site.

9 DR. MEISEL: Can I just comment on that?
10 That is opposite of almost everything we do in
11 healthcare with pharmacy. They're dosed by weight,
12 period, and we don't dose them volumetrically.

13 You have an infusion problem. You program
14 that in. 60 mgs per kilogram per minute, and then
15 that's it, and the calculations happen there.

16 If you ask ISNP or any other patient safety,
17 medication safety organization, what you just
18 described would be totally opposite of what those
19 recommendations would be for a good reason.

20 DR. HART: We have similar concerns.

21 DR. BURGER: Yes. We have smart pumps now
22 that do all that work for us. So just that

1 simplifies things, so I agree with the other folks
2 here.

3 DR. BESCO: Yes. And I guess the other
4 concern is, I'm hearing it would be made by
5 pharmacy, but how would it be made by pharmacy if
6 they're getting it at a sleep center? I guess
7 that's still unclear to me.

8 DR. LaCIVITA: This is Cynthia LaCivita from
9 the Division of Risk Management. We haven't worked
10 out all the details yet on where it could be, so
11 we're going to ask for your input on this, too.
12 But I mean, this is complicated.

13 Preparing the bags is fairly complicated,
14 too, because it's based on weight and they're
15 adjusting the volumes. I would think it would have
16 to be done in a pharmacy. I mean, we haven't
17 worked out all those details.

18 DR. NARENDRAN: What if somebody decides to
19 leave when they're at 90 micrograms and say, "I
20 need to go?" Would you be worried about a seizure
21 if someone offered you to discontinue them and send
22 them on their way?

1 Or would you move them to a taper down or do
2 REMS address that?

3 DR. LaCIVITA: If a patient were to decide,
4 I don't want to continue treatment and I want to
5 leave, I don't know that we would be able to
6 control that in a REMS. I mean, you can't force a
7 patient to stay.

8 DR. MATHIS: Mitch Mathis. I think it might
9 be like many other situations when a patient
10 decides to stop their medicine against medical
11 advice. There are also other situations where you
12 run into adverse events and you have stopped them
13 abruptly, like loss of consciousness, for instance.

14 So we would have to deal with those with
15 this product as we do with others.

16 The REMS would be a difficult thing to ask
17 the REMS to tell the provider what to say, should
18 this happen, in every instance, so that would
19 probably not make the REMS documents.

20 DR. NARENDRAN: Ms. Numann?

21 DR. NUMANN: Sabrina Numann. I have a quick
22 question. What was the cut-off to determine non-

1 responders? Was it 24 hours? Was it the dose of
2 90? Or was it discharge at 72? At what point did
3 they decide the patient was a non-responder?

4 DR. FISCHER: This is Bernie Fischer. They
5 had pre-defined criteria based on HAM-D score,
6 which they assessed at various time points for non-
7 response, so they do have non-responders at 60,
8 which was their primary endpoint, but they also
9 looked at non-responders throughout the assessment
10 points, including the 30 days.

11 DR. NUMANN: Thank you.

12 DR. NARENDRAN: Ms. Witczak?

13 DR. WITCZAK: Kim Witczak, consumer rep.
14 Question about potential unintended consequences
15 and if there's any data on the babies; I know we
16 keep saying that there's little in amounts, but was
17 there any study looking at the babies long term?

18 I know this is for the mother, but I'm
19 always thinking about future unintended
20 consequences. And maybe it's something that goes
21 into the REMS or whatnot?

22 DR. DOW: The studies that were done in

1 humans didn't have moms breastfeeding until 7 days.
2 We do have a pre- and postnatal development study
3 in rats. And the findings are primarily at birth
4 and are most likely due to effects on the mother in
5 terms of rats, babies that were nursing, mothers
6 that receive brexanolone.

7 After postnatal day 4, there were no
8 effects. Also, there was no exposures that were
9 seen in the [indiscernible] that received
10 brexanolone.

11 DR. NARENDRAN: Dr. Turner?

12 DR. TURNER: Yeah, I want to pick up on the
13 pre-clinical evidence of issues, and I think it was
14 dogs that had withdrawal seizure after, what, 5
15 days of exposure or something like that.

16 Now, the exposure that we have, of course,
17 is much shorter and there seems to be new evidence
18 so far of there being withdrawal problems that you
19 might expect from, say, benzodiazepine with longer
20 use.

21 Well, this sort of answers itself, but I'm
22 just wondering about precautions against off-label

1 use and I'm wondering if the prescriber takes the
2 patient out to 60 hours and, lo and behold, the
3 patient doesn't respond as well as they were
4 expecting and say, "You just need another 60 hours.
5 And then you might be talking," -- well, we don't
6 know. We don't know what happens. But you might
7 speculate based upon a pre-clinical evidence more
8 safety issues when it eventually is discontinued
9 and perhaps no additional efficacy.

10 So anyway, we want the REMS to be clear
11 about that hard cut-off at 60 hours. And what's to
12 keep people from continuing on?

13 DR. LaCIVITA: This is Cynthia LaCivita from
14 the Division of Risk Management. The REMS needs to
15 be commensurate with labeling and so a lot of these
16 things would be probably addressed in labeling and
17 then the REMS would reinforce those measures.

18 So you could have requirements in the REMS
19 to say that it needs to be made in a pharmacy. You
20 could address some of those things, information for
21 patients. So does that help you at all?

22 DR. TURNER: How clear or how strong would

1 the language be that you really shouldn't go beyond
2 60 hours?

3 DR. FARCHIONE: This is Tiffany Farchione.
4 So the other issue is that we don't regulate the
5 practice of medicine. So we can't forbid people
6 from doing that, but we can appropriately label the
7 benefits and the risks and what we know about
8 efficacy with a given dose and a given duration and
9 so on.

10 We can tell everybody anything that we know
11 about the drug and then, if they still choose to
12 use it in that way -- Cynthia?

13 DR. LaCIVITA: We do have REMS, though, that
14 limit doses. So I mean, we could say, "Not to
15 exceed 60 hours." We could add something like
16 that, I mean, if that is where we end up.

17 DR. TURNER: Yeah, no, with other drugs.
18 This says, "The safety of," blah, blah, blah, "Has
19 not been evaluated beyond a duration of," so there
20 could be language in the labeling. Might be
21 sufficient.

22 DR. LaCIVITA: It would need to be addressed

1 in labeling.

2 DR. TURNER: Sufficiently strong.

3 DR. NARENDRAN: Sounds like they'll address
4 it. Dr. Dunn?

5 DR. DUNN: Walter Dunn. Circling back to
6 the question of the need for a taper and then the
7 need for a duration of the infusion, were there any
8 patients that discontinued early in the middle of
9 the infusion, were never restarted and which we
10 have outcome data for?

11 DR. FISCHER: There were very few, and I'd
12 have to look and see what the outcome of the
13 patient who discontinued. There was only one who
14 discontinued because of an AE and did not continue
15 the infusion or finish the study, but I don't know
16 what the outcomes were.

17 DR. NARENDRAN: Dr. Valbh?

18 DR. VALBH: I don't mean to keep rehashing
19 the healthcare setting, but my question is around,
20 if a pharmacy does mix the product, you certify a
21 healthcare setting, pharmacy mixes the product,
22 sends it to a healthcare setting like a sleep

1 center.

2 Do they have adequate ability to store the
3 product appropriately, 12 hours room temperature,
4 24 hours refrigerated?

5 Most sleep centers and certain healthcare
6 settings may not have the ability to store it
7 correctly and room temperature could mean a lot of
8 different things within a facility. So that's
9 something to definitely consider, how to check the
10 box around storage of the product as well once
11 mixed.

12 DR. MATHIS: Mitch Mathis. So the REMS
13 would likely define the setting that we feel
14 comfortable using the medications, should we get to
15 that point. And then the individuals settings will
16 have to certify that they can meet those
17 conditions. And they're pretty explicit in most
18 REMS with a temperature range, for instance, for
19 exactly what we mean by room temperature, et
20 cetera. Yes.

21 I think that we would rather do it that way
22 than, say, any sleep center because none of us

1 knows what that means. We'd want to say what we
2 know and then have the facilities match the REMS,
3 not the other way around.

4 DR. NARENDRAN: Dr. Meisel?

5 DR. MEISEL: Steve Meisel. So in keeping
6 with the stability of the bag issue, 12 hours at
7 room temperature is very short. So on a practical
8 basis, if you want to infuse a drug that is at room
9 temperature, you've got to change the bag more
10 often than every 12 hours because, by the time the
11 pharmacy mixes it and sends it upstairs, there's
12 logistics involved with that. Right?

13 You take out the old bag, hook on the new
14 one. You're really talking about 10 hours unless
15 you're willing to infuse something that's ice cold.
16 So is there any data about infusing refrigerator
17 temperature of product and the tolerability of
18 that?

19 DR. FISCHER: Hi, this is Bernie Fischer.
20 Not as far as I know, but the applicant may have
21 knowledge of it.

22 DR. NARENDRAN: Yes. Dr. Unger?

1 DR. UNGER: I'm not an expert on this, but
2 the infusion rate is really slow, so the ability
3 for diffusion of the temperature differences is
4 considerable.

5 DR. FARCHIONE: So sorry. This is Tiffany
6 Farchione. I just asked our chemistry person who
7 knows the stability data and he said that it is
8 stable for 24 hours in the refrigerator and for 12
9 hours at room temperature.

10 DR. MEISEL: Right, which means that, unless
11 you're changing the bag more often than 12 hours,
12 you can be infusing something that is that
13 refrigerator temperature, which, if anybody's ever
14 gotten an IV, that's not comfortable, no matter how
15 slow it is.

16 DR. UNGER: Yes. Right here, it's 3 ccs an
17 hour and that's pretty slow. I keep commenting I
18 don't know anything about, but it's sitting in the
19 pump. And given the slow velocity through the pump
20 at 3 mLs an hour, I would imagine, by the time it
21 gets to the vein, it's going to be pretty close to
22 room temperature anyway.

1 DR. MEISEL: I wouldn't make that
2 assumption. The first hour or so is going to be
3 pretty cold. Does the applicant have any data in
4 that space?

5 DR. SCHACTERLE: We do not have any data for
6 infusion cold. But Dr. Unger is right in terms of
7 it can be mixed up and refrigerated until the time
8 of delivery, and then you could hang the bag and,
9 due to the slow infusion rate, it would warm up as
10 it's going through the infusion tube and into the
11 patient.

12 DR. FISCHER: This is Bernie Fischer. I just
13 also wanted to point out that the stability data
14 wasn't determined until the applicant had submitted
15 the application. And so when the studies were
16 done, they were infused with room temperature bags
17 over the 24 hours.

18 DR. NARENDRAN: Dr. Dunn?

19 DR. DUNN: Walter Dunn. Question, that gave
20 a couple phases. So some of the background
21 literature suggested that it's not really the level
22 of allopregnanolone alone, but perhaps the

1 resetting of the receptors that's giving you the
2 antidepressant effect.

3 So early on, was there any discussion or any
4 studies looking at if you're able to achieve the
5 same effect of an extended infusion of midazolam?

6 DR. FARCHIONE: No. I don't think we have
7 any data like that.

8 DR. NARENDRAN: One thing; Dr. Fischer, I
9 have a question for you. So the sponsor said that
10 the two pump malfunctions led to a higher dose, but
11 you said the PK levels in those subjects did not
12 suggest a higher dose. Is that correct?

13 DR. FISCHER: That's correct.

14 DR. NARENDRAN: Thank you. Dr. Meisel?

15 DR. MEISEL: Could I just follow up on what
16 you said, Doctor? That just struck me. You said
17 that the studies were done with room temperature
18 bags at 24 hours, so it's possible that some of
19 these patients were receiving subpotent infusions?

20 DR. FARCHIONE: It was not a matter of the
21 drug stability. There are microbiology issues, is
22 my understanding. So yes. The drug was a drug.

1 DR. MEISEL: This is Steve Meisel. I'm
2 sorry. I don't get the microbiology issues. I
3 mean, IVs are, if you compare them to clean room
4 (phonetic), good for X. The refrigeration has
5 nothing to do with that. Was there some
6 peculiarity about the preparation that introduced
7 microorganisms that were different than any other
8 way you make an IV?

9 DR. SCHACTERLE: We did chemical stability
10 and microbial growth studies. It is chemically
11 stable for quite a bit, so for at least 24 hours or
12 more. It's the microbial growth and these were not
13 prepared necessarily in a clean room. They were
14 prepared in a pharmacy. That's all that's
15 necessary. Refrigerated, there's no microbial
16 growth, but the formulation does support growth
17 over time. And so we, as a precautionary measure,
18 limited it back to a 12-hour infusion for the
19 labeling so that we could ensure that is safe.

20 DR. FARCHIONE: We've got chemistry over
21 here. He's nodding. He confirms that.

22 DR. NARENDRAN: Thank you. So does anybody

1 else have any other questions, last five minutes?

2 DR. BURGER: Yes, Greg Burger, Stormont Vail
3 Health. So it's beyond-use date versus stability.
4 Beyond-use date is used by USP 797 to prevent
5 microorganism growth. That's the limitation on
6 this product, not stability.

7 DR. CLAFFEY: Yes. David Claffey, and I'm
8 [indiscernible] lead for CMC from OPQ in FDA.

9 DR. NARENDRAN: Thank you. I guess we could
10 break for lunch. We will reconvene in this room 1
11 hour from now. That will be 1:00. Please take any
12 personal belongings you may want with you at this
13 time. Panel members, please remember that there
14 should be no discussion of the meeting topic during
15 lunch, amongst yourselves, or with any member of
16 the audience. Thank you.

17 (Whereupon, at 11:55 a.m., a luncheon recess
18 was taken.)

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A F T E R N O O N S E S S I O N

(1:03 p.m.)

Open Public Hearing

DR. NARENDRAN: Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationships that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial

1 relationships. If you choose not to address this
2 issue of financial relationships at the beginning
3 of your statement, it will not preclude you from
4 speaking.

5 The FDA and this committee place great
6 importance in the open public hearing process. The
7 insights and comments provided can help the agency
8 and this committee in their consideration of the
9 issues before them.

10 That said, in many instances and for many
11 topics there will be a variety of opinions. One of
12 our goals today is for the open public hearing to
13 be conducted in a fair and open way where every
14 participant is listened to carefully and treated
15 with dignity, courtesy, and respect.

16 Therefore, please speak only when recognized
17 by the chairperson. Thank you for your
18 cooperation.

19 Will speaker number 1 step up to the podium
20 and introduce yourself? Please state your name and
21 any organization you are representing for the
22 record.

1 DR. SRINIVASAN: Good afternoon. Thank you
2 for the opportunity to speak today. My name is
3 Dr. Varuna Srinivasan. I'm a physician with a
4 Master of Public Health from Johns Hopkins
5 University. I'm a senior fellow of the National
6 Center for Health Research. We analyze scientific
7 and medical data to provide objective health
8 information to patients, health professionals, and
9 policy-makers. We do not accept funding from drug
10 and medical device companies, so I have no
11 conflicts of interest.

12 We have serious concerns about the safety of
13 this drug, brexanolone. Benzodiazepines have their
14 own safety issues, and barbiturates have strong
15 side effects such as sedation and respiratory
16 depression.

17 Does it really make sense to approve a drug
18 for new mothers that has the characteristics of
19 both these drug classes? At the last, approval
20 should require better evidence of long-term safety
21 and efficacy than the sponsor has provided.

22 In comparison to the placebo group, it

1 appears that all evaluated doses of brexanolone
2 cause increased risk of sedation, somnolence, and
3 loss of consciousness.

4 This is a postpartum drug, so the question
5 is, might the impaired mother accidentally
6 suffocate her baby or accidentally harm herself?
7 Might the mother's oxygen saturation drop to
8 dangerously low levels when given this drug?

9 If a health professional is needed to
10 monitor the patient continuously for two and a half
11 days when given infusions in order to protect the
12 patient's safety, is it realistic to believe that
13 monitoring and multiple infusion bag changes will
14 actually be error-free during those 60 hours?

15 Given the risk and inconvenience, it is
16 noteworthy that the sponsor did not provide any
17 information about whether this drug is as safe or
18 as effective than any other antidepressant
19 currently on the market.

20 While the studies show consistent benefits
21 compared to placebo, the amount of benefit is not
22 that impressive in most of the analyses, and it is

1 unclear if the higher dose is more effective than
2 the lower dose.

3 Given the short half-life of brexanolone, it
4 also appears that the positive effects of this drug
5 seem to be temporary, showing decrease in symptoms
6 only over a very limited period of time. Is it
7 possible the mother was just sedated, confused, or
8 even euphoric when the follow-up scoring was done
9 after infusion?

10 Typically, there is a dose response. With
11 higher dose, with higher drug dose somewhat more
12 effective, then possibly with more adverse events,
13 in the case of this drug it seems to be the
14 opposite.

15 Higher doses are not usually more effective,
16 and with lower doses it resulted in more adverse
17 events. We have to consider that even the
18 significant differences could be due to chance
19 since quite a few comparisons were made in these
20 studies.

21 We are also very concerned about the
22 potential for abuse. FDA reviewers point out that

1 the human abuse potential studies for this drug
2 indicate an abuse potential on par with alprazolam
3 3 milligrams. That is a substantial risk.

4 I respectfully urge this panel to also
5 consider whether approving this drug today for a
6 higher monitored inpatient setting would result in
7 an off-label use that are not so carefully
8 monitored.

9 We also urge the committee to require more
10 persuasive evidence on the safety of this drug. It
11 is our moral obligation to patients to make sure
12 that all drugs with this risk potential are
13 scrutinized and held to a higher standard in the
14 approval process. Thank you.

15 DR. NARENDRAN: Thank you.

16 Will speaker number 2 step up to the podium
17 and introduce yourself? Please state your name and
18 organization for the record.

19 MS. FULWIDER: Hi. I'm Tonya Fulwider, and
20 I'm here representing Mental Health America of
21 Franklin County and our POEM program.

22 Hello. Thank you for your time this

1 afternoon. Again, I'm Tonya Fulwider, and I live
2 and work in Columbus, Ohio. I have not received
3 any payment to speak here today, with the exception
4 of my travel expenses supported by Sage
5 Therapeutics.

6 Twenty years ago, after having my oldest
7 daughter, I struggled with postpartum depression.
8 I've since dedicated the last 20 years to of course
9 raising my children, but also working to ensure
10 that new mothers don't encounter the same obstacles
11 I did to care.

12 The clinical professionals I saw were
13 grossly uneducated. It took several months and,
14 among other interventions, six different
15 medications to find something that could help me.
16 So I co-founded an organization that specifically
17 addresses barriers to care and provides a menu of
18 mental health services for moms and families.

19 Several years ago a local Mental Health
20 America affiliate approached us about a
21 partnership, which resulted in a merger. And I'm
22 proud to say that we're one of the very few general

1 mental health advocacy organizations that provide
2 this necessary specialized maternal mental
3 healthcare.

4 People often ask: What's the key in
5 addressing postpartum depression? There is no key.
6 It's whatever each mother chooses. And I see it as
7 my job to ensure that she has the ability to select
8 that key for herself and use it.

9 New motherhood is hard for everyone. But
10 battling a mental illness in the midst of raising a
11 child is excruciating. We must do all we can to
12 address her barriers and help her move to recovery.

13 In Ohio, the infant mortality rate is among
14 the worst in the country. There are many
15 initiatives looking to address this crisis. But we
16 also know that mental health is a factor, and we
17 must keep mental health at the forefront of that
18 conversation.

19 Our program serves women of all backgrounds,
20 but nearly 70 percent of our approximately thousand
21 clients a year live in poverty. They've
22 experienced trauma. We're battling food and

1 housing insecurity. Our families are among those
2 atrocious infant and maternal mortality statistics.

3 So our challenges for supporting moms in a
4 health start to parenthood are many. But we
5 continue to advocate for her care, particularly
6 around mental health and treatment.

7 I'm pleased to say that we are mostly able
8 to flip that script in Columbus on the statistics
9 of women that actually access care in that about
10 72 percent of our clients connect to care, and we
11 can verify that.

12 But getting that outcome is a real battle,
13 and the more care and treatment available, the
14 better. The most important job in our country is
15 motherhood. It's raising the next generation. We
16 must do all we can to support moms. Thank you.

17 DR. NARENDRAN: Thank you.

18 Will speaker number 3 step to the podium and
19 introduce yourself? Please state your name and any
20 organization for the record.

21 MS. COLEMAN: Good afternoon. My name is
22 Jabina Coleman. I am a licensed social worker, and

1 international board-certified lactation consultant,
2 the owner of LIFE HOUSE Lactation & Perinatal
3 Services. I'm also the co-founder for Perinatal
4 Mental Health Alliance for Women of Color, and a
5 mother of two children.

6 Thank you to the FDA for allowing me the
7 opportunity and the space to speak today. All of
8 my travel expenses were paid for by Sage
9 Pharmaceuticals. My experiences, thoughts, and
10 opinions are my own.

11 I have worked with women, perinatal women
12 and families, for over 10 years, providing
13 psychosocial support and counseling surrounding
14 maternal mental health and perinatal mood
15 disorders, specifically postpartum depression. I
16 am aware of the many social and emotional
17 challenges that women and families face during the
18 perinatal period, especially postpartum.

19 Fourteen years ago I delivered my first
20 child. I was unassessed, undiagnosed, and
21 untreated for major postpartum depression. It was
22 the most darkest and debilitating time of my life,

1 and as many mothers would expect, this is the time
2 that should be the most joyful and the most
3 happiest. I couldn't leave that into the hands of
4 my providers at the time.

5 It is important to me and the work that I do
6 and the families and communities that I serve in
7 Philadelphia, primarily low-income, underserved
8 communities and families, that maternal mental
9 health, specifically postpartum depression, is
10 managed adequately, effectively, and efficiently,
11 whether it is through psychosocial support and/or
12 medication management.

13 We know that postpartum depression is very
14 common, affecting 10 to 20 percent of women. For
15 women of color, it is twice as likely. Sixty
16 percent of women of color do not receive any
17 treatment and are unassessed for postpartum
18 depression and perinatal mental health.

19 Again, we also know that with therapy and
20 medication management that postpartum depression
21 and treatment affects balancing hormones,
22 stabilizing moods, increasing mother-baby bonding,

1 and oftentimes aiding in a more fulfilled
2 experience.

3 As a mother who experienced severe
4 postpartum depression, a lactation consultant, and
5 an advocate for maternal mental health, I fully
6 support any medication management that would aid in
7 the treatment of helping to decrease postpartum
8 depression and the debilitating effects that it can
9 have on the women and the communities that we
10 serve. Thank you.

11 DR. NARENDRAN: Thank you.

12 Will speaker number 4 step to the podium and
13 introduce yourself? Please state your name and any
14 organization for the record.

15 DR. MAXIMOS: Good afternoon. My name is
16 Dr. Bassem Maximos. I'm an obstetrician-
17 gynecologist in private practice from Houston,
18 Texas.

19 I'm here today to speak on my own behalf,
20 but I would like to disclose that I was one of the
21 principal investigators on the clinical trial
22 sponsored by Sage Therapeutics, and Sage also paid

1 the expenses of my travel and accommodations to be
2 here today. I do not have any vested interest, and
3 I am not a stakeholder in Sage Therapeutics.

4 I chose to take the time off from my
5 practice to be here today to share my experience
6 with brexanolone because if it becomes available, I
7 believe it will have a large impact on many of my
8 future patients that might develop postpartum
9 depression.

10 Such a medication with rapid onset of action
11 and high efficacy would give my patients the
12 ability to enjoy bonding with their babies and
13 nurturing them instead of being distant and
14 isolated from their families like many patients
15 with postpartum depressions tend to do.

16 These depressed moms, if left untreated or
17 inadequately treated, most often suffer emotional
18 or physical extremes that can last for a very long
19 time and have a negative impact on their newborns,
20 their spouses, and families.

21 As an OB/GYN for the last 12 years, I
22 rendered care to many women that develop postpartum

1 depression after I delivered them. In most cases
2 the treatments available were not adequate or
3 effective to improve the symptoms to treat the
4 disease.

5 All of the treatments currently available
6 are for major depressive disorders and either
7 require patients to be on them for a long period of
8 time to be effective or the patients to have
9 multiple agents in order to achieve some response.

10 A large number of my OB/GYN colleagues are
11 reluctant to screen for and treat postpartum
12 depression either because the current treatments
13 are not proven effective or not specifically
14 indicated for postpartum depression.

15 If approved by the FDA, brexanolone will be
16 the first medication specifically indicated for the
17 treatment of postpartum depression. This will not
18 just add another option for the treatment of
19 postpartum depression, it would also encourage many
20 of my OB/GYN colleagues to screen more patients for
21 postpartum depression, knowing that there is a
22 specific and effective treatment for the disease.

1 I'd like to share with you my experience
2 during the clinical trials at my research site and
3 the impressive response of my study subjects to the
4 medication when it was administered.

5 As early as 24 hours after the patients were
6 started on brexanolone, symptoms of their
7 depression started to significantly improve. Most
8 of my study subjects became more social and
9 interactive with the staff. They started eating
10 better and taking interest in the social activities
11 available. But more important, they started
12 bonding with their babies, playing and laughing
13 with them instead of asking staff or family members
14 to care for those babies.

15 It was a heartwarming and fulfilling
16 experience for me as a clinician to observe such a
17 response to the treatment administered to my
18 patient, and have such a fast and immediate impact
19 on their lives.

20 At our site, the 60-hour infusion was simple
21 and straightforward, with minimal maintenance
22 required to the infusion pumps. The moms did not

1 mind the small IV line attached to them, especially
2 once they started feeling better.

3 The sedation effects were mostly tolerated
4 by most of our subjects, and some of them welcomed
5 the somnolence because they were deprived from
6 sleep or have had poor sleep for a long period of
7 time since they had the baby.

8 I personally believe that brexanolone could
9 be administered at home with reliable preprogrammed
10 pumps and adequate medical support, and the
11 presence of a family member that could monitor the
12 treatment, and have immediate access to a
13 healthcare professional if the need arises will be
14 of major importance to home infusion.

15 Most patients that had loss of consciousness
16 or excessive sedation during the trials were
17 subsequently aroused with discontinuation of
18 medication without any medical intervention.

19 As a clinician, I believe in advocating
20 increased patient access to any new third party. I
21 believe limiting the medication to be infused in an
22 inpatient setting would limit patient access to

1 treatment.

2 Many inpatient settings do not allow the
3 patients to stay with the mother during hospital
4 stays, and many mothers will decide against
5 treatment in favor of staying home with their
6 babies. Thank you so much.

7 DR. NARENDRAN: Thank you.

8 Will speaker number 5 step to the podium and
9 introduce yourself? Please state your name and any
10 organization.

11 MR. COUNTS: Hi there. Nathaniel Counts,
12 Mental Health America. Mental Health America paid
13 for my time to be here today.

14 I'd like to really thank you today for now
15 spending two straight days considering therapies in
16 mental health. So we really appreciate all the
17 consideration that goes into this.

18 So I won't give you the overview of Mental
19 Health America today, but I wanted to note that
20 Mental Health America as an organization is devoted
21 to the entire life course. But in policy, the vast
22 majority of my work I think focuses on the first

1 1,000 days.

2 Like if you look at I think it was Jim
3 Heckman's study in *Econometrica*, you look at the
4 value of investments across the life course in new
5 families, and the highest impacts are definitely
6 within the first thousand days. And I never
7 thought I'd be at the FDA ever talking about
8 something like this because it's so challenging to
9 invest in this time period, but really excited to
10 be here.

11 So while postpartum depression on its own is
12 a huge, serious concern for the well-being of moms,
13 and I think that'll be a consistent theme
14 throughout the public testimony, I wanted to touch
15 on the two-generation implications that I think
16 really raise the stakes for this beyond sort of
17 like other depressive episodes that we might be
18 thinking about.

19 So the National Academies of Science,
20 Engineering, and Medicine has long highlighted the
21 sort of meaningfulness of these earliest
22 experiences and their later impacts on the life

1 course, starting in I think 2000 with "Neurons to
2 Neighborhoods," the sort of like pivotal study; and
3 then 2009, the report on "Preventing Mental,
4 Emotional, and Behavioral Disorders." There's a
5 new one under development right now.

6 I think all of them hit the consistent theme
7 that these like first moments in the first thousand
8 days and these interactions with families end up
9 being so determinative.

10 I get -- we only have three minutes today.
11 So I could get into some of the developmental psych
12 about the importance of caregiver attachment and
13 early stimulation and engagement for baby brains to
14 develop healthy cognitive and effective skills,
15 which then go into -- and the meaning of this ends
16 up being along the developmental cascade.

17 Whereas you have these developmental assets
18 form in the first thousand days, the way that then
19 the child goes to school, and on to family life, as
20 they go through ages 3 through 5, begin to develop
21 into behavioral -- slight behavioral problems and
22 emotional dysregulation and slight learning

1 problems.

2 Then any issues at that point in the
3 developmental cascade can begin to grow over time,
4 until you have actual, like diagnosable mental
5 health conditions beyond sort of early
6 externalizing and internalizing, And then school
7 failure, and substance use.

8 Because of the relationship between mental
9 health and development and physical health, both
10 through health-related behaviors and allostasis and
11 the interaction between CNS systems and other
12 bodily system, it also puts you at increased risk
13 for obesity, hypertension, and all these other
14 issues, which are empirically validated by some
15 meta-analyses, although I think it's still kind of
16 evolving over time, the way these life course
17 impacts work.

18 So postpartum depression interrupts these
19 earliest activities, making it much more
20 challenging for moms to invest in that early
21 attachment, stimulate engaged babies, all of these
22 kinds of activities. And so the first thousand

1 days, like every day of it ends up being extremely
2 meaningful.

3 So I think any opportunity to innovate in
4 this space -- because we kind of mentioned
5 yesterday, even though we as a society have done
6 very little, I think, to address postpartum
7 depression, sadly, I think just applying existing
8 tools more effectively won't get us to where we
9 need to be, and additional innovation is needed.

10 So I really appreciate everyone's
11 consideration today as we think about the profound
12 two-generation implications of postpartum
13 depression.

14 DR. NARENDRAN: Thank you.

15 Will speaker number 6 step to the podium and
16 introduce yourself? Please state your name and any
17 organization for the record.

18 MS. LONG: Thank you for this opportunity.
19 My name is Rebekah Long, and I was a participant in
20 the Hummingbird PPD study by Sage Pharmaceuticals.
21 I want to thank Sage for providing my travel and
22 allowing me to be here today. I am not being

1 reimbursed for my time as this is a personal
2 journey to help change women's lives.

3 I did not feel any connection with our son.
4 I tried breastfeeding him, but had to feed him via
5 bottle and pumping. I felt like I should be
6 excited about this experience, but it only
7 frightened me to be alone with all my children.

8 I was gripped by sadness, overwhelmed by
9 fear, and too ashamed to talk about it. I tried to
10 go back to work after six weeks, and ended up
11 calling my husband as I couldn't even make a simple
12 decision.

13 My management team couldn't believe that I
14 forgot how to do the simplest task. I quit my job
15 that I was so eager to go back to before I left on
16 maternity leave. All that I could do was sleep and
17 cry. Luckily, my mom was here to support my
18 family. She just didn't know how to help me.

19 I went to my PCM and was given anxiety and
20 depression meds. I also did psychotherapy, but
21 nothing seemed to help. I was not eating and lost
22 15 pounds. Everything seemed so painful. My days

1 became a foggy mess of uncontrollable emotion,
2 frustrating anxiety. My husband kept on telling me
3 that something needed to change.

4 While on Facebook late one night, the
5 Hummingbird study came up. I felt like this was my
6 last hope. If this didn't work, then I would have
7 to go into a psychiatric hospital.

8 I remember getting the IV when I went to the
9 research family, and how throughout the day I felt
10 something change. I was asked the same survey
11 questions over and over. I could tell my answers
12 were changing. I could breathe, laugh, and think.
13 I was able to leave my room and interact with the
14 other clients. I felt like eating a meal, and even
15 called to check on my family.

16 After returning home, my husband, mom, and
17 children noticed a difference. My daughter told me
18 I got magical medicine because I was able to
19 interact with them. The next morning I woke up,
20 cooked them breakfast, and played a game with them.
21 I stayed awake all day and interacted with
22 everyone. I was not afraid of making a mistake. I

1 was able to cuddle and actually breastfeed my son.

2 This drug trial changed my life. Nobody can
3 imagine what PPD feels like unless you have
4 personally gone through it.

5 Thank you for allowing me the opportunity to
6 be part of it. The reason why I felt it crucial to
7 be here is to share my personal experience and
8 hopefully assist other women who are struggling
9 with PPD. Thank you, Sage, for giving me my life
10 back.

11 DR. NARENDRAN: Thank you.

12 Will speaker number 7 step to the podium and
13 introduce yourself? Please state your name and any
14 organization for the record.

15 MS. SMITH: Good afternoon. My name is Ann
16 Smith, and I am speaking on behalf of myself
17 personally as well as Postpartum Support
18 International. Postpartum Support International
19 receives -- well, Sage has been a sponsor of
20 Postpartum Support International's annual
21 conference along with many other sponsors.

22 I am a certified nurse midwife and women's

1 health nurse practitioner, and I personally am a
2 survivor of postpartum depression and anxiety. I
3 am also president of Postpartum Support
4 International, the leading organization devoted to
5 perinatal mood and anxiety disorders.

6 PSI's mission is to inform and support women
7 and their families who are experiencing PMDs,
8 trained mental health and other professionals, in
9 how to screen, diagnose, and treat, and provide the
10 connection between the two so that women can get
11 the treatment they need.

12 This afternoon I would like to talk about
13 numbers, the numbers of women who suffer from these
14 painful and damaging disorders, the numbers who get
15 treatment, and the numbers who actually recover.

16 PSI used the commonly accepted statistic
17 that 1 in 7 women who are pregnant or postpartum
18 suffer from a mood and anxiety disorder. That
19 translates to 14 percent, and with 3.8 million
20 births in the U.S. in 2017, that means
21 approximately 532,000 new moms struggle with a
22 significant mental illness while also struggling to

1 recover from childbirth and adjust to parenting.

2 PSI and other experts in the mental health
3 field use alarming numbers taken from a study in
4 the Journal of Clinical Psychiatry in September
5 2016 showing that barely 30 percent of symptomatic
6 women are actually identified in a clinical
7 setting, no more than 17 percent receive treatment,
8 and well under 10 percent are treated to remission.

9 There are many reasons for this dreary
10 finding: lack of access to care; lack of
11 competent, trained providers; stigma of having the
12 illness, and reluctance to reach out; insurance
13 problems; and perception that there is not
14 effective treatment, although the last one is
15 inaccurate. There is effective treatment. The
16 options are sometimes limited, and they are not
17 effective for everyone.

18 Often I watch as moms who are part of PSI's
19 10,000-strong Facebook support network quit their
20 medications because they take too long to work or
21 the early side effects are unpleasant. Many women
22 are desperate and have lost hope of ever being

1 well.

2 Just as an example of that, three members of
3 the 18-member boards of directors of Postpartum
4 Support International have lost a close family
5 member to suicide and/or homicide.

6 On behalf of Postpartum Support
7 International and myself personally, I see an
8 important role for the development and approval of
9 new, safe, effective, quick-acting medications
10 available to all eligible women.

11 It is my fervent hope that new widely-
12 available medications will mean that less and less
13 mothers and their loved ones need to experience the
14 heartache and agony of depression and anxiety.

15 DR. NARENDRAN: Thank you.

16 Will speaker number 8 step to the podium and
17 introduce yourself? Please state your name and any
18 organization for the record.

19 MR. D'ACHILLE: Hello. My name is Steven
20 D'Achille. I'm here on behalf of the Alexis Joy
21 D'Achille Foundation for Postpartum Depression,
22 also as a husband and a father.

1 I'm here speaking today on behalf of my wife
2 because she can't because she's dead. I'm here
3 speaking on behalf of my daughter, Adrianna Joy,
4 who has the unfortunate burden of growing up
5 without a mother. She's going to grow up with this
6 huge question, and that is: Is it her fault that
7 her mother's no longer here?

8 The reality is, my wife suffered from a
9 disease that affects nearly 1 in 5 new moms, a
10 disease that does not discriminate, a disease that
11 nobody is safe from. Most importantly, I'm here as
12 a man to let everyone know that this disease is a
13 family disease. It affects every single member of
14 the family, not just women.

15 When a woman is sick, everyone suffers. The
16 divorce rates are unfathomable in homes where mom
17 is suffering with a maternal mental health issue.
18 The children end up paying the price. It is our
19 job to give our children to have the opportunity to
20 have the best childhood possible and a limitless
21 future. I know firsthand the effects on children
22 who grow up in homes without moms.

1 August 30, 2013 was supposed to be the
2 happiest day of mine and my wife Alexis's life.
3 Rather, it was the most challenging, eye-opening,
4 brutal reality we had never been prepared for. Our
5 daughter's delivery was a Code Blue delivery. That
6 was the beginning of the end of our perfect lives.

7 Alexis was diagnosed with PTSD due to the
8 delivery. Alexis experienced just about every
9 symptom of maternal mental health disorders
10 starting with PTSD, then postpartum depression,
11 postpartum anxiety, and eventually postpartum
12 psychosis.

13 Alexis was different in that she bravely
14 sought help and treatment. She did not suffer in
15 silence. It's important to note with my wife's
16 symptoms and kind of the unraveling, her postpartum
17 psychosis was, I believe, brought on by the
18 antidepressant she was prescribed.

19 Alexis had been calling her OB/GYN,
20 psychiatrist, and pediatrician during this entire
21 period. Each one said, don't worry, it's just the
22 baby blues. It'll pass. You're fine. Try to

1 relax and enjoy this time.

2 2013 was just five short years ago.

3 However, in those five short years I've watched
4 awareness and access to care change dramatically in
5 the field of maternal mental health. The one thing
6 that hasn't evolved at all is how they medicate and
7 treat the disease.

8 Since my wife's passing, I've dedicated my
9 life to helping find solutions to this disease. I
10 set upon a mission to build a sustainable mother-
11 baby program where women can get treatment with
12 their child. I'm proud to say that we've
13 accomplished that goal and are hoping to have
14 access to women everywhere someday.

15 New medication for MMH issues is a solution
16 to this problem that I wholeheartedly believe in.
17 The United States has a problem with access to
18 mental health professionals, specifically
19 psychiatrists.

20 In our case, my wife had a two-month wait.
21 Because of these issues, she was forced to see her
22 OB/GYN to get psych meds prescribed. In my mind,

1 this is not okay. Poor screening tools were used,
2 if any.

3 Her OB ended up prescribing her
4 antidepressant. She was told that in two weeks she
5 would start feeling better. Two weeks from the day
6 she got on them, instead of feeling better, she
7 hung herself in our basement.

8 Breastfeeding was a major issue for her
9 because she felt that she couldn't and shouldn't
10 take them while breastfeeding. She feared a lot of
11 backlash, kickback from what people would think.
12 We went to seven hospitals in her final 13 days,
13 each time turned away. They doubled her dose of
14 Zoloft and she ended up taking her life.

15 Why would we not give women and families
16 another treatment option? If this option doesn't
17 work, we can always go back to the other normal,
18 more conventional methods. It's too late for
19 myself, my daughter, and my wife, but it's not too
20 late to change the future for your wife, sister,
21 daughter, or friend. I think this is an option
22 that every single woman deserves.

1 DR. NARENDRAN: Thank you. A powerful
2 testimony.

3 Will speaker number 9 step to the podium?
4 Please state your name and any organization for the
5 record.

6 MS. HATHAWAY: Good afternoon. My name is
7 Stephanie Hathaway, and I was a patient in this
8 study. While my travel here was paid for, my
9 personal time is not, and I am speaking today on my
10 own behalf.

11 So these are my girls. Hadley is 4; she
12 loves animals and can make you laugh like no one
13 else. Britney [ph] is 1, with a fierce independent
14 streak and a smile that lights up a room. They are
15 incredible little people who deserve to have a mom,
16 and because of this drug, they do.

17 I gave birth to Hadley when we served as
18 missionaries overseas in China. Having never
19 experienced any form of depression or anxiety in my
20 life and living in a country where such a thing is
21 taboo, you can imagine that when I started having
22 suicidal thoughts, including a plan of exactly how

1 I would carry it out, I was scared to death.

2 I thought that my child deserved a better
3 mom and my husband a better wife. These thoughts
4 and more played on repeat in my head. Ultimately,
5 with medication and being put under 24-hour watch
6 for months on end, I barely made it through
7 unscathed.

8 With the treatment options after my first
9 pregnancy leaving so much to be desired, we did
10 everything we could to reduce my chances of going
11 through that again the second time around,
12 including going back onto medication during my
13 pregnancy.

14 But soon after giving birth the second time,
15 those same thoughts crept back in with a vengeance,
16 this time even worse than the first. I was
17 hospitalized, which was even more traumatizing, and
18 I came away from that feeling like even more of a
19 failure.

20 I couldn't go into my baby's nursery because
21 every time I did I got flashbacks to the night I
22 came closest to killing myself by stabbing a knife

1 in my abdomen at the foot of her crib. The words
2 of affirmation my friends and family used to try
3 and help me only made it worse, and I was left in a
4 lonely and isolated downward spiral that medicine
5 wasn't helping and no one, even trained
6 professionals, understood.

7 Enter this medical trial. Literally on the
8 verge of killing myself, I saw an ad on TV and
9 thought, what could it hurt? I was injected with
10 this drug, and for the first time, I felt an
11 incredible life-changing feeling, hope. Hope for a
12 future with my children. Hope that this acute
13 depression would not define me. Hope that I could
14 go home and have the willpower to actually try to
15 live another day. And that's exactly what I did.

16 This medicine was pivotal in allowing me to
17 not give up but to move forward in finding the
18 treatment that would work long term. Because of
19 that short infusion of medication, I am here today
20 to share this short version of my dark story with
21 you.

22 While it did not fully cure me of my

1 depression, it set me firmly on the course to
2 healing and gave me sweet, cherished moments with
3 my babies that did not end in intrusive thoughts
4 and guilt.

5 Having gone through two bouts of severe
6 depression, one with this medication and one
7 without, I can say with 100 percent certainty that
8 this infusion is worth every moment of
9 inconvenience spent in the hospital to get it.
10 Life and death has no time frame.

11 In closing, those are my girls, and they
12 deserve to have a mom. Because of this drug, they
13 do. Thank you.

14 DR. NARENDRAN: Thank you.

15 Will speaker number 10 please state your
16 name and any organization for the record.

17 MS. McNABB: Hi. My name is Christine
18 McNabb. I'm here for Donna Kreuzer, and here's a
19 video that she has.

20 (Video played.)

21 MS. KREUZER: My name is Donna Kreuzer. My
22 only child, Kristy Marie [inaudible], was born in

1 1974. She was a gift and filled our lives with
2 happiness. Kristy's only child, Vivian Grace, was
3 born in 2010. That same year, in what should have
4 been the most wonderful period of her life, Kristy
5 took her life after a six-month struggle with
6 severe postpartum depression. That was 2,952 days
7 ago.

8 "Kristy's death and the consequences of that
9 tragic decision is why I am making this video in
10 support of brexanolone application. My daughter
11 Kristy was very bright and possessed a spirit of
12 hope, strength, confidence, and happiness and
13 compassion.

14 "She earned three degrees in her life, and
15 all who knew and worked with her would say she was
16 an extraordinary, incredibly well-accomplished
17 young woman with a heart bigger in size than the
18 state of Texas.

19 "Kristy was a beautiful, extremely selfless
20 individual throughout her lifetime. But she did
21 yearn for something very dear to her and her
22 husband. Kristy wanted to become a mother. She

1 had the strongest desire to conceive, deliver the
2 healthiest baby possible, and for her to remain the
3 healthiest and happiest new mommy alive, allowing
4 her to raise and enjoy her child for the duration
5 forevermore.

6 "Unfortunately, conceiving for Kristy and
7 her husband was extremely difficult. But after
8 years of fertility assistance, miscarriage, and
9 thoughts of adoption, finally Kristy had a
10 daughter, our Vivian Grace, who has become a
11 healthy, happy, and most beautiful child.

12 "For the first eight weeks of Vivi's life,
13 Kristy slept alone in silence with PPD, not because
14 we weren't aware of PPD but because of Kristy's
15 undeniably selfless nature and the stigma a mental
16 health disorder carried back then as well as today.

17 "After she revealed that she had been
18 keeping this secret, we immediately sought
19 assistance from a psychiatrist, her fertility
20 specialist, her OB/GYN, her preacher, a cognitive
21 behavioral therapist, support groups, friends and
22 family. You see, we had the resources to help

1 Kristy as much as possible. But nothing seemed to
2 work.

3 "The constant and swift changes of meds
4 prescribed were ineffective and creating many side
5 effects. On October 1, 2010, my beloved Kristy
6 lost all hope of a cure for the battle with severe
7 postpartum depression she had been suffering with
8 and tragically committed suicide.

9 "I know there are other Kristys in the world
10 who are facing the same struggles as our daughter
11 did, who are losing their battles as well. We all
12 lose. Again, that's why I'm speaking in support of
13 the approval of brexanolone. This might have been
14 an answer to my Kristy's prayers and the help other
15 mothers and their families experiencing PPD
16 desperately need today.

17 "Please give my plea serious and thoughtful
18 consideration. Thank you, FDA and your committee,
19 for this opportunity."

20 DR. NARENDRAN: Will speaker number 11 step
21 to the podium and introduce yourself? Please state
22 your name and any organization for the record.

1 MS. McNABB: My name is Christine McNabb,
2 and this is my husband, Brandon McNabb. We're here
3 on behalf of This Mama Wines. Thank you to the FDA
4 for allowing me to share my story. I would like
5 you to know that we have flown down here from New
6 Orleans, Louisiana. All travels and stay have been
7 provided by Sage Therapeutics, but this story is
8 completely ours.

9 I was diagnosed with postpartum depression,
10 anxiety, and psychosis two years ago a few months
11 after having our fourth child. The reality is I
12 should have been diagnosed three children before.
13 I had always had signs of anxiety and depression
14 during and after each child, but it wasn't until my
15 psychotic break when it was evident that I needed
16 help.

17 You see, my husband found me in our room
18 figuring out how I could leave my family. But
19 prior to me making plans to leave, I wanted to kill
20 myself. I could no longer handle the pressure of
21 being a mom and I just did not want to live. Over
22 thinking suicide, I was afraid of not actually

1 succeeding. I did not want to be a failure at
2 suicide. So instead, I decided to leave.

3 When Brandon saw the condition I was in, we
4 made a joint decision to get help. I received my
5 diagnosis after speaking with my OB. I decided to
6 take medication and to seek third party.

7 MR. McNABB: When I found Christine in that
8 state, I was afraid for her, for us, and for our
9 children. I knew at that point I was going to
10 fight for her if she wasn't strong enough to fight
11 for herself.

12 MS. McNABB: Since my diagnosis, the journey
13 hasn't been easy. But I'm glad to be here to share
14 my story. I was one of the lucky ones that could
15 afford treatment. I had insurance, and paying for
16 medication was not a problem. Not all women have
17 that luxury. With brexanolone on the market, women
18 of all walks of life will have access to life-
19 changing treatment.

20 I am here to advocate not only for myself
21 but on behalf of all moms. And because of my
22 story, I started my company, This Mama Wines.

1 Brexanolone is needed so we don't lose another mom
2 or child to mental illness, to postpartum
3 depression.

4 Being pro-life means supporting the lives of
5 mothers, including their mental health. Otherwise,
6 you're just pro-birth. Thank you.

7 DR. NARENDRAN: Thank you.

8 Will speaker number 12 please step to the
9 podium? Please state your name and any
10 organization for the record.

11 MR. SPERLING: My name is Andrew Sperling,
12 and I'm with the National Alliance on Mental
13 Illness. I'm back again today. I'll spare you the
14 introduction of what NAMI is because I did that
15 yesterday.

16 I want to talk a little bit about the burden
17 of postpartum depression. You've heard some of
18 this already, but it bears repeating. Seven to
19 12 percent of pregnancies experience this, many of
20 them women with no history of major depression. So
21 it visits the family, and it's new to them. It's
22 not something they've been through.

1 It's not the baby blues. Although the
2 symptoms do resemble major depression, it is
3 different in its mechanism. It's associated with
4 reduced GABA-A function related to the rapid
5 changes in hormones that occur after childbirth.

6 We do not have any on-label treatments,
7 which is why this is such an enormous breakthrough.
8 We're very excited about it. Instead, clinicians
9 use traditional antidepressants, which as we heard
10 several times today often takes four to six weeks
11 to show any clinical benefit. And this is a
12 critical time for mothers.

13 The impact on families is staggering, not
14 only in terms of suicidal ideation and the things
15 you've heard today from women that have been
16 through this horrific illness, but it also imposes
17 enormous harm and risk to the newborn and later
18 child development.

19 So this is a huge breakthrough therapy.
20 I've been coming to these ad coms for psychiatric
21 drugs for many, many years, and this is really
22 exciting to say this really is a breakthrough.

1 This is a brand new mechanism of action, and we
2 finally have a rapid-acting agent, 2.5 days to show
3 improvement versus placebo.

4 That is staggering and a huge advance in
5 psychiatric drug development, when you compare with
6 antipsychotics and antidepressants and the products
7 that we have that often take four to six weeks to
8 show clinical benefit.

9 We know there are challenges. In the last
10 hour discussion you all had about the delivery of
11 this product, and 60 hours of infusion, and the
12 setting, whether it has to be done in a clinical
13 setting with a nurse around the clock -- all these
14 different issues. I know you're going to have to
15 write a REMS on this. Just make sure it's not
16 overly restrictive.

17 This is a problem we would dream of in terms
18 of showing immediate clinical benefit in suicidal
19 ideation and major depression or psychosis and
20 schizophrenia. We can overcome some of these
21 issues around infusion. This is a therapy we would
22 dream of, with this level of clinical efficacy and

1 immediate, rapid impact in schizophrenia and
2 psychosis.

3 Take this opportunity to allow a
4 breakthrough in psychiatric drug development. We
5 know the slow pace of drug development; we saw some
6 of this yesterday. This is very frustrating for
7 NAMI, to see the companies pull out of this, and
8 the slow pace in which drug development is taking
9 place.

10 This is an opportunity for a breakthrough.
11 Let's seize this opportunity. Thank you very much.

12 DR. NARENDRAN: Thank you.

13 Will speaker number 13 step to the podium
14 and introduce yourself? Please state your name and
15 any organization for the record.

16 MR. POLLOCK: Good afternoon. My name is
17 Michael Pollock. I'm the chief executive officer
18 for the Depression and Bipolar Support Alliance.
19 We do not receive funding from Sage
20 Pharmaceuticals.

21 DBSA is the leading peer-directed national
22 organization focused on mood disorders, depression

1 and bipolar. Unlike any other organization of its
2 kind, DBSA is created for and led by individuals
3 who themselves have a mood disorder. This first
4 person lived experience informs everything we do.

5 The first priority for treatment should be
6 to ensure that a person living with depression is
7 provided a pathway out of crisis and on to
8 stability. However, all too often this baseline
9 stability is also the end goal established for
10 successful long-term care.

11 DBSA believes that every woman deserves the
12 opportunity not just to survive, but to thrive.
13 And to do that we need to ensure true wellness as
14 the end goal for mental health treatment.

15 The cost of settling for reduced symptoms is
16 far too great, as you've already heard. For many
17 it can be a matter of life and death. According to
18 findings published in the American Journal of
19 Psychiatry, moms with postpartum psychological
20 disorders have a four times higher risk of death
21 from natural and unnatural causes during the
22 follow-up period than moms without postpartum

1 disorders.

2 The idea of wellness cannot be embraced
3 without considering the whole health of the woman.
4 The comorbidities associated with depression are
5 not insignificant. For example, according to the
6 U.S. Office of Women's Health, depression and
7 anxiety is common among women living with
8 polycystic ovary syndrome, and the prevalence of
9 major depression among individuals living with
10 other conditions such as heart disease, diabetes,
11 and Alzheimer's, just to name a few, is well-known.

12 Additionally, the prescriber treating
13 postpartum depression is faced with the dilemma
14 that just as each medication is different, so is
15 each mother's clinical reaction. Further, the
16 considerations around medication risks and benefits
17 can often be different.

18 The prescriber may approach the challenge
19 from a clinical perspective, symptom relief, while
20 the mom, on the other hand, may just be seeking to
21 care for and enjoy her child.

22 The patient community is feeling abandoned.

1 Many researchers consider depression a problem
2 already solved due to the number of pharmaceutical
3 interventions available. But nothing could be
4 further from the truth.

5 My hope this afternoon is you take away the
6 following messages as you make your recommendation.
7 First, patient voices count. Patients want and
8 need solutions that support a pathway to wellness.
9 One size does not fit all. Solutions are as
10 complex as the individuals seeking them. And
11 finally, mothers will evaluate on their own the
12 risks and benefits of different solutions based on
13 their own life circumstances.

14 When considering this application, DBSA
15 urges the advisory committee to not abandon the
16 patient community. Thank you.

17 DR. NARENDRAN: Thank you.

18 Will speaker number 14 step to the podium?
19 Please state your name and any organization for the
20 record.

21 DR. DELIGIANNIDIS: Good afternoon. My name
22 is Dr. Kristina Deligiannidis. I'm the director of

1 women's behavioral health at Zucker Hillside
2 Hospital in Queens, New York, and associate
3 professor of psychiatry and OB/GYN.

4 My disclosure is that I have received grant
5 funding to serve as site principal investigator on
6 all three brexanolone trials, and I have consulted
7 for Sage Therapeutics in the past. My travel today
8 will be reimbursed, but my time will not be
9 reimbursed. And my testimony is my own.

10 I'm a board-certified psychiatrist who has
11 specialized in the psychopharmacologic treatment of
12 PPD for over 10 years. You've heard a lot about
13 the clinical presentation of PPD. I'm going to
14 highlight some points, and I'm going to talk about
15 some of the neuro science that is coming out now
16 from our research supporting this mechanism of
17 action.

18 The CDC reports an overall PPD prevalence of
19 about 11.5 percent. PPD is drastically under-
20 detected and more severely undertreated, leaving
21 women with prolonged symptoms and significant
22 impairment.

1 Untreated PPD can have substantial adverse
2 effects on the well-being of the mother and child,
3 with lasting consequences. PPD with onset during
4 pregnancy, not just postpartum, has effects.
5 During pregnancy it's associated with increased
6 risk for maternal substance abuse, preterm
7 delivery, and infant low birth weight.

8 PPD can impair a woman's ability to care for
9 herself and infant, negatively impacting child
10 cognitive, behavioral, and emotional development.
11 Maternal suicide, as you've heard, is the leading
12 cause of direct maternal mortality in the first
13 postpartum year, with 1 in 7 deaths due to suicide.

14 A recent study, which was also briefly
15 mentioned, reported that in women with PPD, only
16 6.3 percent receive adequate treatment, and only
17 half of them achieve remission. This is worse than
18 our rates in MDD. The authors concluded that 95 to
19 97 percent of women with perinatal depression are
20 not successfully treated. There's an obvious
21 urgent need to develop novel therapeutics for this
22 undertreated population.

1 As a neuroscientist, over the past 10 years
2 I've conducted NIH-funded research in how
3 peripartum changes in allopregnanolone interact
4 with brain GABA and functional connectivity in PPD.
5 I recently published the results of a five-year
6 NIH-funded study that strongly supports that
7 peripartum allopregnanolone, through positive
8 allosteric modulatory effects on GABA contributes
9 to PPD.

10 Recognizing the clinical need for novel
11 therapeutics which have molecular targets aligned
12 with the pathophysiology of PPD, I have separately
13 served as PI on the trials. We have no medication
14 today. As a psychiatrist, there is nothing I can
15 prescribe with such rapid onset.

16 The study results demonstrate that
17 antidepressants with novel treatment targets can
18 indeed be developed to address this highly
19 prevalent yet undertreated disorder. Thank you.

20 **Clarifying Questions (continued)**

21 DR. NARENDRAN: Thank you.

22 The open public hearing portion of this

1 meeting has now concluded and we will no longer
2 take comments from the audience.

3 Before we move to the discussion and
4 questions, I wanted to give the sponsor five
5 minutes to answer some of the questions that were
6 pending from the morning. After that I also want
7 to give the agency to talk a little bit more about
8 the REMS to clarify that for the committee. We'll
9 start with the sponsor.

10 DR. SCHACTERLE: Thank you. We just want to
11 remind the committee that brexanolone is equivalent
12 or is identical to allopregnanolone, which is
13 administered approximating the plasma
14 concentrations that are experienced during
15 pregnancy. It also undergoes the same elimination
16 as allopregnanolone does during pregnancy.

17 I'm going to put a slide up that we felt
18 that would clarify some of the questions that were
19 coming up around withdrawal. You can see that the
20 elimination is biphasic, and so there is a very
21 rapid drop.

22 Most of the brexanolone is cleared from the

1 plasma within 40 minutes. And this is why patients
2 wake up so quickly, because the brexanolone is
3 eliminated quickly. And it's why turning off the
4 infusion would be faster than administering any
5 kind of reversal agent.

6 I'd also like to quickly discuss the plasma
7 concentrations around the pump malfunctions in the
8 30 dose. There was a note that there was a loss of
9 consciousness on the 30 dose. That in fact was a
10 pump malfunction so it was not really the 30 dose.

11 This slide looks at the estimated
12 concentrations. And I'll turn it over to
13 Dr. Colquhoun.

14 DR. COLQUHOUN: Thank you. This is Patient
15 A, who had an overdose of about 700 micrograms per
16 kilogram. The solid line is the model-based
17 simulation of what the plasma concentrations would
18 be like in the instance of a bolus dose of that
19 size. You'll see the dots represent the actual
20 plasma concentrations that were taken.

21 There was a statement made that there was
22 perhaps some doubt that the overdose had occurred

1 in the way that we had described because the plasma
2 concentrations on either side of it were within the
3 normal range.

4 So the pharmacokinetics of brexanolone are
5 really, really fast. That is the bonus dose going
6 up with the high rise of the plasma concentration.
7 They turned off the pump, and that is the fall in
8 the plasma concentrations. Our PK model is very
9 reliable. So I think that this is a good estimate
10 of what happened.

11 I can also show you Patient B. We think
12 that they had an overdose perhaps over the
13 90 minutes, which is that you see again the model-
14 based plasma concentrations the line, the actual
15 plasma concentrations the dots, so again reaching
16 maybe 450 nanograms per mL very quickly. Then the
17 pump was turned off and the plasma concentrations
18 fall extremely rapidly.

19 DR. SCHACTERLE: Thank you. I also wanted
20 to mention that with the dose interruptions, those
21 interruptions range from a few minutes to
22 approximately 10 hours. So we did not see any

1 withdrawal symptoms during those times.

2 If I can quickly put up AL-21, we also
3 analyzed whether there was a withdrawal syndrome at
4 the end of infusion for any administration that was
5 longer than 24 hours. You can see there are very
6 few adverse events in these time frames, either
7 during the taper phase or after follow-up.

8 Just moving -- one clarification around the
9 microbial studies that we were mentioning for the
10 bag stability. Chemical stability is up to
11 30 hours. Those microbial studies are spike
12 studies, so we actually purposely put in the
13 microbe and then watched the growth. We did not
14 want anyone to have the impression that there was a
15 growth in any of these bags.

16 Now, quickly going to the questions that
17 were asked, one was to evaluate brexanolone from
18 202B, the adverse event profile. So put that slide
19 up. Dr. Colquhoun will quickly present.

20 DR. COLQUHOUN: Yes. So this shows adverse
21 events in study 202B in more than 3 percent, or
22 3 percent or more of patients. And you'll see that

1 there was headache, dizziness, similar incidences.
2 Somnolence was a bit more prevalent, 18 percent
3 complaint to 5 percent on the 90 dose.

4 DR. SCHACTERLE: The next presentation or
5 the question that was asked was around the adverse
6 events by use of medroxyprogesterone.

7 DR. COLQUHOUN: So you'll see in the
8 highlighted columns, the one on the left is adverse
9 events in those patients who were using MPA, and on
10 the right those that were not. So if you compare
11 the top line, about 25 percent of subjects had at
12 least one adverse event versus 27 percent who did
13 not use.

14 There were only eight patients who were on
15 MPA, so it's not very easy to draw comparisons.
16 But you'll see roughly there was not very much
17 difference in the percentage incidence of adverse
18 events of those who did and did not take
19 concomitant MPA.

20 DR. SCHACTERLE: The next question was
21 around the patient with the vasovagal syncope.
22 Dr. Colquhoun.

1 DR. COLQUHOUN: Yes. I actually talked to
2 the investigator when he called us about this
3 patient. So I can say I am convinced that this
4 patient had a vasovagal faint as a result of fear
5 of needles.

6 We've no evidence that she had had previous
7 vasovagal syncope, but she was known to have a
8 fear of needles. And it was the hour 24 blood
9 sample that triggered this fainting episode.

10 DR. SCHACTERLE: The next question was to
11 look at patients who achieved a response at
12 24 hours and look at their 30-day outcomes versus
13 the patients who responded at 60 hours or took
14 until 60 hours and what were their outcomes at 30
15 days.

16 This is a little bit of a complicated slide,
17 but the top major rows was yes if they were a
18 responder at hour 24, and then what did they look
19 like at day 30. So you can see that over
20 80 percent across the top row for the subjects that
21 were responders at hour 24 continued on to be
22 responders at day 30, for placebo and for

1 brexanolone.

2 The lower major row is no, they are not
3 responders at hour 24. But if you look at the
4 third minor row down, that's a yes at hour 60. And
5 so if you draw across that line, both placebo and
6 brexanolone continue on. If they were yes, a
7 responder, at hour 60, three-quarters of them
8 remained a responder at day 30.

9 Then my last comment is that there had been
10 some discussion around the bag preparation, by
11 concentration, and infusion delivery. Certainly
12 the briefing documents often precede additional
13 discussions that we have with the agency.

14 We wanted to assure you that we are in
15 alignment with the agency to prepare it by
16 concentration so that all of the bags will have the
17 same concentration and can adjust the dose
18 accordingly. Thank you.

19 DR. NARENDRAN: Thank you. Just one
20 question. Dr. Besco.

21 DR. BESCO: Yes. I just have a clarifying
22 question. Can you define what you use as your

1 definition for pump malfunction? And were you
2 using the same pumps throughout all the study
3 sites? It just seems concerning, the level or I
4 guess amount of medication that these two patients
5 received as a result of the malfunction. So I'm
6 just wondering, does malfunction also potentially
7 mean programming error, or is it truly a device
8 malfunction?

9 DR. SCHACTERLE: So each site was required
10 to supply their own pumps. There was a requirement
11 for all sites, and there will be in the labeling,
12 for the pumps to be peristaltic so that theirs is
13 not a wide open fail-safe scenario.

14 Our understanding is that they were pump
15 malfunctions, not necessarily medication errors.
16 The two pump malfunctions occurred at the same
17 site. And that's the information that we have.

18 DR. BESCO: Thank you. We'll hand it over
19 to the agency to comment on the REMS, clarify on
20 the REMS.

21 DR. LaCIVITA: This is Cynthia LaCivita with
22 the Division of Risk Management. I thought it

1 might be just helpful to kind of lay out some
2 framework for the REMS.

3 So the REMS is a risk management plan. It's
4 not a study. But that's not to say that when we
5 receive assessments on the REMS that we don't get
6 additional information that helps inform us about
7 how to mitigate the risk or safety information.

8 In general, the REMS puts forth the
9 requirements to assure safe use. In this case, it
10 would be brexanolone. The plan that the sponsor
11 and the agency are considering are the use of an
12 authorized representative who would sign on behalf
13 of a healthcare setting, and they would attest that
14 the healthcare setting is able to meet the
15 requirements.

16 The requirements could be spelled out in the
17 REMS, such as things that were discussed earlier
18 today such as prepared in compliance with 797, or
19 personnel must be able to perform certain
20 functions. States may dedicate or may have the
21 purview over who can perform certain activities, so
22 we might not be as specific in those circumstances.

1 Or it could lay out specific monitoring
2 requirements.

3 We haven't made a determination on that, so
4 that's part of the discussion this afternoon. So
5 hopefully that's helpful to you all.

6 DR. NARENDRAN: Thank you for the
7 clarification.

8 We will now proceed with the questions for
9 the committee and panel discussions. I'd like to
10 remind the public observers that while this meeting
11 is open for public observation, public attendees
12 may not participate except at the specific request
13 of the panel.

14 DR. NARENDRAN: If there are no questions or
15 comments concerning the wording of the question, we
16 will open the questions to discussion. The
17 division has asked for a change in the order of the
18 question, so we're going to do question number 1,
19 question number 20, and then we're going to do
20 discussion question 4, question 5, and then we're
21 going to go back and vote on question number 3, and
22 then we'll come back to question number 6.

1 I'll take care of the order. Don't worry
2 about it; just the order is going to be switched,
3 and we're going to flip the order around.

4 Dr. Mathis, do you want to give us charge or
5 just present the final comments?

6 **Charge to the Committee - Mitchell Mathis**

7 DR. MATHIS: Sure. So you've heard the
8 discussion. You have heard from the public. The
9 needs that we need from a regulatory point of view
10 are do we have evidence of substantial evidence?
11 Have we characterized the safety? And then the
12 third voting question, which will come after the
13 discussion question, do the benefits outweigh the
14 risks?

15 We've modified that question to say when we
16 use a REMS program that we've defined -- we haven't
17 completely defined the REMS, but I think you
18 understand where we're going with that. We will
19 talk with you about it. We have the options here
20 to design it in a way that would make us
21 comfortable, and we're happy to integrate any
22 suggestions that you have into that.

1 **Questions to the Committee and Discussion**

2 DR. NARENDRAN: Thank you.

3 So we'll start with the first question,
4 which is a voting question. Has substantial
5 evidence been presented by the applicant to support
6 a claim of effectiveness for brexanolone for the
7 treatment of postpartum depression?

8 DR. MEISEL: A clarifying question about the
9 question?

10 DR. NARENDRAN: Okay. One second.
11 Dr. Meisel, you have a qualifying question about
12 the question.

13 DR. MEISEL: Right. The data may have been
14 different based on the severity of the depression
15 coming in. So how we answer this question, how
16 we're to vote on it, are we asking to vote on this
17 in and aggregate or could this be subdivided into
18 two questions; one for major depression with the
19 HAM score greater than 26 and the other for the
20 more moderate depression?

21 DR. NARENDRAN: I assume the question you
22 would vote as how it's written, but the

1 agency -- we can't break it up --

2 DR. MATHIS: No. I can tell you how it got
3 to this point. In the initial designing of this
4 program, it was we who said that we'd like the
5 sponsor to examine not just two studies in severely
6 depressed patients, postpartum depression, but one
7 severe, one moderate. And the endpoint was the
8 60-hour endpoint, which is the substantial
9 endpoint. And then it was we who said can you look
10 for 30 days just to make sure it keeps working in
11 case we -- so we'll know what other treatment
12 options. We might be able to implement another
13 antidepressant, for instance, if that would be
14 necessary.

15 So we would find the greatest public health
16 benefit if we could interpret these studies so that
17 the label could be written for the treatment of
18 postpartum depression. And then in the clinical
19 trial section, describe that there was severe and
20 moderate patients and what the differences were in
21 the treatment responses there.

22 Unless you absolutely feel like you would

1 have a different answer for those two questions, I
2 would rather you just vote on the one.

3 DR. MEISEL: It's so call. It's your
4 questions, the FDA. The 60-hour time frame, we
5 know in the moderate depression, that fades, or at
6 least the placebo catches up, over the course of
7 the following -- however many days that is, 27
8 days.

9 Many people would say that that
10 is -- compared to the risks and everything else,
11 that maybe we're greasing the pump, but by itself
12 it's not all that effective when you see what
13 happens at 30 days, whereas that's a different
14 answer when you're talking about the severe
15 depression.

16 If you say that the definition is 60 hours,
17 period, an draw the line, then that's the way we'll
18 have to answer the question. But I have a hard
19 time with the way that question is framed.

20 DR. MATHIS: And I understand the
21 distinction that you're making, but I would hope
22 you could understand mine, that to have an

1 antidepressant work at 60 hours was an impressive
2 thing for people with postpartum depression. It is
3 true that the placebo patients catch up by 30 days
4 in one of the studies, but we wanted to be able to
5 label the fact that the drug worked quickly and
6 significantly better, if you believe that to be
7 true, in patients no matter the severity of their
8 postpartum depression.

9 DR. TEMPLE: I'm a little puzzled. If a
10 drug took a condition that lasts for a long time
11 and made it go away substantially in a few days or
12 a few hours, or something like that, but the
13 placebo group caught up at 30 days, would that be a
14 bad thing? I mean, maybe the disease tends to go
15 away after 30 days, which it obviously does to some
16 degree. That doesn't mean that there wasn't -- as
17 we heard from the patients, that doesn't mean that
18 the early terrible illness going away fast isn't a
19 benefit, does it?

20 DR. FARCHIONE: I think just for context,
21 for instance, when we get the postmarketing data on
22 other antidepressants in a more typical development

1 program, we usually ask for a randomized withdrawal
2 trial. In the case of those treatments, what we
3 usually are looking for is relapse. So we expect
4 to see relapse in the placebo, and then we want to
5 make sure that if people who keep taking the drug,
6 that the drug keeps working, and the people who go
7 off of it, we're looking for when the depression
8 recurs.

9 In this case, at that 30 days, what we're
10 actually looking for is the durability of the
11 effect. So again, if the folks who had had the
12 drug in the 60 hours had gotten worse and gone up
13 to meet the placebo, that's a different story than
14 the placebo coming down to meet the drug. So I
15 think it's important to put it in that kind of
16 context as well.

17 DR. NARENDRAN: Dr. Unger?

18 DR. UNGER: If we were to approve the drug,
19 we would give an indication that would be probably
20 something along the lines for the treatment of
21 postpartum depression. So it wouldn't be qualified
22 with treatment of postpartum depression at X days

1 or Y days. So the question I think reflects is
2 there substantial evidence to support an indication
3 for postpartum depression? So we have a little
4 trouble parsing it out.

5 DR. NARENDRAN: With everything we've seen
6 so far.

7 There are a couple more questions.
8 Dr. Kulldorf?

9 DR. KULLDORF: Martin Kulldorf, Harvard
10 Medical School. I just wanted to ask, as a
11 biostatistician, a comment that I found the study
12 to be very well designed and executed, accurately
13 analyzed, and well and honestly presented.

14 DR. NARENDRAN: Thank you. Ms. Witczak?

15 MS. WITCZAK: Kim Witczak, consumer rep. I
16 think my whole comment was around what Steven, the
17 postpartum depression being defined as is it an
18 event or is it something that -- because it has the
19 features of the MDD and the potential of what this
20 could be eventually, or is it just being defined at
21 this 60 hours?

22 Can we put that in there or do you want us

1 to just put that in our answer so it's for the
2 record? Because I think there is something to be
3 said about it being in this context of the
4 60 hours, 30 days, but I don't know what it's going
5 to be in 60 days, or for relapses. So that's the
6 distinction for me.

7 DR. MATHIS: Mitch Mathis. Right. We never
8 know when we approve a drug for the acute treatment
9 of depression what's going to happen until after we
10 get our phase 4 data for relapse prevention, and
11 it's even going to keep working.

12 What we wanted to measure here was that in
13 the current episode of postpartum depression, the
14 patients got significantly better on the drug than
15 placebo because of the way they've designed their
16 drug. It has to be given for 60 hours, so the
17 endpoint was put at 60 hours for that reason.

18 So at 60 hours, what the sponsor would like
19 to show you is that they have a significantly
20 different result from the drug than placebo.
21 That's where substantial evidence would be
22 measured, is at the primary endpoint.

1 The secondary look was our own interest in
2 your very question: what do you do now? So now
3 that it's worked, does it keep working? And if so,
4 for how long? Long enough to do something else or
5 you don't have to do anything else. And we still
6 haven't answered all those questions. We never
7 know all the answers to every question until we get
8 more data as we put this out there. If it were to
9 go out there with REMS, and it would have a
10 registry, you could learn from that, if there are
11 postmarketing studies, et cetera.

12 So I appreciate you being uncomfortable with
13 not knowing exactly what to do next. We always are
14 when we approve a new drug, especially one in a new
15 class. So if this were to get approved, we'd have
16 that same discomfort, but we would work through it.

17 DR. TEMPLE: But in this case, they didn't
18 do anything next, they finished the infusion, and
19 then they watched.

20 DR. MATHIS: That's right --

21 DR. TEMPLE: A least for this group of
22 people who knows how selected they did not for the

1 most part recur?

2 DR. MATHIS: All the way to 30 days.

3 DR. TEMPLE: No, they didn't recur in any of
4 them. There was no difference in one of the
5 studies of 30 days. In none of them did they
6 recover.

7 DR. MATHIS: Right. So we have 30 days
8 worth of data.

9 DR. TEMPLE: For it's worth, however, in the
10 randomized withdrawal studies that we see for oral
11 antidepressants, recurrence in 30 days in someone
12 who's stable is very unusual. It's a couple of
13 percent at most. But gradually everybody recurs,
14 but the disease is cyclical, and it doesn't come
15 back instantly, most of the time.

16 MS. WITCZAK: One other thing again, but the
17 diagnostic criteria for postpartum depression, they
18 do limit that to an episode that happens within
19 6 months -- well, that starts within 4 weeks, but
20 that happens within six months of birth.

21 So depending on when these patients came
22 into the trial, if you look past 30 days, you might

1 be looking past what would end up being defined as
2 a postpartum depression. If it recurs at that
3 point, then are you really talking about postpartum
4 depression or are you talking about regular old,
5 run-of-the-mill major depressive disorder?

6 So that's something else to keep in mind,
7 too. That's part of why we didn't want to look too
8 far beyond the acute treatment period. So 30 days
9 I think was almost like a compromise time period
10 because you don't want to go too far out.

11 DR. FARCHIONE: So would that actually be in
12 the label, something to the fact of the --

13 MS. WITCZAK: The studies would be
14 described, yes.

15 DR. FARCHIONE: Yes. And then even
16 6 months, that it wouldn't go past, because I think
17 that's the thing I'm wrestling with is?

18 MS. WITCZAK: The definition of postpartum
19 depression would be --

20 DR. TEMPLE: We don't have 6-month data.

21 DR. FARCHIONE: No. She's asking about if
22 somebody could repeat it in month -- we don't

1 really know what that is. So let's say it comes
2 back in month 3, and they did it on month 1, do we
3 assume that that's going to work? I think it's
4 that idea of just --

5 DR. TEMPLE: Well, you could ask whether
6 that's still postpartum depression anymore, and we
7 don't have those data.

8 DR. FARCHIONE: Because then that's part of
9 this question. So that's why I'm just trying
10 to -- and I appreciate you guys wrestling with the
11 questions, too.

12 DR. NARENDRAN: It sounds like we have heard
13 plenty of information, and I think we should go
14 ahead and vote. And a lot of this seems to be
15 discussion points that could be made, so how you
16 voted at the end.

17 That being said, I'll read the question
18 again. Has substantial evidence been presented by
19 the applicant to support a claim of effectiveness
20 for brexanolone for the treatment of postpartum
21 depression?

22 In terms of the voting, please press the

1 button on your microphone that corresponds to your
2 vote. You'll have approximately 20 seconds to
3 vote. Please press the button firmly after you
4 have made your selection. The light may continue
5 to flash. If you're unsure of your vote or you
6 wish to change your vote, please press the
7 corresponding button again before the vote is
8 closed.

9 (Voting.)

10 MS. BHATT: The voting results yes, 18; no,
11 zero; abstain, zero; no voting, zero.

12 DR. NARENDRAN: So we could start from my
13 right-hand side. Dr. Burger, if you want to start
14 and give us a reason how you voted and why you
15 voted.

16 DR. BURGER: Greg Burger, Stormont Vail
17 Health. The evidence is pretty clear that, to me,
18 that it works right away within that 60-hour
19 period, so that's why I voted yes.

20 DR. VALBH: Tina Valbh. I voted yes. I
21 think that there is substantial evidence showing
22 that the medication works in the time frame at is

1 was outlined.

2 DR. RUHA: Michelle Ruha. I was very
3 comfortable that it works based on the evidence
4 presented.

5 DR. HABEL: Laurel Habel. Yes, I agree that
6 all three studies met the primary endpoint at 60
7 hours.

8 DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz.
9 I voted yes. I think that how quick the patients
10 improved versus any other treatment, we know was
11 important. And seeing the data that there was no
12 rebound, I think it was very convincing. I found
13 that the area under the curve of how many days
14 remember feeling significantly better was an
15 important outcome.

16 DR. MEISEL: Steve Meisel. I voted yes. I
17 comment the applicant here for very well designed,
18 well analyzed studies in this space. I do still
19 have that caveat about the moderate depression and
20 whether or not the benefits that we see, which will
21 be caught up to by placebo by 30 days, if that's
22 just a different beast and should be called out as

1 such in product labeling as opposed to in the
2 studies themselves, but to be called out in terms
3 of specifics in terms of indication.

4 DR. GRIFFIN: Marie Griffin. I voted yes.
5 I think the studies were methodologically strong
6 and clearly presented, and presented a substantial
7 benefit to these patients.

8 DR. BESCO: Kelly Besco. Ohio Health. I
9 also voted yes. I also agree the evidence was
10 confirmatory, and I just also want to state that I
11 appreciate the mothers and fathers for sharing
12 their experiences with us today.

13 MS. NUMANN: Sabrina Numann. I did vote
14 yes. I do feel that evidence was there. Thank
15 you.

16 MS. WITCZAK: Kim Witczak. I voted yes I
17 feel like the evidence was there for the
18 short-term, quick-acting.

19 DR. FIEDOROWICZ: Jess Fiedorowicz,
20 University of Iowa. The results are consistent
21 across all three studies in the primary outcome.
22 The magnitude of the effect is large for severe

1 depression and is sustained. These impressive
2 results with a novel therapy are frankly
3 groundbreaking.

4 DR. NARENDRAN: I do second Jess' comments.
5 I think this drug -- the study is methodologically
6 very sound. I think that mechanistically, it's
7 very rooted and a good foundation, and I think it
8 could be of tremendous help in changing the
9 trajectory for postpartum depression.

10 DR. JAIN: Felipe Jane, Department of
11 Psychiatry at Harvard Medical School. The evidence
12 presented today for moderate and severe postpartum
13 depression was overwhelming and remarkable for its
14 high effectiveness, rapidity of effect in
15 durability of response after the infusion.

16 As a clinician, I've seen patients with
17 postpartum depression who have suffered with the
18 shame it brings at this vulnerable point in their
19 lives. Despite their best efforts, it has
20 interfered with their motherhood and their
21 children's development. I believe that brexanolone
22 may be a game changer in the treatment of

1 postpartum depression. This is what hope looks
2 like.

3 DR. TURNER: Yes. Erik Turner. I voted in
4 favor of substantial effectiveness as well. I felt
5 it was quite convincing. I had a couple of caveats
6 there regarding, say, duration of action. I'm also
7 not totally convinced about the magnitude of the
8 effect compared to other antidepressants with the
9 exception of the first study. The other ones
10 seemed to be more aligned with other
11 antidepressants, but there's no question the
12 rapidity at the onset is impressive. Then we have
13 later questions I think to work out about the need
14 for the higher doses and stuff, but I assume that
15 comes in subsequent questions.

16 DR. DUNN: Walter Dunn, UCLA. I also found
17 the evidence very convincing. In regards to the
18 third study, I actually was convinced that -- less
19 worried that the placebo group caught up with it,
20 the treatment group. Placebo groups are known to
21 do very strange things.

22 DR. IYENGAR: Satish Iyengar from

1 Pittsburgh. I thought the study was well designed,
2 well executed, and I found the results convincing.

3 DR. KULLDORF: Martin Kulldorf, Harvard
4 Medical School. A very well conducted study. The
5 quick effect after 16 hours, very impressive, but I
6 think the fact that you still see effect after 30
7 days without any further medication I think is even
8 more impressive. The fact that the mild depression
9 was significant after 30 days may not be too
10 strange because if we went even further, most
11 postpartum depression resolves itself sooner or
12 later. So if we had gone even further like a year
13 or two years, then obviously there wouldn't be any
14 difference between the two groups because then it
15 would be resolved for even those who got the
16 placebo.

17 DR. WARHOLAK: Terri Warholak, and I voted
18 yes. I felt that there was a preponderance of
19 evidence of effectiveness, and I'd like to thank
20 the sponsor for tackling such an important issue
21 and doing such a nice job of it, and answering our
22 questions with such good evidence in a kind of

1 manner. And thank you to the patients and family
2 members for sharing your stories.

3 DR. NARENDRAN: Summary is everybody agrees
4 the drug works.

5 We'll move to question number 1. Has the
6 applicant adequately characterized the safety
7 profile of brexanolone for the treatment of
8 postpartum depression? Do you believe the loss of
9 consciousness events have been characterized
10 sufficiently to enable safe use of brexanolone?

11 It's another voting question, so I
12 think -- Dr. Meisel?

13 DR. MEISEL: There are questions here.
14 Which one are we voting on?

15 DR. NARENDRAN: I assume you're voting on
16 both.

17 DR. MEISEL: What if we say yes or no or no
18 and yes?

19 DR. FARCHIONE: We put the questions
20 together because we did want to emphasize that the
21 loss of consciousness events were a part of that
22 safety profile, that we're asking whether it's been

1 adequately characterized. If something is
2 adequately characterized, then it's been
3 characterized sufficiently to enable the safe use.
4 So they are related. We just wanted to highlight
5 the one event in particular that we're worried
6 about. We should have had a transition of in
7 particular.

8 DR. MEISEL: Perhaps, but some of that is
9 dependent upon a REMS, right? In a vacuum, maybe
10 the answer is no, but with a
11 REMS, maybe the answer is yes.

12 DR. FARCHIONE: Not quite exactly, and
13 that's why we rearranged the questions a little bit
14 because where the REMS comes in, then you're
15 talking about the benefit versus the risk and how
16 you're going to label it in order to allow for safe
17 use and all of all of that stuff.

18 So for this question, it's just, do you
19 think that you know enough about the adverse event
20 in order to be able to answer that later question
21 about benefit risk. And we moved the two
22 discussion items about the dosing and about the

1 REMS ahead of that benefit-risk question, so that
2 you would have all of that discussion before you
3 have to answer that one.

4 DR. NARENDRAN: Thank you for the
5 clarification. So given what we've seen and what
6 we know, we're going to answer this question, and
7 then we'll assist with the REMS.

8 So voting question, Has the applicant
9 adequately characterized the safety profile of
10 brexanolone for the treatment of postpartum
11 depression? Do you believe the loss of
12 consciousness events have been characterized
13 sufficiently to enable safe use of brexanolone? So
14 let's vote.

15 Just press the button on the microphone to
16 correspond to your vote. Twenty seconds to vote.
17 Continue to press it.

18 (Voting.)

19 MS. BHATT: Voting results, yes, 16; no, 2;
20 abstain, zero; no voting, zero.

21 DR. NARENDRAN: So let's start from this
22 side of the table. Dr. Warholak, if you want to

1 tell us your vote and why you voted.

2 DR. WARHOLAK: I voted yes. I feel like
3 although I am concerned about some of the adverse
4 events, I feel like that can be addressed with the
5 REMS. So I feel like they characterized it
6 sufficiently.

7 DR. KULLDORF: Martin Kulldorf, Harvard
8 Medical School. On the first question, I voted
9 yes, and on the second question, I voted yes. For
10 the future, I would ask FDA to not make two
11 questions like that together, but separate them.
12 Thank you.

13 DR. IYENGAR: Satish Iyengar from
14 Pittsburgh. I also thought that the
15 characterization was there. I think there's still
16 a long way to go with details as the discussion
17 indicates.

18 DR. DUNN: Walter Dunn, UCLA. I voted yes.
19 I believe that loss of consciousness is a risk.
20 It's something that we cannot predict. It does not
21 seem to be dose related, and that occurs during the
22 up titration phase, and that's going to inform how

1 the REMS looks like.

2 DR. DUNN: Yes. I voted no, because I
3 understood -- I think I'm actually nevertheless in
4 a agreement with some of the previous people who
5 just spoke. I believe the word "characterized" to
6 me means understood; do we understand why these
7 people lost consciousness and is it predictable. I
8 don't know that we adequately understand the pump
9 malfunctions and how likely that is to happen once
10 it's out in the real world.

11 So in that sense, I don't feel it's been
12 adequately understood. I believe it can be in the
13 future, and even quite possibly -- and I do believe
14 it can be handled through
15 REMS. But nevertheless I don't feel I understand
16 it well enough to say yes.

17 DR. JAIN: Felipe Jain. I felt that the
18 characterization was adequate and that the loss of
19 consciousness events were transient and consistent
20 with the pharmacodynamic profile of the drug.

21 DR. NARENDRAN: Raj Narendran. I voted yes.
22 I feel comfortable with what has been characterized

1 so far. I think the loss of consciousness probably
2 related to any GABAergic drugs that goes into the
3 brain very quickly. The fact that it's IV can
4 probably mitigate it relatively easily by stopping.
5 I feel comfortable with that, and probably more
6 needs to be learned in the postmarketing.

7 DR. FIEDOROWICZ: Jess Fiedorowicz,
8 University of Iowa. I voted no. While I share the
9 concerns about access with the limitations of the
10 REMS program and come from a state with a large
11 rural population where access might be especially
12 limited, I have concerns about safety that cannot
13 be fully answered with the available data.

14 I am less concerned about the risk of abuse
15 given the limited scope, which is essentially a
16 one-time supervised infusion. I am more concerned
17 about the sedation and loss of consciousness. I
18 also appreciate some of the infusion related issues
19 brought up by my peers. I do agree with the rest
20 of the group here in that I think that in a highly
21 supervised setting outlined in a
22 REMS, that could mitigate these safety concerns

1 while waiting for their postmarketing study.

2 MS. WITCZAK: Kim Witczak. I did vote yes,
3 but I did hit no first. I'm kind of in this -- I'm
4 conflicted with this drug. I do think that they
5 did -- I always say this when there's a new novel
6 treatment that's coming on the market, we don't
7 know what we don't know. And that's the thing that
8 I'm nervous about, but for this drug and what I've
9 seen, I think it is. But the same thing just with
10 the antidepressants, we didn't know what we didn't
11 know when we approved it back how many years ago.
12 So that is still a continuation of a fear of mine.

13 DR. NUMANN: Sabrina Numann. I did vote yes
14 for reasons stated. I do feel the sponsor has
15 adequately characterized it. Thank you.

16 DR. BESCO: Kelly Besco, Ohio health. I
17 also voted yes and was comfortable with the
18 provided information. Loss of consciousness is
19 obviously very concerning, which is why I feel it's
20 prudent that we really take time to deliver a
21 thorough multilayered REMS program. While we
22 obviously we want mothers to receive this

1 groundbreaking treatment, we cannot jeopardize the
2 mother's safety for her family.

3 DR. GRIFFIN: Marie Griffin. I voted yes,
4 and I think the sponsor characterized the episodes
5 very well. I don't think we know everything we'd
6 like to know about them, but I think we can find
7 out postmarketing with the correct REMS program.
8 And I feel good that this new entity, people are
9 getting a very limited exposure to it. So that
10 also makes me feel better about safety.

11 DR. MEISEL: Steve Meisel. I'm a reluctant
12 yes because of the way the question is phrased.
13 Maybe we need to go to question phrasing 101 school
14 or something.

15 (Laughter.)

16 DR. MEISEL: Yes, they characterized it, and
17 by characterizing it, we can figure out how to
18 mitigate some of the adverse events. But that's a
19 different question as to ask whether or not this
20 drug, we think is safe. That's a different
21 question altogether.

22 I want to point out the fact that all of the

1 data and all the discussions are based on a 140
2 patients who received this drug. That's nothing.
3 We have 6 people who passed out That's about a 4
4 and a half percent rate of people losing
5 consciousness in 140 patients. Wait until we have
6 1400, 14,000, 140,000 with populations where it's
7 used beyond words intended, in many respects,
8 because you know what happens when drugs get
9 approved. And when we've just got an N that's much
10 larger, there will be more serious adverse events.
11 That happens with every drug, particularly those
12 that have very limited exposure in the
13 premarketing.

14 So when we say has it been adequately
15 characterized, well, no, because in 140 patients,
16 you can't adequately characterize it. You simply
17 can't. Is it enough to get it approved? That
18 maybe a different question. Is it sufficiently
19 concerning that we need to be worrying what
20 happens, what the possible additional adverse
21 events are and how that will frame the REMS?
22 Absolutely.

1 So therefore, based on the question as it
2 was phrased, the answer is yes, but that's a very
3 reluctant yes.

4 DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz.
5 I voted yes. I think it's clear that there are
6 risks that are common and are serious, but I think
7 they represented with transparency. And even when
8 we had the small sample, I think they were
9 characterized enough for us to inform the REMS and
10 the future collection of data that is going to be
11 needed, of course.

12 DR. HABEL: Laurel Habel. I also voted yes
13 for the reasons that have been described by others.
14 Thanks.

15 DR. RUHA: Michelle Ruha. I voted yes. I
16 do think that the safety profile has been well
17 characterized, and I feel comfortable that the loss
18 of consciousness events are consistent with the
19 GABAergic mechanism. Although we still need to
20 carefully monitor, I think they're predictable
21 responses even if we don't know which patients to
22 predict them in.

1 DR. VALBH: Tina Valbh. I voted yes. I am
2 a little conflicted as well, but I do feel that the
3 sponsor did a great job in characterizing the
4 events, and there was good detail around making me
5 comfortable around the safety profile. However,
6 with only 140 patients, I am a little hesitant.
7 And if this product does get approved, and it goes
8 out into the market, and we are exposing more women
9 to this medication, my hope is that the REMS
10 surrounding this product is extremely detailed and
11 tight and that we are really controlling what
12 entities are allowed to infuse and the collection
13 of details around the patient profile.

14 DR. BURGER: Greg Burger, Stormont Vail
15 Health, Topeka, Kansas. I voted yes. I feel like
16 it's well characterized based on its mechanism of
17 action. The sedation is exactly what you'd expect.
18 There are a lot of unknowns. One that Dr. Besco
19 had mentioned earlier in discussions about hazards
20 to healthcare workers that handle this drug because
21 it is similar to some stuff on some other
22 medications that are on the NIOSH right now, and I

1 could see it land on the NIOSH, and then you've got
2 to have full protection of your healthcare workers
3 as well. Those are unknown at this point, but
4 that's where I stand.

5 DR. NARENDRAN: Okay. Just to kind of
6 summarize, most people voted yes. People felt the
7 sponsor had done an adequate characterization,
8 however, several people, including the people who
9 voted no, had concerns that the N is small and loss
10 of consciousness has to be monitored. So given a
11 very strong REMS, people felt that it could be
12 okay.

13 So we'll move on to the next question, which
14 is a discussion question. I guess you're help
15 craft the REMS. Oh, no. We're going to talk about
16 the dosing.

17 I can read it from the thing. We're going
18 to move to question number 4 in your notebook.
19 It's a discussion question. There's evidence that
20 both the 60-microgram per kilogram per hour and in
21 a 90-microgram per kilogram per hour dose after 24
22 hours are effective. Please discuss if it proved

1 which dose should be the recommended dose, start at
2 90 microgram per kilogram per hour with the option
3 to decrease the dose to 60 micrograms per kilogram
4 per hour based on tolerability, or start at 60
5 milligram per kilogram per hour with the option to
6 increase the dose to 90 microgram per kilogram per
7 hour based on response.

8 Does somebody want to go first? Jess
9 Fiedorowicz, Dr. Fiedorowicz?

10 DR. FIEDOROWICZ: Jess Fiedorowicz,
11 University of Iowa. So I think we all are aware
12 that we simply don't have enough information to
13 answer this question. I very much appreciated this
14 slide from the FDA highlighting the pros and cons
15 of these two options. I might add that the 60
16 microgram per kilogram per hour might also be
17 simpler for titration. There's one less step and
18 two less changes, essentially.

19 We don't have enough evidence to confirm any
20 sort of dose-dependent effect, but improvement with
21 the reduction does imply that some, and with many,
22 that's the case. My bias is to start with the 60

1 microgram per kilogram per hour, but this is a very
2 sort of soft [indiscernible], and I don't have a
3 very strong opinion on that.

4 DR. NARENDRAN: Dr. Meisel?

5 DR. MEISEL: Steve Meisel. I agree from the
6 a simplicity point of view, starting at 60 and
7 working up, with the hope that 60 is going to be
8 adequate for most people is for all the obvious
9 reasons, simpler from bag changes and pump changes,
10 and whatever.

11 That said, we only had 140 patients on all
12 three trials put together. We had 38 on the 60;
13 38. That's almost nothing. We have absolutely no
14 idea whether 38 is as good as better or whatever.
15 The N is simply too small.

16 I agree with the sponsor on this. Let's do
17 what they suggested, do the 90 and maybe back off
18 if you have to. But I would suggest that as a
19 follow up, presuming the drug gets approved, that
20 we ask for a more definitive trial of these two
21 dosing regimens to see if there's a real
22 difference.

1 DR. TEMPLE: Can I ask you, does the fact
2 that in the one trial where they compared the 60,
3 that actually looked better, even though we don't
4 believe it really showed that; does that provide
5 more reassurance or not?

6 DR. MEISEL: To me, no, because the N is too
7 small, and the overlap of the confidence limits
8 were almost all the data points, so there was
9 enough overlap of those confidence limits. So that
10 could just be by artifact, by the fact that it's
11 only 38 patients.

12 DR. TEMPLE: The overlap, it wasn't
13 significantly better, that's true, but it certainly
14 doesn't look like it was worse.

15 DR. MEISEL: But N 38.

16 DR. TEMPLE: N 38.

17 DR. HERNANDEZ-DIAZ: Can I follow up?

18 DR. NARENDRAN: Dr. Hernandez-Diaz?

19 DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz.
20 I think the one thing that convinced me about that
21 is the that curves started to separate before they
22 went to the higher dose. So that's why I thought

1 it was random.

2 DR. TEMPLE: No, that's right. That's why
3 the believability of 60 being better is low because
4 of that, because it started before they were
5 comparing them.

6 DR. NARENDRAN: Dr. Michelle Ruha?

7 DR. RUHA: Yes. Initially at the beginning
8 of the day, I was leaning towards the 60, but I
9 actually think the 90 will offer more patients a
10 chance of success since the numbers are so small.
11 And we really haven't seen that 90 as a riskier
12 dose than 60, and we certainly don't want to
13 approve it and then have it look like it's not
14 working maybe because we didn't approve the dose
15 that has been studied more. So I would I would
16 lean toward the 90.

17 DR. TEMPLE: Can I ask one other question of
18 people? You probably noticed from the course of
19 disease over time, that by 24 hours, essentially
20 all the effect is there. It might go up a little
21 bit more, but hardly at all.

22 So if that's true, that's the 60-milligram

1 dose. Does that make any difference? 60 is all
2 they had at 24 hours.

3 DR. RUHA: I would love to see that further
4 explored post-approval for sure, including
5 eliminating the taper.

6 DR. NARENDRAN: Dr. Fiedorowicz?

7 DR. FIEDOROWICZ: That was going to be my
8 comment.

9 DR. NARENDRAN: Dr. Kulldorf?

10 DR. KULLDORF: Thank you. Martin Kulldorf.
11 I think from a statistical perspective, there's
12 absolutely no evidence that 90 is better than 60 or
13 that 60 is better than 90, neither in terms of
14 efficacy or in terms of adverse events. There's in
15 that sense, no statistical reason to choose one or
16 the other. We would do the comparison.

17 When we do look at the 90 versus placebo,
18 there's very strong evidence that it works. If we
19 look at 60 versus placebo, as Steve was saying, the
20 sample size is very small. So that's an argument
21 for doing 90, but there's also clinical judgment
22 and the knowledge about the biology that may

1 influence this decision.

2 DR. NARENDRAN: Thank you. Dr. Dunn?

3 DR. DUNN: Walter Dunn. There are a couple
4 issues in my mind. I agree with applicant that
5 it's definitely easier to detect adverse events and
6 titrate down than it is to look for a response and
7 titrate up. So that's of course favoring the 90.
8 But to Dr. Temple's point that most of the effect
9 is seen at 24 hours and people are still at 60.
10 But the question remains, do you need to be on that
11 dose for much longer to achieve that 30-day
12 durability? So that's maybe more of a question of
13 how long you're on the infusion.

14 But the other point that we're assuming,
15 that I think we should move away from, especially
16 given these novel mechanisms of action, is more is
17 not always better. We talked about it yesterday,
18 and I think the assumption today is there should be
19 some kind of dose response that if we're going to
20 respond to 60, perhaps we should get even more
21 response at 90.

22 You can't make that conclusion here just

1 because it's based on limited numbers. And if
2 anything, I'm actually somewhat swayed by the fact
3 that numerically, if not statistically, the 60 does
4 look a little bit better than 90, and then 2 to 2B.
5 But I think moving away from this underlying
6 assumption that more is always better, I think for
7 these novel mechanisms of action, we can't really
8 extrapolate our experience from previous
9 antidepressants.

10 DR. NARENDRAN: Dr. Jain?

11 DR. JAIN: Felipe Jain. I think that
12 there's good news in this in that either option
13 appears good. In the face of the essentially
14 statistically equivalence of these two regimens
15 within the very small trial that was done, the
16 clinical arguments I think take precedence in that
17 it is certainly easier to detect adverse effects
18 and reduce the dose, and is a compelling argument
19 for me, for the first labeling option. However, I
20 agree with Dr. Meisel that a postmarketing study
21 would be incredibly useful.

22 DR. NARENDRAN: Dr Griffin?

1 DR. MEISEL: Can I just follow up on that
2 very briefly? In addition to a study like that,
3 characterize some other dosing regimens that
4 perhaps with a shorter taper or that sort of thing
5 might also be of some value; to really fine-tune
6 the dosing would be helpful.

7 DR. NARENDRAN: Yes. And even a possible
8 regimen with a longer lead-in period that might
9 allow the person to develop some tolerance to the
10 sedating effects of the medication could
11 potentially improve the safety profile.

12 DR. GRIFFIN: I just want to weigh in and
13 say that I think that the three studies that we
14 looked at, really, we have three studies on the 90
15 dose, and it includes the 90, getting it from 24
16 hours to 48 hours. And we just don't know what
17 that means, and we don't have that level of data
18 for the 70. So I feel more comfortable with the
19 level of evidence we have for 90.

20 DR. NARENDRAN: Ms. Numann?

21 DR. NUMANN: Even in my limited experience
22 as a patient, I really didn't see too much evidence

1 between the two. The only thing that stood out to
2 me was the loss of consciousness percentage was
3 less than the 60. So the recommended 90, I don't
4 see any reason why it wouldn't be recommended,
5 although my only concern is just to make sure that
6 the REMS address the dose limits. Thank you.

7 DR. NARENDRAN: Dr. Temple?

8 DR. TEMPLE: Granted, you don't have enough
9 data to really make a really great decision, but
10 it's not really true that only 38 people got 60.
11 They all got 60, and the effect was pretty much
12 there, at least 95 percent there, at the end of the
13 60-milligram period. So it's not as though you
14 don't know anything about it, and it's not as
15 though when you move to 90, there was a striking
16 difference between the 24-hour value and the
17 lighter value; maybe a little bit more, maybe not.
18 So I think it's sort of close. On the other hand,
19 the 90 didn't seem to do anything dreadful, so
20 maybe there's not too much to worry about.

21 Also, I have to tell you, we all want more
22 data on this stuff, but nobody's going to allow a

1 placebo-controlled trial anymore on these things.

2 So these are all going to noninferiority studies.

3 What? You think they will?

4 DR. UNGER: Questions that have been asked
5 today are comparing 60 to 90, which everyone would
6 have equipoise for we'd go around the room --

7 DR. TEMPLE: I didn't say you don't have
8 equipoise. I'm saying interpreting the study will
9 be very difficult. Look at how small the
10 difference was between treatment and placebo in the
11 last study. So what is your noninferiority margin,
12 and will you know what it is in a new study in
13 different people? And my answer on the noninferior
14 area is that would be very difficult. It's going
15 to be very hard to do that study.

16 DR. UNGER: I'm just saying we don't need a
17 placebo in these studies, and I'm also saying --

18 DR. TEMPLE: That's the problem, Ellis. If
19 there's no placebo, the interpretation of these
20 studies is going to be very difficult.

21 DR. UNGER: Then one question for the group
22 is, if they were to study 60 versus 90 -- you can't

1 prove any difference except to try to do a
2 noninferiority. So if one doesn't beat the other,
3 would you be satisfied in saying, okay then 60 is
4 as good as 90 if they are not statistically
5 distinguishable? Because that could well be --

6 DR. MEISEL: You'd have to power so you
7 could answer the question.

8 DR. UNGER: That's right.

9 DR. MEISEL: You can't just put 2 people in
10 this and 2 people in that, and say --

11 DR. TEMPLE: Okay, good. How big will it
12 have to be if I -- I want to be able to check the
13 difference of half a point, half a HAM-D point.
14 How big is that study going to have to be? 800?
15 900? 1000? 2000?

16 DR. UNGER: It's going to be big.

17 DR. TEMPLE: It's going to be very big. You
18 won't be able to do it.

19 DR. NARENDRAN: But is it that important if
20 the difference isn't that big? I guess that's the
21 question. So maybe the thing is to
22 allow -- approve it as the trials were conducted,

1 reduce the dose, and see what happens. If it
2 becomes a safety concern, maybe that's the real
3 concern.

4 DR. UNGER: The other question I've heard is
5 the length of treatment. So you could do a
6 randomized withdrawal basically after 24 hours, 36
7 hours, whatever series of times, and figure out how
8 long infusion really needs to be. Everybody would
9 start out on the drug, so there would be no ethical
10 question.

11 DR. TEMPLE: And there you might see a
12 difference in recurrence. We already know you're
13 not going to see any difference out to 30 hours or
14 24 hours because you couldn't see one here. But if
15 you stopped it early, what do you think? Stopped
16 after 12 hours, how would that do in comparison?
17 Maybe the difference is big enough there to see it.

18 DR. FARCHIONE: But if you were to give it
19 for a shorter period of time, we don't actually
20 know that you would see the same thing
21 at -- because we haven't looked at that yet. All
22 we've looked at is 60 hours.

1 DR. TEMPLE: Well, no. You'd keep the same
2 60-hour effect point, but you would treat for only
3 24 hours.

4 DR. FARCHIONE: But when you said that we
5 already know that at 30 days you're not going to
6 see anything different, we don't know that if
7 you're talking about shorter fusion.

8 DR. TEMPLE: Exactly right.

9 DR. FARCHIONE: Okay. Just clarifying.

10 DR. NARENDRAN: I think we have one more
11 person who wants to make some comment. Dr. Turner?

12 DR. TURNER: A very interesting discussion,
13 and I was
14 going to say -- there's the old saying, absence of
15 evidence is not evidence of absence. So in order
16 to -- there seems to be an absence of evidence, in
17 my mind, to be able to answer this question, to
18 pick one A or B. I just don't know. I don't know
19 what I would say. I might have to abstain. But
20 perhaps with postmarketing studies, they can be
21 fleshed out or characterized, as I might put it.
22 And any head-to-head study would be truly -- not

1 need to be placebo controlled but, again, the
2 efficacy would not be the only object of interest,
3 but also the safety, which is also we really don't
4 know whether there's a dose response there in that
5 realm as well.

6 DR. NARENDRAN: Just to summarize, it
7 doesn't sound like we have enough data to make that
8 decision, so we'll just allow the FDA to decide
9 what they have to do. But we heard a broad range
10 of opinions that maybe -- but most people did seem
11 like they leaned towards maybe what the sponsor did
12 from 90, lowering it based on the clinical side
13 effects.

14 We'll move to the next question. Question
15 number 4 is another discussion question. Discuss
16 whether the FDA's proposed REMS would ensure safe
17 use of brexanolone. If no, please discuss what
18 additional safeguards would be needed.

19 Who wants to go first. Dr. Besco?

20 DR. BESCO: Sure. Kelly Besco. Honestly,
21 I've been thinking quite a bit about this all day.
22 I'm under the personal belief that until we have a

1 larger number of patients that have received this
2 medication, I would recommend that we restrict it
3 to an inpatient setting.

4 That being said, trying to think
5 logistically how that would work out, at least
6 where I come from or my facilities, these patients
7 would likely be categorized as an outpatient and an
8 inpatient bed. And the concern with that would be
9 is they'd likely be on a med surge unit where a
10 nurse would have 5 to 6 patients in addition to
11 this patient.

12 So some things I thought that could be a
13 part of a robust layered strategy would be to be
14 very restrictive in the REMS about the frequency of
15 needed sedation monitoring. I would also suggest
16 that maybe there'd be some research on an
17 appropriate sedation scale, one that might be in
18 use to monitor sedation for this purpose.

19 One that came to mind that we use for
20 opioids is the Pasero Opioid Induced Sedation
21 scale. Perhaps that could be modified to fit the
22 need for this therapy to almost be a little bit

1 more objective, and when should I consider reaching
2 out to the ordering physician to determine if I
3 need to stop this solution or infusion, or perhaps
4 when I need to go to that next tier, if it's
5 appropriate to go to the next tier.

6 Also, when a lot of these novel therapies
7 come out, the prescribing guidelines great, but we
8 often have to figure so much about the process out
9 ourselves. So wouldn't it be great if there was an
10 order set that was maybe even worked upon by a
11 multidisciplinary team? It could be a subcommittee
12 that FDA would charter, that could work on
13 something that the entire nation could use. That
14 way we don't have all these different orders sets
15 that everyone has to come up and invent on their
16 own.

17 I'm also not entirely still convinced that
18 there's a need for a pulse-ox monitoring based on
19 the data that was shared today, but I don't
20 disagree necessarily with being over-precautious.
21 That being said, if there is a concern by the
22 company and FDA about hypoventilation, I think

1 capnography would provide an earlier detection of
2 that symptom.

3 So those are just some initial thoughts that
4 I've had throughout the day on how we could
5 generate a multilayered, robust REMS program for
6 this drug.

7 DR. NARENDRAN: Dr. Meisel?

8 DR. MEISEL: Steve Meisel. I agree a
9 hundred percent with everything that Kelly has
10 said, and it was very well said. Let me just add a
11 few more points. First of all, I can't emphasize
12 enough this term "certified health setting," we
13 have to let go of that. This is a hospital-based
14 drug, period. I understand the pressure from the
15 from the applicant and from others to have this
16 done in homes, in alternative care settings, and so
17 on. There is no other setting that can have a 24-7
18 nurse at beck and call, who can manage an IV pump
19 at beck and call. That just doesn't exist. It's
20 got to a hospitalized setting. Now, there can be
21 an outpatient unit in a hospital perhaps, but even
22 there the payments on that may or may not be

1 economically worthwhile from an insurance company
2 point of view. It's got to be an institutional
3 setting, the idea of sleep labs or in places like
4 that.

5 Licensed care providers, we can have a
6 licensed audiologist. Does that count? No. It's
7 got to be an RN, somebody who can manage an IV
8 pump, period; somebody who can provide first aid,
9 CPR, whatever, period. So that to me precludes any
10 setting other than a hospital or hospital
11 outpatient department type of setting. And I think
12 we need to be very, very clear about that.

13 I agree that the assessment frequencies,
14 what does that mean? What are we talking about?
15 Q-15 minutes for 60 hours seems a little heavy, but
16 what is it going to look like? To just say that
17 it's going to be specific -- it's going to be
18 frequent doesn't tell us anything; doesn't give us
19 any guidance. We have to have some guidance in
20 there, is it face to face, what kind of vital
21 signs, whatever.

22 I think the applicant has said this and the

1 FDA has said this, but I think any REMS needs to be
2 very clear that the patients may not independently
3 handled their baby while they are receiving this
4 infusion. Should they fall or should they pass out
5 or whatever, the risk of a baby drop or baby
6 smother is high.

7 The other part of this that I think is very
8 important is that any patient who is on this drug
9 should be considered a high fall risk, and with all
10 of the precautions that any hospital has for
11 patients who are at a high fall risk. I don't
12 think we have to specify what those actions are.
13 Those hospitals have them on their own.

14 But again, we have a serious signal events
15 here. 6 out of 140 people lost consciousness. To
16 me, that's a strong signal that also in my mind
17 deserves a black box warning. People need to be
18 hyper-aware that this is serious. People can fall.
19 Nobody got hurt or injured or died as a result of
20 this in this small sample, but multiply this to
21 1400, 14,000, 140,000, there will be people that
22 fall and hit their heads, and suffer an

1 intracranial bleed and die. There will be people
2 who drop their babies, and the baby will die.
3 That's a guarantee. I'm not trying to be
4 hyperbolic, but that will happen unless we take
5 very careful falls precautions with these folks.

6 I think it was mentioned earlier, this is a
7 breakthrough drug, the likes of which we haven't
8 seen for a very important condition. But if we
9 don't do this right, we're going to end up with
10 some adverse events that perhaps even offset that.
11 But we can do that with a strong REMS.

12 So everything that Kelly said is right, but
13 I black box warning, falls precautions, specify a
14 hospital or hospital outpatient department setting,
15 RN as a healthcare provider, and, and specify the
16 assessments or the frequencies of the assessments,
17 and quality of the assessments.

18 DR. FARCHIONE: Can I ask you a follow up,
19 just going back to your idea that if you need an
20 RN, that you couldn't possibly get this anywhere
21 other than an inpatient setting. So that may be
22 the model of medicine now, but let's think

1 hypothetically here. If this drug were to be
2 approved and we were to outline everything that is
3 needed in order to use it safely, and say a sleep
4 center, as the example that you gave, decides,
5 well, let's hire an RN who's willing to work
6 overnight and be the person to monitor this
7 infusion, would you be opposed to that?

8 I understand your concern based on the
9 current medical model and the way that treatment
10 centers are set up now, but that doesn't mean that
11 that won't change.

12 DR. MEISEL: First of all, I can't fathom a
13 business model where a sleep center is going to
14 hire a nurse to monitor one patient for 24/7.
15 Financially that doesn't fly. Sleep centers are
16 often standalone. So should the patient need a doc
17 or whatever, where is that person going to come
18 from? A rapid response team call or something,
19 where is the assistance going to come from in those
20 standalone sorts of places? That doesn't exist in
21 those environments.

22 Maybe after we've got 14,000 patients,

1 140,000 patients, and can characterize this much
2 better, maybe we can loosen that up. But I
3 wouldn't start that way. I would start with a
4 setting where we know we can provide safe care.

5 DR. NARENDRAN: Dr. Besco?

6 DR. BESCO If I could just add to that.
7 Kelly Besco. I would emphatically agree with that.
8 We've heard today that is ground-breaking therapy.
9 We only need to have one adverse outcome that hits
10 the news media that says we killed -- a mother
11 adversely had an event, and there was a fatal
12 outcome. It will ruin this therapy and the
13 benefits that we've all heard today.

14 So I would caution to be overcautious. We
15 don't know what we don't know until we see this
16 medication used more broadly in a larger number of
17 patients.

18 DR. NARENDRAN: Dr. Fiedorowicz?

19 DR. FIEDOROWICZ: Jess Fiedorowicz,
20 University of Iowa. In spite of the fact that I
21 voted no to question 2 about safety, I have to
22 respectfully disagree with Drs. Besco and Meisel on

1 the need to restrict inpatient settings. There is
2 an assumption here that an inpatient setting
3 eliminates all of this risk that I'm not sure is
4 founded.

5 As I stated earlier, I'm comfortable with
6 the FDA approved REMS for administration medically
7 supervised settings as was done in the pivotal
8 trials. I do agree with Dr. Meisel that they need
9 to carefully define what this is in the REMS and
10 will defer that to the FDA. But I believe our
11 prior discussions already urged the agency to do
12 so. I also agree with the recommendation by
13 Dr. Meisel for a black box warning.

14 DR. NARENDRAN: I do kind of want to follow
15 up those comments myself. I do kind of second
16 Dr. Fiedorowicz's comments. I feel like the new
17 model, other people talked about a mother/baby,
18 which is not really an inpatient psychiatric unit,
19 but it's just sort of like a crisis -- it's sort of
20 a residential level program.

21 So if they can fit all these guidelines,
22 like they can do the frequency monitoring, they

1 have someone to watch you every 20 minutes or 30
2 minutes, whatever you guys decide, do the sedation
3 scales and stop the infusion, I think it should
4 allow to do that because you can't
5 restrict -- these units -- I work in one, so
6 obviously it's clear for me to say that. I work in
7 a crisis residential program, which is unattached
8 to a hospital, but the hospital delivers stuff from
9 us, UPMC, we're a big organization.

10 So they can deliver the medication to us.
11 We can have a nurse there. We can pull in a couple
12 of people. We can even have our own postpartum
13 units with the baby, and someone can watch the
14 baby.

15 I think you should have to allow people to
16 be a little bit more creative if they can satisfy
17 everything that's listed in the REMS as opposed to
18 just saying this should be done in inpatient units.
19 Where is it going to happen? Just in OBs? They
20 don't want to admit people for just a few days to
21 give an infusion or pediatric units. So I think
22 it's important to keep that in mind. Layout what

1 you think needs to happen as opposed to specifying
2 the setting where it should happen.

3 I'll turn it to Dr. Dunn.

4 DR. DUNN: Walter Dunn, UCLA. So it sounds
5 like we've got discussion looking at three levels
6 of monitoring. You've got the inpatient, you've
7 got these certified health settings, whatever they
8 may be, and going home. So we really only have the
9 data for what was done during the study, and as the
10 FDA stated, that's what we have the data on. We
11 saw these adverse events. They were able to be
12 headed off early before it became potentially
13 life-threatening.

14 So I'm confident that the FDA can work out
15 the details to establish guidelines, as Raj
16 mentioned, essentially to recreate what was done
17 for this study.

18 I certainly agree and cannot argue that an
19 inpatient setting is probably the safest level we
20 can have. As Jess mentioned, we can't prevent
21 every single adverse event, and then we have to
22 weigh that against what's the potential for an

1 additional barrier of access?

2 I can certainly imagine not enough hospital
3 beds. We've got a lot of patients who are unable
4 to get their infusions, and it comes out in the
5 news that my wife, my mother, my sister killed
6 herself because she had to wait 2 weeks before she
7 could get a date into the infusion unit or into the
8 inpatient unit. So I think balancing out the cost
9 of the barriers that we potentially put up in the
10 name of safety and find the best balance between
11 those two.

12 DR. NARENDRAN: Agency comments?

13 DR. STONE: Hi. I'm Marc Stone. I'm the
14 deputy director for safety in the Division of
15 Psychiatry. What struck me about these comments
16 about the need for inpatient coverage in a hospital
17 is that there's no mention of skilled nursing
18 facilities. You can see a problem with a sleep
19 center, but skilled nursing facilities have RNs
20 generally available around the clock, and they're
21 used to giving infusions. And I don't see why that
22 hasn't been part of the discussion and

1 consideration.

2 DR. NARENDRAN: Dr. Jain, and then I'll come
3 back to Dr. Besco.

4 DR. JAIN: Felipe Jain. I'd like to echo
5 the comments of my psychiatric colleagues,
6 Drs. Dunn, Fiedorowicz, and Narendran, that
7 postpartum depression is extremely serious,
8 extremely disabling. And if we consider the risk
9 of the loss of consciousness events, let's say
10 5 percent, and the potential benefit in terms of
11 treating a patient -- let's be much more
12 conservative than the data presented here and let's
13 say there's a 40 percent response or remission
14 rate, that is in my view still a risk that as a
15 clinician I would absolutely take it, and I think
16 many of our patients would be comfortable in a
17 supervised setting.

18 Although my heart is with outlining the REMS
19 and even allowing it to be administered and less
20 intensively monitored settings, I think that it is
21 wise to follow the clinical trials data and to
22 limit it to the kinds of settings in which it's

1 demonstrated efficacy and in which was voted by the
2 committee 16 to 2 that it had demonstrated safety.

3 DR. NARENDRAN: Dr. Besco?

4 DR. BESCO: Yes. I just want to say I
5 appreciate the other comments that have been made
6 about if you're able to uphold the level of
7 monitoring and mirror an inpatient facility. My
8 concern just stems from some of the examples that
9 were -- I guess some of the care sites that were
10 utilized and the studies that were shared, urgent
11 care centers, which from my experience are MA
12 driven. I'm not even sure in my state they're
13 allowed to operate in IV pumper or administer IV
14 infusion.

15 So I agree if you're able to uphold the
16 level of care at an alternative care site. I would
17 be completely appropriate with that. It's just that
18 a sleep center or an urgent care that's open 24
19 hours and the majority of time, at least in my
20 state, I'm just not sure that those are a right fit
21 for the level of safety that we want to achieve as
22 a recommendation.

1 DR. NARENDRAN: Dr. Griffin?

2 DR. GRIFFIN: Yes. I just want to urge FDA
3 not to stifle innovation. I think it's really
4 important to set the parameters for monitoring, but
5 the hospital, at least in my experience, is not
6 always the safest place. And I think people will
7 come up with other ideas. But I think we want a
8 high level of safety, but I think who's ever
9 certified to give this will have to make sure that
10 they are finding that setting, and I think people
11 will be innovative about that.

12 DR. NARENDRAN: Dr. Ruha?

13 DR. RUHA Yes, actually that's what I was
14 just going to say is that being inpatient in a
15 hospital does not guarantee anything. So I think
16 as long as the criteria that you want are laid out,
17 like 24 hour monitoring -- I do think a pulse
18 oximetry or capnography sounds important -- and
19 mother -- I would let them hold the baby but maybe
20 they have to be sitting down and observed holding
21 the baby. But I think that any facility that can
22 meet the criteria for monitoring should be

1 appropriate to make access, provide more access to
2 care for the people who need it.

3 DR. JAIN: Just one follow-up comment, if I
4 may? Felipe Jain. In all of the loss of
5 consciousness events, except for the one syncope,
6 patients could tell that they were getting more and
7 more tired and fatigued. So providing some
8 guidance regarding the risks of loss of
9 consciousness in the setting of subjectively
10 experiencing more sedation and administering
11 sedation scale is saying, I think would help and
12 administering a sedation scale, as Dr. Besco was
13 saying, I think would help to appropriately
14 mitigate the risk.

15 DR. NARENDRAN: Dr. Valbh?

16 DR. VALBH: Tina Valbh. I just have a
17 clarifying question for the FDA. Are you also
18 proposing restricted distribution under your REMS?
19 So while you may certify a healthcare setting, does
20 that also mean that the distribution and access to
21 purchase the product will also be restricted?

22 DR. LaCIVITA: Hi. This is Cynthia LaCivita

1 from the Division of Risk Management. If the sites
2 would need to be enrolled in the REMS program, then
3 distribution would only be through those sites.
4 That would technically be a type of restricted
5 distribution.

6 DR. VALBH: My concern comes with -- and
7 maybe this is something also for the sponsor -- is
8 while we can certify a site and say that a site has
9 been certified, if the sponsor allows many
10 different wholesalers to access the product, then
11 the product still leaks out into the channel.

12 DR. LaCIVITA: In most programs in REMS
13 programs -- in REMS programs where we have those
14 types of requirements, the distributors would need
15 to verify that the site is in the REMS program
16 before they're allowed to ship to that site.

17 DR. VALBH: And then my other question was,
18 are you also proposing that the staff, for example,
19 the nurse, that is administering the product is
20 certified and trained specifically around the
21 product, or if you're in a healthcare setting where
22 the setting is certified, then anybody in that

1 setting can come in and administer

2 DR. LaCIVITA: What would be your
3 recommendation?

4 DR. VALBH: That the staff is certified to
5 administer and trained.

6 DR. MATHIS: Mitch Mathis. I think that as
7 far as we got into the details of REMS, where that
8 we wanted to make sure that the facility was
9 certified and able to handle the elements of the
10 REMS, and that one of those elements would be that
11 staff would require certain certification as well.
12 We hadn't thought about the details. We hadn't
13 thought about whether it was RN and above, although
14 that has been mentioned. But we were thinking the
15 right place and the right people, if you will.

16 DR. VALBH: And last comment, just a lot of
17 discussion around a healthcare setting. I do
18 believe that this is a breakthrough product. I do
19 believe that we have to allow access to many women
20 to this product. And if we limit it to inpatient,
21 then we essentially do that. There are a lot of
22 alternative sites, infusion centers, pharmacies

1 that have infusion centers that are well equipped
2 to do this, but the question definitely becomes can
3 they handle overnight for 2 and a half days? And I
4 think that's where the strict REMS really has to
5 come in place.

6 DR. NARENDRAN: Dr. Burger?

7 DR. BURGER: Not in rural Kansas; there's
8 not a lot of infusion centers out in western
9 Kansas. I just recently graduated with an EMT
10 certification here this last spring, and I didn't
11 know how much that would actually be beneficial
12 here, but I know in the state of Kansas I can't
13 touch a pump. It doesn't matter if I know that
14 it's an insulin pump and somebody's getting
15 hypoglycemic from it, I'm not able to touch a pump
16 as an EMT in the state of Kansas.

17 So yes, there has to be some level of
18 certification or whatever that is, And I agree with
19 my colleagues, I think that's an RN. The other
20 concerning things that we haven't talked about yet
21 was the stability and sterility. I think that
22 hearing from some of the data that they presented

1 here this afternoon that the bags don't need to be
2 changed as much if we look at that data a little
3 bit closer. And also this 4-bag thing is total
4 nonsense, and it's going to cause craziness and
5 medder after medder [indiscernible], who will be
6 reporting them to ISNP one after another.

7 So standardized a concentration just like
8 what the American Society of Health System
9 Pharmacists is trying to accomplish with
10 Standardize 4 Safety. If you don't know what that
11 is, go look that up. One bag, one concentration; 2
12 bags if it's 30 hour and make it simple. Make it
13 easy to do the right thing and hard to do the wrong
14 thing is my motto. Thank you.

15 DR. NARENDRAN: Thank you. Ms. Witczak?

16 MS. WITCZAK: Kim Witczak, consumer rep.
17 I'm going to agree with some of the things that
18 were said earlier about the black box warning. But
19 is there a way through the patient registration
20 that it's going to ensure that it is being only
21 used for postpartum depression?

22 Obviously, I like that we have something

1 new. Clearly, it's an issue, but I heard Andrew I
2 think from NAMI, who said the schizophrenic
3 population, we've got MDD, and because this has a
4 lot of the same kind of qualities, could there
5 potentially be -- is this the gateway for other
6 people wanting to get their hands on this? And
7 it'll probably be more investigational, but I would
8 just be really -- that's just something I'm
9 concerned with, the potential off label and how
10 easy would that be to get somebody into something
11 if they had the money, they had the access,
12 et cetera.

13 So I just want to make sure that we've put
14 some of those safeguards in place for potential off
15 label or the gateway to something.

16 DR. NARENDRAN: Dr. Meisel?

17 DR. MEISEL: Steve Meisel. Hearing the
18 discussion, I guess conceptually I agree that if we
19 can find an alternative setting that would meet all
20 of the things we've talked about, okay. But I'm
21 skeptical that we would find an alternative setting
22 that would meet everything we've talked about.

1 Maybe a skilled nursing facility, somebody
2 mentioned that before, perhaps, but I'm very
3 skeptical if those really exist, that have 24/7
4 nurses in places like that.

5 I do want to disagree with the notion that
6 we ensure that every provider, whether it's a
7 physician, or nurse, or pharmacist, whoever,
8 especially trained in this drug. That is a common
9 default to REMS programs, and I think as an
10 administrative, that is highly overrated in terms
11 of efficacy.

12 We have a million things that we're supposed
13 to be educating people about. You give them a
14 flyer. You give them a two-slide online thing that
15 they're supposed to sign off on. Once a year it
16 becomes part of the annual requirement learnings
17 along with 400,000 other things, that people just
18 kind of pass through the slides to sign off on. and
19 it becomes a paper exercise.

20 If you set up your systems right internally
21 in your hospital or wherever, where you've got the
22 monitoring built in and you've got the jerk [ph]

1 information built, and you've got the right
2 concentrations, and you've got your indications and
3 all that sort of stuff built in, then adding those
4 five slides and having people sign off on it, the
5 administrative burden of that just, the difference
6 of that is like this.

7 So I would encourage building in safety
8 systems as opposed to trying to build in education.
9 Not that education is
10 bad, but not to require that as a -- then you've
11 got new nurses that come on. You got to hire them,
12 and this is what you're going to teach them about,
13 and then you've got a hundred other things.

14 Dr. Warholak?

15 DR. WARHOLAK: Terri Warholak, and I also
16 wanted to reiterate that I do think that
17 standardization of the bag concentration would be
18 very good, especially if we could make it so that
19 the bags have to be changed less often. And we're
20 talking now about a lot of directions. And I can
21 agree with Dr. Meisel that a lot of times training
22 is suppose to happen and perhaps doesn't.

1 So one of the things I implore the company
2 to do, and perhaps FDA already does this, and I
3 don't know about it, is working with human factors
4 experts in providing not only the front-facing
5 labels for the bags, as well as directions that can
6 be at a glance understood and followed. I think
7 that would be very beneficial.

8 DR. NARENDRAN: Thank you. The one other
9 thing that we didn't talk much about in the REMS
10 discussion, I thought, was the drug interactions.
11 If you do increase GABA levels, you're probably
12 going to increase the affinity of the other
13 compounds like at benzodiazepine site. So there's
14 probably a higher risk for interactions GABA, this
15 drug, and benzodiazepines to cause more increased
16 adverse events.

17 I don't know if you can somehow look at
18 urine drug screens before they do people on benzos,
19 and you're also concerned about people on opioids.
20 So I think those might be something to include in
21 the REMS to maybe be aware of. Until we understand
22 more about the loss of consciousness, you may want

1 to avoid benzos and opioids. I know it's difficult
2 and probably unreasonable to think we should avoid
3 antidepressants, but those two I think are
4 concerning.

5 Any other comments? Ms. Numann?

6 MS. NUMANN: Yes, thank you. Sabrina
7 Numann. I feel like we've been going through both
8 of these discussion points together. I've had just
9 about every thought that's been expressed here, and
10 I feel like I've changed my mind like four times.
11 As everybody talks, I'm like, "Oh, yeah, yeah,
12 that, too." I don't know if I have a specific
13 recommendation. I kind of feel like everybody has
14 expressed every concern I can think about, and I
15 would leave that to the FDA in their discussion.

16 But with respect to the public
17 comments -- and thank you for your stories
18 today -- I do understand the need for this product,
19 for PPD, but I do feel that the FDA's proposed REMS
20 ensures safe use for this product. So I am
21 recommending, based on what's been discussed today,
22 more strict guidelines for what sounds to be

1 inpatient settings.

2 Some of my concerns as a patient, one of my
3 first thoughts that came to mind was how am I going
4 to pay for that? Is my insurance going to cover
5 it? Will my insurance require me to be inpatient
6 in the hospital? Will they pay for 3 days for me
7 to be there? Are they going to tell me I can only
8 do this at home? How are they going to code this
9 and bill me for it?

10 Those are a lot of questions that came to my
11 mind, even if I was in this state of mind. And as
12 a patient with MDD, I do understand that state of
13 mind, but those questions are of high concern. So
14 those are things to consider as well when making
15 this product available to real-world women out
16 there. Thank you.

17 DR. NARENDRAN: Thank you. Two more
18 comments? Dr. Burger?

19 DR. BURGER: Greg Burger. One thing that we
20 didn't mention, too, is the titration at these
21 weird hours, 4 hours, 24 hours, so I appreciate the
22 comment about human factors engineering and the

1 possibility of having the sponsor company team up
2 with a pump company that does the ambulatory pumps,
3 and have that preprogrammed. I have enough trouble
4 getting my nurses just to decrease the rate of
5 amiodarone from 1 milligram per minute to point
6 0.5 milligrams per minute at 6 hours.

7 It doesn't happen. It goes 12 hours, goes
8 15 hours, and then, oh, we are supposed to decrease
9 it down. And that's in a hospital setting, so
10 imagine doing this at home; are we hitting those
11 targets and getting it titrated at the right times?
12 And again, using human factors engineering, using
13 our technology to preprogram these pumps to be able
14 to help our clinicians who are distracted and in
15 this complex environment is an important
16 consideration. Thank you.

17 DR. NARENDRAN: Last comment, Dr. Valbh?

18 DR. VALBH: Tina Valbh. I just wanted to
19 add a couple of comments about the training and
20 education. I've been involved in implementing and
21 operationalizing a lot of REMS programs for
22 products that have side effects that are probably

1 worse than this. And on a training perspective, I
2 do agree, it is a massive burden in training the
3 entire staff.

4 However, if we're looking at inpatient
5 application of this product, then I agree, then on
6 the training perspective, hospitals are better
7 equipped to put forth programs and protocols where
8 you don't need to potentially certify every staff
9 member that's administering.

10 However, if we are considering other
11 healthcare settings, their protocols, their
12 processes are not the same, and we are relying on
13 their internal processes to say, yes, that staff
14 member was trained or not trained, or that facility
15 was trained. I just think it's too scary to allow
16 this in alternative sites without saying that a
17 certified professional will be administering it.

18 So yes, undue burden for sure, but the
19 alternative is if this goes out and lots of other
20 infusion centers have access, then we've got to
21 make sure that the people administering it
22 understand what they're doing and what they're

1 monitoring for.

2 DR. NARENDRAN: Okay. So it sounds like you
3 guys got a lot of feedback on the REMS. Some of it
4 seemed conflicting, but it sounds like the core
5 issue is to make sure every aspect of it is covered
6 in a safe way; implement some very structured ways
7 of monitoring; frequency; instruments like sedation
8 scales; how to interrupt it; not to hold your baby
9 when the dose is being titrated; have adequate
10 things like CPR, access to emergency medical stuff.

11 There was also a lot about simplifying the
12 protocol in terms of IV bags, pre-program pumps,
13 and making a training, and not only the site but
14 also the personnel, although people felt that could
15 be burdensome. It seems like there has to some
16 structured way to ensure that everybody that's
17 doing this knows what to do and how to administer
18 it.

19 I guess that kind of summarizes that, and
20 we'll move to the next question, which is a voting
21 question.

22 Given the efficacy as presented and when

1 using a certified facility by a qualified staff,
2 and as outlined in the FDA's proposed REMS, do the
3 benefits outweigh the risks brexanolone for the
4 treatment of postpartum depression? Please vote.

5 DR. MEISEL: A clarifying question, for the
6 question of the question?

7 DR. NARENDRAN: Sure.

8 (Laughter.)

9 DR. MEISEL: What is the FDA's proposed REMS
10 that we're talking about? There was a proposal
11 we've had about 150 ideas thrown out here in the
12 last 20 minutes as to how to modify that, so what
13 is the REMS that we are evaluating this against?

14 DR. HART: Hi. This is Leah Hart with the
15 Division of Risk Management. I think that the
16 details we still really need to hammer out, but I
17 think the proposal from our end is to certify
18 healthcare facilities and have a certain list of
19 criteria that those facilities need to attest to or
20 to say that that's what they can do or what they
21 will do, and then that will certify the healthcare
22 facility.

1 The second portion that we think is really
2 important is a patient registry because we do need
3 more information. Given the small number of
4 patients after postmarketing, we can get more
5 information using a patient registry. So our
6 proposed REMS includes certifying healthcare
7 facilities that are capable of doing this
8 monitoring and ensuring that the patient can
9 receive the drug safely, and a patient registry to
10 collect more information on the risk to better
11 characterize that.

12 DR. MATHIS: Leah, certifying the facility,
13 are you certifying the level of training of the
14 provider who can do the infusion, for instance? It
15 has to be someone who's infusion qualified.

16 DR. HART: We can detail or I guess mandate
17 what credentials a healthcare provider must have.
18 So we can certainly say that the healthcare
19 facility must attest that only nurses, RNs, LPNs
20 are going to be able to administer the drug. In
21 terms of how we normally train and educate, if it's
22 in a certified healthcare facility, we usually

1 depend on that certified healthcare facility to
2 provide policies and procedures that will train all
3 staff in the risks. all relevant staff that
4 administer the drug, or dispense the drug. So rely
5 on them for policies and procedures.

6 DR. TEMPLE: But we will presumably be
7 fairly detailed on what training and expectations
8 we have.

9 DR. FARCHIONE: But for the purposes of
10 voting and talking about this particular question,
11 maybe it would be helpful to put FDA, slide 50 back
12 up on the screen, from Leah's presentation. Yes,
13 that one.

14 Those are the broad strokes of the outline,
15 and then like we said, the details, the
16 nitty-gritty bits will need to be worked out from
17 here with all of the feedback that we've gotten
18 from you guys.

19 DR. NARENDRAN: That seems sufficient. I
20 think we can go ahead and vote.

21 (Voting.)

22 MS. BHATT: Voting results, yes, 17; no, 1;

1 abstain, zero; no voting, zero.

2 DR. NARENDRAN: I think we can go around the
3 table, starting with Dr. Burger.

4 DR. BURGER: I voted yes, crossing my
5 fingers and hoping that you say and do what we
6 suggested; otherwise, it's going to be a nightmare.

7 DR. VALBH: I voted yes. I feel that the
8 FDA will do the right thing in putting together the
9 right checkpoints and making sure that this product
10 is safely administered, monitored, and definitely
11 we won't restrict access because of that.

12 DR. RUHA: I also voted yes. This is a
13 really exciting new drug, and as long as it's
14 administered in a safe environment, I think it's
15 going to help a lot of people.

16 DR. HABEL: Laurel Habel. I also voted yes.
17 I think that as long as the FDA incorporates many
18 of the suggestions today regarding patient
19 monitoring, I think it can be administered safely.

20 DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz.
21 I voted yes. I think while there are clear risks,
22 I believe the benefits outweigh the risks,

1 particularly for the most severe patients.
2 And with the REMS in place and the registry to
3 optimize the benefit risk while hopefully
4 maintaining the access, I think that the balance is
5 positive.

6 Another thing that I throw into the balance
7 is that now with the treatment, the screening for
8 postpartum depression will be justified potentially
9 further, increasing the benefit at the public
10 health level.

11 DR. MEISEL: Steve Meisel. I voted yes. I
12 do think this is an important addition to the
13 therapeutic realm here. I think you've heard a lot
14 from all of us, and especially me, in terms of the
15 concerns about risks here. And if you can
16 incorporate those in a way that satisfies those
17 concerns, I'm comfortable.

18 I think we also need to be concerned about
19 some things that maybe are not REMS specific but
20 are important. And we've already heard about the
21 concentration, that that's part of that. I think
22 that's probably behind us.

1 The issue about growth in the medium over
2 time, bacterial growth, I think that needs to be
3 further fleshed out again. That's not REMS, but
4 that's something that needs to be looked at. And
5 then the changing doses, I think it ought to be
6 clear in the labeling that the IV pumps ought to be
7 able to accommodate multiple changes of doses over
8 a course of time. If you try to use pumps that
9 don't those kinds of capabilities, you're setting
10 yourself up for additional work and additional
11 error.

12 DR. GRIFFIN: Marie Griffin. I voted yes.
13 I think PPD is a condition with very high morbidity
14 and mortality, and because of that, I think the
15 breakthrough path was the right way. We'd all like
16 more safety data, but I feel comfortable about
17 getting that post licensure.

18 DR. BESCO: Kelly Besco. I also voted yes,
19 pending that we do have a robust multi-layered risk
20 strategy in place. And I'll just say personally as
21 a mom, it felt really good to be a part of today's
22 meeting.

1 MS. NUMANN: Sabrina Numann, patient
2 representative. I did vote yes for every single
3 reason that was stated here. I thank the sponsor.
4 I'm very excited a new approach is being given, and
5 this kind of opportunity is now available. Thank
6 you.

7 MS. WITCZAK: Kim Witczak. I did vote no,
8 and again this has been probably the most
9 conflicted meetings I've personally have had.
10 First of all, I want to say thanks to all the
11 people out there that told your real stories. And
12 I heard it yesterday, and we've heard it a long
13 time about we need new treatments, antidepressants.
14 The current treatments aren't working. So I want
15 to say thank you for you guys doing and finding new
16 novel.

17 But I struggled because the idea of like
18 crossing my fingers and hoping that it gets done
19 that way, I just have to do that for the potential
20 of what could come down the line. And I know
21 that's not what this is really about; it's for this
22 particular thing. But that is what -- I have to

1 put -- and it's not that I don't trust you guys
2 because I think this has been one of the
3 most -- these last two days. But I can't rely on
4 trust or crossing fingers. Thank you.

5 DR. FIEDOROWICZ: Jess Fiedorowicz,
6 University of Iowa. I voted yes, and it's an
7 enthusiastic yes. I did have the safety concerns I
8 mentioned before, but I feel like this program will
9 address them, and I look forward to future study of
10 this promising job [indiscernible].

11 DR. NARENDRAN: Raj Narendran. I voted yes.
12 I think this is truly a well done study, a very
13 exciting breakthrough, probably since you guys ever
14 approved Prozac. I think this is one of the
15 greatest approvals you've ever seen. And I think
16 this drug can truly change the trajectory of people
17 with postpartum depression.

18 It's not that often you think that
19 psychiatry has a drug. I wish this drug had been
20 around 10 years ago. It could have saved so many
21 lives and made people's lives so much better. I
22 think this is truly one of those medications, so I

1 do commend the sponsor for having done a fantastic
2 job.

3 DR. JAIN: Felipe Jain. I voted yes for
4 reasons previously stated. However, the
5 unfortunate history of dissemination of new drug
6 therapies is that they do not reach underserved
7 communities, in that minorities such as black and
8 Hispanic mothers are undertreated. This is
9 particularly true of technologically demanding and
10 expensive therapies.

11 If the FDA approves this application, as I
12 believe it will, I would charge each of you here
13 from Sage Therapeutics with reversing this trend
14 and honoring the minority participants who gave you
15 their trust, including some of whom by being here
16 and speaking on your behalf today, by intentionally
17 targeting accessibility and affordability for
18 minority communities.

19 Provide financial incentives to open
20 infusion sites and regions that serve minority
21 populations and make the drug affordable for those
22 who are currently least served and have poor

1 insurance for their treatment of postpartum
2 depression.

3 I would also ask that the FDA work with the
4 company to the extent it is able to ensure that
5 postmarketing efforts and anything within its
6 jurisdiction target and are required to fully
7 socioeconomically and racially and ethnically
8 diverse and representative populations.

9 DR. TURNER: Erick Turner, Oregon Health and
10 Science University, and I also voted yes. In my
11 mind, you have the efficacy -- the evidence in
12 favor outweighs the evidence against, and I'm
13 trusting the FDA to do the right thing and hammer
14 out the details to flush things out. There are
15 some lingering questions that I'm hoping can be
16 answered either through collecting data via REMS
17 program or phase 4.

18 I wasn't planning on this. And I'll pick up
19 on Dr. Jain's point and introduce a phrase of
20 financial toxicity. I know it's outside the
21 purview of the FDA to get into these things, and
22 they say, "Well, sorry, we don't regulate pricing,"

1 but perhaps it's something for the sponsor to think
2 about. We talk a lot about side effects, but we're
3 also reading more and more about the devastating
4 effect of new medications on people and families
5 finances. So it's just something to consider.
6 Thank you.

7 DR. DUNN: Walter Dunn, UCLA. I voted yes.
8 I think even though the details of the REMS have to
9 be worked out, I trust the FDA will err on the side
10 of caution. Although the discussion recently has
11 been more on the up titration of medical setting,
12 we should get the infusion.

13 I think we did hear earlier, at least I
14 heard earlier, that the FDA certainly could
15 consider down titrating to talb [ph] infusions if
16 the data shows that this is a perfectly safe -- or
17 not perfectly safe, but reasonably safe, and that
18 there's evidence that the safety profile could be
19 maintained in a less restrictive environment.

20 DR. IYENGAR: Satish Iyengar from
21 Pittsburgh. I also voted yes, I think in large
22 part because of the personal testimonies that I

1 heard. They were really quite moving, and I do
2 have faith that the FDA will implement the REMS
3 appropriately.

4 DR. KULLDORF: Martin Kulldorf, Harvard
5 Medical School. I voted yes. I'm very impressed by
6 the excellent work that both Sage and FDA has done
7 concerning this drug. I think that a very
8 important part of the REMS that wasn't discussed
9 that much is the patient registry. There is so
10 much about this drug that we do not know yet, both
11 on the adverse event side, but also on the efficacy
12 side.

13 I think that during the next few years,
14 you're going to have to make a change from doing
15 the randomized clinical trials to now doing
16 observational studies. But observational studies
17 can provide a lot of very important and reliable
18 information. And as you move to doing more
19 observational studies, I think, you will learn a
20 lot more about this drug during the next few years,
21 and I think you're going to have a few years that
22 are very interesting, both in Sage and FDA as you

1 do so. So thank you and good luck.

2 DR. WARHOLAK: Terri Warholak, and I voted
3 yes. I think that the benefits clearly outweigh
4 the risks. I think that a REMS will be essential,
5 and I feel like administration and only medically
6 supervised setting is essential for now.

7 I feel like hopefully someday with the
8 registry, we'll have enough information where we
9 can predict who's going to have a problem, and then
10 make appropriate precautions for those people. But
11 it would definitely increase access over time to
12 work with human factors, experts, and others to be
13 able to get this into a place where we can
14 administer it. So it's kind of exciting.

15 DR. NARENDRAN: Thank you. We'll move to
16 the last question of the day, which is a discussion
17 question.

18 If approved, what additional data will be
19 needed to support safe use of brexanolone at home
20 and address outstanding issues?

21 DR. FARCHIONE: Sorry to interrupt for a
22 second, because we didn't have our afternoon break

1 today, could we maybe take a --

2 DR. NARENDRAN: Okay. I was trying to get
3 people out of here.

4 DR. FARCHIONE: And I do appreciate that,
5 but you know.

6 (Laughter.)

7 DR. NARENDRAN: We'll take a 10 minute
8 break?

9 (Laughter.)

10 DR. NARENDRAN: We'll meet at 3:54.i

11 (Whereupon, at 3:44 p.m., a recess was
12 taken.)

13 DR. NARENDRAN: I guess we're start. If
14 people want to take their seats. So last question,
15 I'll read the question again, and then we'll try to
16 see if everybody could kind of focus on providing
17 new information that we haven't already talked
18 about.

19 Question number 6, if approved, what
20 additional data will be needed to support the safe
21 use of brexanolone at home and address outstanding
22 issues? Who wants to go first? Dr. Dunn?

1 DR. DUNN: Walter Dunn, UCLA. So we heard a
2 lot of moving testimony from the public today, and
3 it struck me that a lot of these cases that they
4 described potentially would not have qualified for
5 this study. And I know that the FDA label will
6 probably say postpartum depression.

7 Unfortunately, I'm assuming that the cost of
8 this treatment will be prohibitive and that
9 third-party payers potentially may look at what was
10 done during the trials and say, if there's a
11 history of psychosis, if there's a history of a
12 suicide attempt, if you have bipolar disorder,
13 we're not going to pay for this because there's no
14 evidence that this will be effective for you.

15 I can potentially understand the motivations
16 of the sponsor to exclude those three conditions,
17 however, I don't know if there's compelling
18 evidence, based off the mechanism of action, that
19 this may elicit a manic episode, that this could
20 worsen psychosis.

21 So I would urge the sponsor and perhaps FDA
22 to require a postmarketing study that includes

1 patients with psychotic depression, those with a
2 suicide attempt, and also look at patients with
3 bipolar disorder, the first comment.

4 Then the second comment brought up by
5 Dr. Ellis [sic] and Dr. Unger in terms of what type
6 of postmarketing studies we should look at, 30
7 versus 60 as opposed to potentially look at doing a
8 randomized withdrawal to see how long do you
9 actually have to infuse for to get the benefit and
10 maintain.

11 I agree that the potential benefit for 30
12 versus 60 is going to be minimal, probably not
13 feasible given the numbers of people we'll have to
14 enroll, but I think based off the safety data and
15 efficacy data, we're not going to gain that much
16 additional benefit with that study. However, with
17 a study looking at the randomized withdrawal to see
18 if we can get most of these patients better at 24
19 or 36 hours, I think if that came out positive,
20 that would provide a huge benefit to patients
21 because I think the 60 hours, irrespective of the
22 location of infusion, still presents a huge barrier

1 to a lot of patients.

2 So I think looking at where to put our money
3 for postmarketing studies, I think looking at those
4 three indications that I mentioned before, these
5 are our sickest patients, and then we're looking
6 really for a risk benefit. And I think those
7 patients would potentially derive the most benefit.
8 And the second, looking to see if we can shorten
9 the duration of infusion and still maintain that
10 antidepressant effect.

11 DR. NARENDRAN: Thank you. Dr. Kulldorf?

12 DR. KULLDORF: Thank you. Martin Kulldorf.
13 If 1 in 1,000 women on this drug has a serious
14 life-threatening event, that's a problem for home
15 use. If 1 in 2,000 have a life-threatening event
16 that needs immediate medical care by a skilled
17 nurse or a physician, that's a problem for home
18 use.

19 In order to evaluate if that exists or
20 not -- because right now we have no idea. To
21 evaluate that, we would need an observational study
22 with maybe at least 10,000 people from the REMS

1 deceased registry. So that's what I would suggest,
2 10,000 people in the REMS deceased registry and an
3 observational study on that.

4 DR. NARENDRAN: Dr. Meisel?

5 DR. MEISEL: Steve Meisel. I agree with all
6 that, and you took away some of my thunder. I
7 think at point, to have it at home is a non-starter
8 for the reasons that you just described. If only 1
9 in 1,000; that sounds like a low, and it is a low
10 number, but it's a high number if you're the one
11 who falls and hits their head in the bathtub or
12 something.

13 Maybe this is artifact; maybe it's a signal,
14 and my gut tells me it's a signal. I've seen way
15 too many wonder drugs over the years -- I've been
16 doing this a long time -- come and go because the
17 initial data are promising, and then adverse events
18 come up that cause it to be withdrawn from the
19 market.

20 I think we can manage that with, at least
21 based on what we know today, by having this in a
22 carefully controlled environment. But I'm not

1 sure; unless we can get to the 10 to 20,000 people
2 in a study and find that this is not a signal, that
3 it's artifact, that it really can be used safely at
4 home.

5 One other -- and this is really minor, and
6 maybe the applicant already knows the question. I
7 should've asked this earlier, but forgot. Are
8 we're talking about the weight-based dosing of 60,
9 90 mgs per kilogram, is it total body weight? Is
10 it lean body weight? Is it ideal body weight?

11 That sort of thing, I think that's a
12 technical point that needs to be clarified and be
13 helpful, if in the product labeling we can specify
14 what that is and what happens over the course of 2
15 and a half days, and because of fluid shifts or
16 whatever, the patient gains 5 pounds. Do we change
17 the dose based on the weight that the patient
18 started at? That kind of technical detail may
19 sound trivial, but it's important to practical use.

20 DR. NARENDRAN: Dr. Hernandez-Diaz?

21 DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz.
22 I was taking notes of things that I think we would

1 like to know today, and maybe with more data from
2 the registry and the REMS, we can answer. One is I
3 think the malfunction of the pumps I think is of
4 concern because 2 of the 5 severe events were
5 coming from that, so making sure that we have safe
6 pumps will be a key thing.

7 Another question is can we try to reduce the
8 dose to reduce the adverse events, if that happens,
9 without affecting the benefit? Can we reduce the
10 number of hours needed of infusion to potentially
11 reduce the risk and increase the access and
12 simplify the process without reducing the benefits.

13 Then following up to capture other potential
14 effects, both potentially beneficial effects like
15 child development effects from living with a mother
16 with less severe depression, and that I think from
17 the registry we can collect if we have a control
18 group. And also other effects in terms of negative
19 effects; less common events that we have not seen
20 in this relatively small sample.

21 Then maybe we can also follow up to evaluate
22 what to do with the non-respondents and find the

1 best clinical treatment for them or follow up. The
2 REMS will define the safest way to administer these
3 treatments hopefully in them.

4 Lastly, can we identify patients with the
5 registry, the postmarketing studies, can we
6 identify those groups of patients with the largest
7 benefits so that we can maximize the benefit-risk
8 for them?

9 DR. NARENDRAN: My only comment to add is
10 one of the things that I keep thinking is, is there
11 a way that these moms can come with an interrupted
12 protocol; if they just come for 5 days in a row, get
13 4 or 5 hours worth of infusion, would that be as
14 effective as the 60-hour protocol? Because that
15 could be so much more easier. They can just come
16 on a 5-days outpatient basis, 30 hours, be done. I
17 think it would be so much more practical.

18 So something like that; so not just try to
19 see if we can send this drug into the home and then
20 home nursing and all that stuff, but if there is
21 any other way mechanistically to alter the protocol
22 where it can be administered to make it more

1 accessible, it would be great.

2 I think that's all we have. Just to kind of
3 summarize what I heard was people wanted to look at
4 data in psychosis, bipolar disorder, suicide,
5 postpartum, as well, maybe optimizing the dose to
6 30 micrograms versus 60 microgram versus 90
7 microgram, and any different; shortening the
8 duration; looking at the responders at 24 hours
9 versus 60 hours; some more data on that; an
10 observational study in a very large sample that
11 could be informed more about the safety risks;
12 reduce the hours, maybe reduce the dose, and
13 identify specific groups of patients who could
14 benefit by this.

15 I think that kind of summarizes the
16 discussion for the postmarketing studies.

17 Dr. Unger, do you have any questions?

18 (Dr. Unger gestures no.)

19 DR. NARENDRAN: Before we adjourn, are there
20 any last comments from the FDA? Do you guys have
21 any last comments for the committee?

22 DR. MATHIS: This is Mitch Mathis. I'd just

1 like to thank you for your time, especially over
2 the two days. I know that was a lot to ask. It's
3 been extremely helpful for us, and I think this
4 concludes the meeting. Thank you very much for
5 your service.

6 DR. TEMPLE: I also want to endorse the
7 breadth of the committee's discussion, it was very
8 good, and to commend the people who spoke from the
9 audience, too.

10 DR. MATHIS: Yes, I'd like to third that. I
11 don't know about thanking you for your time; I
12 guess we can. But I'd like to thank you for all
13 your insight. I've got pages and pages of notes,
14 and usually we come away from meetings with less to
15 think about. It's very unusual. I can't even
16 think of another meeting where we're actually going
17 to leave the meeting with more things to think
18 about than when we came in, which is great.

19 I would really like to thank the public
20 speakers. I think some of them came in and told
21 some compelling stories that I think were very
22 difficult to tell in public, and we really

1 appreciate that.

2 **Adjournment**

3 DR. NARENDRAN: Thank you. Panel members,
4 please leave your name badge here on the table so
5 they may be recycled. Please take all personal
6 belongings with you, as the room is cleaned at the
7 end of the day. Meeting materials left on the
8 table will be shredded for you. We'll now adjourn
9 the meeting. Thank you.

10 (Whereupon, at 4:04 p.m., the meeting was
11 adjourned.)

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