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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE PSYCHOPHARMACOLOGIC
ADVISORY COMMITTEE (PDAC) AND THE DRUG SAFETY AND
RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM)

Tuesday, February 12, 2019

8:00 a.m. to 4:07 p.m.

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

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P R O C E E D I N G S

Call to Order

Introduction of Committee

DR. NARENDRAN: Good morning. I think we'll start our meeting now. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Sandy Walsh. If you are here, please stand. She's right there.

My name is Raj Narendran. I'm the chairperson for today's meeting. I will now call the Joint Meeting of the Psychopharmacologic Drug Advisory Committee and the Drug Safety and Risk Management Advisory Committee to order.

We'll start by going around the table and introduce ourselves. We'll start with the FDA to my left and go around the table.

DR. FARCHIONE: Hi. I'm Tiffany Farchione. I'm the acting director of the Division of Psychiatry Products.

DR. POTTER: Andrew Potter,

1 biostatistician, Division of Biometrics I.

2 DR. STAFFA: Good morning. I'm Judy
3 Staffa. I'm the associate director for public
4 health initiatives in the Office of Surveillance
5 and Epidemiology.

6 DR. LaCIVITA: Good morning. I'm Cynthia
7 LaCivita. I'm the director of the Division of Risk
8 Management and the Office of Surveillance and
9 Epidemiology.

10 DR. EVERETT: I'm Anita Everett, director
11 of the Center for Mental Health Services at the
12 U.S. HHS, SAMHSA .

13 DR. RUDORFER: Good morning. I'm Matthew
14 Rudorfer. I'm a psychiatrist and program officer
15 in the Division of Services and Intervention
16 Research at the National Institute of Mental
17 Health.

18 DR. HILLEFORS: Mi Hillefors. I'm program
19 chief for the translational therapeutics program in
20 the Division of Translational Research at the
21 National Institute of Mental Health.

22 DR. PINE: Danny Pine. I'm a psychiatrist

1 at the National Institute of Mental Health
2 Intramural Research program.

3 DR. NARENDRAN: Dr. Fiedorowicz, are you on
4 the phone?

5 DR. FIEDOROWICZ: This is Jess Fiedorowicz.
6 I'm an associate professor of psychiatry,
7 epidemiology, and internal medicine at the
8 University of Iowa, where I direct the Mood
9 Disorders Center.

10 MS. BHATT: Good morning. I'm Kalyani
11 Bhatt. I'm with the Division of Advisory Committee
12 Consultants Management.

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

15 DR. W. DUNN: Good morning. Walter Dunn,
16 assistant professor at the University of California
17 at Los Angeles and the Mood Disorders director at
18 the West Los Angeles VA Medical Center.

19 MS. WITCZAK: Good morning. Kim Witczak,
20 consumer representative on the psychopharm
21 committee.

22 MR. KUNGEL: Terry Kungel. I've been the

1 chairman and CEO of the Maine Coalition to Fight
2 Prostate Cancer for the last 10 years, and I'm a
3 patient representative.

4 DR. BESCO: Good morning, Kelly Besco. I'm
5 the medication safety officer for the Ohio
6 healthcare system in Columbus, Ohio.

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

10 DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz,
11 pharmacoepidemiologist, Harvard Chan School of
12 Public Health.

13 DR. RUHA: Hi. I'm Michelle Ruha. I'm a
14 medical toxicologist at the University of Arizona
15 College of Medicine in Phoenix.

16 DR. BILKER: Warren Bilker, professor of
17 biostatistics at the University of Pennsylvania.

18 DR. COMPTON: Wilson Compton. I'm the
19 deputy director at the National Institute on Drug
20 Abuse.

21 DR. ZITO: Julie Zito, University of
22 Maryland pharmacoepidemiologist, emerita.

1 DR. HOFFER: Lee Hoffer, associate
2 professor of medical anthropology at Case Western
3 Reserve University in Cleveland, Ohio.

4 DR. NARENDRAN: We have Dr. Conley on the
5 phone.

6 DR. CONLEY: Hi. This is Dr. Rob Conley.
7 I'm the chief science officer for neurology
8 development at Lilly, and I'm the pharma
9 representative.

10 DR. TEMPLE: I'm Dr. Robert Temple, deputy
11 center director for clinical science.

12 DR. NARENDRAN: Thank you.

13 For topics such as those being discussed at
14 today's meeting, there are often a variety of
15 opinions, some of which are quite strongly held.
16 Our goal is that today's meeting will be a fair and
17 open forum for discussion of these issues and those
18 individuals can express their views without
19 interruption. Thus, as a gentle reminder,
20 individuals will be allowed to speak into the
21 record only if recognized by the chairperson. We
22 look forward to a productive meeting.

1 In the spirit of the FDA Federal Advisory
2 Committee Act and the Government in the Sunshine
3 Act, we ask that the advisory committee members
4 take care that their conversations about the topic
5 at hand take place in the open forum of the
6 meeting.

7 We are aware that members of the media are
8 anxious to speak with the FDA about these
9 proceedings, however, FDA will refrain from
10 discussing the details of this meeting with the
11 media until its conclusions.

12 Also, the committee is reminded to please
13 refrain from discussing the meeting topic during
14 breaks or lunch. Thank you.

15 Now, I will pass it to Kalyani Bhatt, who
16 will read the Conflict of Interest Statement.

17 **Conflict of Interest Statement**

18 MS. BHATT: Good morning. The Food and
19 Drug Administration is convening today's Joint
20 Meeting of the Psychopharmacologic Drugs Advisory
21 Committee and the Drug Safety and Risk Management
22 Advisory Committee under the authority of the

1 Federal Advisory Committee Act, FACA, of 1972.
2 With the exception of the industry representative,
3 all members and temporary voting members of the
4 committees are special government employees or
5 regular federal employees from other agencies and
6 are subject to federal conflict of interest laws
7 and regulations.

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

14 FDA has determined that members and
15 temporary voting members of the committees are in
16 compliance with federal ethics and conflict of
17 interest laws. Under 18 U.S.C. Section 208,
18 Congress has authorized FDA to grant waivers to
19 special government employees and regular federal
20 employees who have potential financial conflicts
21 when it is determined that the agency's need for a
22 special government employee's services outweighs

1 his or her potential financial conflict of
2 interest, or when the interest of a regular federal
3 employee is not so substantial as to be deemed
4 likely to affect the integrity of the services
5 which the government may expect from the employee.

6 Related to the discussions of today's
7 meeting, members and temporary voting members of
8 the committees have been screened for potential
9 financial conflicts of interest of their own as
10 well as those imputed to them, including those of
11 their spouses or minor children and, for purposes
12 of 18 U.S.C. Section 208, their employers. These
13 interests may include investments; consulting;
14 expert witness testimony; contracts, grants,
15 CRADAs; teaching, speaking, writing; patents and
16 royalties; and primary employment.

17 Today's agenda involves discussion of the
18 efficacy, safety, and risk-benefit profile of new
19 drug application, NDA 211243, esketamine
20 28 milligrams single-use nasal spray device,
21 submitted by Janssen Pharmaceuticals for the
22 treatment of [sic -- treatment-] resistant

1 depression.

2 This is a particular matters meeting during
3 which specific matters related to Janssen
4 Pharmaceuticals's NDA will be discussed. Based on
5 the agenda for today's meeting and all financial
6 interests reported by the committee and temporary
7 voting members, no conflict of interest waivers
8 have been issued in connection with this meeting.

9 To ensure transparency, we encourage all
10 standing committee members and temporary voting
11 members to disclose any public statements that they
12 have made concerning the product at issue.

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

21 We would like to remind members and
22 temporary voting members that if the discussions

1 involve any other products or firms not already on
2 the agenda for which an FDA participant has a
3 personal or imputed financial interest, the
4 participants need to exclude themselves from such
5 involvement, and their exclusion will be noted for
6 the record. FDA encourages all participants to
7 advise the committee of any financial relationships
8 that they may have with the firm at issue. Thank
9 you.

10 DR. NARENDRAN: There's one more
11 introduction.

12 DR. KIM: I'm Jean Kim. I'm a medical
13 officer at FDA in the Division of Psychiatry
14 Products.

15 DR. NARENDRAN: Thank you.

16 We will now proceed with the FDA's
17 introductory remarks, presented by Dr. Tiffany
18 Farchione, division director.

19 **FDA Opening Remarks - Tiffany Farchione**

20 DR. FARCHIONE: Good morning, everyone. I
21 just want to start off by saying thank you to
22 everyone who is actually here today. In

1 particular, I'm glad to see that we have such a
2 full audience despite the somewhat later-than-usual
3 notification in the Federal Register.

4 As some of you may remember, we recently
5 had a government shutdown, and although we were
6 diligently preparing for this meeting prior to the
7 shutdown, unfortunately, the Federal Register was
8 shut down during that period, and we couldn't make
9 the announcement early.

10 So this meeting almost didn't happen, so I
11 am particularly glad to be here today. Also, I'd
12 like to specifically thank the folks who stepped in
13 to be part of the PDAC at the last minute to
14 replace some people who changed their plans when we
15 initially cancelled the meeting. So thank you to
16 everyone for being here and for participating in
17 this event.

18 Today we're going to be talking about
19 esketamine, which has been granted breakthrough
20 therapy designation by the agency for its potential
21 to be a rapid-acting anti-depressant treatment for
22 a severe condition, treatment-resistant depression.

1 These are folks who have failed a couple
2 antidepressant trials already, and if the drug
3 works the way that it is intended to, then people
4 would start to improve rapidly, hence the name.
5 This is a new molecular -- well, it's not exactly a
6 new molecular entity. It is an enantiomer of
7 ketamine. It is the first in class for this
8 indication.

9 There was no way we were going to do this
10 without having an advisory committee. So despite
11 the shutdown, despite all the snafus, despite the
12 weather, everything else that seemed to come down
13 the pike that was thrown in the way of this
14 meeting, we're here and we're having it today.

15 In terms of some housekeeping issues that
16 we need to take care of prior to the start of the
17 meeting, there were a few things that the company
18 had asked for in terms of errata to our briefing
19 document.

20 Normally, when there aren't 6,000 snafus
21 leading up to a meeting, we would have a
22 conversation with the company. We would go back

1 and forth a little bit. We would publish those
2 errata in an addendum to the briefing document, but
3 today, I'm going to just go ahead and talk about
4 those here so that they are on the record.

5 A lot of the things that the company had
6 asked for are either things that are still under
7 review and trying to decide if we agree with them
8 or not, and other things are kind of nuanced
9 text-edit type things, but a couple that are really
10 important to point out.

11 On page 14 of the briefing document, where
12 we describe how the applicant proposes to
13 administer intranasal esketamine, we basically put
14 in our document a description of the way that the
15 drug was administered during the studies, which was
16 in combination with a newly initiated
17 antidepressant. But they are proposing, just
18 generally, that it should be administered in
19 conjunction with an oral antidepressant. That is
20 one clarification.

21 On page 21, they were asking us to note
22 that the comparator group was an active comparator,

1 but we're actually not using that terminology
2 because the direct comparison is between the
3 intranasal esketamine and the placebo. Everybody
4 had an oral antidepressant on board, so we haven't
5 been using that terminology in our presentations.
6 So that will just be something to pay attention to
7 in terms of the differences between the company's
8 presentation and ours.

9 In terms of the list of serious adverse
10 events that were observed in the trial, the company
11 actually lists additional serious adverse events
12 such as vertigo, dizziness, anxiety, insomnia,
13 feelings of despair, each of which occurred in one
14 patient and those aren't on our table.

15 There's a case of multiple injuries.
16 That's actually the same patient as the road
17 traffic accident, so we didn't include both numbers
18 because it was the same person. But the important
19 distinction is in terms of the difference in number
20 of cases of suicidal ideation in study 3001, which
21 in their documents, they note 0 and we had 4.

22 There was actually early on in the review

1 some disagreement in terms of characterization of
2 serious adverse events. So they were in the case
3 narratives. Although the identified serious
4 adverse event was something else, in the case
5 narrative, there was a description of suicidal
6 ideation with a patient.

7 So where we actually landed on that, from
8 our perspective, was that there were 3 cases of
9 suicidal ideation. Our table still is wrong; it
10 has 4 instead of 3, but it should be 3 from our
11 perspective.

12 Then on page 53, where we discuss a patient
13 who experienced severe sedation late in the study,
14 it actually wasn't clear from the narrative that
15 that patient received midazolam, so we thank you
16 for that clarification.

17 That probably does explain why that
18 patient's sedation occurred late, later than the
19 usual course of sedation, but we're still going to
20 have that information in our slides and present
21 that case in terms of an example of how the
22 sedation fluctuates in some of the patients. We

1 still think that it's difficult to predict when it
2 happens. I'm going to try not to give too many
3 spoilers, actually.

4 Those were the main things. There are a
5 couple of other things that are still under review,
6 so I will just leave it at that.

7 Without taking any more of your time, we'll
8 get right into the presentation, starting with the
9 company. Thank you.

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

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

1 outcome of the meeting.

2 Likewise, FDA encourages you, at the
3 beginning of your presentation, to advise the
4 committee if you do not have any such financial
5 relationships. If you choose not to address this
6 issue of financial relationships at the beginning
7 of your presentation, it will not preclude you from
8 speaking.

9 We will now proceed with Janssen
10 Pharmaceuticals's presentation.

11 **Applicant Presentation - David Hough**

12 DR. HOUGH: Good morning. My name is David
13 Hough, and I'm a psychiatrist with addict
14 qualifications in geriatric psychiatry. I have
15 over 10 years of clinical experience, as I served
16 as an Army psychiatrist. I'm the esketamine team
17 leader and have been working in psychiatric
18 medication research for more than 16 years.

19 On behalf of Janssen, I'd like to thank the
20 committee as well as the representatives of the
21 Food and Drug Administration for the opportunity
22 today to present esketamine nasal spray as a new

1 treatment option for patients with treatment-
2 resistant depression.

3 This is the agenda for our presentation
4 this morning. After my introduction, Dr. John Rush
5 will discuss the needs for new therapies for
6 treatment-resistant depression. He will be
7 followed by Jaskaran Singh, who will highlight the
8 program findings, including the rapid onset of
9 effect and sustained efficacy and maintenance.

10 Dr. Vanina Popova will discuss in detail
11 the well-characterized esketamine safety profile.
12 Dr. Andrew Krystal will review the abuse potential
13 of esketamine and the low rates of ketamine abuse.

14 Next, I'll explain our risk mitigation
15 program, which includes a risk evaluation and
16 mitigation strategy or REMS. I'll then summarize
17 the benefit-risk assessment showing that the
18 totality of evidence supports a positive
19 benefit-risk profile for esketamine nasal spray.

20 Finally, Dr. Madhukar Trivedi will provide
21 the clinician's perspective based on his
22 observations as an investigator in the esketamine

1 clinical trial program.

2 Esketamine has a unique mechanism of action
3 and mode of administration. Esketamine works at
4 the NMDA receptor. And NMDA receptor antagonism or
5 blocking facilitates glutamate release. Glutamate
6 acts on AMPA receptors, resulting in activation.
7 AMPA activation increases signaling of neurotrophic
8 factors and synaptic plasticity, supporting both
9 rapid onset and long-term antidepressant effects.

10 Our proposed indication is treatment-
11 resistant depression, or as we refer to it, TRD.
12 TRD may be defined in different ways. However,
13 health authorities have aligned on a single
14 definition. TRD is defined as major depressive
15 disorder in patients who have not responded
16 adequately to at least two different
17 antidepressants of adequate dose and duration to
18 treat the current depressive episode.

19 The proposed dosing and administration is
20 unlike any other antidepressant. The proposed
21 label states, "Esketamine should be given in
22 conjunction with an oral antidepressant." And

1 while the oral antidepressant is given daily,
2 esketamine dosing is intermittent.

3 For the first 4 weeks, treatment is twice
4 weekly. In maintenance, the antidepressant effect
5 can be maintained with less frequent dosing of once
6 a week or once every 2 weeks. Like many
7 antidepressants, esketamine treatment uses flexible
8 dosing, which can be tailored to each individual
9 patient's clinical presentation.

10 The recommended starting dose in adults is
11 56 milligrams, which uses 2 devices and can be
12 increased based on the patient's response as well
13 as their tolerability. Subsequent doses can be 56
14 or 84 milligrams using 3 devices. The recommended
15 starting dose for patients 65 and older is
16 28 milligrams.

17 Esketamine is administered through a nasal
18 spray device. Nasal spray administration provides
19 a rapidly absorbed non-invasive, convenient, and
20 accessible route of delivery compared to
21 IV infusion. The device is single use and
22 dispenses a total of 28 milligrams. It delivers

1 2 sprays, one in each nostril. Esketamine will
2 only be accessed by patients at the site of care
3 under direct observation and medical supervision.

4 The esketamine TRD program was designed in
5 consultation with FDA. This comprehensive program
6 consisted of 19 phase 1 studies, 4 phase 2 studies,
7 7 phase 3 studies, 5 of which are completed.

8 Over 1700 patients have been exposed to
9 esketamine in the phase 2 and 3 TRD program. While
10 IV ketamine studies in major depression have been
11 reported in the literature, what we'll be
12 discussing today is the first rigorous set of
13 double-blind controlled studies of esketamine in
14 depression.

15 Starting at the left in blue and moving to
16 the right, the phase 3 program consisted of three
17 short-term studies, including a dedicated study in
18 patients 65 and older. It also contained a
19 maintenance of effect study, SUSTAIN-1, which is
20 generally not included in initial submissions for
21 new antidepressants.

22 The fifth study is an open-label, long-term

1 safety study with no control arm, where patients
2 were treated for up to 1 year. There are two
3 ongoing studies, TRD3006, which is a short-term
4 study enrolling patients from the U.S. and China.
5 SUSTAIN-3 is an open-label extension study to allow
6 continued esketamine access to patients who
7 participated in our phase 3 program.

8 The critical trial program has two
9 statistically positive pivotal phase 3 studies,
10 TRANSFORM-2 and SUSTAIN-1. On the right-hand side
11 of this graphic, we are displaying the two-sided
12 p-values.

13 There were also three statistically
14 positive phase 2 TRD studies and a positive phase 2
15 study in a related population of patients with
16 major depression. The positive phase 2 studies
17 provide supportive evidence of esketamine's
18 efficacy. There were two phase 3 studies,
19 TRANSFORM-1 and TRANSFORM-3, that did not meet
20 statistical significance.

21 Now, Dr. John Rush will describe the very
22 significant unmet medical need in patients with

1 treatment-resistant depression.

2 Dr. Rush?

3 **Applicant Presentation - John Rush**

4 DR. RUSH: Good morning. I'm John Rush,
5 professor emeritus at the Medical School in
6 Singapore and adjunct professor of psychiatry at
7 Duke in North Carolina. My research has focused on
8 the diagnosis and treatment of depressive and
9 bipolar disorders as communicated in over 800
10 publications.

11 As CEO of Curbstone Consultant, LLC, I
12 provide research, design, and academic career
13 consultation to individuals and organizations. I
14 am a paid consultant, but I have no financial
15 interest in the outcome of this meeting.

16 Major depressive disorder or MDD is a
17 global public health problem. The World Health
18 Organization estimates that 300 million people
19 worldwide are now living with depression, of whom
20 over 17 million are here in the United States. In
21 addition, we estimate that over 2 million U.S.
22 patients are not adequately treated, namely persons

1 with treatment-resistant depression, those for whom
2 at least two different medications have failed to
3 make them well.

4 Depression affects core life functions;
5 eating, sleeping, energy level, self-worth,
6 intellect, problem-solving capacity, and even the
7 desire to live. Depressed patients in fact rate
8 their health state worse than patients with cancer,
9 diabetes, or heart disease. More than half of
10 these patients report impaired work function,
11 social life function, and home responsibility
12 functions, which is why depression is a leading
13 cause of disability worldwide and in the U.S.

14 Furthermore, depression brings on or
15 worsens the outcome of other general medical
16 conditions like heart disease, diabetes, and
17 cancer. In fact, a depressed person's lifespan is
18 shortened by an average of 10 years.

19 The main point I want to make is that our
20 current treatments fail most patients with
21 treatment-resistant depression, as in fail to bring
22 them into remission. Response means a substantial

1 clinical benefit associated with better quality of
2 life and function. Remission, however, is the gold
3 standard because remission means the patient
4 achieves a symptom-free state associated with a
5 much better quality of life and function.

6 The data from the largest multistep
7 depression treatment trial, the STAR*D, or Sequence
8 Treatment Alternatives to Relieve Depression trial,
9 clearly showed that our current monoamine
10 pharmacotherapies, whether used as monotherapy, or
11 in combination, or as augmentation, leave over
12 80 percent of patients with TRD inadequately
13 treated with active ongoing illness.

14 STAR*D in the bar graph showed us that
15 current treatments cannot get patients with TRD
16 well. In addition, the KM curve, giving us
17 follow-up data, show that even when our current
18 treatments do work for the minority of patients
19 with TRD, they fail to keep them well.

20 STAR*D showed us that patients who require
21 more treatment steps are more likely to relapse and
22 to relapse in a shorter period of time; that is,

1 for 15 percent of patients with TRD who do achieve
2 remission acutely with current therapies,
3 60 percent will relapse within the next 6 months.

4 The clinical, personal, and care system
5 consequences of TRD for patients is substantial.
6 These patients have higher rates of many other
7 general medical conditions, hypertension, diabetes,
8 heart failure. They are hospitalized more often.
9 They stay in the hospital longer. And for those
10 who are hospitalized, there's a much higher risk of
11 suicide than for non-TRD.

12 Patients with TRD have told the FDA that
13 they want treatments that bring them into remission
14 quickly and that keep them well over time.
15 Presently, we have only a few treatment options for
16 TRD, noted in the FDA briefing booklet, with
17 substantial limitations to each. First, our
18 current pharmacotherapies largely target a single
19 mechanism of action for TRD, which itself is a
20 clearly heterogeneous syndrome.

21 Secondly, we have only one approved drug
22 for TRD, but with side effects that can affect the

1 patient's health and quality of life acutely; and
2 only 1 approved somatic therapy, transcranial
3 magnetic stimulation or TMS, with limited data
4 showing its long-term effects.

5 Electroconvulsive therapy, or ECT, is also
6 an option for severe cases of depression or TRD,
7 but there is a high stigma, daunting side effects
8 such as memory loss for a subset of patients, and
9 clear evidence that for many patients, beneficial
10 effects don't last over time.

11 So the bottom line; our current approaches
12 for TRD are not what patients want, a treatment
13 that can get them well quickly and that keeps on
14 working over time.

15 In summary, TRD is a chronic, recurrent,
16 and obviously difficult-to-treat condition that
17 limits health, productivity, quality of life, and
18 longevity in over 2 million Americans. Our need
19 for better therapies is clear with more than
20 200,000 hospitalized depressed patients annually.

21 Time is against our patients. We cannot
22 offer them the same slow-acting inadequate drugs

1 with the same mechanism of action and expect a
2 different outcome for patients with TRD. What we
3 need are new proven options with new mechanisms of
4 action that can quickly bring patients with TRD
5 into remission and get them well.

6 Dr. Jan Singh will take you through the
7 clinical data from the esketamine trials in persons
8 with TRD.

9 **Applicant Presentation - Jaskaran Singh**

10 DR. SINGH: Good morning. My name is
11 Jaskaran Singh. I'm the clinical leader for
12 esketamine at Janssen Research and Development. My
13 work in ketamine started in 2004 while I was at the
14 National Institute of Mental Health. We conducted
15 a controlled study in patients with severe
16 treatment-resistant depression who were inpatients
17 at the NIMH for months prior to participating.

18 The improvement we saw in depression within
19 hours after a single dose of intravenous ketamine
20 was astounding. This study was done with
21 intravenous. Janssen provided the opportunity to
22 continue this research. However, we wanted to

1 develop a non-invasive formulation.

2 Esketamine was selected over racemic
3 ketamine for our clinical program because of its
4 higher potency towards the NMDA receptor. This
5 allows for a lower volume of esketamine to be
6 administered intranasally.

7 The primary endpoint in our phase 2 and 3
8 esketamine studies was measured using the
9 Montgomery-Asberg Depression Rating Scale. The
10 Montgomery-Asberg Depression Rating Scale, or the
11 MADRS, is a valid and reliable scale used to
12 measure severity of depression. It includes
13 10 symptoms of depression and the total scores
14 shown on this slide reflect the categorical cutoff
15 thresholds used for severity.

16 We analyzed the MADRS from a number of
17 perspectives, total MADRS score over time, response
18 rate defined as a 50 percent reduction from
19 baseline, and remission rate total MADRS score less
20 than or equal to 12. As a reference, the average
21 group treatment difference between an
22 antidepressant and placebo for most approved

1 antidepressants is approximately 2 points on the
2 MADRS.

3 Our first study was a proof-of-concept
4 study with intravenous esketamine. Intravenous
5 doses of esketamine 0.2 milligram per kilogram and
6 0.4 milligram per kilogram were selected for study
7 2001 based on the ketamine literature. Rapid and
8 robust effects were seen with esketamine. Based on
9 this study, a nasal formulation was developed to
10 match the plasma concentration from the 0.2
11 milligram per kilogram intravenous dose.

12 This is the plasma concentration profile of
13 the 0.2 milligram per kilogram intravenous dose.
14 We chose 3 intranasal doses from phase 1 studies
15 that bracketed this plasma concentration. These
16 doses were 28 milligram, 56 milligram, and 84
17 milligram.

18 Esketamine nasally administered is rapidly
19 absorbed. Peak drug levels are achieved at
20 40 minutes. Esketamine is extensively metabolized
21 and rapidly cleared from systemic circulation.
22 Nineteen phase 1 studies were conducted to fully

1 characterize the pharmacokinetics of intranasal
2 esketamine. Data from these studies suggest that
3 esketamine intranasal can be used without any need
4 for dose adjustment based on body weight, sex,
5 renal impairment, hepatic impairment, or nasal
6 congestion.

7 No clinically relevant pharmacokinetic
8 drug-drug interactions were discovered. This is
9 important because in the TRD population,
10 comorbidities are common and polypharmacy is
11 prevalent.

12 Now, going back to phase 2, in parallel to
13 study 2001, we assess dose frequency. Published
14 data showed that antidepressant effects from a
15 single 0.5 milligram per kilogram dose of ketamine
16 lasts about 5 days. This suggested intermittent
17 dosing was possible. Therefore, in study 2002, we
18 assess efficacy of 2 and 3 times per week. Both
19 schedules had positive and similar results. These
20 findings led us to select a lower frequency.

21 Our next phase 2 study evaluated dose
22 response with intranasal esketamine. This

1 successful dose-response study with intranasal
2 esketamine showed onset of response within hours
3 after the first dose. The 56- and 84-milligram
4 were significant and therefore selected for further
5 evaluation in phase 3.

6 With these doses chosen and the frequency
7 of dosing in hand, we collaborated with the FDA to
8 design the phase 3 program. We begin with the
9 three short-term studies that were designed to
10 assess the acute efficacy of esketamine. The
11 phase 2 studies just discussed were conducted as an
12 add-on adjunctive treatment with comparison to
13 placebo. The design of the phase 3 studies was
14 different. All patients were switched to a new
15 oral antidepressant at the start of the treatment
16 phase.

17 For a TRD indication, the FDA required the
18 comparator to be an antidepressant for two main
19 reasons. First was to maintain consistency with
20 treatment guidelines, which state that you should
21 not continue an ineffective treatment for
22 non-responders. Second was to evaluate maintenance

1 of effect with an oral antidepressant alone.

2 We worked backwards with the end goal in
3 mind so that a new antidepressant was started in
4 the short-term studies. The new antidepressant was
5 administered with a placebo nasal spray, and I'll
6 refer to these two as a new antidepressant control.

7 As established in phase 2, esketamine
8 dosing visits were twice weekly. These visits were
9 highly interactive, involving multiple interactions
10 with the clinicians typically over a few hours.
11 The primary efficacy assessment was not done by the
12 clinician, but by independent blinded remote
13 graders by telephone using a structured interview
14 guide for the MADRS scale. This was done to
15 protect against unblinding. In addition, a
16 bittering agent was added to the placebo nasal
17 spray to mask taste.

18 Our first short-term study, TRANSFORM-1,
19 was in adult TRD patients 18 to 64 years of age.
20 Eligible subjects discontinued their oral
21 antidepressant treatment prior to randomization and
22 were switched to a new oral antidepressant at the

1 start of the induction phase. All patients
2 randomized to esketamine were started on
3 56 milligram. Those in the 84-milligram treatment
4 group started this dose on day 4 and stayed on it.

5 The study was powered to detect a treatment
6 difference of 6.5 on the MADRS. TRANSFORM-2 was a
7 flexible dose study. This study had a design
8 similar to the fixed-dose studies except had 2 arms
9 instead of 3. Patients started on dose of
10 56-milligram and could remain on that dose or
11 increase to 84-milligram based on clinical
12 judgment.

13 TRANSFORM-3 was a dedicated study in
14 patients over 65. Starting dose was 28-milligram
15 and the dose could be increased to 56- or
16 84-milligram based on clinical judgment. The
17 primary objective of the short-term studies was to
18 evaluate the efficacy of esketamine and the
19 antidepressant versus a new antidepressant control
20 as measured by change in the MADRS total score from
21 baseline to day 28. The first key secondary was to
22 show onset by day 2, which is defined as reduction

1 in MADRS by 50 percent by day 2 and sustained in
2 subsequent visits.

3 Change in function and associated
4 disability was assessed using the Sheehan
5 Disability Scale. Change in patient-rated symptoms
6 of depression was assessed using the Patient Health
7 Questionnaire PHQ-9.

8 The demographics for all three studies were
9 consistent with TRD population. Two-thirds of the
10 patients were female consistent with the prevalence
11 of depression. The mean age was in the mid-40s for
12 TRANSFORM-1 and 2 and 70 for TRANSFORM-3.

13 On average, patients had depression for
14 more than a decade, and the average duration of the
15 current episode was greater than 1 year. At
16 baseline, patients had to have non-response to at
17 least 2 antidepressants. Between 30 to 50 percent
18 across studies had non-response to more than 2.

19 Patients in the study had severe
20 depression. The baseline MADRS is consistent with
21 severe depression. Baseline Sheehan Disability
22 Scale is in the severe range of functional

1 disability. The Health Status Index is in the
2 range that is typically seen with moderate
3 Alzheimer's disease.

4 Now, the first fixed-dose study was
5 TRANSFORM-1. The vertical axis shows change in
6 total MADRS score. The 84-milligram arm was tested
7 first in a fixed-sequence hierarchy and was not
8 statistically significantly different from the new
9 antidepressant control. Therefore, the 56-
10 milligram arm could not be formally tested.

11 However, the treatment difference between
12 the esketamine doses and the new antidepressant
13 control was 3 to 4 points on the MADRS scale. This
14 exceeds the 2 points seen from approved
15 antidepressants against placebo. The treatment
16 difference for 56-milligram arm was 4.1 and the
17 nominal two-sided p-value was 0.027.

18 The key contributor to the 84-milligram arm
19 not achieving statistical significance was the
20 discontinuation rate. In the 84-milligram dose
21 arm, the discontinuation rate is substantially
22 higher, 19 compared to 6. However, 11 of the

1 19 patients in the 84-milligram were after the
2 first dose of 56-milligram. These patients never
3 received the 84-milligram even though they're
4 accounted for in the 84-milligram group to which
5 they were assigned.

6 Poorer tolerability to the higher reason
7 was not the reason, as 5 of the 7 who withdrew due
8 to an adverse event had never received the
9 84-milligram dose.

10 The flexible dose study in adults was
11 TRANSFORM-2. The primary endpoint showed
12 clinically meaningful and statistically significant
13 difference from the new antidepressant control with
14 a two-sided p-value of 0.02 at day 28. The onset
15 of effect was generally seen as early as 24 hours
16 after the first dose and the improvement continued
17 over the next 4 weeks, numerically favoring
18 esketamine at all time points.

19 There was a greater improvement observed
20 for esketamine compared with the new antidepressant
21 control; 85 to 90 percent of the patients completed
22 the study. At day 28, based on the mean, patients

1 had decreased from severe depression to mild
2 depression, while the new antidepressant control
3 group patients were still, on average, moderately
4 depressed.

5 If you overlay the graphs from the two
6 studies, the results are nearly superimposable.
7 Notably, two-thirds of the patients in the flexible
8 study, TRANSFORM-2, were on the 84-milligram at
9 endpoint. The between-group difference in mean
10 change from baseline on the MADRS scale was 3 to 4
11 points.

12 Now, in order to understand the clinical
13 relevance of this group difference of 3 to 4 points
14 on the MADRS, we looked at the MADRS from a
15 different perspective of response and remission,
16 which is what clinicians use to guide the course of
17 treatment.

18 Response was defined as 50 percent
19 reduction from baseline in the MADRS total score.
20 Response was achieved by almost 70 percent of
21 esketamine TRANSFORM-2 patients. Remission was
22 defined as MADRS score of less than or equal 12,

1 which indicates resolution of all clinical symptoms
2 and is associated with functional recovery.
3 Remission was achieved in 52 percent of esketamine
4 patients in TRANSFORM-2.

5 Now, moving to the first key secondary
6 endpoint, a more stringent definitional response
7 looked at patients who achieved at least a
8 50 percent improvement by day 2 and maintained
9 through day 28. This could not be formally tested
10 in TRANSFORM-1 due to the statistical hierarchy and
11 was not statistically significant in TRANSFORM-2.
12 But the pattern of response consistently favored
13 esketamine.

14 The other secondary endpoints of Sheehan
15 Disability Scale and the Patient Health
16 Questionnaire 9 could also not be formally tested
17 due to the hierarchy.

18 The third short-term study was TRANSFORM-3.
19 This focused on patients 65 and older. With the
20 aging of a population, we considered it important
21 to assess efficacy and safety in a separate
22 dedicated study. The least score mean difference

1 was 3.6, favoring esketamine, while the two-sided
2 p-value was 0.059.

3 The treatment difference at endpoint was
4 consistent with the results in our other studies.
5 The figure only shows separation during the last
6 week, suggesting a much slower course of
7 improvement. This could be due to starting with
8 28-milligram, which is starting low and going slow
9 for this older population.

10 One of the prespecified subgroups was
11 patients with 65 to 74 and those over 75. The
12 improvement with esketamine was only seen in the 65
13 to 74 years-of-age group where the separation
14 starts at week 1. Notably, the number of patients
15 in the 75 years of age group is small. There's
16 also a larger reduction in the comparator group,
17 and the reason for this is not apparent.

18 The data from all three short-term studies
19 are consistent in terms of the effects seen. In
20 all three short-term studies, there was a
21 consistent and clinically meaningful benefit for
22 esketamine across studies and scales on the MADRS,

1 the Sheehan Disability Scale, and the Patient
2 Health Questionnaire.

3 All of the point estimates are well to the
4 left of the 0 line with similar magnitude of
5 benefit across the studies. Additionally, the
6 difference represents clinically meaningful
7 improvements on each of the scales. The
8 improvement also consistently observed across
9 patient subgroups.

10 This looks at the pooled results of
11 TRANSFORM-1 and 2. In general, the treatment
12 effect within subgroups is consistent with overall
13 effect across the adult short-term studies.

14 Now, let's look at the long-term
15 maintenance study. We looked at whether esketamine
16 dosing could be reduced in frequency to sustain the
17 antidepressant effects or could esketamine be
18 discontinued entirely with the effect maintained on
19 antidepressant alone.

20 The primary objective was to assess with a
21 continuation of esketamine is important to delayed
22 relapse in patients who are in stable remission.

1 The secondary objective was a separate patient
2 population who were stable responders not
3 overlapping with remitters.

4 The primary endpoint was time to relapse in
5 stable remitters. Stable remission was defined as
6 a MADRS total score less than or equal to 12 for at
7 least 3 of the last 4 weeks prior to randomization.
8 Stable response was defined as more than 50 percent
9 reduction in the MADRS total score from baseline in
10 each of the last 2 weeks prior to randomization but
11 does not meet criteria for stable remission.

12 After 4 weeks of induction on esketamine
13 given twice a week, responders received esketamine
14 and the antidepressant for 12 weeks in the
15 optimization phase where the frequency was reduced
16 to weekly or every other week.

17 If a patient was in remission, they went on
18 every-other-week therapy. But if remission could
19 not be sustained, they were boosted by weekly
20 treatments for 4 weeks. Then at the end of the 16
21 weeks of total treatment, patients were randomized
22 to stay on esketamine and the antidepressant or

1 discontinue esketamine and continue on the oral
2 antidepressant alone.

3 The duration of the maintenance phase was
4 variable. One interim analysis was performed after
5 31 relapses to either stop for efficacy or perform
6 a sample size re-estimation. The definition of
7 relapse was MADRS total score greater than 22 for 2
8 consecutive weeks.

9 The occurrence of clinically relevant event
10 could also count as relapse. These included
11 hospitalization for worsening depression or suicide
12 prevention, attempted or completed suicide, or
13 other clinically relevant events suggestive of a
14 relapse that were assessed by an independent
15 blinded adjudication committee.

16 This is the Kaplan-Meier curve for the
17 stable remitters, which shows the number of
18 relapses over time. Each drop represents a
19 relapse. The results show a statistically
20 significant longer time to relapse in patients
21 randomized to continue esketamine compared with
22 those randomized to discontinue esketamine and

1 receive antidepressant alone.

2 This was an event-driven study. The risk
3 of relapse on esketamine was reduced by half with
4 hazard ratio of 0.49. The p-value for the primary
5 endpoint is 0.003. At 6 months, in the maintenance
6 phase, 65 percent of esketamine patients were
7 relapse free compared to 51 percent who had
8 discontinued esketamine.

9 Because of the low rate of relapse on the
10 esketamine arm, the median time to relapse could
11 not be estimated. The median time to relapse for
12 patients who discontinued esketamine was 9 months.

13 A similar pattern was seen in stable
14 responders as well. Stable responders had a
15 statistically significant longer time to relapse.
16 At 6 months in the maintenance phase, 76 percent of
17 the esketamine patients remained relapse free
18 compared to 42 percent who discontinued esketamine.
19 In fact, this result is similar to those who remain
20 relapse free among the stable remitters.

21 The risk of relapse on esketamine was
22 reduced by 70 percent with a hazard ratio of 0.3.

1 The two-sided p-value for this result was less than
2 0.001. The estimated median time to relapse on
3 esketamine was about 21 months compared to about
4 3 months for those who discontinued esketamine.

5 For this more wonderful population of
6 stable responders who had not achieved remission
7 and are at a higher risk of relapse compared to
8 stable remitters, this high percentage of
9 relapse-free patients is notable.

10 Looking across the long-term studies, we
11 see a consistent benefit favoring esketamine across
12 subgroups. Here, the number of patients are
13 smaller, but there's still a clear benefit in terms
14 of relapse across subgroups with most point
15 estimates to the left of 0.

16 There is a consistent demonstration of
17 efficacy across subgroups, studies, and
18 assessments. Nearly half of the patients
19 randomized who discontinued esketamine relapsed in
20 the first 4 weeks, which is faster than that
21 typically seen in studies with major depression.

22 A key question in a randomized withdrawal

1 study is would the absence of a side effect after
2 discontinuing the active drug and switching to
3 placebo lead to functional unblinding and impact
4 the results?

5 During the study conduct, we took great
6 care in maintaining the blind. All MADRS
7 assessments were performed pre-dose by telephone,
8 by remote independent graders who were blinded to
9 patient treatment and safety information. In
10 addition, a bittering agent was added to the
11 placebo nasal spray.

12 One of the side effects associated with
13 esketamine is dissociation, which could potentially
14 lead to functional unblinding. We performed
15 additional analyses to assess the potential impact
16 of dissociation on the treatment effect in
17 SUSTAIN-1.

18 We used the Clinician-Administered
19 Dissociative States Scale to assess the severity of
20 dissociation. The total score range is from 0 to
21 92. A score of 4 or less is considered in the
22 normal range.

1 If patient is experiencing dissociation
2 while on esketamine and then does not experience
3 dissociative symptoms upon discontinuing
4 esketamine, functional blinding may occur. If
5 functional unblinding led to relapse, it would be
6 expected to occur shortly after switching, after
7 discontinuing esketamine.

8 We examined the CADSS plot for 19 patients
9 who relapsed within the first 4 weeks after
10 discontinuing esketamine. The majority of patients
11 did not have dissociative symptoms, i.e., the CADSS
12 score was 0, prior to discontinuing esketamine as
13 dissociative symptoms tend to reduce in severity
14 over time with repeated dosing.

15 There were only 3 patients who had CADSS
16 greater than 0 while on esketamine, which can be
17 seen to the left of the orange dotted line and did
18 not have these symptoms after discontinuing
19 esketamine to the right.

20 A sensitivity analysis censoring the above
21 3 patients was performed. The results show a
22 hazard ratio of 0.5 with a two-sided p-value of

1 0.008, which is consistent with the primary
2 analysis. Furthermore, an effect such as presence
3 or absence of dissociation may be correlated with
4 treatment but does not necessarily cause the
5 treatment effect.

6 A mediation analysis attempts to
7 distinguish between the correlation and causation.
8 The oral treatment effect on an outcome can be
9 decomposed into a direct effect causing the outcome
10 or indirect effect leading to the outcome.

11 An indirect effect, as shown in the orange
12 line, is treatment effect on the outcome that is
13 accounted for by the mediator. A direct effect, as
14 shown on the green line, is treatment effect on
15 outcome that is over and above its effect on the
16 mediator.

17 Here are the results of the mediation
18 analysis from SUSTAIN-1. For the direct effect,
19 the randomization and continuation of esketamine
20 will decrease the number of relapses by 2 persons
21 per day per 1,000 persons. There was essentially
22 no indirect effect for time to relapse. Results

1 indicate that the treatment effect accounted for by
2 dissociation is 0.

3 The early relapses may reflect a
4 heterogeneous treatment-resistant depression
5 population. Dr. Rush had presented early on the
6 faster relapses in TRD patients relative to the
7 depression patients from STAR*D studies.

8 In conclusion, the totality of the evidence
9 supports the efficacy of intranasal esketamine in
10 the treatment of treatment-resistant depression.
11 The rapid reduction of symptoms is evidenced as
12 early as 24 hours after the first dose.

13 The rates of response and remission were
14 high and robust after induction. The benefits were
15 also observed over the long term in the maintenance
16 studies with a reduced, individualized dosing
17 frequency. The results indicate that esketamine is
18 efficacious for the treatment of TRD.

19 Now, Dr. Popova will present the safety
20 data.

21 **Applicant Presentation - Vanina Popova**

22 DR. POPOVA: Good morning. My name is

1 Vanina Popova, and I am study physician for the
2 esketamine program at Janssen Research and
3 Development. I will present the safety data from
4 the esketamine studies starting with the safety
5 exposure.

6 The safety database of the completed
7 phase 2 and 3 TRD studies comprises 1,708 patients
8 with treatment-resistant depression who received at
9 least 1 dose of esketamine. Considering the number
10 of patients exposed to esketamine for 6 and
11 12 months, as well as the number of exposures in
12 patients aged 65 and older, the database provides
13 safety information for a cumulative exposure of 611
14 patient-years of esketamine. In comparison, the
15 cumulative exposure of all antidepressant plus
16 intranasal placebo was 100 patient-years.

17 A comprehensive assessment plan was
18 included in the program to evaluate both short and
19 long-term safety. Even though ketamine has been on
20 the market as an anesthetic for more than 50 years,
21 there is little systematic data regarding the
22 safety of repeated doses over time.

1 Case reports from street users and other
2 studies have highlighted safety concerns from
3 long-term, high-dose use of ketamine. To
4 understand their potential relevance to
5 intermittent use of esketamine, the clinical
6 program comprised a comprehensive safety
7 evaluation, which included multiple components such
8 as adverse events, clinical laboratory, ECG, and
9 further to that, scales assessing safety topics of
10 special interest.

11 The safety database, including this
12 expensive evaluation, provides a well-characterized
13 safety and tolerability profile of esketamine. The
14 timing of most adverse events is predictable. In
15 general, onset of adverse events occurs shortly
16 after dosing and resolution generally occurs by
17 1 and a half hours on the same day of dosing. The
18 safety profile is similar for the proposed doses 56
19 and 84 milligram across subgroups, including age
20 and with long-term exposure.

21 In this presentation, we will cover adverse
22 events data overall. A data-pooling strategy was

1 applied for the short-term studies aged 18 to 64 to
2 provide a better comparison to placebo. This will
3 be followed by a review of topics of special
4 interest, including suicidal ideation and behavior,
5 post-dose effects associated with discharge
6 readiness, in particular blood pressure
7 dissociation, and sedation, and safety parameters
8 related to long-term exposure like cognition,
9 interstitial cystitis, and liver function.

10 The most common adverse event in the
11 esketamine-treated group in the pooled studies in
12 patients aged 18 to 64 was nausea. This is
13 followed in descending order by symptoms of
14 dissociation, dizziness, vertigo, and headache.

15 In patients 65 years of age and older in
16 TRANSFORM-3, the most common adverse events profile
17 was similar, with the most common adverse events of
18 nausea, dissociation, headache, and vertigo
19 reported in lower rates in this population compared
20 to 18 to 64 years.

21 Adverse events reported at higher incidence
22 in esketamine-treated patients 65 years and older

1 were blood pressure increased and fatigue. Both
2 doses, 56 and 84 milligram of esketamine, appeared
3 to be safe and tolerated.

4 The type and rates of adverse events were
5 generally similar between those receiving the
6 56-milligram and 84-milligram dose of esketamine.
7 However, a slightly higher rate of dissociation was
8 reported in the 84-milligram esketamine dosing.

9 In both age groups, the pattern of adverse
10 events remains similar with long-term exposure up
11 to 1 year. In terms of severe events, these were
12 infrequent, reported in higher rates in the
13 esketamine group, and generally occurred during the
14 earlier treatment phases.

15 Across the completed phase 3 studies, the
16 most common severe adverse events in the
17 esketamine-treated group included dissociation
18 followed by vertigo, dizziness, and dysgeusia,
19 bitter metallic taste. The most common adverse
20 events categorized as severe in the controlled
21 group were headache and anxiety.

22 Adverse events associated with esketamine

1 occurred shortly after dosing when patients will be
2 under the supervision of a healthcare professional
3 and typically resolved within 90 minutes of dosing.
4 Over 90 percent of all adverse events in the pooled
5 short-term studies aged 18 to 64 years and over
6 85 percent in the short-term study of those 65
7 years and above occurred and resolved on the day of
8 dosing.

9 Of the adverse events associated with
10 esketamine treatment, the frequent individual
11 events reported as not resolved on the day of
12 dosing were headache, nausea, and anxiety. In
13 these controlled studies, rate of occurrence and
14 same-day resolution of adverse events were higher
15 in the esketamine group compared with controlled
16 group. The same pattern was observed across both
17 long-term studies and for severe adverse events.

18 Overall the discontinuation rates due to
19 esketamine-related adverse events were low.
20 Discontinuations were reported in approximately
21 5 percent to 6 percent of patients in all
22 short-term study age groups. The rates of

1 discontinuation of esketamine treatment due to
2 adverse events were highest shortly after treatment
3 initiation.

4 In SUSTAIN-1, the rate of discontinuations
5 to esketamine-related events was higher in the
6 earlier treatment phase compared to the subsequent
7 phases. The overall discontinuation rate observed
8 with esketamine exposure of up to 1 year was
9 9.5 percent.

10 The most common adverse events leading to
11 esketamine discontinuation presented here were
12 similar across studies and categorically associated
13 with symptoms of major depressive disorder or
14 common esketamine adverse events. There were no
15 new safety events observed, which resulted in
16 discontinuation with long-term exposure.

17 In the completed phase 3 studies, serious
18 adverse events were reported at low rates. The
19 serious adverse events considered related to
20 esketamine by investigators were those associated
21 with underlying depression, esketamine post-dose
22 effects, or associated with other comorbidities

1 common in this patient population.

2 Across the phase 2 and 3 studies in TRD,
3 6 deaths occurred in esketamine-treated patients.
4 None of the events occurred on dosing day. There
5 was 1 death which has occurred in one of the
6 short-term controlled studies. The remaining
7 5 deaths were reported during the treatment phase
8 of completed ongoing open-label studies and
9 follow-up phase. It is important to note that
10 these studies did not include control arm.

11 Three of these 5 cases were completed
12 suicide. Based on the severity of patients
13 underlying illness and the lack of a consistent
14 pattern, these cases were considered unrelated to
15 esketamine treatment.

16 The all-cause mortality rate of
17 0.39 -- that's per 100 patient-years of
18 treatment -- observed in our TRD studies does not
19 appear to be higher than the all-cause mortality
20 rate of 0.79 deaths per 100 patient-years of
21 treatment reported in a registry consisting of over
22 15,000 patients with treatment-resistant

1 depression.

2 To further evaluate the potential effects
3 of esketamine treatment on risk of experiencing
4 treatment-emergent suicide-related events, we
5 thoroughly looked for trends in suicidality
6 assessment throughout the course of the studies.

7 The Columbia-Suicide Severity Rating Scale
8 was conducted at every visit to prospectively
9 assess potential suicidal ideation and behavior.
10 Patients with suicidal ideation were included in
11 the studies. However, patients with a history of
12 suicidal ideation with some intent to act within
13 the prior 6 months or suicidal behavior within the
14 preceding year were excluded.

15 Across all phase 2 and 3 studies, suicidal
16 ideation assessed by C-SSRS showed a decrease from
17 baseline to the endpoint in the esketamine
18 treatment groups. Based on the data, there is no
19 evidence to suggest that esketamine is associated
20 with increased risk of treatment-emergent suicidal
21 ideation and behavior.

22 Based on the C-SSRS evaluation, we saw

1 similar rates of treatment-emergent suicidal
2 ideation in the esketamine and control groups in
3 the short-term studies. No worsening with
4 long-term exposure was observed in SUSTAIN-1 and 2.

5 Among patients treated with esketamine,
6 10 patients, 2 in the studies with the comparator
7 and 8 in the open-label long-term study SUSTAIN-2,
8 reported suicidal behavior post-baseline based on
9 the C-SSRS. All 10 patients had a lifetime history
10 of suicidal ideation or behavior, and 5 of these
11 patients had suicidal ideation at baseline.

12 Esketamine administration is associated
13 with transient blood pressure increases after
14 dosing. The TRD program was designed to allow an
15 extensive assessment of blood pressure effects.
16 All phase 3 trials followed specific pre- and
17 post-dose blood pressure monitoring guidelines.

18 Patients were only to be dosed if systolic
19 blood pressure was equal or below 140 millimeter
20 for 18 to 64, respectively; 150 millimeter for
21 65 years and older; and diastolic blood pressure
22 was equal or below 90 millimeter for both age

1 groups.

2 At any time post-dose, if a patient met
3 study-defined criteria for acute hypertension,
4 dosing was interrupted and treatment resumed only
5 after evaluation by specialists. Patients whose
6 post-dose blood pressure increased to above or
7 equal to 200 systolic or above or equal to 120
8 diastolic for age 18 to 64, and above or equal to
9 190 systolic or above or equal to 110 diastolic for
10 age 65 years and above were discontinued from
11 treatment.

12 Post-dosing blood pressure changes observed
13 in the completed studies are consistent in pattern
14 with the esketamine pharmacokinetic profile. The
15 blood pressure elevations are typically observed
16 within 40 minutes of dosing and subsequently
17 returned to or near to pre-dose values by 1.5 to
18 2 hours post-dose.

19 These elevations did not appear associated
20 with adverse clinical outcomes. The magnitude of
21 blood pressure elevations is in the range of dosing
22 with normal daily activity.

1 The mean maximum elevations in blood
2 pressure compared to pre-dose in the pooled studies
3 were 13 millimeters systolic and 9 millimeters
4 diastolic, respectively. In the fixed dose study
5 TRANSFORM-1, the difference between the 56- and
6 84-milligram doses is not suggestive of a dose
7 response.

8 Blood pressure effects were greater in
9 patients 65 years and older with mean ranges
10 16 systolic and 10 diastolic, respectively. The
11 pattern and magnitude of blood pressure changes
12 remains consistent across visits, and as seen from
13 the long-term data, there appears to be no
14 cumulative effect with long-term exposure.

15 All patients were assessed for clinically
16 relevant treatment-emergent increases in blood
17 pressure. A small number of patients met the
18 criteria for acute hypertension.

19 Treatment-emergent post-dose systolic blood
20 pressure greater than or equal to 180 or diastolic
21 blood pressure greater than or equal to 110 were
22 reported at rates 3 to 7 percent across patients

1 aged 18 to 64. These elevations were reported more
2 frequently in the controlled study in patients
3 65 years and above.

4 Incidence did not increase with long-term
5 treatment up to 1 year. Overall, 68 percent of
6 patients had a single occurrence of acute
7 hypertension. These increases were transient,
8 mostly single occurrences limited to post-dose
9 period, and did not appear to be associated with
10 adverse clinical outcomes such as myocardial
11 infarction or cerebrovascular accidents.

12 Blood pressure increases typically returns
13 to or near to pre-dose values by 1 and a half,
14 2 hours post-dosing. In 9 to 15 percent of visits,
15 in each of the short-term controlled studies, at
16 1 and a half hour post-dose, systolic blood
17 pressure was at or above 10 millimeter compared to
18 pre-dose.

19 In the longer-term studies, a similar
20 pattern of systolic blood pressure normalization
21 was observed. Across all studies at all visits,
22 the return of diastolic blood pressure to or near

1 to pre-dose levels was near 100 percent at 1 and a
2 half-hour post-dose.

3 In summary, provided patients' blood
4 pressure is under control prior to treatment
5 initiation and is assessed prior to each dosing,
6 there appear to be no acute or long-term risk
7 associated with transient post-dose blood pressure
8 changes. The proposed label includes the
9 recommendation that elevated blood pressure should
10 be controlled before initiating esketamine and that
11 blood pressure should be monitored after doing.

12 The most common psychological effects of
13 esketamine are dissociative and perceptual effects.
14 These include transient distortion of time and
15 space, change in the perception of what people
16 feel, see, or hear; for example, sounds appearing
17 louder, colors brighter, or the subjective feeling
18 of being separated from environment or body.

19 The Clinician-Administered Dissociative
20 Symptom Scale, CADSS, is an instrument for
21 measurement of present-state dissociative symptoms.
22 CADSS was administered in the program at every

1 dosing session pre- and post-dose to assess the
2 treatment-emergent dissociative effects.

3 The total score range is from 0 to 92 and a
4 score of equal or less than 4 is considered to be
5 within normal range. Across all phase 2 and 3
6 studies, a similar pattern of change for the CADSS
7 total score was observed.

8 The CADSS score peaked at 40 minutes
9 post-dose with maximum mean values not exceeding 10
10 across the studies and returned to pre-dose values
11 at 90 minutes post-dose. Over time, the mean CADSS
12 score decreases with consecutive doses from 8.4 on
13 day 1 to 3.6 on day 25.

14 Another common effect associated with
15 esketamine administration is sedation. This effect
16 was monitored objectively in the phase 3 program
17 using the Modified Observers' Assessment of
18 Alertness and Sedation Scale, referred to as
19 MOAA/S. The MOAA/S scores ranged from 0, which
20 corresponded to a state of general anesthesia, to
21 5, corresponding to being fully awake.

22 A consistent pattern in the effects of

1 sedation were observed in the completed phase 3
2 studies; 40 to 50 percent of esketamine patients
3 did not experience sedation. Generally, for
4 patients that experienced sedation, onset was
5 around 15 minutes into dosing, peak was at 30 to 45
6 minutes post-dose. Symptoms of sedation
7 spontaneously resolved by 1 to 1 and a half hours
8 post-dose. Sedation was not associated with
9 hypoxemia.

10 In both short-term controlled studies, age
11 18 to 64 years, the incidences of any sedation
12 defined as MOAA/S score of 4 or lower were higher
13 in esketamine-treated patients, 50 to 59 percent,
14 compared to the controlled group, 11 to 13 percent.

15 In TRANSFORM-1, the sedation incidence in
16 esketamine 84-milligram group was 59 percent, which
17 was slightly higher than the 50 percent rate
18 observed in the esketamine 56-milligram group. In
19 patients 65 and older who participated in
20 TRANSFORM-3, the incidence of sedation was observed
21 at a lower rate compared to TRANSFORM-1 and 2.

22 There were no increases in incidence rates

1 during the long-term studies. Across the completed
2 phase 3 studies with over 31,000 dosing days, there
3 were 11 patients who experienced a level of
4 sedation corresponding to MOAA/S score 0 or 1.

5 In all but 2 cases, the onset of severe
6 sedation corresponding to score 0 or 1 was reported
7 within 45 minutes of dosing initiation. One case
8 was identified as a data entry error. The second
9 case, MOAA/S score was 4 at 45 minutes, and by
10 60 minutes, the patient was fully awake at a score
11 5. However, due to an adverse event of acute
12 anxiety, the patient received intravenous
13 midazolam, 5 milligrams, at 60 minutes and
14 subsequently was observed to be severely sedated
15 with MOAA/S score of 1 at 2 hours post-dose.

16 None of the 11 patients had associated
17 respiratory depression at the time of sedation, and
18 in all patients, sedation resolved spontaneously.

19 The next 3 topics to be discussed relate or
20 are associated with long-term exposure. Changes in
21 cognition have been reported in chronic illicit
22 high-dose ketamine users. To evaluate the

1 potential effects of esketamine on cognition, a
2 comprehensive cognitive test battery was conducted
3 in the phase 3 studies. The Cogstate Battery
4 provides an assessment of multiple cognitive
5 domains, including processing speech, visual
6 learning and memory, working memory, and executive
7 function. The Hopkins Verbal Learning Test Revised
8 measures verbal learning and memory.

9 In the short-term phase 3 studies and in
10 the relapse prevention study, SUSTAIN-1, there were
11 no differences in cognitive performance between
12 esketamine groups and placebo groups. In the
13 long-term open-label study SUSTAIN-2, there was
14 some evidence of slowing reaction time in patients
15 65 years of age and above. However, there was a
16 high intraindividual variability making it
17 difficult to distinguish drug effects from other
18 factors.

19 In this group, 65 years and above, more
20 complex aspects of cognition like learning, and
21 memory, and planning, and decision making were not
22 influenced at all by 12 months' treatment.

1 Next topic of interest to be discussed is
2 interstitial cystitis. Severe and permanent
3 ulcerative cystitis is an identified complication
4 of ketamine, particularly among daily recreational
5 users of the drug. Because of this, patients in
6 the clinical program were thoroughly assessed for
7 these events.

8 The Bladder Pain Interstitial Cystitis
9 Symptom Score Scale was used to monitor patients at
10 every visit for lower urinary tract symptoms and
11 cystitis. Patients meeting a prespecified cutoff
12 on the scale were sent for diagnostic work-up. No
13 cases of esketamine-related interstitial cystitis
14 were observed in any of the studies, which involved
15 treatment for up to a year.

16 The last topic of interest relates to liver
17 function. Liver function was monitored in the
18 phase 2 and 3 studies through laboratory
19 assessments and evaluation of adverse events.
20 There is no evidence supporting the potential for
21 esketamine to induce liver toxicity.

22 Esketamine was not found to produce

1 clinically meaningful changes in liver enzymes or
2 bilirubin. No persistent increases in liver
3 enzymes were observed. Across all studies, there
4 were no cases that met criteria for severe
5 drug-induced hepatocellular injury as defined by
6 Hy's law.

7 In patients with elevated baseline liver
8 enzymes, no elevated total serum bilirubin above
9 2 times upper limit of norm and/or equal to or
10 above 2 times baseline values were observed.

11 In summary, the safety profile of
12 esketamine has been well-characterized in the
13 clinical program. The most common adverse events
14 reported were transient and predictable. The
15 long-term studies showed no new safety findings.

16 While the safety profile is well
17 established in the clinical program, more needs to
18 be learned in the real-world setting. To gather
19 more information on extended exposure such as
20 long-term cardiovascular effects, we will implement
21 a comprehensive real-world data and evidence
22 strategy. This will include data from several

1 sources such as long-term clinical studies and
2 electronic health records and claims data.

3 Our goal is to cast a broad net so we are
4 better positioned to address potential safety
5 issues earlier and faster, identify subpopulations
6 who appear to be at risk, and refine existing
7 predictive models to help clinicians optimize
8 patient selection and follow-up.

9 I will invite now Dr. Andrew Krystal to
10 discuss the abuse potential of esketamine.

11 **Applicant Presentation - Andrew Krystal**

12 DR. KRYSTAL: Good morning. I'm Andrew
13 Krystal, professor of psychiatry at the University
14 of California San Francisco and emeritus professor
15 of Duke University. I've received research funding
16 from Janssen, and my brother is an inventor on a
17 patent that's licensed by Janssen. I'm paid to be
18 here today, but have no financial interest in the
19 outcome of these proceedings.

20 I have extensive experience treating
21 patients with major depression and abuse potential,
22 as well as prescribing many treatments, which are

1 controlled substances. Let's begin by reviewing
2 the abuse potential data collected during the
3 esketamine clinical program.

4 Data obtained from studies of esketamine
5 are the most direct indicator of abuse- and
6 misuse-related risks. Results from esketamine
7 trials indicate no drug seeking, no abuse, misuse,
8 overdose, or withdrawal. During the trial, there
9 were no cases of respiratory depression, which is
10 among the most common causes of overdose death.

11 It's helpful to turn to ketamine to further
12 estimate the abuse, misuse-related risks of
13 esketamine. This is because ketamine
14 administration includes administering esketamine.
15 When patients receive ketamine, they receive
16 esketamine.

17 Unlike the most commonly abused
18 prescription treatments, which are given directly
19 to patients, esketamine will only be administered
20 in medical settings by healthcare professionals, as
21 is the case for ketamine.

22 Ketamine is a Schedule III drug. Results

1 of an abuse potential study indicate that
2 esketamine has comparable likeability and suggest
3 that it, too, should be Schedule III. Given these
4 similarities, it is useful to consider available
5 data with ketamine to estimate the abuse- and
6 misuse-related risks of esketamine, but first, a
7 brief introduction to ketamine.

8 Ketamine became available in the 1960s and
9 is critical in first-response settings. Ketamine
10 is listed on the World Health Organization
11 Essential Medicine List. These are medicine
12 considered most safe and effective and needed in
13 any health system worldwide.

14 In addition to its use in hospitals and
15 emergency rooms, ketamine is used off label in a
16 growing number of pain and depression clinics. In
17 all cases, it's administered by healthcare
18 professionals, and administered in this context,
19 the abuse rate of ketamine is far lower than
20 medications with abuse potential that are
21 prescribed directly to patients.

22 SAMHSA is an agency within the U.S.

1 Department of Health. Their annual report tracks
2 misuse of prescription medications, the green bars
3 in the figure, and illicit drug use appearing in
4 gray. The abuse rate of ketamine is so low that
5 its individual rate is not reported. Instead, it
6 appears in the far-right column grouped with
7 5 other drugs.

8 In 2017, the combined abuse rate of these
9 6 drugs was only 0.2 percent. This is lower than
10 the rate of misuse of prescription pain relievers,
11 stimulants, and benzodiazepines. Of note, despite
12 the rapid proliferation of ketamine clinics in the
13 United States, there has been no increase in
14 ketamine abuse.

15 We'll now discuss overdose risks, which is
16 a concern associated with the abuse of some
17 medications. Ketamine is not listed among the top
18 15 drugs involved in overdose deaths as reported by
19 the Centers for Disease Control. Drug overdose
20 deaths are primarily associated with two pathways,
21 respiratory depression, often seen with opioids and
22 sometimes benzodiazepines, and cardiac arrest,

1 which can occur with stimulants such as cocaine and
2 amphetamines.

3 Neither of these are a significant risk
4 with ketamine. This is reflected in the rarity of
5 deaths that occur with this medication. In fact,
6 deaths related specifically to ketamine are
7 exceedingly rare. Across two reports covering
8 different 13-year periods, ketamine was identified
9 in a total of 35 cases. For 28 cases, deaths were
10 not attributed to ketamine.

11 During these periods, there were only
12 3 deaths in the European Union and United States
13 and 4 in the United Kingdom where ketamine was the
14 only substance identified in toxicology. Now,
15 contrast this with a number of overdose deaths
16 reported by the Centers of Disease Control. In
17 2016 alone, there were over a thousand deaths
18 reported for amphetamine, which was ranked 15th in
19 drug overdose frequency.

20 In summary, the esketamine trials indicate
21 no drug seeking, abuse, or misuse, or overdose, or
22 withdrawal of esketamine, and there was no

1 respiratory depression. Real-world use of ketamine
2 provides the best opportunity to assess the abuse-
3 and misuse-related risks of esketamine. The abuse
4 risks are relatively low, and there is minimal risk
5 and overdose.

6 But esketamine will have a significant
7 advantage over ketamine and other available
8 clinical therapies for treatment-resistant
9 depression. Currently, ketamine is administered
10 without benefit of an FDA label or associated
11 education and monitoring programs. Esketamine
12 approval will address these limitations of
13 ketamine's rapidly expanding off-label use for
14 treatment-resistant depression.

15 Finally, these risks will be mitigated by a
16 comprehensive REMS program, which Dr. David Hough
17 will now present.

18 **Applicant Presentation - David Hough**

19 DR. HOUGH: The risks of treatment with
20 esketamine nasal spray are well-characterized and
21 manageable. The risk mitigation strategy that
22 we're proposing includes a constellation of

1 measures to protect patients and public health.

2 We will focus in this presentation on the
3 elements highlighted in blue. The sponsor is in
4 agreement with FDA on the risk evaluation and
5 mitigation strategy or REMS goals. The REMS goals
6 are to mitigate the risks of misuse, abuse, and
7 serious adverse outcomes from dissociation and
8 sedation resulting from esketamine administration.
9 In addition, the sponsor is proposing to add blood
10 pressure changes to these events.

11 These goals will be accomplished by
12 ensuring that esketamine is only dispensed and
13 administered in a medically supervised healthcare
14 setting that can provide patient monitoring,
15 enrollment of patients in a REMS to further
16 characterize the risks and safe use of esketamine.
17 In subsequent slides, I will review how we will
18 implement these goals in more detail.

19 Wholesalers and distributors will only ship
20 esketamine to REMS-certified pharmacies and
21 certified healthcare settings. Therefore, patients
22 will not receive esketamine directly. Patients

1 will self-administer esketamine only under direct
2 supervision and monitoring by a healthcare
3 professional at the site of care.

4 Used devices will be disposed of as medical
5 waste according to local and federal regulations.
6 There are a number of important requirements for
7 healthcare settings. REMS enrollment in
8 certification is required for all healthcare
9 settings through a sponsor-approved process.

10 Esketamine will only be administered at
11 DEA-licensed sites authorized to handle controlled
12 substances. Each site must have the necessary
13 infrastructure to support dosing and monitoring.
14 Each setting must also have an authorized
15 representative who will attest that the site has
16 appropriate processes and procedures in place. For
17 example, the patients are supervised during and
18 post-dosing and that all appropriate personnel are
19 trained.

20 Janssen will audit sites for REMS
21 compliance and perform knowledge and behavior
22 surveys of staff and patients regularly. Post-dose

1 monitoring is an important component of the REMS.

2 To further characterize safe use, all
3 patients will be enrolled in the REMS. Based on
4 data from our phase 3 program, all patients will be
5 monitored for a minimum of 1 and a half hours to
6 capture the onset of interest events. Events of
7 interest include sedation, dissociation, and blood
8 pressure changes, and these will be recorded on the
9 patient monitoring form, including the time of
10 onset and resolution.

11 Patients will be monitored until clinically
12 stable and ready for discharge based on clinical
13 judgment, but no earlier than an hour and a half
14 after dosing, and the time of discharge will be
15 recorded. In the phase 3 program, 90 percent of
16 patients were ready for discharge in 1 and a half
17 hours, and this was based on an objective
18 assessment.

19 Another aspect of our risk mitigation plans
20 includes the RADARS system. This monitors for
21 signals of abuse, misuse, and diversion. The
22 researched abuse-, diversion-, and addiction-

1 related surveillance system, which is also known as
2 RADARS, can prospectively collect data on abuse,
3 misuse, and diversion of prescription medications.
4 RADARS employs a mosaic approach with expert
5 analysis across multiple data sources. These
6 include surveillance systems, surveys, and web
7 monitoring. We will prospectively collect data for
8 both ketamine and esketamine.

9 The design of the device itself further
10 deters abuse. Each single-use disposable nasal
11 spray device delivers 28 milligrams in two sprays.
12 Limited pack sizes are available with 1, 2, or
13 3 devices to deliver 28, 56, or 84 milligrams,
14 respectively. After dosing, there's only a small
15 residual volume left in the device of about
16 30 microliters, which is difficult to extract. The
17 used devices will be difficult to obtain because
18 they are disposed of as medical waste. Any unused
19 devices are returned to the pharmacy or disposed of
20 according to local and institutional SOP.

21 Suspicious order monitoring is a critical
22 element to identify possible inappropriate use of

1 esketamine. Janssen currently has a suspicious
2 order monitoring program for its existing scheduled
3 products. Esketamine will be added to this program
4 which deters unusual orders of quantity, frequency,
5 or patterns suggestive of inappropriate prescribing
6 or diversion. Suspicious activity identified will
7 be reported to DEA and state agencies per local and
8 federal regulations.

9 In summary, this is a comprehensive risk
10 mitigation program. The REMS is an important part
11 of our risk mitigation strategy in addition to a
12 number of other programs which we haven't discussed
13 this morning, including labeling, scheduling, and
14 enhanced pharmacovigilance. Overall, this risk
15 mitigation program is designed to assure the safe
16 use of esketamine in TRD patients.

17 I'll now discuss benefit-risk. To this
18 point, we've described the esketamine clinical
19 program, unmet need, efficacy, safety, abuse
20 potential, and risk mitigation. To summarize,
21 Dr. Rush explained that major depression is a
22 serious and life-threatening condition and that the

1 burden of TRD is substantial.

2 TRD has high rates of hospitalization,
3 suicidal ideation and behavior, and medical
4 complications compared with major depression.
5 Current treatment options are limited and there's
6 an urgent need for rapidly acting, more efficacious
7 alternatives.

8 Esketamine provides significant clinical
9 benefits for patients, including a rapid onset of
10 effect, high rates of response and remission,
11 prolonged duration of benefit, low rates of
12 relapse, and high rates of patient retention and
13 engagement with the treatment.

14 The risks of esketamine use are
15 well characterized and manageable. Transient
16 dissociation, sedation, and blood pressure changes
17 were observed post-dosing in the clinical program.
18 These will be addressed through a proposed REMS and
19 labeling.

20 Administration will only occur under direct
21 observation of a healthcare professional in a
22 certified healthcare setting, and that supervision

1 by the healthcare professional will occur during
2 and post-dosing.

3 Potential long-term consequences of blood
4 pressure changes will be addressed through specific
5 blood pressure criteria for dosing that will be
6 included in the label as well as with a real-world
7 observational study.

8 Abuse potential is a known risk with
9 controlled substances. Ketamine is being used off
10 label for pain and depression, and this use has
11 been increasing in recent years as outlined in the
12 FDA background document. Despite this increased
13 use, as ketamine abuse remains uncommon.

14 This abuse potential risk will be addressed
15 with a REMS in which a controlled medication
16 distribution program and other critical elements
17 will be included such as suspicious order
18 monitoring, RADARS, and enhanced pharmacovigilance.

19 Esketamine has demonstrated benefits and a
20 well-characterized safety profile. This graphic
21 shows the risk differences and 95 percent
22 confidence intervals for key benefits and harms in

1 our adult short-term studies.

2 The efficacy benefits of esketamine are
3 similar across the studies. It shows that for a
4 theoretical 100 TRD patients who are treated with
5 esketamine and an oral antidepressant compared with
6 100 TRD patients treated with oral antidepressant
7 alone, estimates to the left of the Y axis favor
8 esketamine. In this analysis, all remitters were
9 also responders.

10 If we first consider patients who respond
11 to esketamine, it would be 15 to 17 more responders
12 with esketamine treatment compared to oral
13 antidepressant alone. If we consider only
14 remitters, there would be 5 to 21 more remitters
15 with esketamine-treated patients.

16 Considering safety on the bottom half of
17 this slide and moving down, there was a single
18 death in the double-blind short-term studies. More
19 patients would experience serious or severe common
20 adverse drug reactions with esketamine than oral
21 antidepressants.

22 Most of these events, however, resolve on

1 the day of dosing. There are few differences in
2 events that last beyond the day of dosing or occur
3 on a non-dosing day. The occurrence of suicidal
4 ideation numerically favors esketamine, meaning
5 there was less suicidal ideation in the
6 esketamine-treated folks, but the 95 percent
7 confidence interval does cross 0.

8 The risk difference results in maintenance
9 treatment are similar. If we consider again a
10 theoretical 100 TRD patients treated with
11 esketamine and oral antidepressants who achieved
12 stable response or stable remission, there would be
13 19 to 32 fewer relapses due to esketamine treatment
14 compared with treating these same patients with
15 oral antidepressant alone.

16 Considering safety and moving down, there
17 were no deaths in the relapse prevention study.
18 There would be one more discontinuation due to an
19 adverse drug reaction and 5 more serious or severe
20 adverse drug reactions with esketamine.

21 Similar to the short-term studies, most of
22 these events resolve on the day of dosing and few

1 occur on a non-dosing day. The occurrence of
2 suicidal ideation, again, slightly favors
3 esketamine.

4 We conducted a patient preference study to
5 better understand the perspectives of TRD patients
6 who will be taking this treatment. In
7 collaboration with Duke Clinical Research
8 Institute, we asked patients for their opinion
9 about the benefit-risk.

10 We measured preferences in 159
11 esketamine-treated patients and about 300 TRD
12 patients, most of whom had not received esketamine
13 or ketamine. The results showed that TRD patients
14 highly value treatments that provide the level of
15 efficacy, response, and remission observed in the
16 esketamine studies.

17 Transient adverse events, monitoring, and
18 an inability to drive on the day of dosing were
19 considered by patients of low importance when
20 compared with the efficacy benefits. TRD patients
21 were even going to accept more significant
22 potential risks that were seen in ketamine

1 substance abuse patients in the medical literature
2 in exchange for efficacious treatments. The
3 benefit-risk assessment for the patient perspective
4 is favorable.

5 Now, Dr. Madhukar Trivedi will present his
6 clinical perspective as an expert psychiatrist who
7 specializes in mood disorders and was an esketamine
8 investigator.

9 Dr. Trivedi?

10 **Applicant Presentation - Madhukar Trivedi**

11 DR. TRIVEDI: Good morning. I am Madhukar
12 Trivedi. I'm professor of psychiatry at UT
13 Southwestern Medical Center in Dallas and also the
14 chief of the Division of Mood Disorders and the
15 founding director of the Center for Depression,
16 Research, and Clinical Care. I am a paid
17 consultant to Janssen, but I have no financial
18 interest in the outcome of this meeting.

19 I have focused my work on
20 treatment-resistant depression for over 35 years.
21 At my center, which focuses on TRD, the biggest
22 challenge I face is to identify new options for

1 patients who have not benefitted from the current
2 treatments.

3 Most people know me as one of the leaders
4 of the landmark STAR*D study. When we designed and
5 began our work on STAR*D, the thought at the time
6 was to use a rational approach to help our patients
7 to get better. Our hope was that through STAR*D we
8 could identify a valid design treatment sequence
9 that could get everyone, or almost everyone, well.
10 We were ambitious about the overall outcomes we
11 could accomplish.

12 What we found, however, was that after two
13 failed treatments, getting to and staying in
14 remission became unlikely for a majority of
15 patients. STAR*D also told us that, unfortunately,
16 there was little we can do for patients who have
17 had multiple treatment failures.

18 Clinically, the only current option is to
19 try something else. However, the frustrating
20 reality is these options are almost identical in
21 terms of mechanism of action as the treatments they
22 have already tried. With each treatment that does

1 not work, these patients are losing hope that they
2 can ever get better. It weighs on them that they
3 are not contributing to their families and society,
4 and sadly, some end up taking their own lives.

5 When we completed STAR*D, we had therefore
6 concluded that the current drug development at that
7 time had not offered any significant advances to
8 the monoaminergic system and more work was badly
9 needed.

10 As was mentioned, I also served as an
11 investigator in the esketamine clinical trials.
12 During the participation in these TRD studies, I
13 saw some of my most difficult-to-treat patients get
14 better and stay well. For the first time, we now
15 have something that works completely differently
16 and is not a monoaminergic agent. We have an
17 opportunity to unlock hope and transform the future
18 of how these patients are treated and what's
19 possible for this.

20 The trials we've heard about today are a
21 springboard for a new generation of research. The
22 trials on this medication have ignited new

1 possibilities. We are witnessing the research
2 community come together to realize the
3 opportunities these and other trials with novel
4 mechanisms have unlocked.

5 In summary, I'd like to remind you we
6 started this journey with STAR*D in 1999, thinking
7 we could end TRD. STAR*D's publications in 2006
8 and subsequently have taught us that the new
9 options are badly needed. Now, almost 20 years
10 later, we have opened a new window with esketamine.

11 Finally, at least this gives us some hope.
12 Every day, I see patients with little hope because
13 of the unending refractory nature of their illness
14 and repeated treatment failures. These patients
15 are desperate for new treatments, and they are also
16 really asking for treatments that will work rapidly
17 and will keep them well. Hopefully, esketamine may
18 provide this opportunity.

19 Thank you. I'm going to ask Dr. Hough to
20 come back.

21 DR. HOUGH: This concludes the sponsor
22 presentation. In addition to the speakers that

1 you've heard from so far, we have three additional
2 experts listed here who are available to answer
3 questions for the committee.

4 **Clarifying Questions to Applicant**

5 DR. NARENDRAN: We will now take clarifying
6 questions to the sponsor, Janssen. Please remember
7 to state your name for the record before you speak.
8 If you can, please direct questions to a specific
9 presenter.

10 It is a large panel. I do want to try to
11 see if people can limit their questions to one
12 question and maybe one follow-up if it's relevant.
13 Then, if there's extra time after other people have
14 asked their questions, we can kind of come back to
15 your second burning question.

16 Again, clarifying questions is really just
17 for clarification. There will be plenty of time
18 for discussion later. So we'll start with
19 Dr. Dunn.

20 DR. W. DUNN: Walter Dunn. This is a
21 question for Dr. Singh. This is regarding the
22 withdrawal maintenance study. I just wanted to

1 clarify, it looked like in the remitters' and
2 responders' analysis, the hazard ratios are
3 actually a little bit better for the responders
4 versus remitters. If I understand correctly,
5 that's comparing within that subpopulation of
6 responders and remitters, respectively.

7 So I guess maybe the question is, if you
8 stated time to relapse, are the remitters still
9 doing better than responders?

10 DR. SINGH: Sure. Thank you. The program
11 was really designed to maximize the number of
12 patients who would achieve remission by both dosing
13 and frequency and maximize the oral antidepressant
14 to make sure that they would be able to stay well,
15 even with the antidepressant alone.

16 The responder group is an independent
17 group, which is a more vulnerable population. You
18 would expect both of them to kind of relapse very
19 quickly. I think the data -- can show slide 1
20 please? This slide shows you the stable remitters
21 who remained relapse free.

22 If you could show slide 2, this is the

1 group that shows the stable responders. The
2 relapse rate primarily defers to the comparator
3 group, but the number who remain well on esketamine
4 is remarkably similar.

5 DR. NARENDRAN: Next question,
6 Dr. Rudorfer?

7 DR. RUDORFER: Thank you.

8 Dr. Hough, a very basic question; I realize
9 the protocols were developed by the company with
10 the FDA, but why no esketamine monotherapy arm?

11 DR. HOUGH: Sure. The intention of the
12 phase 3 program was always to use esketamine dose
13 intermittently while patients remained on their
14 oral antidepressant because the intent was
15 potentially, understanding the logistical hurdle of
16 coming for administration and dosing, that patients
17 could potentially just remain on the oral
18 antidepressant alone during maintenance treatment.
19 That was one of the objectives of the relapse
20 prevention study, to determine if that were
21 possible.

22 DR. NARENDRAN: Next question, Dr. Michelle

1 Ruha?

2 DR. RUHA: Thank you. Michelle Ruha. I
3 think my question is for Dr. Singh. I'm just
4 curious about the TRANSFORM-3 study with the
5 esketamine flex dose. How many participants
6 actually continued the 28-milligram dose through
7 the end?

8 I see that there wasn't a significant
9 difference from placebo until day 28, and I'm
10 wondering if that was because no one was on
11 28 milligrams anymore and that that dose maybe
12 just isn't effective.

13 DR. SINGH: In TRANSFORM-3, all patients
14 started on 28-milligram, and then the dose could be
15 increased to 56 or 84 based on clinical judgment,
16 and the overall guidance we gave them was to start
17 low and go slow.

18 If you could show slide 1 please, this
19 gives you the proportion of patients who stayed on
20 28 or increased to 56 or 84. The overall number,
21 as you can see at the endpoint, was about
22 6 patients on the 28-milligram versus 16 on 56 and

1 40 on the 84-milligram dose.

2 Was there a second part to that question?

3 DR. RUHA: I hadn't asked it, but I was
4 wondering if you could also show how the adverse
5 events in that population related to the dose they
6 were on.

7 DR. SINGH: I don't think we have an
8 analysis in this study by dose. I think we have
9 just overall results. We can request that specific
10 analysis if that would be helpful.

11 DR. HOUGH: We can get back with you, and
12 we will try to do that analysis. But I'd like to
13 also add to what Dr. Singh said. In the phase 2
14 study, we did a study with 28, 56, and 84, and we
15 found that 28 did not have a persistent enough
16 efficacy effect for us to take it into phase 3, so
17 the only 2 doses we took for adults was 56 and 84.

18 We did find that with the older elderly,
19 they did have higher plasma levels or blood levels,
20 so we determined it would be best to start for
21 tolerability knowing that elderly or more
22 vulnerable patient population, but it was not

1 really thought that for adults, that this would be
2 an efficacious treatment.

3 DR. NARENDRAN: Dr. Bilker?

4 DR. BILKER: Yes. Hi. I wanted to make a
5 point about slide 52. I think this question is for
6 Dr. Singh. On that slide, the esketamine plus AD
7 group, you have it dropping to probability of 0 of
8 surviving without relapse at about, what, 91? I
9 don't think that curve should be dropping to 0
10 since you have many people who are censored.

11 DR. SINGH: To make sure, are you looking
12 at the very last patient? So that was only really
13 1 patient in the study at the time. The study was
14 discontinued when the number of relapses were met,
15 so the rest of the patients who were still in the
16 study were censored.

17 There was 1 patient who relapsed on the
18 very last day that the study was stopped, and
19 that's the patient that you see at the very end of
20 that curve.

21 DR. BILKER: That's right, but the censored
22 patients didn't relapse. At least, you don't know

1 if they relapsed. It shouldn't be dropping to 0.

2 I hope not.

3 DR. NARENDRAN: Dr. Pine?

4 DR. PINE: Yes. I had a question for
5 Dr. Singh. It was a question about powering the
6 phase 3 studies. I think I heard you say that that
7 they were powered for a 6-point difference, but I
8 also heard you say that the typical difference is 2
9 to 3 points on the MADRS in studies.

10 So I wondered what was the thinking in
11 terms of powering the studies for 6 points when the
12 past work suggested 2 to 3 points.

13 DR. HOUGH: I would like to call up our
14 statistician, Ms. Rosanne Lane, who can address the
15 powering of the phase 3 studies.

16 MS. LANE: So we based the powering of the
17 phase 3 studies based on our phase 2 study. There,
18 we saw differences of almost 9 in the 84-milligram
19 group. So we did bring it down a bit lower, but
20 not to the 4 or 3 that you see in the phase 3
21 studies.

22 DR. PINE: But if I understood it

1 correctly, the phase 3 studies were fundamentally
2 different from the phase 2 studies in that the
3 phase 2 studies did not change and add a new
4 antidepressant where the phase 3 studies did do
5 that. Is that correct?

6 MS. LANE: Yes, that's correct.

7 DR. NARENDRAN: Dr. Compton?

8 DR. COMPTON: Thank you. I had a question
9 about the inclusion and exclusion criteria as it
10 relates to the abuse potential. Could you clarify
11 for us what substances and what substance use
12 disorders were part of the exclusion criteria?

13 DR. HOUGH: Sure.

14 DR. COMPTON: Does it include alcohol,
15 illicit substances? And what about tobacco?

16 DR. HOUGH: I'll have Dr. Singh address
17 that in detail.

18 DR. SINGH: The overall studies, we
19 included patients who were using some substances,
20 but excluded patients who either met dependence
21 criteria within the last 1 year or severe use
22 criteria within the past 6 months. Very

1 specifically, we allowed patients who were smoking,
2 so there was no exclusion at all based upon
3 nicotine.

4 If you could show slide 1, please. These
5 are the very specific exclusion criteria listed for
6 those patients, so as defined, a history of
7 moderate to severe substance or alcohol use within
8 the past 6 months.

9 The two things that we allowed
10 specifically, which we didn't exclude, were
11 nicotine or cannabis. Only cannabis dependence was
12 excluded, so that if they could show a negative
13 urine screen at the start, they were allowed to
14 enter the study.

15 DR. COMPTON: Thank you.

16 DR. NARENDRAN: Dr. Everett?

17 DR. EVERETT: Thank you. I have a question
18 about the risk mitigation strategy. In light of
19 our current experience with oxycodone, pill mills,
20 and things like that, which you may include or may
21 not include at ketamine infusion sites, I would
22 like to know a little bit more about the company's

1 proposal for that piece of the certification and
2 monitoring of the certification of these sites.

3 It sounds like the conceptual intention is
4 that this be provided in the context of a
5 healthcare setting like we saw from the University
6 of Texas, but we could all envision a
7 period -- what keeps that intact versus prevents a
8 basic franchise of ketamine mills, so to speak,
9 from happening?

10 DR. HOUGH: Sure. In a moment, I'll ask
11 Dr. Michelle Kramer, who's our medical affairs
12 leader, to walk you through the details of the
13 certification of the healthcare settings as well as
14 the monitoring period, so she'll speak to that
15 detail.

16 But I'd like to first make an opening
17 comment that as opposed to opioid stimulants,
18 benzodiazepines, and other substance abuse, which
19 patients can get up to a month's supply at their
20 local pharmacy or have it shipped to their home and
21 then administer it themselves at will, this is a
22 program which has been very thoughtfully considered

1 and in consultation with FDA.

2 It includes this controlled medication
3 distribution program where patients can only access
4 the product at a certified site of care and receive
5 it under direct observation of a healthcare
6 professional. But let me have Dr. Kramer speak to
7 the details.

8 Dr. Kramer?

9 DR. KRAMER: Thank you. So as was
10 mentioned, the key first component is that patients
11 will not be able to pick up the product from a
12 pharmacy or have it shipped to them. They will
13 require a treatment center to be treated. Those
14 treatment centers will only be able to receive
15 shipment if they are certified under the REMS.

16 The certification includes -- that
17 attestation that sites will have to take includes
18 assigning an individual authorized representative
19 at the site level who is responsible for insuring
20 that processes and procedures are in place for the
21 facility, including a number of different elements.

22 Importantly, they will be required to train

1 not just the prescriber, but all relevant personnel
2 at the site on how to manage the product on the
3 REMS elements, on important safety elements as
4 well. They will be required to maintain
5 documentation as part of the attestation, and they
6 will agree to an audit, which the company will
7 perform on an annual basis of a representative
8 number of centers.

9 In addition, we will be performing a number
10 of knowledge and behavior assessment surveys of
11 downstream providers and pharmacists to assure that
12 they are indeed trained on the important elements,
13 and we'll be monitoring all of that data on a very
14 regular basis.

15 DR. NARENDRAN: Next question is on the
16 phone, Dr. Fiedorowicz?

17 DR. FIEDOROWICZ: Yes, hello. This is Jess
18 Fiedorowicz from the University of Iowa. I'm
19 calling from Iowa City, and I have a question for
20 Dr. Singh.

21 I appreciate the analyses involving the
22 dissociation to explore for any potential impact on

1 blinding, and there were several other immediate
2 adverse effects such as anxiety, dizziness,
3 vertigo, sedation, nausea, taste changes.

4 I have concerns about the apparent
5 assumption that only the adverse effect of
6 dissociation could lead to unblinding. I'm
7 wondering if any other analyses were conducted to
8 look at other symptoms or some composite of
9 symptoms, or if at any point during this study
10 patients were asked whether they thought they were
11 receiving esketamine or placebo.

12 DR. SINGH: We did perform similar analyses
13 based on other adverse events also. One of the
14 other more common ones is sedation, so we looked at
15 both, patients who had sedation or those who had
16 dissociation and sedation.

17 If you could show slide 2, please? There's
18 only about 5 patients who have both sedation and
19 dissociation, and this shows you the results. If
20 you censored those patients, that would remain
21 significant. We have not done specific analyses
22 based on some of the other adverse events such as

1 vertigo or nausea that tend to appear early on and
2 lesser during that phase, but that's something we
3 could do.

4 Regarding your second question, we didn't
5 ask very specifically to guess which treatment they
6 were on, whether they were on esketamine or
7 placebo. The reason for really not asking that
8 question was based upon us using that questionnaire
9 in our prior phase 1 and phase 2 studies, where
10 upon asking that question, patients went on to do
11 research and then would try to say, "Well, I guess
12 I'm this, but this is what I am now," and they'd
13 end up spending more time thinking about what that
14 specific answer could be, so it was
15 counterproductive.

16 Another way of understanding this thing is
17 if you look at the number of patients who have, for
18 example, dissociation who discontinue it, there's a
19 very high number, even on placebo after
20 discontinuing it, suggesting that there was some
21 degree of blinding maintained.

22 DR. NARENDRAN: Next question, Ms. Witczak?

1 MS. WITCZAK: Kim Witczak. I guess I had
2 one question on the secondary outcome where it was
3 the patient-reported where it said it was not
4 statistically significant, because that leads to a
5 question like the PHQ-9 form and whatnot, when it
6 gets into real-world implementation.

7 Who is the ideal candidate for this when it
8 goes into marketing? Will my GP be able to say
9 what the criteria is and what would make me
10 available to have this treatment?

11 DR. HOUGH: I'd like to address that in two
12 ways. Slide 1 up, please. This is the PHQ-9 that
13 you specifically mentioned, and you can see that
14 the point estimates and confidence intervals are to
15 the left of 0. However, because of the statistical
16 hierarchy of testing in the short-term studies, we
17 were not able to test either the Sheehan Disability
18 Scale or the PHQ-9. So because of the statistical
19 analysis plan, we were not able to determine if
20 they were statistically significant, but the point
21 estimates are consistent with the MADRS changes.

22 I'd like to also say that I'm not sure that

1 general practitioners will all be prescribing this
2 kind of medicine. I think, being that this is
3 treatment-resistant depression, it's much more
4 likely to be prescribed by psychiatrists and by
5 others who are experienced in the assessment and
6 treatment of patients with depression.

7 There are a number of healthcare
8 requirements, as Dr. Kramer mentioned, about the
9 healthcare setting they would have to have, and
10 they would all have to be REMS certified.

11 DR. NARENDRAN: Next question,
12 Dr. Hillefors?

13 DR. HILLEFORS: Mi Hillefors from NIMH.
14 This may be for Dr. Singh and maybe the
15 statistician. I just want to look at the age
16 group, above 65 or older, it was only in the
17 TRANSFORM-3 study if I understood correctly, which
18 has about 123 subjects that completed day 28.

19 The change in the MADRS total score was
20 less than 4 points. What was the clinical
21 significance of that? Also, do you believe that
22 that is sufficient efficacy data to support

1 treating this potentially more vulnerable age
2 group?

3 DR. HOUGH: I'd like to address your
4 question in two ways. I'll have Dr. Singh speak to
5 the actual data that we observed in the clinical
6 trial program, but then we also have Dr. Eric
7 Lenze, who is an expert psychiatrist in geriatric
8 psychiatry to speak to the clinical relevance of
9 this change and the clinical meaningfulness of it,
10 given that this is a very vulnerable treatment
11 population.

12 DR. SINGH: The study was really conducted
13 very specifically as a separate study so that we
14 could really assess efficacy as well as safety,
15 which is often not done in most programs. The
16 overall treatment difference, as you correctly
17 point out, was really not seen for the first
18 3 weeks and really only the last week.

19 To understand what drove the distance, I
20 think one is just the dose was started low and went
21 up slow. If you can look at these specific
22 subgroups, there were two predefined subgroups.

1 Could you show slide 3, please? These are
2 two subgroups. These were prespecified. The left
3 side is the 65- to the 74-year-old group, and then
4 the right side is 75. I think what's really
5 puzzling is the group on the right, where you have
6 initial improvement really more so with the placebo
7 arm than even with the comparator arm, that's
8 driven by three outliers, and I really do not have
9 any good explanation for what explains those three
10 outliers that drive it.

11 On the left side is your larger group, your
12 65 to 74 group. That is consistent, except a
13 slower onset occurred, which is very consistent
14 with what you would see in older patients. And to
15 add some clinical meaningfulness to it, I'll
16 request Dr. Lenze, who had some clinical impression
17 on that.

18 DR. LENZE: Hi. I'm Eric Lenze. I'm a
19 professor of psychiatry at Washington University.
20 I'm a geriatric psychiatrist and treatment-
21 resistant depression specialist there. I'm here as
22 a paid consultant. I have no other financial

1 conflicts.

2 I just wanted to take a minute to talk
3 about what treatment-resistant depression looks
4 like in the older adult population.

5 Symptomatically and in terms of suffering and
6 suicide risk, it's actually quite common and
7 similar to what we see in younger adults, but
8 exacerbated by greater health risks, including
9 cognitive health with older adults with depression
10 having four- to sixfold increased dementia rates.

11 Right now, there are very limited options
12 for treatment-resistant depression in this age
13 group with heightened risk. Lithium augmentation
14 is one such option, but it contains risks of
15 tremors and renal toxicity.

16 Second-generation antipsychotics are also
17 an option, but have extrapyramidal side effects
18 such as Parkinson's for a risk. There is a clear
19 need for something new in older adults.

20 With respect to the difference in MADRS
21 scores, a 2-point difference being a minimally
22 clinically significant difference, that's actually

1 the same difference that we use in our NIMH-funded
2 study of aripiprazole augmentation in older adults,
3 which is to date the only published full-scale
4 study of an antidepressant in this treatment-
5 resistant population.

6 DR. NARENDRAN: Thank you. Next question,
7 Dr. Meisel?

8 DR. MEISEL: Steve Meisel. I just want to
9 go back to the REMS. Have you thought
10 through -- let's propose a scenario where you have
11 somebody that lives in the middle of NoPlace, North
12 Dakota, has to drive 3 hours to a facility that is
13 certified, is doing well, never has any side
14 effects.

15 Over the long haul, this person is going to
16 say let me do this at home or let me do this at my
17 local family practice office, who's not certified,
18 or another scenario where somebody's doing really
19 well, they're taking a dose once a week, but now
20 they want to go on a 3-week cruise and the cruise
21 ship doesn't have a facility.

22 Have you thought through the practical

1 implications of the REMS in those kinds of
2 scenarios?

3 DR. HOUGH: I would like to address your
4 question in two ways. One, let me take the second
5 part of your question first about someone going on
6 vacation for an extended period of time. During
7 the phase 3 clinical trial program, we only tested
8 once a week or once every 2 weeks. However, we
9 have a very large continuation of care study, 3008,
10 in which we have approximately 900 subjects.

11 In that study, we've been allowing
12 investigators to extend the time between
13 treatments, and there are a number of patients who
14 are on monthly treatment, and they're able to
15 maintain their response or their remission. So
16 that's one opportunity, but it was not part of the
17 submission package and not something that we are
18 proposing at this moment. We need more data to
19 understand that.

20 Secondly, you raised a very good point, and
21 this is something difficult. On one hand, we as a
22 sponsor want to do the responsible thing for

1 patient safety. We understand the abuse potential
2 and the need for a REMS as well as certification of
3 healthcare sites. But on the other side of the
4 coin, we also understand that this is an important
5 new treatment and that there are places as you
6 describe in rural parts of the country or places
7 that are underserved by psychiatrists in which we
8 might be limiting patient access.

9 So we want to have consultation. We want
10 to get your ideas from the committee and have
11 further discussion with FDA about what's the
12 appropriate balance between access and between
13 making sure that patients are safe.

14 DR. NARENDRAN: Next question, Dr. Besco?

15 DR. BESCO: Kelly Besco. I noted that many
16 of the patients who experienced the more serious
17 sedation-related events were also taking
18 concomitant benzodiazepines, and I was just
19 wondering if there's any data available on how many
20 patients were taking concomitant benzodiazepine
21 therapy that also experienced a post-administration
22 sedation event.

1 DR. HOUGH: I don't think we have that
2 exact analysis, but you're right, that patients
3 with depression often suffer from anxiety and
4 insomnia and are taking either benzodiazepines for
5 anxiety or non-benzodiazepine medications for
6 sleep. I don't have that exact analysis of which
7 ones were taking those concomitant medicines and
8 which ones might have more, but we can try to look
9 for that answer and get back to you later.

10 DR. NARENDRAN: Next question, Dr. Zito?

11 DR. ZITO: I'm not sure who to address the
12 question to, but in general, what proportion of
13 patients had suicidal ideation versus suicidal
14 behavior? Secondly, I'm curious of the logic about
15 the decision that the suicides are unrelated to
16 esketamine. I can't understand the logic of that
17 inference.

18 DR. HOUGH: Sure. I'll have Dr. Popova
19 come up in a moment to discuss the background rate
20 and how we came to that conclusion, but let me
21 first start with a couple of opening comments and
22 to provide some perspective here.

1 Suicide is always a tragic outcome, and
2 it's far too common in our patients with major
3 depression, and as Dr. Rush pointed out, in
4 patients with treatment-resistant depression, it's
5 far higher than those in major depression.

6 We as a company take a responsible approach
7 when we do a clinical trial because we understand
8 that some patients are receiving placebo, some are
9 receiving the active drug. So in each and every
10 visit, we do a Columbia Suicide Severity Rating
11 Scale in order to understand what level of suicidal
12 ideation and behavior the patient is experiencing
13 at that moment.

14 But it's important to understand that the
15 Columbia Suicide Severity Rating Scale is a
16 snapshot in time. It's not a predictor of future
17 suicidal behavior. Suicidal behavior is a complex
18 interaction of the medication, the underlying
19 disease, psychosocial factors and stressors, and
20 psychological factors, so it's important to
21 understand the background rate.

22 We did have 3 suicides in this particular

1 program, but we have to see that in context of the
2 TRD patient population. None of these patients'
3 suicides occurred during the double-blind, so we
4 don't have a comparator group. So the only active
5 comparator group is, if we want to understand an
6 apples-to-apples comparison, we have to look at the
7 background rate, and I'll have Dr. Popova explain
8 that.

9 DR. POPOVA: I will start by saying that
10 patients with suicidal ideation were allowed in our
11 programs. However, patients with suicidal ideation
12 with some intent or plan or suicidal behavior
13 within the last 6 months prior to enrollment were
14 not permitted in the program.

15 If we can have slide number 3, please.
16 Overall, in the program -- this is the two
17 controlled studies in adults -- we saw that
18 patients either stayed within the same category of
19 suicidal ideation or improved. As you can see,
20 this is a comparison, baseline day 4 and endpoints
21 for the two short-term adult studies. As you see,
22 the patients overall improved into a category.

1 The incidence of suicidal behavior -- slide
2 number 2, please -- this slide presented in the
3 core, overall, we had 10 patients who reported
4 post-baseline suicidal behavior, 8 of which were in
5 the open-label studies, and then only 2 were in the
6 controlled studies. Out of these patients, 5 had
7 pre-existing suicidal ideation prior to study
8 entry.

9 DR. HOUGH: Just to add to what Dr. Popova
10 said, in terms of relatedness, that was part of
11 your question as well, that each time a suicide
12 occurs, we do a very thorough retrospective
13 assessment of that case, as well as the
14 investigator does.

15 The investigator independently determines
16 the relatedness of the event to the study
17 medication, and in each of those 3 cases, the
18 investigator determined, independent of the
19 sponsor, that the event was not related to the
20 underlying medication.

21 DR. NARENDRAN: I have a more general
22 question. I know you're probably aware that AJP

1 published this paper from Dr. Schatzberg's group
2 that ketamine doesn't work very well for people on
3 naltrexone, and then I think there's some
4 discussion about that, and then John Krystal's
5 group recently published that it did work for
6 people on naltrexone.

7 Do you have any data on esketamine's
8 affinity for the mu opioid receptor or any PET data
9 to suggest what the occupancy is? Are you worried
10 about that?

11 DR. HOUGH: Yes, and I can address that in
12 two ways. Dr. Wayne Drevets will come up and speak
13 to the fact that we do not believe that the opioid
14 receptors are directly impacted as part of the
15 mechanism of action, and he'll also make some
16 comments on the Williams paper.

17 DR. DREVETS: In the antidepressant dose
18 range, ketamine and esketamine do not directly
19 stimulate the opioid receptors, but are rather
20 relatively selective as an NMDA receptor
21 antagonist. This is partly evident, but as you
22 allude by looking at the affinities of those

1 compounds for B opiate and NMDA receptors -- and
2 this has been characterized by a measurement of the
3 inhibitor constant or Ki values. The lower the Ki
4 value, the lower the concentration of a drug needed
5 to potently bind a receptor.

6 Slide 2 up, please. This graph shows the
7 median Ki reported for the esketamine at NMDA
8 receptors at 0.5 micromolar. In contrast, the
9 median Ki reported for mu opioid receptors for
10 esketamine is 11 micromolar, about 20-fold higher.
11 The blue line shows the average estimated brain
12 concentration of esketamine after an 84-milligram
13 dose of esketamine nasal spray, which approaches
14 the Ki value for NMDA receptors.

15 In this range, we and others find
16 significant effects on NMDA receptors, but no
17 significant impact on mu opioid receptors. If one
18 wanted to achieve the same occupancy at mu opioid
19 receptors, conceivably, you could do it by a
20 20-fold elevation plasma level, which would take
21 conceptually about 60 of our 28-milligram nasal
22 spray devices.

1 However, above the recommended dose range,
2 the rise in plasma level is less than dose
3 proportionate, so it would be practically
4 impossible to get to that same level of occupancy
5 with our esketamine nasal spray.

6 Now, the occupancy of esketamine and also
7 of antidepressant levels of racemic ketamine at
8 antidepressant doses are about 30 percent.
9 Notably, it takes a greater proportion of the
10 receptor occupancy to activate mu opioid receptors,
11 so that actually gives you even wider moat around
12 the mu opioid receptor relative to esketamine.

13 In preclinical studies, it has taken
14 concentrations that have been 2 to 3 orders of
15 magnitude higher, 100- to 1,000-fold higher, to
16 actually activate mu opioid receptors. So in
17 summary, mu opioid receptor stimulation does not
18 occur at antidepressant doses of esketamine nasal
19 spray.

20 DR. NARENDRAN: Thank you. Dr. Kungel?

21 MR. KUNGEL: I'm not a doctor. I am a
22 patient. My question is to Dr. Hough. When we're

1 trying to do statistical significance, we're
2 comparing the esketamine plus oral antidepressant
3 against the placebo and oral antidepressant?

4 DR. HOUGH: Yes, that's correct.

5 MR. KUNGEL: I would make the case that if
6 you look at the study 3002 total score at 28 days,
7 the MADRS score for the folks on esketamine was
8 down 20 points, but it was down 15 for the placebo.

9 When I look at these charts, I'm looking at
10 the placebo tracking the medical piece very
11 closely, and it raises the question of are we
12 really looking at a placebo? Because if you look
13 at the patients that are here that have been on
14 TRD, we're telling them that there's a new option
15 that they've never had before.

16 We've got these people seeing doctors twice
17 a week. They're establishing a relationship.
18 They're on a new antidepressant, and even the
19 placebo nasal gives them an impression something's
20 going on.

21 So I would make the case that the placebo
22 is a very active group, and particularly because of

1 the cognitive and emotion issues with TRD patients,
2 what we're measuring are two very active groups
3 that have responded, and that perhaps we need to
4 look at the esketamine against folks on oral
5 antidepressants only because I think the case that
6 the placebo is a placebo in this situation may not
7 actually be the case.

8 DR. HOUGH: I agree with your argument
9 about why we saw such a high response in the
10 comparator group. It's our opinion that starting a
11 new antidepressant at baseline is a much higher bar
12 than starting a placebo at baseline and I think
13 helps explain some of the results we saw in
14 phase 3.

15 DR. NARENDRAN: Thank you.

16 I think we're out of time, so we'll take a
17 15-minute break and try to meet at 10:35. Thank
18 you.

19 (Whereupon, at 10:21 a.m., a recess was
20 taken.)

21 DR. NARENDRAN: We will now proceed with
22 the FDA presentations, starting with Dr. Jean Kim.

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FDA Presentation - Jean Kim

DR. KIM: Good morning. I'm Jean Kim. I'm a medical officer and a clinical reviewer on this application for esketamine. Generally today, I'm going to go over the definition of treatment-resistant depression, the background of esketamine, and the studies submitted for the efficacy of esketamine.

Treatment-resistant depression has no formally agreed-upon DSM-5 definition or diagnostic criteria in the psychiatric community. However, the current general consensus often defines it as major depressive disorder or an episode, such as the current one, is unresponsive to at least 2 antidepressants of adequate dose and duration.

TRD, as with major depression, is considered an extremely serious life-threatening condition with high clinical morbidity, including increased suicide rates, hospitalizations, and overall impairment in daily functioning, leading to deterioration in jobs, relationships, and the ability to care for oneself.

1 As a clinician myself who worked with
2 patients with major depression in hospital settings
3 for a decade, I can attest to the gravity of this
4 condition and the crucial life-saving importance of
5 finding additional effective treatment options for
6 TRD.

7 The overall prevalence of major depression
8 in the United States and worldwide is listed here.
9 Estimates of the prevalence of TRD range from about
10 a third to half the population that has major
11 depression and even higher according to some
12 estimates. This indicates several million people
13 are currently suffering from TRD.

14 Although we have numerous drugs approved
15 for the treatment of major depression, we only have
16 one that is officially approved for the indication
17 of TRD, olanzapine plus fluoxetine. We also have a
18 few atypical antipsychotics approved for the
19 indication of adjunctive therapy to partial
20 response in major depression, which from a
21 regulatory standpoint indicates a treatment
22 population slightly less ill than TRD, whose

1 definition I'll discuss in a minute.

2 We also have several devices approved for
3 TRD under slightly different regulatory standards
4 by the Center of Devices and Radiological Health,
5 electroconvulsive therapy, vagus nerve stimulators,
6 and transcranial magnetic stimulation.

7 There are also many drugs being used off
8 label for both adjunctive therapy and partial
9 response and for TRD such as oral antidepressants
10 combined from multiple classes, lithium, thyroid
11 hormones such as Cytomel, buspirone, and other
12 antipsychotics.

13 Also notably in recent years, ketamine has
14 been used off label for depression, which is
15 currently FDA approved as an anesthetic
16 administered either intravenously or
17 intramuscularly. Because of esketamine's
18 pharmacologic similarity to the drug ketamine, I'll
19 briefly provide some contextual information on
20 ketamine use.

21 From 2013 to 2017, ketamine sales nearly
22 doubled in the United States from 1.2 million vials

1 in 2013 to 2.1 million as shown here. While we
2 can't surmise the exact indications for ketamine
3 use from the data here, one potential component of
4 this increase may be related to the growing
5 clinical use of ketamine for off-label indications.
6 These indications have been mentioned in published
7 research literature for the treatment of major
8 depression, pain, and other conditions.

9 The flurry of research and promising
10 anecdotal reports from the off-label use of
11 ketamine are part of what led the applicant to
12 pursue their esketamine development program.
13 Esketamine is the S-enantiomer of ketamine that
14 works primarily as a non-competitive NMDA receptor
15 antagonist. The characteristics of esketamine have
16 similarities to racemic ketamine, although it's
17 noted to be more selective for NMDA receptors and
18 more potent as an anesthetic than racemic ketamine.
19 Esketamine is eliminated more quickly from the body
20 than racemic ketamine.

21 Esketamine has been approved in other
22 countries as an anesthetic, but not for any

1 psychiatric indications yet. For this new drug
2 application, the proposed indication is for
3 treatment of treatment-resistant depression using
4 an intranasal spray formulation of esketamine.
5 There's a separate investigational new drug program
6 ongoing for the indication of treatment of major
7 depression with imminent risk of suicide.

8 The proposed dosing of esketamine for the
9 TRD indication mirrors that used in a clinical
10 trial program. Intranasal esketamine is to be
11 administered twice weekly on top of a newly
12 initiated oral antidepressant taken daily for the
13 first 4 weeks of treatment, then for maintenance,
14 esketamine is stepped down to weekly dosing for
15 4 weeks, which you will see the applicant sometimes
16 refer to as the optimization phase in the studies,
17 then weekly or every other week ongoing thereafter.
18 Typical treatment for an episode of major
19 depression lasts at least 6 months.

20 In general, the use of esketamine for
21 depression differs from that for anesthesia and
22 that the doses used are much lower, but are

1 administered repetitively on a potentially
2 long-term basis. Accordingly, the esketamine
3 program incorporated long-term maintenance of
4 effect and safety studies, including a multi-year
5 study which is currently ongoing. If approved, the
6 drug is currently proposed for administration only
7 in settings supervised by a REMS-certified
8 clinician. In other words, patients cannot take
9 the spray home and use it themselves alone.

10 The primary outcome measure used in the
11 esketamine TRD study program is the MADRS, which is
12 a well-established scale used for many other major
13 depression drug approvals. The higher the score,
14 the more severe the illness. Some general severity
15 categories correspond to the following scores; 0 to
16 6 being asymptomatic, 7 to 19 being mild
17 depression, 20 to 34 being moderate depression, and
18 greater than 34 being severe depression.

19 Of note, MADRS evaluations in the phase 3
20 studies were conducted using remote independent
21 blinded raters via telephone to improve blinding.

22 In a May 2012 meeting with the applicant,

1 FDA agreed to a regulatory definition of TRD for
2 their program, which is failure of response defined
3 by less than a 25 percent reduction on the MADRS
4 with a minimum score of greater than 28 for adults
5 and 24 for geriatric, to treatment with at least
6 two prior antidepressants as monotherapy, given at
7 adequate dose and duration of at least 6 weeks.

8 The phase 3 esketamine program consists of
9 the following studies. There were three short-term
10 studies in adults lasting 4 weeks. Two of these
11 studies, study 3001 and 3002, studied esketamine in
12 adult patients 18 to 64 years old. Study 3005
13 studied esketamine in geriatric patients 65 and
14 older.

15 3001 was a fixed-dose study comparing 56-
16 and 84-milligram doses to placebo. Study 3002 and
17 3005 were flexible dose studies using either 56 to
18 84 milligrams for adults, or 28, 56, or
19 84 milligrams for geriatric subjects. 3003 was a
20 randomized withdrawal study of non-geriatric adults
21 on 56 and 64 milligrams of esketamine. There is
22 also a 1-year open-label safety study, 3004, whose

1 results were submitted with this NDA, and there is
2 also the multi-year study I mentioned, which is
3 ongoing.

4 Of note, the type of evidence we have for
5 this program is somewhat unusual relative to other
6 antidepressant development programs. Typically, we
7 have two positive adequate and well-controlled
8 short-term studies at the time of initial approval
9 with a randomized withdrawal conducted as part of a
10 postmarketing commitment for a maintenance claim.

11 A randomized withdrawal trial is still an
12 adequate and well-controlled trial. However, it
13 involves an enriched population of patients who
14 have already both responded to and tolerated the
15 drug.

16 The same basic design was used in all the
17 phase 3 short-term studies and also for the
18 open-label direct entry group, which is part of the
19 maintenance study. There was a screening phase
20 where treatment-resistant status was assessed,
21 including subjects who are still receiving a second
22 oral antidepressant for at least 2 weeks before

1 screening.

2 If subjects remain non-responders during
3 screening, they entered randomization into the
4 double-blind induction phase of 4 weeks of
5 treatment. They were either randomized to
6 intranasal esketamine or intranasal placebo with
7 both arms also initiated on the new oral
8 antidepressant, 1 of 4 choices they had not
9 previously taken.

10 The intranasal medication will be dosed
11 twice weekly and the oral antidepressant daily.
12 After the induction phase ends, they end intranasal
13 treatment, and they could enter a follow-up phase
14 anywhere from 2 to 26 weeks, depending on the
15 study, or they would continue intranasal treatment
16 by entering a long-term study, either 3003 or a
17 long-term safety study.

18 The primary efficacy endpoint for all the
19 short-term studies was a change from baseline on
20 the MADRS total score at day 28 with a difference
21 in least-score means between esketamine and placebo
22 groups compared using mixed-effects model for

1 repeated measures analysis.

2 Here we have the design diagram where you
3 see the patients who are non-responders to previous
4 treatment randomized to either receive the fixed
5 dose of 56 milligrams from the beginning or
6 84 milligrams. They actually started dosing at 56
7 for the first dose and then were titrated up to 84
8 by the second dose in the 84 arm, or they were
9 randomized to placebo.

10 3002 was the flexible dose study where you
11 have a combined intranasal esketamine arm, where
12 they all started at 56 for the first dose, and
13 then, according to investigator discretion, based
14 on efficacy and tolerability, they could titrate up
15 to 84 milligrams. Then, in the geriatric study,
16 that was also a flexibly dosed study, where they
17 all started at 28 milligrams. By the next dose,
18 they could go up to 56 and then to 84.

19 The criteria cutoffs used for the phase 3
20 studies, which are also agreed upon in sponsor
21 meetings, to define treatment remission and
22 response are as follows: remissions defined as a

1 MADRS total score less than 12 and the clinical
2 response is defined as greater than 50 percent
3 reduction in the MADRS total score from baseline
4 without meeting criteria for remission.

5 These cutoffs are used as the entry
6 criteria for the randomized study population for
7 3003, which is therefore an enriched population for
8 esketamine responders. The criteria were also used
9 for an exploratory secondary endpoint in the
10 short-term studies comparing percentages of
11 patients responding or remitting on esketamine
12 versus placebo.

13 This is the design schematic for the
14 randomized withdrawal design. Subjects came either
15 after completing the induction phase in 3001 or
16 3002 or via direct entry group, who underwent
17 open-label 4-week treatment.

18 With the exception of those originally on
19 placebo in 3001 and 3002, who remained on
20 intranasal placebo to maintain blinding and they
21 were not included in the primary analysis, all of
22 the transferred and direct-entry patients were

1 given intranasal esketamine, open label, for 12
2 weeks during the optimization phase, weekly for the
3 first 4 weeks, then weekly or every other week
4 depending on their MADRS total score response
5 criteria, which was reassessed every 4 weeks.

6 Subjects who were found to be stable
7 remitters and stable responders per these
8 predefined criteria were admitted into the
9 randomized withdrawal phase. At the start of
10 randomization, subjects either remained on
11 esketamine or were switched to placebo. They
12 continued either weekly or every-other-week dosing
13 based on the MADRS total scores until official
14 relapse was designated. Oral antidepressant was
15 continued in all phases and all arms.

16 The primary efficacy endpoint was time to
17 relapse based on MADRS score increased cutoff where
18 a clinically significant event such as suicide
19 attempt or hospitalization with esketamine and
20 placebo groups compared via log rank test. The
21 number of relapses required to detect an effect and
22 end the study was calculated by an interim

1 analysis.

2 We are considering two of the phase 3
3 studies submitted by the applicant as adequate and
4 well-controlled trials necessary to support
5 efficacy for esketamine. Study 3002, the flexible
6 dose parallel group study, was statistically
7 significant on its primary endpoint. Study 3003,
8 the randomized withdrawal study, was also
9 statistically significant on its primary endpoint.

10 This slide summarizes the results of the
11 phase 3 short-term studies on the primary efficacy
12 endpoint of least square mean MADRS total score
13 change from baseline. As noted before, 3002 was
14 the only study of these three that was
15 statistically significant on its primary endpoint.
16 There was nominal statistical significance for the
17 56-milligram esketamine arm in study 3001. Due to
18 a prespecified testing sequence, the lower dose
19 could not be formally tested if the higher dose
20 failed.

21 This graphic shows the response curve for
22 the positive study 3002. There was a fairly

1 consistent differentiation from placebo starting at
2 day 2, although not meeting nominal significance at
3 day 15, and then reaching significance by day 28,
4 the primary endpoint.

5 This analysis illustrates the range of
6 change in baseline in MADRS total scores for 3002
7 study subjects. For nearly all categories of
8 response thresholds, particularly in the more
9 robust range that generally corresponds with our
10 previously mentioned definitions of remission and
11 response, the percentage was higher on esketamine
12 than placebo. This information points to a
13 clinically relevant subgroup of patients with TRD
14 who respond very well to esketamine.

15 Overall, 3002 is an adequate and
16 well-controlled study that was statistically
17 significant on its primary endpoint with a
18 numerical improvement on the MADRS of minus 4.2.
19 Overall response and remission rates on esketamine
20 were numerically greater than placebo consistently
21 across most time points and score distributions,
22 indicating at least a clinically relevant subgroup

1 of patients with TRD who responded well to
2 esketamine versus placebo, although these were not
3 statistically compared.

4 There were no major uncertainties with this
5 study, although there is a general overarching
6 concern about potential unblinding bias in the
7 esketamine studies, which we'll discuss in more
8 detail with study 3003.

9 Now, I'll let Andrew Potter, the
10 statistical reviewer, go over the results from
11 study 3003.

12 **FDA Presentation - Andrew Potter**

13 DR. POTTER: Good morning. Thank you,
14 Dr. Kim. I'm Andrew Potter, the statistical
15 reviewer, and I'll present the results of the
16 randomized withdrawal trial, study 3003.

17 Study 3003 consists of two separate
18 randomized populations, stable remitters and stable
19 responders. A primary efficacy analysis was
20 conducted in the stable remitter population,
21 subjects who continued to score less than 12 on the
22 MADRS throughout the pre-randomization phase minus

1 an excursion.

2 Comparing time to relapse between
3 esketamine and placebo arms, subjects on esketamine
4 had a statistically significant longer time to
5 relapse with a two-sided p-value at 0.003 and a
6 hazard ratio of 0.49. The p-value and hazard ratio
7 were adjusted for an interim analysis that
8 re-estimated the sample size.

9 Here, we see the Kaplan-Meier estimates of
10 the cumulative probability of relapse with days
11 since randomization along the horizontal axis.
12 Placebo subjects, the dark gray curve, have a
13 greater probability of relapse compared to
14 esketamine subjects, the red curve.

15 The curves start to separate within the
16 first month after randomization, denoted by the
17 dashed green line, with placebo subjects relapsing
18 rapidly. This rapid relapse on placebo is
19 different than is seen in most other oral
20 antidepressant randomized withdrawal trials.

21 The reasons for this more rapid relapse are
22 unclear, with several hypotheses, including rapid

1 relapse because of disease severity, the drug
2 effect not persisting due to its rapid-acting
3 profile, and changes in the subject's perception of
4 their treatment assignment; these are changes in
5 their experience of esketamine's immediate effect.

6 The secondary endpoint compared to time to
7 relapse between esketamine and placebo in the
8 population of stable responders, subjects who
9 showed a greater than 50 percent MADRS reduction
10 who did not meet the criteria for remission. These
11 results were also statistically significant in
12 favor of greater maintenance of effect on
13 esketamine compared to placebo. P-value and hazard
14 ratio were not adjusted for the interim analysis.

15 In the stable remitter population,
16 Kaplan-Meier cumulative probability curves show a
17 similar pattern to observe in the stable remitter
18 population. Placebo subjects, again denoted by a
19 gray line, relapse faster compared to the
20 esketamine subjects. Again, note the same rapid
21 rise in relapse probability in the first month.

22 Because of acute, within-2-hours, side

1 effects of esketamine, we explored concerns that
2 subjects became unblinded to their treatment
3 assignments after randomization to placebo and
4 whether this influenced the relapse rate in the
5 placebo arm. A potential proxy measure of change
6 in patients' perception of their treatment
7 assignments is dissociative side effects.

8 In study 3003, dissociation is measured by
9 the Clinician-Administered Dissociative States
10 Scale. As the applicant previously discussed the
11 scale, its total score ranges from 0 to 92 and
12 subjects reported most dissociation at 40 minutes
13 post-dose. There was a change in CADSS after
14 randomization of placebo, but the question that we
15 have to ask is do subjects notice this change?

16 In this graphic, we see the trajectory of
17 the CADSS score at 40 minutes post-dose during the
18 optimization and maintenance phases of study 3003.
19 In the optimization phase, to the left of the
20 dotted line, all subjects receive esketamine even
21 though there are some plotted in the placebo group.

22 Day zero was the date of randomization to

1 continue on esketamine or switch to placebo. Red
2 represents the patients who relapsed during
3 follow-up and gray represents the patients where no
4 relapse was observed. The top panel represents the
5 CADSS trajectories in patients who remain on
6 placebo. Notice that the CADSS score remains
7 elevated after randomization.

8 In the bottom panel, the same trajectories
9 are presented for placebo subjects. In these
10 subjects, the average CADSS score declines after
11 randomization even though some patients still
12 report non-zero CADSS scores.

13 This pattern raises concerns about
14 potential changes in the subject's perception of
15 their treatment assignments, but cannot show any
16 definitive connections to time to relapse.

17 In terms of data integrity, one concern for
18 study 3003 was whether the total efficacy outcome
19 swung on the results of 1 site, where 16 out of
20 16 subjects on placebo all relapsed compared to 2
21 out of 9 subjects on esketamine. This includes
22 both remitters and responders. On the reassuring

1 side, the hazard ratio in the stable remitter
2 population only changed to 0.58 from 0.49, even
3 though the confidence interval now included 1, and
4 for stable responders, the hazard ratio only
5 changes from 0.30 to 0.37.

6 In summary, the maintenance of effect
7 study, 3003, has positive results on both the
8 primary and secondary endpoints of time to relapse
9 on esketamine versus placebo. This indicates that
10 patients who respond well to esketamine maintain
11 treatment gains due to the drug than without, even
12 with an ongoing oral antidepressant.

13 However, there are some concerns about
14 relying on this randomized withdrawal study design
15 as a confirmatory trial for study 3002. Given the
16 higher number of early relapses in the study
17 compared to oral antidepressant randomized
18 withdrawal trials, are the study results partially
19 being influenced by change in subject perception of
20 their treatment assignments, where patients are all
21 familiarized with esketamine and some are switched
22 to placebo and could notice the change?

1 Are there concerns about one large study
2 site affecting the overall study result important?

3 Finally, is it reasonable to use a study
4 with an enriched population as a confirmatory trial
5 for 3002? Will the results generalize to an
6 esketamine-naïve population or at least a
7 clinically relevant subpopulation of responders?

8 Thank you. Dr. Kim will finish presenting
9 the efficacy results.

10 **FDA Presentation - Jean Kim**

11 DR. KIM: Thank you, Andrew.

12 Here we have the primary endpoint results
13 comparing each of the two short-term studies that
14 were not statistically significant and then
15 comparing it to the positive study 3002.

16 First, we have 3001, which was a fixed-dose
17 adult study. Of note here, the response curve for
18 3001 generally parallels that of 3002 with a change
19 from placebo noted as early as day 2. This seems
20 to provide some hypothetical confirmation of the
21 efficacy trend from 3002, although again, the
22 results of 3001 were not statistically significant.

1 Uncertainties about study 3001 include the
2 fact that the higher dose arm, 84 milligrams, was
3 not statistically significant for efficacy versus
4 placebo, and accordingly, subsequent primary and
5 secondary endpoints could not be formally tested
6 due to the prespecified testing sequence to control
7 type 1 error.

8 Also, given that the higher dose failed in
9 a fixed-dose study, we as yet do not have
10 conclusive evidence of a dose response for
11 esketamine other than some indication of higher
12 adverse event rates on 84 milligrams such as blood
13 pressure, elevation, and sedation.

14 The phase 2 study, 2003, indicated a
15 potential dose response, which is why they selected
16 56 and 84 milligrams as the doses for phase 3, but
17 the larger phase 3 study did not confirm these
18 results. There were also higher dropouts noted in
19 the 84-milligram arm, but they were not necessarily
20 due to issues with increased drug intolerability at
21 that dose, as the majority of dropouts occurred
22 only after the first dose, which is 56 milligrams.

1 It's unclear if the dropout rate affect the
2 efficacy results for the 84-milligram arm.

3 In contrast, the response curve for
4 study 3005 was different and somewhat odd compared
5 to the other two short-term studies, with no early
6 onset of effect, even accounting for the difference
7 in dosing; so it's difficult to interpret the
8 results of this study and esketamine's efficacy in
9 the geriatric population. We do not necessarily
10 agree with the applicant's characterization of 3005
11 as a supportive study for the efficacy of
12 esketamine.

13 This slide shows ranges of MADRS mean score
14 data from previous antidepressant trials used to
15 support FDA approval. The numerical score data for
16 esketamine is comparable to these other trial
17 results, and notably in a population with a higher
18 baseline mean MADRS score, indicating more illness
19 severity in the esketamine trials.

20 Although efficacy of the drug is primary in
21 our assessment here, there are practical concerns
22 weighing into our benefit-risk assessment with

1 esketamine. They include its potentially faster
2 onset of action, which would render it different
3 than previous oral antidepressants, which typically
4 take weeks to kick in.

5 Although the phase 3 studies were not
6 significant for the secondary endpoint of early
7 response onset with continued sustained response
8 through day 28, they were still nominally
9 statistically significant at several of the early
10 time points.

11 While it's difficult to interpret the
12 clinical relevance of this early response without
13 the sustained response, you may still make a
14 clinical difference in individual patients who feel
15 these effects more quickly, potentially opening
16 them up to other interventions during
17 hospitalizations, crises, and so forth.

18 Esketamine is being given through
19 intranasal dosing, which is less invasive than
20 intravenous or intramuscular, which are the main
21 routes of administration for off-label ketamine.
22 There is also better quality control than the

1 compounded intranasal ketamine, which is also
2 available.

3 Esketamine will be the first antidepressant
4 approved in its class, which means a different
5 mechanism of action that may work in some patients
6 with depression and may have different tolerability
7 profiles that work with a given patient.

8 Drug interactions are noted to be fewer
9 than for most oral antidepressants. The dose is
10 given twice a week initially and is infrequently as
11 every other week during maintenance, which is more
12 convenient than other options such as TMS, where
13 you would typically have to visit the office daily.
14 Unlike other interventional TRD options, there's no
15 complications from surgery or general anesthesia.

16 To summarize our efficacy results for
17 esketamine, we have two positive phase 3 studies, 1
18 flexible dose short-term study, and 1 randomized
19 withdrawal maintenance of effect study in the
20 enriched population of stable remitters and
21 responders to esketamine.

22 When looking at distribution of response

1 with MADRS total scores in 3002, there was a
2 numerically higher number of subjects with greater
3 decreases in MADRS scores relative to baseline on
4 esketamine compared to placebo. This points to a
5 clinically relevant group of patients with TRD who
6 are particularly responsive to esketamine. The
7 results from the maintenance study 3003 still
8 pertain to this clinically responsive population.

9 Given the clinical morbidity and
10 dangerousness of a serious condition like TRD,
11 whereby definition the subjects have not responded
12 to at least 2 prior treatments, we must consider
13 the benefit-risk assessment in this clinical
14 context.

15 We have the following main concerns about
16 the evidence reviewed, though. Study 3001 was not
17 statistically significant on its primary endpoint,
18 which was the higher dose studied, 84 milligrams.
19 Study 3005, the geriatric study, also was not
20 statistically significant on its primary endpoint.

21 Finally, a general concern is the study
22 design for the phase 3 studies with esketamine,

1 whether there was a contribution of change of
2 perception of their treatment assignments helping
3 to drive the early relapse rate when switched to
4 placebo for 3003, and whether there was a
5 contribution of expectation bias in all the studies
6 if patients perceived they were on esketamine,
7 given its common immediate effects of dissociation
8 and sedation.

9 With that, I will hand over the discussion
10 to Dr. Qi Chen, who will review the safety profile
11 of esketamine in the NDA study program.

12 **FDA Presentation - Qi Chen**

13 DR. CHEN: Good morning. I'm Qi Chen. I'm
14 going to present the safety findings of the
15 esketamine development program. The safety
16 population in the esketamine development program
17 includes 1,708 subjects in six phase 2 and 3
18 studies, 1 study, 2003, in phase 2, and 5 studies
19 in phase 3. There were a total of 1,601 subjects
20 in phase 3 studies.

21 As Jean previously mentioned, 3001, 3002,
22 and 3005 were 4-week, randomized, double-blind

1 placebo-controlled trials. Subjects in 3001 and
2 3002 were less than 65 years old and the subjects
3 in 3005 were 65 years or older. Study 3003 was a
4 randomized withdrawal study that included three
5 phases: induction, optimization, and then a
6 randomized maintenance phase. Study 3004 was a
7 single-arm, long-term, open-label study.

8 The three short-term studies included
9 418 subjects who had received 3,074 treatments. In
10 the randomized withdrawal study, 3003, 87 subjects,
11 over 50 percent, received more than 10 esketamine
12 treatments. In long-term open-label studies,
13 442 subjects received more than 20 esketamine
14 treatments and 118 subjects received more than
15 40 treatments.

16 There were 6 deaths, including 3 suicides.
17 All six had been receiving esketamine treatment.
18 Two of the deaths were in randomized controlled
19 trials. The remaining four were in uncontrolled
20 open-label studies. There were no deaths on
21 placebo. The last death was not included in the
22 applicant presentation. It was in an ongoing

1 study, 3008, reported in the applicant's 19-day
2 safety report.

3 There was no consistent pattern that would
4 suggest a relationship between esketamine and the
5 particular cause of death. One potentially
6 concerning death case was a 41-year-old man, who
7 26 hours after his last dose of esketamine drove
8 his motorcycle into a tree.

9 Given that esketamine-induced sedation
10 normally lasts no more than 6 hours and the
11 applicant's depression had been improving and he
12 had not shown any suicidal intention, it seems less
13 likely that esketamine played a role in this
14 accident.

15 Regarding the suicides, it seems unlikely
16 that a direct effect of esketamine, other than lack
17 of efficacy, could have contributed to a suicide
18 occurring 3 days or more after the last treatment.
19 There was no evidence of suicidal intention,
20 ideation, or behavior immediately at following
21 treatment.

22 Adverse events are categorized using the

1 Medical Dictionary for Regulatory Activities,
2 MedDRA, verbatim reports from subjects who are
3 coded to preferred terms based on standard MedDRA
4 terms. To capture complex phenomena like
5 dissociation, we grouped multiple terms potentially
6 suggestive of these adverse events of special
7 interest.

8 The applicant submitted categorization of
9 preferred terms for several adverse events of
10 interest. We added more terms into categories for
11 dissociation, sedation, increased blood pressure,
12 lethargy, anxiety, and headache. For example, we
13 added loss of consciousness into sedation and
14 migraine into headache.

15 We also made two categories for cystitis-
16 suggestive adverse events and for suicidal ideation
17 or behavior. The following analysis of
18 patient-reported adverse events are based on these
19 categorizations.

20 This table shows adverse events that
21 occurred in at least 5 percent of esketamine-
22 treated subjects and at more than twice the rate in

1 placebo in the two short-term randomized controlled
2 trials for subjects younger than 65. Adverse
3 events of interest are in yellow. The most
4 commonly reported adverse events were dizziness or
5 vertigo, dissociation, nausea, and sedation. Other
6 adverse events of interest were increased blood
7 pressure and cystitis-suggestive adverse events.

8 Vomiting in orange was not initially
9 identified as an adverse event of interest, but
10 when both sedation and vomiting are common adverse
11 events, it would be concerning if a patient
12 developed both at the same time, putting the
13 patient at risk of pulmonary aspiration. I will
14 discuss this further when we get to sedation.

15 In this table, the frequencies are
16 different than the applicant provided for two
17 reasons. First, we added preferred terms into
18 categorization of several adverse events of
19 interest, as I previously mentioned.

20 Second, because of the difference in
21 randomization ratio between studies 3001 and 3002,
22 we averaged incidence among the two studies,

1 weighting by sample size. When we analyzed
2 subjects 65 or older, the distribution of adverse
3 events was similar to subjects younger than 65,
4 except the difference of cystitis-suggestive
5 adverse events between esketamine and placebo
6 groups are very small in senior subjects.

7 Anxiety was reported with higher incidence
8 in placebo than esketamine group. Sedation in
9 senior subjects was reported in less than
10 5 percent, so it's not listed here.

11 Randomized withdrawal study, as Jean
12 mentioned before, all the subjects in this study
13 were exposed to esketamine for at least 16 weeks
14 and then randomized to either continuing esketamine
15 or to placebo. In this randomized withdrawal
16 study, there continued to be a higher incidence in
17 the esketamine group of many of the adverse events
18 seen in the short-term study except viral upper
19 respiratory tract infection in yellow. No adverse
20 events were more common with placebo than with
21 esketamine, suggesting no withdrawal effects.

22 The most concerning transient adverse

1 events after esketamine use were sedation,
2 dissociation, and increased blood pressure and
3 heart rate. Although the phase 3 trials only
4 included monitoring for 1 and a half hour after
5 dose for most subjects, we do know more about time
6 course of adverse events because of longer
7 monitoring that occurred in earlier clinical
8 pharmacology trials.

9 Transient adverse events were correlated
10 with serum esketamine level. The half-life of
11 plasma esketamine is 2 to 3 hours. Blood pressure
12 effects last up to 4 hours, and the sedation and
13 dissociation lasts up to 4 to 6 hours.

14 Sedation; ketamine was approved as an
15 anesthetic; thus, the adverse effects of sedation
16 is one of our main concerns. Sedation was
17 evaluated by adverse event reports and using the
18 modified observer's alert list, sedation scale,
19 MOAA/S at pre-dose and every 15 minutes post-dose
20 until 90 minutes, then every 5 to 15 minutes if
21 subjects were sedated until sedation resolved.

22 In the MOAA/S scale, 5 means responds

1 readily to name spoken in normal tone, and 0 means
2 no response after painful trapezius [indiscernible]
3 squeeze. For most people, 0 is in deeper sedation
4 than falling asleep in clinic while waiting.
5 MOAA/S score is more sensitive to sedation than
6 adverse events reports.

7 This graph shows comparison of incidence of
8 sedation in the three short-term randomized
9 controlled trials and the long-term randomized
10 withdrawal study 3003. Based on the MOAA/S scale,
11 there was a substantially higher incidence of
12 sedation in esketamine-treated patients than in
13 placebo-treated patients.

14 As you can see here, 41 to 61 percent of
15 esketamine-treated patients experienced a sedation
16 versus 10 to 19 percent of placebo-treated
17 patients. In study 3001, the sedation incidence
18 was slightly higher in the esketamine 84-milligram
19 group than in the esketamine 56-milligram group,
20 suggesting possible dose effect.

21 In randomized controlled trials, there were
22 11 subjects who experienced a severe sedation.

1 This was defined by a MOAA/S score of 2 or less,
2 which means response only after shaking or painful
3 squeeze or no response at all. Some subjects
4 experienced severe sedation on more than 1 visit.
5 All visits with severe sedation were with
6 esketamine treatment and in subjects less than
7 65 years old.

8 Two subjects experienced sedation with
9 score 0. In other words, they did not respond even
10 after painful squeeze. One subject was transferred
11 to the emergency room when this occurred. The
12 other subject experienced this level of sedation at
13 5 different visits with onset 15 to 30 minutes
14 after receiving esketamine. These episodes lasted
15 between 15 and 35 minutes.

16 There was a total of 528 subjects who
17 experienced sedation after esketamine treatment in
18 studies 3001, 3002, and 3003. This graph shows in
19 subjects less than 65 years old, the percentage of
20 subjects who experienced sedation at different time
21 points by onset, peak, and resolution time. The
22 blue dot in the red circle shows about 55 percent

1 of subjects started feeling sedation at 15 minutes
2 post-dose.

3 As the applicant previously presented, the
4 onset of sedation was usually shortly after
5 esketamine administration, typically peaked at 30
6 to 45 minutes post-dose and resolved by 60 to
7 90 minutes post-dose. However, we found some
8 subjects had much later onset, peak, and resolution
9 time.

10 In this graph, we can see, among all the
11 esketamine-treated subjects who experienced
12 sedation in these studies, about 18 percent peaked
13 after 45 minutes and about 3 percent resolved after
14 90 minutes. The latest onset peak and the
15 resolution time was 90 minutes, 120 minutes, and
16 210 minutes, respectively. This indicates some
17 patients with late onset sedation may need longer
18 observation time.

19 Among all subjects aged 65 and older who
20 experienced sedation after receiving esketamine,
21 sedation began at 60 minutes for around 6 percent.
22 The latest onset peak and resolution time for

1 elderly subjects was 60 percent, 60 minutes,
2 90 minutes, and 105 minutes, respectively.
3 Compared to subjects less than 65 years old,
4 sedation was not as severe in subjects 65 years or
5 older. No score was lower than 3 and was shorter
6 in duration.

7 When patients started to recover from
8 sedation, did they steadily become more alert? In
9 most cases, yes. However, in several subjects,
10 severe sedation showed markedly fluctuating
11 patterns. This is a graph of extreme cases in
12 4 subjects demonstrating severity of sedation by
13 MOAA/S score: 5 is alert; 0 is no response to
14 painful squeeze and post-dose time. Each line
15 represents a subject.

16 Severity of sedation, time of onset, peak,
17 and the resolution varied among visits in some
18 subjects. It appears that the experience of
19 previous visits cannot accurately predict future
20 onset, peak, or resolution time, or the degree of
21 severity.

22 Sedation and vomiting; as I mentioned

1 previously, subjects who experienced both sedation
2 and vomiting at the same time could be at risk of
3 pulmonary aspiration. In short-term randomized
4 controlled trials 3001, 3002, and 3005, 10 subjects
5 out of 418 in the esketamine group reported both
6 sedation and vomiting on the same day.

7 No placebo subjects reported both vomiting
8 and sedation. Sedation severity was scored at 3 or
9 4 for these subjects. No pulmonary aspiration
10 cases were reported in clinical studies.

11 Little data on sedation were collected
12 after one half-hours in phase 3 studies. However,
13 sedation was monitored for an extended period in
14 the phase 1 study 1005. In this study, sedation
15 was assessed using the Karolinska sleepiness scale
16 at regular intervals through 6 hours post-dose.
17 Although most subjects reported that they were
18 alert by 6 hours, there were subjects who reported
19 feeling sleepy around 4 to 6 hours post-dose in
20 both placebo and esketamine groups.

21 Because of the late onset and the
22 fluctuating pattern of sedation in some subjects

1 and the potential severity of sedation events,
2 patients will need to be monitored following
3 administration of esketamine until sedation
4 resolves or until they have passed the period of
5 greatest risk for sedation.

6 In the clinical development program,
7 sedation resolved within 2 hours of dosing with
8 rare exceptions. Thus, it seems reasonable to
9 monitor patients for at least 2 hours following
10 administration of esketamine to mitigate the risk
11 of adverse events caused by excessive sedation.

12 Dissociation; ketamine is abused as a club
13 drug because of its dissociative properties.
14 Dissociation is described as feeling weird, spacey,
15 loopy, floating, visual disturbances, trouble
16 speaking, confusion, and numbness. Dissociation
17 was evaluated by Clinician-Administered
18 Dissociative States Scale, CADSS, questionnaire at
19 pre-dose and 40 and 90 minutes post-dose.

20 The CADSS questionnaire includes 23 items
21 scored from 0, not at all, to 4 extremely, with
22 component scores for amnesia, depersonalization,

1 and derealization. The total score ranges from
2 0 to 92, and the total score of 4 or less is
3 considered normal.

4 This graph compares the incidence of
5 dissociation defined as CADSS increase more than
6 4 points from pre-dose. In the 3 short-term
7 randomized controlled trials and the long-term
8 randomized withdrawal study, 3003, the incidence of
9 dissociation was substantially higher with
10 esketamine treatment than with placebo.

11 As you can see here, 60 to 79 percent of
12 esketamine-treated patients experienced a
13 dissociation versus 9 to 23 percent of
14 placebo-treated patients in the three short-term
15 studies, 3001, 3002, and 3005.

16 In 3001, incidence of dissociation was
17 higher in the esketamine 84-milligram group than in
18 the esketamine 56-milligram group, suggesting dose
19 effect, which we will explore in detail with a
20 mixed model analysis later.

21 Another thing I want to point out is the
22 incidence of dissociation among esketamine-treated

1 subjects. In randomized withdrawal study 3003, it
2 was 42 percent, which is lower than any short-term
3 studies. Given that subjects in 3003 had been
4 exposed to esketamine for 16 weeks before the
5 study, this could suggest the dissociation effect
6 from esketamine diminished with time. We will also
7 explore this in detail later with a mixed model
8 analysis.

9 This box plot shows the distribution of
10 CADSS score in esketamine and the placebo groups in
11 studies 3001, 3002, 3005, and 3003. All the black
12 dots represent outliers. Among the esketamine-
13 treated subjects who experienced dissociation, some
14 of the CADSS symptoms could be as severe as the
15 score above 16 on the scale of 0 to 92.

16 Findings from a repeated measure mixed
17 model shows scores in the esketamine group were
18 higher than in the placebo group with average
19 increase relative to placebo of 5.8 at 40 minutes
20 and 0.7 at 90 minutes. It appears there may be
21 partial attenuation of dissociation with repeated
22 treatment.

1 The CADSS score at 40 minutes averaged
2 6.0 points higher with esketamine than with placebo
3 after the initial treatment. This difference
4 decreased with subsequent treatments for the first
5 4 weeks, then plateaued at an average increase of
6 2.4 points relative to placebo at 40 minutes.

7 In study 3001, a dose effect was seen at
8 40 minutes with an average increase of 1.3 points
9 for 84 milligrams relative to 56 milligrams. No
10 dose effect on dissociation was observed at
11 90 minutes.

12 Blood pressure was observed to be elevated
13 after esketamine treatment. In phase 3 studies,
14 blood pressure was measured at pre-dose,
15 40 minutes, 60 minutes, and 90 minutes post-dose.
16 The average peak increase in esketamine-treated
17 subjects relative to baseline and placebo was
18 8-millimeter mercury in systolic blood pressure and
19 5 in diastolic blood pressure.

20 The proportion of subjects with markedly
21 increased blood pressure on at least one occasion,
22 defined as systolic blood pressure increase of

1 20-millimeter mercury or more to at least 180 or
2 higher, or a diastolic blood pressure increase of
3 15 or more to at least 105 millimeter mercury, was
4 about 10 percent with esketamine compared to
5 2 percent with placebo in subjects younger than 65.

6 There were few increases of these magnitude
7 in subjects 65 or older in study 3005, but lesser
8 increases such as to systolic blood pressure of 160
9 or more were more likely in the esketamine group.
10 Of the subjects with markedly increased blood
11 pressure, about 80 percent has blood pressure less
12 than 140 over 90 at pre-dose.

13 For most subjects, the highest systolic
14 blood pressure was observed at 40 minutes. Data
15 from clinical pharmacology study 1013 showed blood
16 pressure effects lasts for about 4 hours and
17 closely follows esketamine plasma levels.

18 Heart rate; in most phase 1 and 2 studies,
19 esketamine treatment was associated with increasing
20 heart rate. This effect was not observed in
21 studies 3001 and 3005. In study 3002, an average
22 increase in heart rate relative to placebo of about

1 5 beats per minute was observed at 40 minutes.

2 Given that the time pattern of heart rate
3 changes, seen in study 3002, and the phase 1 and 2
4 studies matched the time pattern of changes in
5 blood pressure and esketamine from pharmacokinetic
6 profile, it is likely that esketamine does cause an
7 increase in heart rate in some patients despite the
8 absence of this observation in studies 3001 and
9 3005.

10 There are several serious risks or
11 potential risks with ketamine. The racemic
12 mixture, including both enantiomers, are ketamine
13 and esketamine. This is based on safety data with
14 ketamine repeated dose administration for various
15 medical conditions or in the setting of ketamine
16 abuse.

17 Urinary bladder toxicity, including
18 interstitial cystitis and ulcerative or hemorrhagic
19 cystitis, has been reported in the medical
20 literature and to the FDA adverse event reporting
21 system, FAERS.

22 Ketamine labeling includes a description in

1 the adverse event section. The medical literature
2 discusses the potential risk of persistent
3 cognitive impairment based on cognitive testing and
4 neuroimaging in individuals who heavily abuse
5 ketamine. In addition, animal studies with
6 ketamine have demonstrated increased neuronal
7 apoptosis and neurodegeneration depending on
8 species, age of animals, and other conditions.

9 Serious liver injury with ketamine has been
10 reported and published case series and reported to
11 FAERS. Some foreign regulatory agencies have
12 issued communication about the risk.

13 Ketamine-related urological symptoms;
14 recreational abuse of ketamine and chronic
15 off-label use can cause interstitial or ulcerative
16 cystitis. The most common symptoms of
17 ketamine-induced cystitis are dysuria, increased
18 urinary frequency, urgency, urge incontinence, and
19 hematuria. Cystitis was reversible after
20 discontinuation of ketamine in the early course of
21 the disease but could be irreversible later.

22 Because of the known risk of ketamine, we

1 considered cystitis and adverse events suggestive
2 of cystitis as adverse events of special interest
3 in our safety analysis. I grouped urinary
4 discomfort or pain, cystitis or UTI, frequency or
5 nocturia, urgency, and abnormal sediment, or odor
6 into a single category of cystitis-suggestive
7 adverse events. I included urinary tract infection
8 because symptoms of cystitis could be misreported
9 as UTI due to similarity of symptoms.

10 This graph compares the proportion of
11 subjects with cystitis-suggestive adverse events in
12 the three short-term studies. Cystitis-suggestive
13 adverse events occurred in 6 to 10 percent of
14 esketamine-treated subjects compared to 1 to
15 3 percent of subjects receiving placebo in studies
16 3001 and 3002, subjects less than 65 years old, and
17 around 8 percent with both esketamine and the
18 placebo in study 3005, subjects at least 65 years
19 old.

20 The most commonly reported
21 cystitis-suggestive adverse events in esketamine-
22 treated subjects were urinary frequency and

1 dysuria, which is consistent with the clinical
2 symptoms of ketamine-related cystitis. However, no
3 cases of interstitial or ulcerative cystitis were
4 identified during the clinical trials.

5 Long-term cognition; again, because of the
6 known effects of ketamine, we were concerned about
7 the potential for cognitive impairment with
8 esketamine. In the phase 3 studies, cognition was
9 evaluated by the Cogstate Computerized Test
10 Battery, which includes assessments of multiple
11 cognitive domains and the revised Hopkins Verbal
12 Learning Test, which is a measure of verbal
13 learning and memory.

14 The evaluation was conducted at baseline,
15 the end of induction phase and during the follow-up
16 phase. There was no change or a slight improvement
17 in cognition with esketamine compared to placebo in
18 studies 3001, 3002, 3003, and 3005.

19 Also based on what we know of ketamine's
20 effect, we looked closely at esketamine's hepatic
21 effects. In study 3001, 3002, and 3005, there was
22 no clinically significant increase in liver enzymes

1 relative to placebo.

2 Suicidal ideation and behavior was assessed
3 using both adverse events report and the Columbia
4 Suicide Severity Rating Scale. There was no
5 statistically significant difference between
6 esketamine and the placebo groups in studies 3001,
7 3002, 3005, and 3003 based both on adverse event
8 report and the C-SSRS scale.

9 Conclusion; main adverse effects identified
10 from the esketamine development program include
11 sedation, dissociation, increased blood pressure,
12 and the urinary symptoms. Sedation, dissociation,
13 and blood pressure increase were transient and
14 correlated with serum esketamine level.

15 No serious urinary adverse effects were
16 observed, but sample size and duration of
17 observation may have not been sufficient to rule
18 out serious or long-term effects.

19 Next, I'm going to hand it to my colleague,
20 Dr. Somya Dunn, to talk about risk management.

21 **FDA Presentation - Somya Dunn**

22 DR. S. DUNN: Good morning. My name is

1 Somya Dunn, and I work in the Division of
2 Management. I will present a discussion on risk
3 management for esketamine nasal spray. I will
4 begin with a background on risk evaluation and
5 mitigation strategies or REMS. I will discuss
6 safety concerns associated with the use of
7 esketamine nasal spray, the agency-proposed risk
8 management strategies, and a comparison of the
9 agency and applicant proposals. I will start with
10 a background on REMS.

11 A REMS is a drug safety program that can be
12 required by the FDA for certain drugs. A REMS is
13 designed to mitigate risks associated with drug use
14 and includes strategies beyond labeling to ensure
15 the benefits outweigh the risks of the drug.

16 The FDA Amendments Act of 2007 gave the FDA
17 authorization to require applicants and application
18 holders to develop and comply with REMS if
19 determined necessary. The FDA has the authority to
20 require a REMS pre- or post-approval.

21 A REMS can include a number of components
22 such as a medication guide, a communication plan,

1 elements to assure safe use, an implementation
2 system, and must include a timetable for submission
3 of assessments.

4 If determining a necessary component of a
5 REMS, the elements to assure safe use can include
6 the following: certification and/or specialized
7 training of the healthcare providers that
8 prescribed the drug; certification of pharmacies or
9 other dispensers of the drug; limited settings for
10 dispensing or administration of the drug; having
11 each patient using the drug subject to certain
12 monitoring; the drug is dispensed or administered
13 only with evidence of safe use conditions, for
14 example, a pregnancy test or a liver function test;
15 or enrollment of treated patients in a registry.

16 Additionally, ETASU must align with the
17 serious risks listed in labeling. They cannot
18 cause undue burden on patient access to the drug,
19 considering in particular patients with serious or
20 life-threatening diseases or conditions and
21 patients who have difficulty accessing healthcare.

22 I will now discuss safety concerns for

1 which a REMS is being considered. The agency is
2 concerned about sedation and dissociation caused by
3 esketamine nasal spray. We are also concerned
4 about the potential for misuse and abuse of the
5 product.

6 Sedation was experienced at high rates in
7 patients treated with esketamine. Typical onset
8 was about 15 to 30 minutes, peaked at 30 to
9 45 minutes, and for most, it resolved by an hour
10 and 15 minutes. Sedation fluctuates with visits
11 and there are outliers, such as 1 and a half hour
12 onset and a 3 and a half hour resolution.

13 Twenty-four out of 855 esketamine-treated
14 patients versus 0 out of 287 placebo-treated
15 patients experienced severe sedation. Patients are
16 at risk for accidents due to impaired motor
17 activity as a result of the sedation effect.

18 The score in the Clinician-Administered
19 Dissociative State Scale in the esketamine group
20 was significantly higher than in placebo. Patients
21 experienced visual disturbances, trouble speaking,
22 confusion, numbness, and feelings of dizziness or

1 faintness. They also experienced a distortion of
2 time and space and had illusions and sensations of
3 derealization and depersonalization.

4 Typical resolution was seen by 1 and a
5 half hours after administration. The dissociation
6 effect decreases for about 4 weeks, and then there
7 is a plateau effect where there is no further
8 decrease. Patients are at risk for potential
9 accidents if they experience these dissociative
10 effects and leave the setting prior to resolution.

11 As described in the FDA's background
12 package, ketamine has known abuse potential, and in
13 1999, ketamine and its salts were designated as
14 Schedule III substances under the Controlled
15 Substances Act.

16 Ketamine is abused for its dissociative and
17 hallucinogenic effects and is often associated with
18 so-called rave or nightclub scenes. According to
19 the DEA, major sources of illicit ketamine include
20 diversion or theft from healthcare settings,
21 particularly veterinary clinics and smuggling from
22 outside of the U.S.

1 FDA's review of current ketamine abuse data
2 indicates that ketamine abuse continues to occur
3 most commonly in young adults, but is relatively
4 uncommon in the general population. Available data
5 also suggest no increases in ketamine abuse,
6 despite growing sales of the drug.

7 Ketamine abuse is associated with some
8 adverse effects as evidenced by poison center
9 calls, emergency department visits, and spontaneous
10 adverse event reports, but available data suggest
11 that, in general, abuse of ketamine alone
12 infrequently results in hospitalization or other
13 serious outcomes.

14 In the clinical program, esketamine was
15 self-administered under medical supervision in
16 healthcare settings, therefore, misuse and abuse
17 were not observed. Dissociation effects are seen
18 with esketamine, and the agency is concerned that
19 esketamine nasal spray could be misused and abused.

20 I will now discuss the agency-proposed
21 REMS. The proposed agency goal for esketamine
22 nasal spray is to mitigate the risks of misuse,

1 abuse, and serious adverse outcomes from
2 dissociation and sedation as a result of esketamine
3 administration by ensuring that esketamine is only
4 dispensed and administered in medically supervised
5 healthcare settings that can provide patient
6 monitoring and enrollment of patients in a registry
7 to further characterize the risks and safe use of
8 esketamine.

9 Agency-proposed ETASU include
10 administration of esketamine only in certain
11 healthcare settings that ensure patient monitoring
12 by a healthcare provider for at least 2 hours after
13 administration. Pharmacies, practitioners, or
14 healthcare settings that dispense the drug are
15 specially certified in the REMS program. They
16 ensure that esketamine is not dispensed directly to
17 a patient.

18 The agency also recommends enrollment of
19 patients in a registry to better characterize the
20 risks associated with esketamine administration and
21 informed risk mitigation strategies.

22 The agency believes that limiting

1 esketamine administration to a medically supervised
2 healthcare setting decreases the likelihood of
3 potential serious adverse outcomes from sedation
4 and dissociation and decreases the likelihood that
5 the medication will be misused or abused.

6 The agency believes that a patient registry
7 will serve to inform patients about the REMS during
8 the enrollment process and will also provide
9 additional long-term data to assess use, safety
10 concerns, and confirm and evaluate monitoring
11 times. Certification of healthcare settings and
12 pharmacies ensure that these processes occur.

13 The REMS continues to be under discussion
14 and review, and the agency and applicant are mostly
15 in alignment on the REMS program. The agency is
16 recommending that the length of monitoring
17 post-administration be at least 2 hours, a patient
18 registry that will inform patients, and
19 all-healthcare setting certification. The agency
20 is also considering how blood pressure and/or blood
21 pressure monitoring would be included in the REMS.

22 The agency is concerned about misuse,

1 abuse, and serious adverse outcomes from sedation
2 and dissociation. We would like the committee to
3 consider if the agency-proposed REMS with ETASU
4 program will ensure safe use of esketamine nasal
5 spray.

6 **Clarifying Questions to FDA**

7 DR. NARENDRAN: Thank you.

8 Are there any clarifying questions for the
9 FDA? Please remember to state your name for the
10 record before you speak. If you can, please direct
11 questions to a specific presenter. We'll try to
12 stick to the same rule of one question per person,
13 and if there's extra time, we'll come around the
14 table.

15 Dr. Hernandez-Diaz, first question?

16 DR. HERNANDEZ-DIAZ: Thank you. Sonia
17 Hernandez-Diaz. This is a clarification question
18 about study 3003 -- sorry; like, 35 or
19 so -- regarding the uncertainties and the issues
20 about two things, the blinding and the using in the
21 patients that are not naïve.

22 If I understood correctly, the question we

1 wanted to answer with that part of the study is
2 whether a medication can be used in an acute phase,
3 and then stop using it and using the oral
4 antidepressants, and if that was going to be okay.
5 So a positive outcome would have been that,
6 actually, it can be stopped and things would be
7 okay, and that's not what we see.

8 So I don't understand these two things.
9 One is why is there concern for the interpretation
10 about the blinding since the lack of blinding, if
11 anything, is going to make it more similar to what
12 would happen in clinical practice where stopping
13 the medication, the patient would be aware of that,
14 and, if anything, the relapses would be lighter, so
15 that will support continuation of maintenance in
16 any case?

17 The related second question is the comment
18 that we have to keep in mind that this is in
19 patients that are not naïve. I don't think that's
20 a problem because that was the question. We were
21 not considering not giving aid to patients that
22 were not responding, but among those that respond

1 to discontinuation.

2 I think, in any case, what we are seeing
3 informs and will give us the same answer to the
4 question, can we discontinue or do we need to
5 maintain the medication afterwards.

6 DR. FARCHIONE: Actually, I think that's
7 the part about when you're in clinic -- sorry; this
8 is Tiffany Farchione -- their comment about when
9 patients are in clinic, they know that you're
10 stopping the medication, that's a reasonable point.
11 In real life, you would be unblinded, so we hadn't
12 really taken that into consideration.

13 What we were looking for was just the idea
14 that this medication is different. There are
15 things about it inherently that make it difficult
16 to blind. And we were just trying to dig through
17 to see if there was any way we could tease out an
18 effect of unblinding versus your usual run-of-the-
19 mill relapse. And essentially, what we came down
20 to is that there's just not a way you can tease
21 those things apart.

22 DR. NARENDRAN: Dr. Meisel, you have a

1 person you can identify?

2 DR. MEISEL: Yes. Steve Meisel. I'm going
3 to take two questions, but they're both yes/no
4 questions, so they'll be very, very fast.

5 For Dr. Chen, IV ketamine is associated
6 with nightmares, night terrors, that sort of thing.
7 I've heard nothing about that in terms of the
8 adverse effect list either from the sponsor or from
9 the FDA.

10 Has that not been noted at all in any of
11 these trials?

12 DR. CHEN: No, nightmares. I won't say
13 there's not one case, but the incidence is not high
14 enough for us to notice it.

15 DR. MEISEL: Okay. And the second very
16 quick question for Dr. Potter, the studies that
17 didn't show a statistical significance, the trend
18 lines were still clearly similar, I heard from the
19 sponsor earlier that they were powered for MADRS
20 reduction of about 6, but most antidepressants have
21 a 4.

22 Had these been powered for a 4, would those

1 have been statistically significant? I know you
2 can't go back and redo the trial, but had that been
3 the case, would that have changed the statistical
4 significance?

5 DR. POTTER: Andrew Potter, a very good
6 question. There has been a lot of internal debate
7 about that, and we haven't been able to come to any
8 conclusion about if there had been more sample
9 size.

10 If I could go to the backup slide from the
11 FDA presentation, slide 68, this might help. In
12 this slide, the dark line on top is 84-milligram
13 esketamine, the treatment difference at 28 days
14 between placebo. The bottom lighter gray line is
15 the 65-milligram -- 56, thank you. The red dashed
16 line is the time of the interim analysis. The blue
17 dashed line is the final analysis that the sponsor
18 conducted.

19 I don't know how much we can -- and this is
20 overlap study. I don't know, at 339, if we had
21 extended to maybe 4[00] or 500 patients, I don't
22 know if we could -- I'd be very hesitant to extend

1 out that line, but this is the trends that we saw.

2 DR. NARENDRAN: Dr. Temple?

3 DR. TEMPLE: Not being burdened by being a
4 statistician, it's fairly clear that the results
5 were leaning highly favorably. The reason you
6 couldn't analyze the lower dose was that the
7 primary endpoint was the effect of the higher dose.
8 So although the lower dose was nominally
9 significant, you couldn't get there. But we obey
10 these rules; we believe in them. But it was fairly
11 obviously close. And if the same effect size were
12 seen in a study of twice the size, of course it
13 would have been significant.

14 3005, I think, is more difficult because
15 all of the effect shows up on that last visit,
16 which is completely implausible to me. I think
17 that's a bigger problem.

18 DR. NARENDRAN: Next question, Dr. Besco?

19 DR. BESCO: Hi. Kelly Besco. My question
20 is for the last presenter; Dr. Dunn, sorry.

21 My question is -- I'm just more interested
22 because I don't know that I've ever asked this

1 before -- at what frequency are the results of a
2 REMS program intervention, reviewed by the agency,
3 to just characterize the observed risk and evaluate
4 the effectiveness of the mitigation strategies?

5 DR. S. DUNN: We have the company submit
6 assessments at regular intervals. They have an
7 entire plan to evaluate the REMS, and it usually
8 starts coming in at about 6 months after the
9 program is implemented or the drug is approved, and
10 after that, can be yearly. We can change that, I
11 suppose, if needed, but that's generally the way
12 that it comes in, the assessment.

13 DR. NARENDRAN: Next question, Dr. Bilker?

14 DR. BILKER: Yes. Hi. This is Warren
15 Bilker. I have a question about the elements to
16 assure safe use as part of the REMS program. I
17 thought I understood from previous panels that I
18 was on that the certification of the specialized
19 training for healthcare providers could be
20 suggested but not mandated.

21 I want to know if that's really the case
22 and, if it is, is that the case of any of the other

1 ETA, the other elements? Can they be suggested,
2 but not mandated?

3 DR. S. DUNN: If it's in ETASU and it's
4 requiring a certification, it would be required.
5 If it's training that is offered, then it's not
6 required. This program, we did not propose a
7 program that had healthcare provider certification.
8 We're suggesting that we would have healthcare
9 center certification and pharmacy certification.

10 In that process, the healthcare providers
11 would be informed and trained on what they need to
12 do. So they themselves are not certifying, but if
13 that's a requirement, if that's an ETASU, then
14 there is a certification process, and it is a
15 requirement.

16 Does that answer your question?

17 DR. BILKER: Yes.

18 DR. S. DUNN: Okay.

19 DR. NARENDRAN: Dr. Compton?

20 DR. COMPTON: I believe this is a question
21 for Dr. Kim, if I'm remembering right. In the
22 slide when you compared the MADRS changes for the

1 esketamine trials to other antidepressants, I found
2 that very helpful, sort of providing a broad
3 context for response.

4 Could you describe the differences in the
5 pattern of response as well? So you're looking at
6 the overall score changes, but presumably, one of
7 the advantages of esketamine is the rapid response.

8 Was that apparent in contrast to some of
9 the other trials that you referenced, and are there
10 any similar results for devices in addition to the
11 medications you list?

12 DR. KIM: I don't think I specifically
13 looked at the trajectory in all the antidepressant
14 trials, although we could look back and do that.
15 But just from common knowledge of how oral
16 antidepressants work, they take typically 2 to
17 4 weeks.

18 In terms of -- what was your second
19 question?

20 DR. COMPTON: About devices.

21 DR. KIM: Oh, devices. I think it was in
22 the backgrounder, we looked at some of the MADRS

1 changes and some of the previous approvals for
2 devices. I don't have it right here, but it's in
3 the backgrounder.

4 DR. TEMPLE: In the acute trials, you don't
5 see any separation of drug and placebo until about
6 3 weeks, so this is quite different.

7 DR. NARENDRAN: Dr. Dunn?

8 DR. W. DUNN: Walter Dunn. This is a
9 question for Dr. Chen regarding the patients who
10 experience adverse events. In the spirit of trying
11 to develop a REMS that's least burdensome to
12 patients, from your analysis, can we predict which
13 patients will have problems with blood pressure and
14 sedation maybe during the first 4 weeks or are
15 these events completely random? They'll experience
16 no blood pressure rises during the induction phase,
17 but suddenly spike during the maintenance phase.

18 On a related question, we know that the
19 dissociation severity seems to decrease with repeat
20 administration. Do we see the same trend with
21 blood pressure and sedation?

22 DR. CHEN: For the majority of the

1 subjects, they do have a consistent onset of the
2 sedation, but there are some subjects that it
3 varies. And for the majority, it's not like
4 50 minutes and then next time, 50 minutes. It
5 maybe varies from like this time, 45 minutes, next
6 time, an hour. So it has some variability. It's
7 difficult to predict.

8 For the trend of the attenuation, I didn't
9 see that in sedation and blood pressure.

10 DR. NARENDRAN: Next question, Dr. Everett?

11 DR. EVERETT: Thank you. This is a
12 question that relates probably to Dr. Dunn and
13 ETASU. I'm wondering specifically how much detail
14 we have about the definition of healthcare setting;
15 and what I'm particularly wondering is whether a
16 requirement could be made that the setting have
17 skills and experience in a full range of treatment
18 for depression, not a very narrow one like a
19 drop-in clinic that offered only one modality, this
20 modality, for instance.

21 DR. S. DUNN: From the perspective of the
22 REMS, we would want all the healthcare settings

1 certified. So it would be inpatient, outpatient,
2 private practices, wherever the patient's going to
3 get their dose administered or self-administer
4 their dose. That setting would need certification.

5 There's also regulation, since it's a
6 controlled substance through the DEA, for where
7 that product can be stored and kept. But it would
8 be any healthcare setting that the patient can get
9 the medication administered. So as long as they
10 can meet the requirements that they're going to
11 have to attest to on the form, they would be able
12 to get certified so the patient could be treated.

13 DR. FARCHIONE: This is Tiffany Farchione.
14 I think that this also speaks, to some degree, to
15 the earlier question about balancing safety and
16 access.

17 We didn't want to be overly prescriptive
18 and say this has to be tertiary care facilities
19 with psychiatrists who are highly specialized in
20 treating TRD, because if a patient sees a
21 psychiatrist, they think that this is appropriate,
22 but they don't have the capability to administer

1 this in their hung-out-shingle, in private
2 practice, single-provider, no-ancillary-staff kind
3 of situation, they might be able to refer the
4 patient to, say, a primary care physician who was
5 willing to go through the certification process.
6 But again, as long as the facility can meet the
7 criteria outlined in the REMS, then that facility
8 would be acceptable.

9 DR. NARENDRAN: Next question, Dr. Pine?

10 DR. PINE: This is a question for
11 Dr. Potter, and it's both a specific and a more
12 general question, really, about heterogeneity
13 related to your slide 34. You made comments about
14 the one site in study 3003, about it being -- I
15 won't call it an outlier but somewhat extreme. You
16 made that as an isolated comment.

17 I wondered if you could comment a little
18 more generally about heterogeneity in response, and
19 in particular, across sites. I took your
20 discussion to mean that by some formal statistical
21 analysis, you were not concerned about this and
22 you're not concerned with the overall heterogeneity

1 across sites either in this study or in the other
2 two, or the other positive study, but I wanted you
3 to just comment on that.

4 DR. POTTER: Yes. Andrew Potter. When we
5 looked at all the sites by treatment effect, this
6 site was clearly different in all the studies. I'm
7 trying to remember back. There wasn't a ton of
8 variability in some of the other sites.

9 DR. PINE: But when you fit interactions
10 with site as a factor, was the overall
11 heterogeneity significant among all the sites?

12 DR. POTTER: We did not conduct an
13 interaction test. We excluded a site, saw if there
14 was significant change in the treatment effect, and
15 did that for all the sites, and then compared
16 those.

17 DR. PINE: So this might just be anecdotal?

18 DR. POTTER: It might be anecdotal, might
19 not. There's nothing further about beyond.

20 DR. PINE: Got it.

21 DR. FARCHIONE: This is Tiffany Farchione.
22 I would point out also that that particular site

1 was inspected, and we didn't find any reason to
2 question the data integrity.

3 DR. NARENDRAN: Dr. Hillefors?

4 DR. HILLEFORS: Mi Hillefors, NIMH. I had
5 a question about the two studies that's really the
6 basis for this application, study 3002 and 3003,
7 the short-term and the long-term. There seems to
8 be both a difference in the clinical efficacy
9 timing and an overlap.

10 The 3002 is really short-term efficacy,
11 4 weeks, versus a longer term several months for
12 the maintenance, 3003. There seems like there's
13 one study supporting short term and one study
14 supporting longer term, so that doesn't make two
15 studies.

16 How does FDA deal with -- there is an
17 overlap in the subpatient population, because the
18 short-term study, the patients feed into the
19 long-term studies. So there are not truly
20 independent studies from each other.

21 DR. POTTER: Andrew Potter from FDA. For
22 independence, since the statistical analyses are

1 done separately and aren't combined, the
2 statistical analyses will be separate even though
3 there is overlap between the patient population.

4 I'll let my colleagues answer the other.

5 DR. FARCHIONE: One of the main questions
6 that you guys are going to be asked has to do with
7 whether they've met the standard for substantial
8 evidence of effectiveness. I had actually been
9 scribbling down some comments to make during the
10 charge to the committee, but I suppose I
11 can -- spoiler alert, you might hear this again.

12 The idea here is that we do have two
13 positive adequate and well-controlled studies. The
14 populations, though, as you mentioned, are
15 different, and they are looking at different
16 aspects of the same disease. So this is really one
17 of the key questions that we're asking you guys, is
18 whether or not you think they have met that
19 standard.

20 One thing I would note, though, is when you
21 do get to the point of saying, yes, we have the two
22 positive, adequate, and well-controlled studies, it

1 is then legitimate to look to the other studies for
2 any supportive evidence, whether you see other
3 trends or anything that either adds weight to or
4 against what your prior conclusion is based on
5 those two studies.

6 So there is a lot to consider when you
7 think about question 1 later on today.

8 DR. NARENDRAN: Next question is on the
9 phone, Dr. Conley?

10 DR. CONLEY: Yes. Thanks very much. This
11 is Dr. Rob Conley, and my question is to
12 Dr. Potter. It's sort of along the same lines.
13 Since this is one of the first times the FDA has
14 considered a randomized withdrawal design, I think
15 one of the concerns you said was about the, quote,
16 "enriched population."

17 I might have been missing something; that's
18 why I'm asking for clarification here. I would
19 think that, by definition, a randomized withdrawal
20 design must have an enriched population, I think
21 from the way you were saying it, because it has to
22 be taken from responders. But maybe I wasn't

1 following that line of thinking very well. That's
2 why I was asking for some clarification here.

3 Thank you.

4 DR. POTTER: Yes, that's our understanding
5 as well.

6 DR. TEMPLE: This is Bob Temple. It's
7 definitely an enriched population, and our draft
8 enrichment guidance cites it as an example of
9 enrichment. You're studying the people who
10 responded. That's one of the things that's
11 attractive about it. They're more likely to
12 respond than an unselected population, but it still
13 should give you an answer for that population.

14 DR. CONLEY: That's what I was thinking.
15 It felt like what was being said that there was a
16 worry about getting it after, Bob, but I thought
17 it's a reasonable design. But thank you for that.

18 DR. NARENDRAN: Next question,
19 Dr. Rudorfer?

20 DR. RUDORFER: Yes, thank you. Matthew
21 Rudorfer. I guess a question for anybody from the
22 FDA. I'm still concerned about the antidepressant

1 comparator. I'm thinking, if we're looking at a
2 4-week acute treatment trial, wouldn't we want to
3 see esketamine nasal spray active versus esketamine
4 nasal spray placebo without other drugs that some
5 people might start to respond to within 4 weeks and
6 some won't, some might develop adverse effects to
7 the comparator antidepressant and some won't?

8 DR. FARCHIONE: This is Tiffany Farchione
9 again. When we were working together with the
10 company in designing the studies, this is something
11 obviously we talked a lot about. When you have a
12 population that is seriously ill that has failed a
13 number of treatments before, it really was hard for
14 us to stomach the idea of just having them in a
15 trial with no treatment at all.

16 So having everyone on a new antidepressant
17 seemed like a good way to deal with that in terms
18 of just from an ethical perspective.

19 Then also, we don't really expect to see
20 much happen with the oral antidepressant for the
21 first few weeks. If we could see any effect of the
22 drug earlier than that, we would expect that effect

1 to be primarily due to the esketamine that was
2 added on.

3 DR. TEMPLE: Tiffany, you actually do have
4 a phase 2 study, which gave a pretty strong result,
5 in which there was no background.

6 There was?

7 FEMALE VOICE: There could have been
8 background [indiscernible - off mic].

9 DR. TEMPLE: Well, there could have been,
10 but it wasn't required in the same way. What's
11 interesting is that showed a numerically
12 considerably larger effect. Whether that had
13 anything to do anything is not so clear.

14 DR. NARENDRAN: Next question, Dr. Zito?

15 DR. ZITO: I would like to think about
16 diversion and the risk of diversion more,
17 particularly in terms of the loose definition of
18 healthcare clinics because in my experience, there
19 can be quite a range in terms of, one, having staff
20 who become salesmen for the product; but two, how
21 to deal with severe adverse events with the
22 patient; and three, is driving going to be

1 permitted on the day of medication, and how are you
2 going to enforce that sort of thing?

3 DR. FARCHIONE: I mean, we can't shackle
4 patients to the chair, but it is part of the REMS
5 to say that patients should not drive on the day of
6 the study; that they should have somebody come with
7 them to the clinic and plan to drive.

8 I'm sorry. This is Tiffany Farchione again
9 for the transcript.

10 In terms of diversion and things like that,
11 the way that the product is packaged, although it's
12 probably not the greenest option you could come up
13 with, with all of these different containers and
14 everything, it does make it really difficult to get
15 an abuseable quantity out of the devices; not
16 impossible, obviously.

17 DR. ZITO: I would suggest that there are
18 very smart folks who can handle all of these
19 problems.

20 DR. FARCHIONE: Right, but you've got to
21 basically take a crate of esketamine home with you.
22 That's an exaggeration. Obviously, I don't want to

1 minimize the concern or seem like I'm being
2 dismissive, but we can do so much. And I do think
3 that they've done quite a bit in terms of trying to
4 address this risk.

5 DR. ZITO: I do appreciate the efforts that
6 are being made, and I don't want to sound cynical,
7 but I do think that this delivery system is quite
8 different from IV, and this will really encourage a
9 lot of creative chemistry.

10 DR. NARENDRAN: I'm going to move to the
11 next question. Mr. Kungel?

12 MR. KUNGEL: Terry Kungel. Quick question
13 to Dr. Farchione. We have a number of different
14 oral antidepressants that were in this program.
15 Did we ever look at the individual drugs to see if
16 there was a MADRS effect associated with specific
17 depressive drugs?

18 DR. KIM: This is Jean Kim. We did look at
19 the comparison, and there was no remarkable change
20 between the different oral antidepressants.

21 DR. NARENDRAN: Next question on the phone,
22 Dr. Fiedorowicz?

1 DR. FIEDOROWICZ: Yes, hello. This is Jess
2 Fiedorowicz from the University of Iowa. I just
3 had a quick follow-up question to Andrew Potter.
4 This was in prior discussion about the sites,
5 study 3003 that had all the responders. I believe
6 it was [indiscernible] from the materials provided.
7 He had said that the site was, quote, "clearly
8 different than all the studies," end quote.

9 Did this imply that the results differed
10 for the site not just in study 3003, but the other
11 studies as well, or was that just a misspeaking?

12 DR. POTTER: It did not differ in the other
13 studies. It was compared -- let me clarify. It
14 was distinct only looking at the sites in 3003.

15 Does that help?

16 DR. FIEDOROWICZ: Yes. Thanks for
17 clarifying. When you said all the studies, I
18 wasn't sure if there were different -- if this
19 pattern showed across -- if this site was
20 participating in other studies and if the pattern
21 showed this. So it sounds like you were referring
22 specifically and only to study 3003.

1 DR. POTTER: Yes.

2 DR. FIEDOROWICZ: Thank you.

3 DR. KIM: This is Jean Kim. Just to
4 clarify, in 3002, we did not have that concern
5 about an outlier site.

6 DR. NARENDRAN: Next question, Ms. Witczak?

7 MS. WITCZAK: Yes. Looking beyond just
8 this initial clinical trial and looking more
9 forward to real-world implications. If the
10 estimates of 16.2 million have MDD and anywhere
11 from 29 to 46 percent have TRD, do you have a
12 thought on if you think this should be -- again, I
13 keep going back to the general practitioners and
14 having limited access to psychiatrists, and then
15 once advertising and knowing how the public thinks,
16 we want quick -- because there is something
17 attractive about it, a quick reaction.

18 But I wanted to know your thoughts on where
19 this should actually be handled because there are
20 going to be limitations on psychiatrists and we've
21 got to be realistic; anywhere from 29 to 46 percent
22 of people, of 16.2 million, where this is going to

1 be ultimately being recommended.

2 DR. S. DUNN: Well, at this time, we're
3 still discussing what the attestations will be for
4 the healthcare setting. We do want to make sure
5 that the patients have a safe place to stay while
6 they're being monitored, and that that practitioner
7 that's at that setting is able to do appropriate
8 monitoring; that they have the devices to check
9 blood pressure and a place for the patient to stay
10 and wait that's not around other people and that
11 sort of thing.

12 It is a controlled substance, so it'll be
13 regulated in that way in terms of how it's going to
14 go to the patient and be regulated. We don't want
15 to make it so difficult for patients to access the
16 medication and didn't feel that we needed to be
17 overly prescriptive with the healthcare settings.

18 So at this time, it is our intention to try
19 to enable clinics and practitioners that feel they
20 are able to handle those requirements, to have the
21 patients administer the drug there.

22 But we are interested to know, from the

1 committee as well, if there are particular concerns
2 that you believe need to be worked into the REMS,
3 that will be part of the discussion hopefully
4 later. But right now, we're working with
5 healthcare settings that can meet those
6 requirements. And basically, it would be
7 monitoring the patient until they're clinically
8 stable and for that minimum 2-hour time period.

9 DR. NARENDRAN: I'm going to give
10 Dr. Hoffer has a chance. He hasn't asked his
11 question.

12 DR. HOFFER: Yes. Lee Hoffer. My question
13 goes back to a little bit about what Tiffany was
14 asking or talking about. Just how much medicine
15 are doctors going to get to treat one patient? So
16 they get the little inhaler and they might have 50
17 of those for one patient over the course of
18 6 months. Is there any kind of idea of just scale
19 per patient?

20 DR. S. DUNN: In most situations, the
21 medication would be going to a patient specifically
22 for that particular patient or it would be in a

1 healthcare setting, like a large healthcare setting
2 like a hospital or something like that, that keeps
3 that stocked and secure, and that's also regulated
4 by the DEA.

5 However, there are ways that maybe there
6 could be a large clinical setting where they could
7 stock and store it for patients that haven't come
8 in yet. That is a possibility. So we are planning
9 on asking through the REMS for data to reconcile,
10 have the company reconcile how much was given to
11 patients and what was at that facility.

12 If there are any discrepancies, we would
13 ask for audits, and that's something that we're
14 discussing in more detail right now. But we are
15 working on a program to try to help ensure that
16 that doesn't happen.

17 DR. NARENDRAN: We're almost up. I'll give
18 5 minutes for rapid-fire questions for a second
19 round.

20 Dr. Pine, very sharp-focused questions,
21 please.

22 DR. PINE: Sure. This is for Dr. Temple in

1 discussing the randomized discontinuation design.
2 I seem to recall from other discussions that you
3 had thought that that was not only a legitimate
4 efficacy design, but a good one.

5 Could you just comment on that?

6 DR. TEMPLE: As a general matter, I like
7 enrichment because it helps you win. The problem
8 with it, the limitation of it, and everybody has
9 known this, that it's not a general population.
10 You don't get an answer as to what the response
11 rate is when you first use the drug. It's not for
12 that.

13 What it does is confirm the fact that the
14 other studies did identify populations who
15 responded, and it confirms the fact that the drug
16 did what you hoped it would do. So there are
17 generalizability issues that have to be discussed,
18 but does it confirm the fact that the drug did what
19 it's supposed to if you're not worried about
20 unblinding? Yes, and in a good way.

21 DR. NARENDRAN: Next question,
22 Dr. Hernandez-Diaz?

1 DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz.
2 This is going back to the p-values because it's
3 going to affect how I interpret the effectiveness
4 of medication. I'm not concerned about the
5 p-values but about the reasons for them to be so
6 borderline. One, of course, could be the sample
7 size; with a lighter sample size, we will have
8 crossed that. I would be concerned regarding
9 whether the sample size was decreasing because of
10 withdrawal on adverse events.

11 Mainly, my concern is about the tiny
12 effects that we see on top of placebo, and it was
13 asked before. We see the placebo dropping 14,
14 16 points and a complicated treatment adding 3.5,
15 4 points extra.

16 I wonder -- we seem to count in
17 p-values -- if the FDA has any advice for what is
18 considered effective in the antidepressant research
19 if 4 points in the scale is considered relevant, if
20 there is any guidance, because we have heard that
21 that can be clinically relevant, but I wonder if
22 there is any rule.

1 DR. FARCHIONE: We know that placebo
2 response is a huge problem in antidepressant
3 clinical trials just generally. In most approved
4 antidepressant programs, you'll see somewhere
5 around 3 points versus placebo because you see
6 improvement in both groups. So even though you
7 might see a 12- or 15-point drop overall, it's only
8 a couple points better than placebo.

9 In this case, you're still a couple points
10 better than placebo, but you're 4 points, and in
11 this case, you do see that effect. Very early on,
12 you see the separation very early on, and then that
13 separation remains pretty consistent throughout.

14 So even if that's not a placebo effect,
15 even if, for instance, the underlying
16 antidepressant is starting to do something, it's
17 doing it in both arms, and it's doing it in the
18 same pattern, but still, you have that separation
19 and you maintain it throughout. It's a reassuring
20 pattern.

21 DR. NARENDRAN: The last question,
22 Dr. Dunn?

1 DR. W. DUNN: This is Walter Dunn. This is
2 a question for Dr. Dunn. I also wanted to say
3 that, and thanks for squeezing me in.

4 (Laughter.)

5 DR. W. DUNN: It's a question about the
6 REMS. I'm certainly not advocating for this, but
7 are you guys thinking about or even discussing any
8 restrictions on maximum dose, frequency of dose,
9 increasing it beyond twice a week, or the time
10 frame between doses?

11 It looks like, in the study, the minimum
12 time was 72 hours. Are there any restrictions as
13 far as doing it the day after?

14 DR. S. DUNN: That would be actually a
15 question for the review division. That's not
16 really something that would be regulated through
17 the REMS program. Those would be labeling
18 recommendations. I guess I'll let the review
19 division answer that.

20 DR. FARCHIONE: If the drug were to be
21 approved, it would be labeled to be administered
22 similar to the way that it was in the clinical

1 trials. Although, I can see your point that if we
2 are looking into are people using it more, or more
3 often, or worried about a pill mill or something
4 like that, one potential signal could be that
5 you've got a patient who is somehow getting it
6 every day or twice a day, and that would be a red
7 flag. But we haven't really discussed that in
8 terms of tracking or adding that. I'm not even
9 sure if there's a mechanism by which we could do
10 that.

11 DR. LaCIVITA: That may be something that
12 the sponsor reports to us in the assessment
13 reports, because I know that they had mentioned
14 that they'll be looking for deviations. So that
15 could be something that's picked out from that
16 perspective.

17 DR. NARENDRAN: I think with that, we will
18 now break for lunch. We will reconvene in this
19 room at 1:15, roughly 50 minutes from now.

20 Please take any personal belongings you may
21 want to. Panel members, please remember that there
22 should be no discussion of the meeting topic during

1 lunch amongst yourselves or with any member of the
2 audience. Thank you.

3 (Whereupon, at 12:23p.m., a lunch recess
4 was taken.)

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A F T E R N O O N S E S S I O N

(1:17 p.m.)

Open Public Hearing

DR. NARENDRAN: We're going to start now.

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.

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4 the beginning of your statement, it will not
5 preclude you from speaking.

6 The FDA and this committee place great
7 importance in the open public hearing process. The
8 insights and comments provided can help the agency
9 and this committee in their consideration of the
10 issues before them. That said, in many instances
11 and for many topics, there will be a variety of
12 opinions.

13 One of our goals today is for this open
14 public hearing to be conducted in a fair and open
15 way, where every participant is listened to
16 carefully and treated with dignity, courtesy, and
17 respect. Therefore, please speak only when
18 recognized by the chairperson. Thank you for your
19 cooperation.

20 Will speaker number 1 step up to the podium
21 and introduce yourself? Please state your name and
22 any organization you are representing for the

1 record.

2 DR. FOX-RAWLINGS: Thank you for the
3 opportunity to speak today on behalf of the
4 National Center for Health Research. I am
5 Dr. Stephanie Fox-Rawlins. The center analyzes
6 scientific and medical data to provide objective
7 health information to patients, health providers,
8 and policymakers. We do not accept funding from
9 the drug or medical device companies, so I have no
10 conflicts of interest.

11 A drug that reduces symptoms of
12 treatment-resistant depression within a few days
13 could be very valuable. Esketamine is particularly
14 interesting because it works differently from other
15 antidepressants on the market. Even if it was only
16 practical or even only effective for a few weeks or
17 months, it would still be beneficial.

18 The data from the clinical trials for
19 esketamine nasal spray are encouraging, but they're
20 still important questions concerning its safety and
21 efficacy. Of greatest concern, only 1 of the 3
22 short-term phase 3 efficacy studies had significant

1 effects. This could mean that the positive result
2 of that trial was due to chance or that the
3 treatment is only effective for a narrow subset of
4 patients or only under particular circumstances.

5 The randomized withdrawal trial also
6 suggests that the drug is effective, but the
7 results were largely driven by one study site, and
8 since the drug can cause immediate side effects, it
9 is likely that many patients in the study were not
10 truly blinded.

11 Esketamine could have a role in treating
12 treatment-resistant depression with either
13 short-term and/or long-term effects, but these
14 effects should be clearly demonstrated before FDA
15 makes a decision about approval. If the drug is
16 only effective for a definable subset of patients,
17 the indication should specify those patients
18 because it would be important information for
19 clinicians and patients.

20 There are several major safety concerns
21 that need to be addressed. The imbalance in death
22 is of great concern. Six patients taking

1 esketamine died compared to zero patients taking
2 placebo. Three of these deaths were due to
3 suicide. Other antidepressant medications can also
4 increase the risk for suicidal thoughts and
5 behaviors.

6 Esketamine works very differently from
7 those other antidepressants, and if it increases
8 the risk for suicide, it is important to note if
9 this is higher or lower compared to other
10 antidepressants. Clinicians and patients need to
11 know if the drug can increase this risk.

12 It is essential that patients receive the
13 correct dose. The human factors study demonstrated
14 that users were confused about the strength and
15 dose of the product. This confusion increases the
16 risk for avoidable serious harm. If the drug is
17 approved, it is important that the company develop
18 packaging and labeling to make sure that patients
19 are given the proper dose.

20 For that reason, a study demonstrating that
21 the product can be used properly should be required
22 before approval.

1 The applicant and the FDA proposed REMS to
2 reduce the risks for patient harm due to adverse
3 events and the risk for misuse and abuse. The
4 proposed REMS, including education and
5 certification for providers, patient education, and
6 clinical administration, and patient monitoring for
7 at least 2 hours could help keep patients safe, but
8 only if these are actually carried out.

9 These REMS should be required, not
10 voluntary. If sites are lax in their training,
11 dispensing, and monitoring practices, patients are
12 likely to be harmed. The REMS need to be carefully
13 evaluated before widespread implementation and
14 continuously monitored to ensure that they are
15 working.

16 Although we have strong concerns about this
17 drug, it may be a better option for some patients
18 than other FDA-approved treatments for refractory
19 depression, such as ECT.

20 In conclusion, esketamine has the potential
21 to help patients. Please carefully consider the
22 results of the clinical trial. There are still

1 important efficacy and safety questions. New
2 treatments need to have strong evidence that they
3 work and can be used safely before approval.
4 Another clinical trial, if it showed statistical
5 and clinically meaningful results, would provide
6 important information about dosage and appropriate
7 patients. Thank you for your time.

8 DR. NARENDRAN: Thank you.

9 Will speaker number 2 step up to the podium
10 and introduce yourself? Please state your name and
11 any organization you are representing for the
12 record.

13 Speaker number 2 is not here, so we'll move
14 to speaker number 3.

15 MS. COHEN: Hello. My name is Joy Cohen.
16 I'm a 69-year-old wife, mother of one daughter, and
17 grandmother of one granddaughter. My husband and I
18 will be married 48 years in May, and we live in a
19 suburb of Boston. I have been in esketamine trials
20 3005, 3004, and 3008 at Adams Clinical in
21 Watertown, Massachusetts. Adams Clinical is
22 reimbursing my travel and lodging expenses for

1 coming here today.

2 I have suffered from chronic
3 treatment-resistant depression for over 25 years.
4 I've been to numerous doctors, psychiatrists,
5 psychopharmacologists, and therapists, too many to
6 count. I've tried many antidepressant drugs over
7 the years, including imipramine, Prozac, Celexa,
8 Effexor, Wellbutrin, Lamictal, Trintellix, Remeron,
9 Seroquel, buspirone, and Abilify. None of these
10 drugs have worked for me. Actually, two
11 medications did work initially, but they petered
12 out after just 3 months.

13 I've suffered many side effects from these
14 medications, including agitation, shakiness,
15 nausea, and difficulty sleeping and eating. It's
16 been very difficult trying each new medication as
17 it takes time to reach a therapeutic dose, see if
18 it works, and then if it doesn't, slowly wean
19 myself off of it.

20 It hasn't been done doing this time after
21 time. It's been an extremely painful process over
22 many years. Depression is a terrible thing. It

1 takes life's happiness away. No matter how hard
2 you try, you just don't feel right. The sadness
3 is overwhelming. The darkness is always present.
4 It's so difficult to accomplish your everyday
5 chores and to put on a happy face for your friends
6 and family, wanting them to think you are normal.

7 I always ask my psychopharmacologist to
8 think of me when he would go to medical conferences
9 and seminars to keep an ear open for any new drug
10 or idea, no matter how out of the box it may be.
11 Finally, he came back from a meeting where he met
12 Dr. Daniel Rutrick, who told me of a trial he was
13 running with esketamine for people with
14 treatment-resistant depression over 65 years of
15 age.

16 My doctor was kind enough to get
17 Dr. Rutrick's contact information and nice enough
18 to discuss it with me and give me the information.
19 I called Dr. Rutrick at Adams Clinical immediately
20 and was able to get an appointment right away. I
21 went to see him, and we talked for quite a while.
22 Dr. Rutrick asked me numerous questions to see if I

1 would be a good for his study, then he explained to
2 me about the study and how it would work.

3 I was quite excited when I was accepted to
4 the study. There are not a lot of trials for
5 people in my age group. It was a big decision, but
6 I felt I had -- every other avenue and wanted to
7 try esketamine.

8 When I went to get my first dose of
9 esketamine, I was a little nervous as I was every
10 time I tried a new medication. The experience was
11 certainly unique, but not unpleasant. Esketamine
12 is easily administered and as its effects diminish,
13 you return to normal with no side effects.

14 I continued to go for my treatments
15 faithfully, and after a very short time, I started
16 to feel different, better. My husband and daughter
17 said they saw an improvement in my mood. Then my
18 friends said they did, too. I felt better. I
19 don't feel that constant, overwhelming sadness
20 these days.

21 I'm so grateful to have found this
22 medication that actually helps me and has no

1 adverse side effects. I am so glad the trial was
2 available to people over age 65. I feel so lucky
3 to have been accepted into this esketamine trial.
4 It has made a real difference in my life.

5 I hope you will approve esketamine and that
6 it will be able to help many more people. Thank
7 you for your time.

8 DR. NARENDRAN: Thank you.

9 Will speaker number 4 step up to the podium
10 and introduce yourself? Please state your name and
11 organization you are representing for the record.

12 MR. SCHARF: Good afternoon. My name is
13 Eric Scharf. I am the efficacy advisor to the
14 Depression and Bipolar Support Alliance. DBSA has
15 received funding from Janssen for support on
16 sponsorship of our peer support program. However,
17 today, I have not been given any remuneration to be
18 here or any travel expense. I'm also a person who
19 lives with treatment-resistant depression.

20 DBSA is the leading peer-directed national
21 organization, focusing on mood disorders,
22 depression, and bipolar disorder. Unlike any other

1 organization of its kind, DBSA is created for and
2 led by individuals who themselves have a lived
3 experience of a mood disorder. It is this
4 first-person lived experience that informs our
5 comments.

6 DBSA's vision is wellness for people with
7 mood disorders, and we believe that an open and
8 collaborative approach to treatment that accounts
9 for the whole person. Whether she or he is right
10 now, it is what allows people to achieve what they
11 personally define as wellness.

12 In the 60 years that have passed since the
13 first antidepressant medications were approved by
14 the FDA, there have been significant advances in
15 scientific understanding of depression and better
16 recognition of the challenges faced by many who
17 live with this condition, however, innovation has
18 been incremental.

19 People electing such treatment are
20 consequently frustrated by and losing hope of a
21 medical product solution. Last year, DBSA
22 distributed a survey to its community to understand

1 how they define and prioritize aspects of wellness
2 while living with a mood disorder. Of the over
3 6400 responses, nearly one-third of the respondents
4 reported having 10 or more discrete episodes of
5 severe depression. Thirty-six percent indicated
6 that its impact is persistent. These findings are
7 consistent with the literature on this condition
8 that affects 21 million Americans.

9 The first priority for treatment is
10 ensuring that a person living with depression is
11 provided a pathway out of the crisis and on to
12 stability. However, all too often, this baseline
13 stability is also an end goal established for
14 successful long-term care. Stable or better is
15 not always synonymous with well.

16 DBSA believes that every person deserves
17 the opportunity not just to survive but to thrive,
18 and to do that, we need to ensure true wellness as
19 the end goal for mental health treatment. DBSA
20 urges the committee to consider implications of
21 chronic versus episodic experiences of mood
22 symptoms.

1 Success should not be defined by
2 controlling this week's, month's, or even this
3 year's episode of a mood disorder, but by reducing
4 the severity and eliminating the reoccurrence of
5 symptoms over the entire lifetime. Further, the
6 idea of wellness cannot be embraced without
7 considering the whole health of the individual.

8 Comorbidities associated with depression
9 are not insignificant. The prevalence of major
10 depression among individuals living with heart
11 disease, diabetes, Parkinson's disease,
12 Huntington's disease, multiple sclerosis,
13 polycystic ovary syndrome, and Alzheimer's, to name
14 just a few, is well known. The effect depression
15 can have on attaining positive outcomes of comorbid
16 conditions is significant.

17 Even more challenging than understanding
18 the whole health ramifications of pharmacological
19 interventions associated with comorbidity is the
20 realization that no one medication typically
21 provides the entire range of symptom relief.
22 Additionally, the risk-benefit tolerances are

1 different for each individual.

2 Just as significant, prescribers treating
3 major depressive disorder are faced with a dilemma
4 that each patient's clinical reaction to the same
5 medication can vary. Further, the considerations
6 around medication risks and benefits are often
7 different from patient to patient. The prescriber
8 may approach the challenge from the clinical
9 perspective, symptom relief, and the patient on the
10 other hand may be seeking other well-being
11 outcomes.

12 These variables often result in a
13 frustrating trial-and-error period for both
14 prescribers who want to help their patients and the
15 patient who was looking for improvement.
16 Unfortunately, during this trial-and-error period,
17 many patients reach a point where they abandon hope
18 in a pharmacological intervention or other type of
19 a treatment.

20 If I've communicated anything today, I hope
21 it is this. Patients count. Patients want and
22 need solutions that support a pathway to wellness.

1 Depression is not a problem solved. One size does
2 not fit all. Solutions are as complex as the
3 individuals seeking them, and individuals will
4 evaluate the risks and benefits of solutions based
5 on their own life circumstances.

6 I respect that there are many variables
7 taken into account when considering this
8 application. However, I urge the advisory
9 committee to prioritize patient-desired treatment
10 outcomes as part of your evaluation. Thank you.

11 DR. NARENDRAN: Thank you.

12 Will speaker number 5 step up to the podium
13 and introduce yourself? Please state your name and
14 any organization you are representing for the
15 record.

16 MS. REINERT: Good afternoon. My name is
17 Maddy Reinert, and I'm here to speak on behalf of
18 Mental Health America and our constituents. I did
19 not receive compensation for my time or travel here
20 and have no interest in the outcome of these
21 deliberations. I would like to begin by thanking
22 the committee for their time and effort in

1 considering this important issue.

2 MHA is the nation's leading community-based
3 nonprofit dedicated to addressing the needs of
4 those with mental illness and to promote the
5 overall mental health of all Americans. Our work
6 is driven by our commitment to promote mental
7 health as a critical part of overall wellness,
8 including prevention services for all, early
9 identification and intervention for those at risk,
10 and integrated care, services, and supports for
11 those who need it with recovery as the goal.

12 Depression is the leading cause of
13 disability worldwide and is one of the highest
14 burden disease conditions in the United States.
15 This problem persists despite the availability of a
16 number of antidepressants and a number of
17 initiatives to deploy existing antidepressants more
18 effectively.

19 This is undoubtedly helpful for many, but
20 current antidepressants are not sufficiently
21 effective for many Americans. About half of people
22 with depression are not helped by the first

1 antidepressant prescribed by their doctor and
2 one-third of patients don't respond to several
3 attempts at treatment, indicating they likely meet
4 criteria for treatment-resistant depression. Even
5 among those with TRD, 30 percent of patients do not
6 respond to any treatment.

7 Beyond the problems of effectiveness, most
8 antidepressants do not provide immediate relief of
9 symptoms. Most people do not see any improvement
10 in depressive symptoms for at least 4 weeks and
11 studies have shown that the full benefits of
12 antidepressants may not take effect for up to
13 3 months.

14 During this time, people often experience
15 the side effects of these medications without the
16 benefits and give up on treatment and hope of
17 recovery. Nearly half of patients discontinue
18 antidepressant treatment within 6 months. These
19 challenges increase the burden of depression and
20 reduce the likelihood that individuals will try
21 medication-based options that can provide relief.

22 It is imperative that we continue working

1 so that people dealing with depression have more
2 innovative, effective, tolerable, and fast-acting
3 options to choose from when addressing their
4 symptoms.

5 At Mental Health America, we asked people
6 to share what mental illness feels like to them on
7 social media, and I think it's worth taking a
8 moment to consider their responses. One user
9 stated, "I fear starting a medication because I
10 don't know what sort of side effects I'll
11 experience. I want to feel some relief, but it
12 almost doesn't seem worth it. I've felt awful for
13 so long, I've gotten used --" [inaudible - mic
14 fades].

15 Others described their fear that they'll
16 never find a suitable treatment and the
17 hopelessness that comes with drastically increasing
18 their dose or switching to a new medication, only
19 to feel worse rather than better.

20 We need to aspire to more than the
21 therapies we currently have for the millions of
22 people in this country that struggle with

1 depression and provide them with treatment options
2 that work quickly enough that they may make
3 stronger connections between the medications they
4 take and their improvement in symptoms, improving
5 utilization and adherence to treatment that truly
6 works.

7 Despite mental health being something that
8 more and more people are talking about, far too
9 many people are still suffering. People are simply
10 not receiving the treatment they need to live
11 healthy and productive lives and too many don't see
12 a way out. We simply must do more to provide
13 additional effective options for those dealing with
14 depression in this country.

15 In closing, we want to thank the committee
16 for its careful attention to this treatment that
17 helps us feel much relief and a renewed hope about
18 the future of treatment options for depression.
19 I'm happy to answer any questions you may have.
20 Thank you.

21 DR. NARENDRAN: Thank you.

22 Will speaker number 6 please step up to the

1 podium? Please state your name and organization
2 for the record.

3 MR. SPERLING: Good afternoon. My name is
4 Andrew Sperling. I'm with the National Alliance on
5 Mental Illness. I have received no compensation or
6 reimbursement for being here today other than my
7 salary as an employee of NAMI.

8 NAMI, as you may know, is the nation's
9 largest organization representing people living
10 with serious mental illness in their families. We
11 have more than 500 local organizations all across
12 the country providing advocacy, support, and
13 education for people living with these devastating
14 disorders, and treatment-resistant depression is
15 among the most devastating.

16 People living with TRD experience enormous
17 frustration. It's been discussed earlier. These
18 are individuals that have repeatedly failed on two
19 different medications, but even three, or four, or
20 five, and failed to get any symptom relief
21 whatsoever.

22 We know that this is about a third of

1 people that have been diagnosed with depression.
2 This is by no means a small population. There's an
3 enormous public health burden associated not only
4 with the cost of care but lost productivity
5 approaching, by many estimates, as much as
6 \$64 billion a year in this country. So it's
7 enormously expensive in terms of public health
8 burden.

9 We also know about the dramatically higher
10 risk of both suicidal ideation and suicidal
11 actions. We know that mortality from suicide
12 [inaudible - mic fades] -- for breast cancer and
13 prostate cancer combined. It's about 40,000
14 Americans a year, and we don't see any improvement
15 of really changing that curve over the near term.
16 So we desperately need newer and better therapies
17 to address that associated with suicide as an
18 epidemic in this country.

19 We know that there are limited options now
20 for treatment-resistant depression. We have very
21 few on-label medications. One antipsychotic is
22 adjunctive therapy. We know about the side effects

1 associated with that particular compound in terms
2 of weight gain and other types of problems that are
3 devastating for people. We know about ECT. It can
4 work for a small fraction of people, but the side
5 effects associated with ECT can be severe; and same
6 with some of the vagus nerve stimulation and
7 transcranial magnetic stimulation. These are not
8 viable treatment options for many, many patients
9 living with treatment-resistant depression.

10 Now, we have a breakthrough, a real
11 promising new intervention that's really going to
12 give hope to people living with treatment-resistant
13 depression. It's been discussed here earlier
14 today, an immediate response.

15 Imagine the challenge for someone living
16 with treatment-resistant depression, when you're
17 getting no clinical benefit, yet your physician
18 continues to tell you, "Wait another 3 or 4 weeks.
19 Wait another 3 or 4 weeks and, hopefully, we're
20 going to get some clinical response." This is
21 immediate response, which is enormously valuable
22 for patients, not having to wait 4 to 6 weeks.

1 Easy administration with this new
2 technology and very, very important in terms of
3 adherence. We have enormous problems with
4 adherence with oral medications. We're not going
5 to have an adherence problem with this particular
6 product.

7 Minimal side effects was discussed earlier,
8 both in the presentations by the FDA staff and the
9 sponsor. It is enormously important, given some of
10 the side effects associated with existing
11 antidepressants out there that can be very
12 challenging for patients.

13 Finally, the REMS, which has been discussed
14 at this meeting on behalf of the FDA and the
15 sponsor, are going to ensure that there's
16 absolutely minimal or no risk whatsoever of
17 diversion or abuse, which is very, very important
18 going forward.

19 This is real hope for people living with
20 treatment-resistant depression, and NAMI would urge
21 the committee to give every consideration to this
22 problem. Thank you.

1 DR. NARENDRAN: Thank you.

2 Will speaker number 7 step up to the
3 podium? Please state your name and organization
4 for the record.

5 MS. KELLEY: I am patient 20015525 from
6 site A51 US 10055, patient emeritus of the Janssen
7 3002 study and current participant in the 3008
8 open-label long-term study. I am here unsolicited
9 to ask you to approve the esketamine 28-milligram,
10 single-use nasal spray device in its current
11 application for the treatment of
12 treatment-resistant depression.

13 I was neither approached by staff at my
14 study site nor at Janssen to speak to this panel.
15 Rather, it was I who approached the study lead
16 doctor to inquire about the timing of an FDA
17 hearing, and then a contact at Janssen to confirm
18 the scheduling of this meeting.

19 I have secured and paid for my own travel
20 today. I am here upon my own account, inspired by
21 my own experience, and driven by the necessity that
22 viable treatments must be available to persons

1 suffering from treatment-resistant depression.

2 In fact, I could be shooting myself in the
3 financial foot by testifying and requesting
4 approval for esketamine. If the FDA approves it
5 for depression, then it moves from the clinic to
6 the pharmacy, where it may become difficult to
7 acquire, complicated to administer, and impossible
8 to afford, depending upon how the FDA decides to
9 classify it.

10 No matter, this is too important not to
11 approve. I will take my chances, and I will
12 continue to get esketamine if it means it will
13 become available to others who need it as much as I
14 needed it when I first entered the study two years
15 ago.

16 Let me be clear. Esketamine is
17 life-saving, period. It not only saved my life,
18 but it also gave me a semblance of one back. You
19 have heard a lot of complicated and confusing data
20 on efficacy today; at least it was complicated and
21 confusing today. I am offering real-world proof of
22 efficacy, and that is I am both alive and here

1 today because of esketamine.

2 My plea today is the same regardless of
3 whether or not experimental treatments get
4 approved. We still need them. We need you and we
5 need the research. Those of us who cannot help
6 ourselves, who cannot save ourselves, need to be
7 helped and saved. This is not possible without
8 risk from the industry and encouragement from the
9 agencies that oversee them. If you kill these
10 studies, you kill the people who would enroll in
11 them.

12 Despite your expertise in pharmacology and
13 statistics, administration, regulation, biology, or
14 first do no harm, neither this panel nor the
15 industry has had my experience. Since available
16 treatments for treatment-resistant depression have
17 not been successful throughout my years of
18 suffering with this illness until now, I am going
19 to quote from a previous testimony that I presented
20 to an FDA panel back in 2004.

21 It reads, "The medical community does not
22 accept death as a cure for treatment-resistant

1 depression. It asks us to continue to hang on and
2 continue to live, yet offers us no viable
3 treatments. Trust me, it's not that we don't want
4 to live. We don't want to live like this.

5 "Our illness is embedded in our physical
6 bodies, ourselves. We are prisoners there, and our
7 sentence is life: menacing insomnia, isolation,
8 fear, anxiety, sadness, hopelessness, general
9 malaise, lingering fatigue, physical exhaustion,
10 apathy, lack of motivation.

11 "You all are familiar with this
12 short-sheeted laundry list of symptoms. Now,
13 imagine having them all at once, imagine passing
14 from one room to another in the house of pain,
15 where some symptoms are more prevalent than others,
16 sometimes exacerbated by the very medications that
17 were meant to alleviate them."

18 Thank you for obliging me to revisit that
19 description of depression. I thought it necessary
20 to give a personal account of what it's like to
21 live like this all day, every day, and I want to
22 humanize the data.

1 My data show esketamine works and continues
2 to work. I am not naïve. I know that esketamine
3 is not a cure for depression. At this time, only
4 suicide is, but esketamine is the only treatment
5 that has saved me from persistently contemplating
6 that cure. Besides, as I mentioned, the medical
7 community does not accept death as a cure; ergo,
8 that challenges the industry with proving and the
9 FDA with approving viable treatments like
10 esketamine, 28 milligram, single-use nasal spray in
11 its current application for treatment-resistant
12 depression. Thank you.

13 DR. NARENDRAN: Thank you.

14 Will speaker number 8 please step up to the
15 podium and introduce yourself? Please state your
16 name and organization for the record.

17 MS. GURLEY: My name is Susan Gurley, and
18 I'm the executive director of the Anxiety and
19 Depression Association of America. Janssen has not
20 paid for my travel. They do provide us educational
21 support for our annual conferences.

22 The Anxiety and Depression Association of

1 America is a nonprofit membership organization that
2 represents millions of sufferers of mental illness
3 as well as those professionals who provide them as
4 different types of treatments. ADAA's board of
5 directors is comprised of mental health experts in
6 the field who deal with patients suffering from
7 depression daily. Many of our board members as
8 well as our members at large are also engaged in
9 cutting-edge mental health research.

10 As you know, we have all watched as suicide
11 rates have continuously risen, up 25 percent since
12 1999. We now lose 45,000 people to suicide each
13 year, and depression is the number one reason for
14 this. Many people never even get into treatment
15 because of the stigma of admitting to mental
16 illness, and when they do, they confront the fact
17 that their chances of responding fully to a
18 medication is nowhere near what it should be. At
19 least of the patients of our members don't really
20 get well, and their lives and those of their
21 families are disrupted by the symptoms they endure.

22 Living with depression, as you have heard

1 from many of the people before me, is often not
2 living. Many of our members/patients watch as life
3 goes on around them, finding it difficult to muster
4 up the energy to engage. Their children are often
5 collateral damage, both because the risk of
6 depression is increased, but also because they
7 sometimes feel as though they are growing up
8 without their parents.

9 Everyone in the life of the sufferer
10 watches helplessly as their loved ones turn within,
11 losing their connections with the things that
12 should bring them joy, but cannot, and the legacy
13 that depression leaves the next generation is
14 indelible.

15 As many of our members who provide
16 treatment to those who suffer depression, they see
17 its impact every single day. Fortunately, they
18 have seen also what happens after multiple
19 medication trials. Their patients finally begin to
20 respond to medication. They watch them become the
21 friend, colleague, spouse, and parent that they
22 haven't been in months or years, and they see the

1 ripple effect it has on their relationships and the
2 lives of so many around them. The medication that
3 finally works saves not only one life but touches
4 so many others and fully changes the trajectory for
5 all.

6 The way that you successfully treat someone
7 with treatment-resistant depression is trying to
8 fulfill everything in your toolkit until you find
9 one medication or a medication combination that
10 ultimately gets the result you need. To be able to
11 get people well, we need to have many treatment
12 options, and treatment options that work in new,
13 unique, and different ways.

14 Our pharmaceutical companies have given us
15 many tools, but we need many more, and we need
16 those companies to commit their resources to the
17 neuroscience space. Pharmaceutical research
18 dollars for psychiatric drugs have dropped by
19 70 percent, and we cannot let that number get
20 worse. Our policymakers and regulatory bodies need
21 to see this as the public health emergency that it
22 is and do what is necessary to encourage and fund

1 research and development of new and different
2 treatments.

3 As an organization, our website visitors
4 numbered 27 million in 2017 and have soared to
5 38 million in 2018. The public is reaching out to
6 ADA and the other organizations who have spoken
7 before me for resources and information, and these
8 numbers speak for themselves. People are
9 absolutely desperate for information.

10 The public wants treatments, and your
11 committee can make decisions that will make more
12 treatments potentially available to them. Please
13 consider all the lives that depression touches when
14 you make your decisions today and in the future.
15 Thank you very much.

16 DR. NARENDRAN: Thank you.

17 The open public hearing portion of this
18 meeting is now concluded and we will no longer take
19 comments from the audience. The committee will now
20 turn its attention to address the task at hand, the
21 careful consideration of the data before the
22 committee as well as the public comments.

1 Next, we'll do the charge to the committee.
2 Dr. Tiffany Farchione will provide us with the
3 charge to the committee.

4 **Charge to the Committee - Tiffany Farchione**

5 DR. FARCHIONE: Thank you again. At this
6 point, we've heard presentations from the
7 applicant, and we've heard presentations from FDA,
8 as well as the comments that we just got during the
9 open public hearing.

10 I think that we can all agree that
11 treatment-resistant depression is a serious
12 condition and that we need new options for
13 treatment. We've sort of heard that universally
14 from all sides. We also all agree that the
15 potential for rapid treatment is an advance over
16 available treatment. From FDA's perspective, that
17 potential is the reason why this program was
18 granted a breakthrough therapy designation.

19 As the applicant noted earlier, there was a
20 lot of interaction and collaboration with FDA along
21 the way in terms of study design. There was
22 agreement on the definition of TRD, the endpoints

1 used, the statistical analysis plan, which adverse
2 events of special interest to look at, the safety
3 monitoring, all of these things.

4 But despite all of this agreement, there's
5 still quite a bit for the committee to discuss.
6 Most of the committee members have been here
7 before, so the questions that we're going to ask
8 you today will probably sound familiar.

9 The first voting question is related to
10 effectiveness, and the regulatory definition of
11 substantial evidence of effectiveness calls for
12 positive, adequate, and well-controlled
13 investigations, plural, usually meaning two
14 positive studies; though in certain circumstances,
15 one statistically very persuasive study is enough.

16 But the one-study standard isn't the
17 question here today. In this case, though, I do
18 think it serves for us to look at the rest of the
19 substantial evidence definition. So it calls for
20 adequate and well-controlled investigations on the
21 basis of which it could fairly and responsibly be
22 concluded that the drug will have the effect it

1 purports or is represented to have, under the
2 conditions of use prescribed, recommended, or
3 suggested in the labeling or proposed labeling
4 thereof.

5 Here, we have agreement that both studies
6 3002 and 3003 are positive. That's not an issue.
7 But one is a short-term study and one is a
8 randomized withdrawal study in an enriched
9 population. So as you consider your vote on the
10 substantial evidence question, you should take the
11 proposed conditions of use into account and decide
12 whether you think the applicant has met the
13 standard.

14 That said, you'll recall that data from
15 other studies was presented as well from phase 2,
16 the other phase 3 studies. Given that we have the
17 two positive studies to start with, it is
18 reasonable to look at those other studies for
19 patterns or trends that could support or tend to
20 refute the evidence of effectiveness. Those
21 studies can provide some context, basically. So
22 there's a lot in there for you guys to consider as

1 you think about your vote on question 1.

2 The next question that we have for you
3 today relates to safety and whether you think the
4 risks of esketamine have been adequately
5 characterized. We're not asking if you think it's
6 safe. Obviously, we had two big presentations, one
7 from the applicant, one from us, describing the
8 risks that have been identified in the program.
9 What we're asking is whether you think the risks
10 have been identified and characterized.

11 The final voting question will take both
12 benefits and risks into account as well as the
13 proposed strategy for mitigating some of the
14 identified risks. With those factors in mind, the
15 question is whether you think the benefits of
16 esketamine outweigh the risks in the treatment of
17 treatment-resistant depression.

18 Finally, following the votes, we'll also
19 have two discussion questions designed to hear from
20 you what you think the missing pieces are and how
21 we might address those. So first, we'll ask you to
22 consider whether additional safeguards are needed

1 in the REMS, and then we'll ask what additional
2 data you would like to see, either premarketing or
3 postmarketing, to address any outstanding
4 questions.

5 With that, I'll hand it back to Raj.

6 **Questions to the Committee and Discussion**

7 DR. NARENDRAN: Thank you.

8 We'll now proceed with the questions to the
9 committee and the panel discussions. I'd like to
10 remind public observers that while this meeting is
11 open for public observation, public attendees may
12 not participate except at the specific request of
13 the panel.

14 I'll read the first question. Question
15 number 1, has the applicant provided substantial
16 evidence of the effectiveness of esketamine for the
17 treatment of treatment-resistant depression?

18 Are there any questions, thoughts the panel
19 wants to talk about?

20 DR. MEISEL: Just for a point of order, are
21 we voting and then discussing or are we discussing
22 and voting?

1 DR. NARENDRAN: I think we discuss if you
2 have questions about the question, and then we can
3 just kind of go around the table and say why we
4 voted.

5 Does that work? Dr. Hillefors?

6 DR. HILLEFORS: Mi Hillefors, NIMH. My
7 question is, is the question related to one
8 specific esketamine for treating in TRD or would
9 the FDA consider subpopulations, either a duration
10 or age group or a subpopulation of patients, or is
11 that something that would be considered later.

12 DR. FARCHIONE: What kinds of things did
13 you have in mind?

14 DR. HILLEFORS: I think I heard from some
15 of the discussions earlier today, both from the
16 sponsor presentation and FDA presentation, the
17 questions about the efficacy data from, for
18 example, the 65-and-older age group.

19 So the question would be, even though that
20 study was not a basis because it didn't show the
21 efficacy but it was still being presented, and the
22 studies that have shown efficacy were all in the

1 age group below 65, would, for example, FDA
2 consider limiting the age group there or is it a
3 vote for all the adults?

4 DR. FARCHIONE: The question is asking
5 whether you think they've met the standard for
6 effectiveness overall, treatment-resistant
7 depression. Now, I think it's important to
8 remember that in a lot of studies that we see, we
9 don't have patients over 65 even in the studies,
10 and we don't restrict the age range on those
11 indications.

12 In this case, the one thing that we have an
13 option to do is put information about the study
14 in -- in the labeling, there's special populations
15 in section 8. You can put geriatric patients in
16 there. That could be one way to inform people.
17 There are a lot of ways that we could address it,
18 but overall, the question is just with the
19 indications writ large.

20 DR. NARENDRAN: Anybody else have thoughts
21 or questions you want to get clarified? Dr. Ruha?

22 DR. RUHA: I guess, just regarding the

1 28-milligram dose, that in particular, I didn't
2 really see evidence of efficacy. It looked like
3 only 6 people in the entire study were still on
4 that dose at the end of the study.

5 I understand the question, but that would
6 just be my one thought, the 28-milligram dose, I
7 didn't see evidence of efficacy.

8 DR. FARCHIONE: Right. So the proposal is
9 for the starting dose to be 56.

10 DR. MEISEL: If I understand correctly,
11 they'd be packaged in 28-milligram containers, so
12 it would be two containers per dose. Each
13 container has two sprays. I can see where the
14 confusion would be that was talked about in the
15 briefing document about how to dose this thing
16 properly and make sure you don't mix it up and mess
17 it up.

18 DR. NARENDRAN: That's it? Any other
19 thoughts or questions? Dr. Rudorfer?

20 DR. RUDORFER: Just to clarify, the studies
21 we've reviewed combined esketamine with an oral
22 antidepressant. Should that be part of the

1 question?

2 DR. FARCHIONE: The proposed labeling
3 includes that provision, that the esketamine would
4 be given with an antidepressant.

5 DR. NARENDRAN: That's it? I'll read the
6 question again, and then we can vote.

7 Has the applicant provided substantial
8 evidence of the effectiveness of esketamine for the
9 treatment of treatment-resistant depression?

10 Please press the button on your microphone
11 that corresponds to your vote. You will have
12 approximately 20 seconds to vote. Please press the
13 button firmly. After you have made your selection,
14 the light may continue to flash. If you are unsure
15 of your vote or you wish to change your vote,
16 please press the corresponding button again before
17 the vote is closed.

18 (Voting.)

19 MS. BHATT: The voting results, yes, 14;
20 no, 2; 1, abstain. No voting is zero.

21 DR. NARENDRAN: So if we just want to go
22 around the room and want to mention what your vote

1 was and if you have any closing thoughts on that
2 vote. We can start from that side of the table.

3 Dr. Hoffer?

4 DR. HOFFER: It's a little confusing with
5 the protocol, but it seemed to be effective with
6 the step dose versus placebo with the on-board
7 antidepressant.

8 MS. BHATT: Dr. Zito?

9 DR. ZITO: I voted no because I found that
10 there were a number of limitations to a persuasive
11 demonstration of effectiveness. Symptom control by
12 itself over a short term doesn't rule out
13 expectancy effects and other good things that
14 happen when people come into trials that are well
15 run.

16 Also, I think that we have a statistical
17 difference and perhaps not a clinical significant
18 difference. A 4-point score on the MADRS scale
19 seems to be quite narrow or small. There is no
20 indication of functional improvement, which seems
21 so crucial for such a very sick population of
22 individuals.

1 The treatment-resistant definition, I think
2 was rather narrowly operationalized. I can imagine
3 that there are many, many people with mild to
4 moderate depression who have failed two trials in
5 the last whatever undefined period called the
6 episode.

7 Then there's this functional unblinding
8 that's been mentioned and really can't be ruled
9 out. The variation in findings across the studies
10 is not so persuasive. I'm also concerned about the
11 term "transient" of -- well, I guess I should stop
12 there. This is effectiveness. That's safety.
13 Thank you.

14 DR. COMPTON: This is Wilson Compton. I
15 voted yes. While I think the evidence was
16 borderline in some cases, I was persuaded not only
17 by the two positive trials, but even by the partial
18 evidence in the third trial that was at least
19 pointing in the same direction.

20 I remain a little concerned about the high
21 placebo response rate. For a treatment-resistant
22 group, this seems a little odd to me that they

1 haven't responded to two other treatments, and
2 adding a third one, they suddenly have a pretty
3 good response.

4 Both groups looked a little concerning, but
5 the very consistent separation between the
6 esketamine and the antidepressant-only group, I
7 found persuasive. I liked the second trial. It
8 was an unusual design from my perspective, and I
9 appreciated that one. I thought that's strong
10 evidence because it's sort of on and then off,
11 showing evidence in the same direction, I found
12 persuasive.

13 DR. BILKER: Warren Bilker. I voted yes.
14 I felt that the data provided sufficient evidence
15 of effectiveness across all of the studies.

16 DR. RUHA: Michelle Ruha. I voted yes. I
17 agree. I was convinced that there was a
18 significant effect and that it's a hopeful
19 treatment.

20 DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz.
21 I voted yes because I think the preponderance of
22 the evidence suggests a modest beneficial effect of

1 the population of patients, but it may be helping
2 some specific patients significantly or
3 meaningfully, and we can identify who they are
4 maybe in postmarketing studies.

5 DR. MEISEL: Steve Meisel. I voted yes
6 because there isn't an option to say, "yes, but."
7 There's no doubt that two of these trials
8 statistically showed effectiveness. The other two
9 were pretty marginal, except for the patients over
10 the age of 65, where it clearly did not show a
11 benefit. I think that came up earlier, and I think
12 we have to point that out, despite the testimonial
13 that we heard from the public comments. Maybe it
14 does work in some people, but the evidence doesn't
15 demonstrate that.

16 I agree that the magnitude is small on
17 average, but I think there are individual people
18 who would likely have a benefit that exceeds
19 average, and obviously there are some that it
20 wouldn't work at all. So that 4-point scale is the
21 average improvement, but there may be some people
22 that would substantially benefit from this

1 medication. I think that's important.

2 It occurs to me that we don't really
3 understand how this drug works. There is some
4 suggestion by the vendor as to what it might be,
5 and I know, in some of the written comments that
6 were posted, there is some suggestion, well, maybe
7 there is a high effect because of mu receptors or
8 something of that sort.

9 I wonder, in my own mind, whether or not
10 this is effective not because it's serving as an
11 antidepressant, but because it's providing some
12 sort of a high, like a party drug type of high, and
13 that lasts for a week or two or whatever, and then
14 it wears off, and you got to do it again.

15 At the same time, I said to myself, well,
16 even if that's the case, so what? If this is a
17 condition that is very difficult to treat, as we've
18 heard from many of the speakers, it's life
19 threatening and life endangering, and impacts
20 everybody; and even if the effectiveness is because
21 we're giving a high and not as antidepressant, to
22 me, that's evidence of efficacy.

1 So I've got some reservations about the
2 magnitude of the effect, the lastness [ph] of the
3 effect. There's no doubt that the over-65
4 population needs more work in this space, but I do
5 think there is substantial evidence, at least for
6 some people, that this could be a game changer.

7 DR. BESCO: Kelly Besco. I also voted yes
8 for many of the reasons that have already been
9 expressed. I do want to reemphasize Dr. Meisel's
10 earlier comment about worrying about patient
11 confusion over the dose administration when the
12 patient would require more than one device to
13 complete their first dose. I think that will be
14 confusing for patients, so I just want to make sure
15 that is considered as this moves forward.

16 MR. KUNGEL: This is Terry Kungel. I voted
17 yes. I thought there were two positive studies,
18 and I thought the third was also good evidence. I
19 would make the case I made earlier today, which is
20 the placebo effect here is so huge, getting over
21 that placebo effect and having statistical
22 significance is huge, getting over that placebo

1 effect and having statistical significance is huge.

2 You look at why do we have the placebo
3 effect, and we heard it from the audience. There's
4 no hope for a lot of the people with treatment-
5 resistant depression, and with the option of
6 thinking you've got a new drug and a totally new
7 process, it's not surprising to me that we saw the
8 placebo effect be as big as it was.

9 MS. WITCZAK: Kim Witczak. I voted yes,
10 and I usually -- I was kind of torn on this one,
11 but when you further described what substantial
12 was -- I know it's a novel mechanism. I think
13 there was evidence in the trials that were there.
14 I think it's looking at it from a fresh perspective
15 outside of the regular antidepressant treatments.

16 DR. W. DUNN: Walter Dunn. I voted yes. I
17 believe there is compelling evidence that
18 esketamine is an effective treatment for this
19 highly treatment-resistant population. There are
20 two aspects about the studies that I was very
21 impressed by.

22 Number one, the addition of a new, active

1 antidepressant both in the placebo arm and active
2 arm. I think that really mirrors what we see in
3 clinical practice. I think that was important for
4 the clinicians to see. If anything, probably, in
5 reality, you have patients on two or three
6 antidepressants by the time they've failed two.

7 The second aspect was the maintenance
8 trial. I really commend the FDA for considering
9 this to be one of the pivotal trials because I
10 think from our experience with IV ketamine
11 off-label use for the last 10-plus years, we know
12 it works, and we know it works fast.

13 The question is will the effect last, and I
14 think the maintenance trial really demonstrated
15 that there is potential for a long-term benefit for
16 this patient population that will undoubtedly be
17 required, probably for the rest of their lives
18 until something else better comes along.

19 DR. NARENDRAN: Raj Narendran. I voted
20 yes. I felt very comfortable that the one
21 short-term trial and the randomized withdrawal
22 trial complemented each other in terms of its

1 efficacy.

2 I do share the comments that Dr. Meisel
3 made. At some point I kept thinking, well, does it
4 just make them feel good because it's a drug, it's
5 a party drug, and it's probably going to go down
6 the line of -- ecstasy is going to be there, MDMA,
7 or psilocybin. All this is kind of cooking in the
8 academia.

9 I kind of felt, with the two complementary
10 designs and the 10 years' experience of what we
11 know about how ketamine works, it works rapidly, it
12 seems to clearly offer a benefit for these people,
13 not just in the short term, but long term. It's
14 also intermittent dosing, so all that kind of moved
15 me to feel more comfortable and convince me that it
16 does work.

17 Dr. Fiedorowicz on the phone?

18 DR. FIEDOROWICZ: This is Jess Fiedorowicz,
19 University of Iowa. I was concerned about blinding
20 with esketamine with its immediate recognizable
21 effects. The rationale that was brought up for not
22 directly assessing the blind by the sponsor, the

1 concern that patients might be motivated to unblind
2 themselves seemed not compelling and anecdotal to
3 me. It seemed analogous to suggesting that asking
4 someone about suicidal ideation will prompt them to
5 think or act on thoughts. It's very common for
6 participants in the trial to wonder and be
7 interested in what treatments they're getting
8 regardless of whether they're asked.

9 The analyses looking at dissociation and
10 presumably sedation, although we didn't see those
11 directly, were appreciated, but really didn't fully
12 capture whether the blind was broken or any
13 expectancy of benefit.

14 Ultimately, there's almost certainly a bias
15 away from the null hypothesis here related to these
16 issues, and it's difficult to underestimate the
17 magnitude of that, and it could be substantial,
18 given the subjective outcomes being used.

19 I subsequently cannot say that the
20 applicant has provided substantial evidence of
21 effectiveness. I'm abstaining rather than voting
22 no, which seemed unfair, given that the FDA

1 ultimately approved the design, albeit after
2 recommending the use of an active intranasal
3 placebo.

4 DR. PINE: Danny Pine. I voted yes. I
5 found the data reasonably compelling to the point
6 where I feel comfortable voting yes in terms of
7 efficacy. I think the only other point that I
8 would add is that I think there were a lot of
9 challenges in that there is a high degree of
10 novelty, both with the compound, the nature of the
11 questions, and the designs, and I thought that the
12 novelty of those issues has much to do with some of
13 the questions that came up, at least for me, as did
14 issues related to efficacy.

15 Again, the term "comfortable," I would
16 agree with that. I feel entirely comfortable.

17 DR. HILLEFORS: Mi Hillefors, NIMH. As I
18 noted, I'm one of two that voted no. I do want to
19 recognize I think that all the data is very
20 compelling, as my fellow committee members have
21 said, and I think it's done through a very thorough
22 and very thoughtful program in an area that's

1 really is a public health importance. But
2 different from maybe some of the other committee
3 members, I did come down a little bit on the other
4 side, where I wasn't convinced that the
5 effectiveness here had yet been demonstrated, maybe
6 because we have several trials that did not show an
7 effect.

8 The two studies that did have the basis for
9 the effectiveness here are also very different, and
10 it's not clear to me yet how well they complement
11 each other when it comes to effectiveness.

12 I do want to make note that I really was
13 trying to stick to the question 1 and not put in 2
14 and 3 and how compelling it is in context to other
15 perspectives.

16 DR. RUDORFER: Matthew Rudorfer. I voted
17 yes. I agree with most of my colleagues. I think
18 the sponsor has provided substantial evidence for
19 the effectiveness of esketamine. I too wish that
20 the evidence was a bit more overwhelming, but I
21 appreciate these are very difficult studies to do,
22 and I appreciate the novelty of the design and the

1 evidence we were given.

2 DR. EVERETT: Great. So this is Anita
3 Everett again from SAMHSA. I also voted yes. I
4 felt like there was sufficient information to
5 justify that. I do wish, as you mentioned, it were
6 more robust, if the difference were more robust.

7 With regards to the placebo effect, I'm
8 interested in that and that we can talk about that
9 later as something to look at, but I wonder myself
10 about the high touch that's required by the
11 frequency of these visits and the duration of the
12 visits.

13 We certainly see that or we propose that
14 that's part of the mechanism for why Clozaril seems
15 to work in populations where there's mandatory
16 contact with health providers in a caring
17 environment pretty often. So I voted yes, but I
18 wish the data were more strong.

19 DR. NARENDRAN: Just to summarize, it seems
20 like most people felt comfortable that the evidence
21 was there. Not only the short-term trial, but the
22 randomized withdrawal design also provided

1 compelling evidence that was persuasive enough that
2 most people voted for it.

3 I did hear that even the people who voted
4 for it felt the effect could have been modest.
5 However, it seemed like it does seem to help a
6 substantial number of people, so in that way, it
7 kind of swayed people.

8 On the other side of the coin, I felt there
9 were similar reasons that led to people voting
10 against it, felt like the effect size was too small
11 and how would this translate clinically. They
12 weren't fully swayed by the trials

13 So that's my summary. We'll move to
14 question number 2. Question number 2, has the
15 applicant adequately characterized the safety
16 profile of esketamine for the treatment of
17 treatment-resistant depression?

18 Are there any questions, discussions, or
19 clarifications that the panel needs about question
20 number 2? Dr. Hoffer?

21 DR. HOFFER: Are we talking about the
22 applicant's packet or the FDA's packet? Because

1 there were some differences, it seemed like, in how
2 safety was -- the profile was presented.

3 DR. FARCHIONE: Both.

4 DR. NARENDRAN: Dr. Meisel?

5 DR. MEISEL: Again, just for clarity, do we
6 think that we understand what the adverse event
7 profile is? Is that really the question?

8 DR. FARCHIONE: Yes, exactly.

9 DR. NARENDRAN: Any other clarifications on
10 the safety profile? Sure. Go ahead, Dr. Zito.

11 DR. ZITO: Yes. Are you asking that you
12 have defined -- you're saying have you defined the
13 safety profile adequately?

14 DR. FARCHIONE: Basically. For every drug
15 that gets labeled, you have to be able to put the
16 warnings and precautions, the adverse reactions.

17 DR. ZITO: Right.

18 DR. FARCHIONE: Do you think that we have
19 enough information to be able to write that label
20 and to inform people what they should be aware of
21 when they're deciding who to prescribe this for and
22 what to warn their patients about?

1 DR. TEMPLE: It doesn't mean there's no
2 existing question. As our presentation said, there
3 are still some things we want to know more about,
4 eventually.

5 DR. NARENDRAN: Dr. Pine?

6 DR. PINE: So there wasn't any discussion
7 of this issue in the presentations, but there was a
8 fair amount of material in the packet that we
9 received. I wondered if maybe somebody from the
10 FDA might comment on it, and that was vacuolization
11 and concerns about neurotoxicity.

12 My reading of that material is that this
13 issue was raised, and it was evaluated fairly
14 critically and in depth, and that the reason that
15 we didn't hear about it here in the public hearing
16 is from your standpoint, you did not think that
17 there were any lingering questions for us.

18 Is that correct?

19 DR. FARCHIONE: That's essentially correct.
20 We did ask for certain studies. The applicant
21 conducted them. We have the data that we think
22 that we need to be able to label it accordingly and

1 to describe the risks and what was seen.

2 DR. NARENDRAN: Does the division want to
3 provide a clarification? One second.

4 DR. HILLEFORS: Can I just clarify? The
5 question is about the Olney lesions that the FDA
6 has discussed before about these [indiscernible]
7 agents.

8 DR. PINE: Well, that was the general
9 question, but there was a fair amount of material
10 in the packet that made it clear that additional
11 studies were done and that, just by the fact that
12 it wasn't discussed at all and my take on the
13 material that I reviewed, I came away thinking that
14 was not an issue. But it does pertain to this
15 issue and it hasn't been explicitly said. So it
16 would be nice to just hear from the FDA standpoint
17 that there are no concerns that we need to discuss.

18 DR. MATHEW: Hi. I'm Shiny Mathew. I am a
19 pharm-tox reviewer within the division. I am the
20 one who reviewed the Olney lesion studies. So for
21 an NMDA antagonist receptor and diagnosis, you know
22 we're very concerned about an NMDA receptor

1 antagonist, especially the blockers of the
2 channels. We're concerned about the Olney lesions.
3 And Olney lesions, as you know, are vacuolations
4 that can go on to degenerate. We had the sponsor
5 conduct a number of studies.

6 The one pivotal study that I want to allude
7 to today is the single-dose acute neurotoxicity
8 study, where they tested doses up to more than
9 20-fold with esketamine, and there were no findings
10 of neuronecrosis at the 3-day sacrifice time point.

11 I do want to note that there was no head-
12 to-head comparison with ketamine in that study, so
13 it was esketamine intranasally administered, a
14 single dose, compared with MK-801, which is the
15 positive control, and it was negative.

16 The time point for vacuolation was not
17 examined in that pivotal study. So I think it's
18 safe to say that intranasally administered
19 esketamine at a single dose does not cause
20 irreversible neuronecrosis according to the study
21 conducted here.

22 DR. PINE: And you had no additional

1 concerns about repeated dosing, then, either,
2 right? Because that's how the clinical studies
3 were performed.

4 DR. MATHEW: Right. Regarding repeated
5 dosing, it is a different question altogether. The
6 sponsor conducted studies in both dogs and rats,
7 9 months in dogs and 6 months in rats. The
8 exposure margins there at the high dose were
9 minimal, 0.6 times the MRHD, maximum recommended
10 clinical dose compared to the rat. And in dogs,
11 it's 1.3 times based on ASE exposure.

12 In those studies, based on standard
13 histopathological analysis, we did not see any
14 findings within the brain. But we do know that
15 ketamine in published literature has showed that
16 repeated dose administration does cause neuronal
17 apoptosis in the adolescent brain. We see that in
18 primates, in mice, and a number of species.

19 That sort of a study was not conducted
20 here. It was just the basic standard
21 histopathology studies that were conducted in the
22 6-month rat and the 9-month dog studies.

1 DR. HOUGH: Mr. Chairman, this seems like
2 an important issue. Could I have a moment for the
3 sponsor to respond and provide the data that we've
4 gathered?

5 DR. NARENDRAN: Sure.

6 DR. HOUGH: That might be reassuring to the
7 committee. I'll invite Dr. de Waal to come up and
8 speak about the very extensive preclinical program
9 we did. We were aware of this as an issue, and we
10 decided not to move forward until we had
11 appropriate therapeutic safety margins, and
12 Dr. de Waal will describe this extensive number of
13 studies that were done.

14 DR. DE WAAL: Good afternoon. Can I have
15 slide 2 up first? This is a comprehensive list of
16 the studies in rats and dogs that were just
17 mentioned, where we looked into the potential of
18 intranasal esketamine to induce histopathological
19 brain lesions.

20 In collaboration with the FDA, we designed,
21 in particular, the acute neurotoxicity study in
22 rats as well, as was not mentioned yet, the 14-day

1 repeat dose study in rats, where we also looked for
2 neurotoxicity. And as already mentioned, we also
3 did long-term studies like the 9-month dog study,
4 the 6-month rat study, carcinogenicity study, where
5 basically the rats were exposed during their entire
6 lifetime.

7 In all these studies, there was no evidence
8 of histopathological changes in the brain. Also,
9 in the 6-month rat study and in the 9-month dog
10 study, we did functional endpoints, and also those
11 endpoints don't point to the direction of any
12 evidence for neurotoxicity.

13 DR. NARENDRAN: Does that answer your
14 question?

15 One of the things that amazes -- I know the
16 long-term cognitive effects of ketamine have been
17 reported in drug abusers, but it seems like in
18 their data, they didn't really have that.

19 Do you feel like they have adequately
20 characterized them in terms of the Cogstate and the
21 1-back/N-back [ph] is what they did, if I remember.
22 That's not super sensitive to detect subtle

1 deficits, I would think, but are you guys worried
2 about that? It's something that they could
3 probably get during the long-term postmarketing.

4 DR. FARCHIONE: Then that would be
5 question 5, the discussion question.

6 DR. NARENDRAN: All right. Thanks. I was
7 just curious if it could be added in the REMS or
8 something. That's fine.

9 I'll move to question number 2. Based on
10 what we've seen, has the applicant adequately
11 characterized the safety profile of esketamine for
12 the treatment of treatment-resistant depression?

13 It's a voting question; same thing. Please
14 press the button on your microphone that
15 corresponds to your vote. You will have
16 approximately 20 seconds to vote. Press the button
17 firmly. If you want to change it, you can change
18 it. If you're unsure, it's registered; you can
19 press it again.

20 (Voting.)

21 MS. BHATT: The voting results, yes, 15;
22 no, 2; abstain, zero; and no voting is zero.

1 DR. NARENDRAN: If the panel just wants to
2 go around, we'll start with Dr. Everett.

3 DR. EVERETT: Yes. I voted -- I do feel
4 like they have adequately characterized the safety
5 profile. Thank you.

6 DR. RUDORFER: Matthew Rudorfer. I voted
7 yes as well. I thought the sponsor took safety
8 very seriously and adequately characterized the
9 safety profile.

10 DR. HILLEFORS: Mi Hillefors, NIMH. I
11 voted yes. I do think that the applicant took a
12 lot of effort to profile the safety. I do also
13 think that there's a lot of information from the
14 use of ketamine, even though it's been off-label.
15 So it's esketamine in that way, not completely
16 novel, and we don't know much.

17 I do think that it will be important, if
18 esketamine gets approved, to follow and really
19 study more the long term and also get the data from
20 the SUSTAIN-2 study that's going to provide even
21 further safety data. So I think the long-term
22 data, still, we don't have enough of it.

1 DR. PINE: Danny Pine. I voted yes. There
2 are clear safety concerns, but I feel that they
3 were adequately characterized.

4 DR. NARENDRAN: Dr. Fiedorowicz on the
5 phone?

6 DR. FIEDOROWICZ: This is Jess Fiedorowicz
7 from the University of Iowa. I voted yes. The
8 safety profile appears to be characterized well
9 enough, and importantly, beyond the short term, in
10 this repeated administration.

11 DR. NARENDRAN: Raj Narendran. I voted yes
12 as well. I felt like the safety profile, there are
13 risks, but it's well-categorized and manageable in
14 the context of how it would be labeled. But the
15 long-term concerns are shared as well, which can be
16 dealt later.

17 DR. W. DUNN: Walter Dunn. I voted yes. I
18 think the adverse effects are consistent with our
19 experience with IV ketamine used off label, and
20 those are being dosed at higher than what we've
21 seen in the study.

22 I do share the concern about the long-term

1 cognitive effects specifically. I anticipate
2 patients to be on this for decades. That can't be
3 addressed in some of these studies, but that's
4 something that should definitely keep an eye out
5 for.

6 MS. WITCZAK: Kim Witczak. I voted no
7 mostly around how the FDA characterized some of the
8 safety and how the applicant did. So I
9 distinguished that because it said applicant,
10 especially around the deaths is pretty important.
11 Then I also have a long -- which I know can't
12 necessarily be resolved in the short term, but I do
13 have concern with the long-term safety of this
14 drug.

15 MR. KUNGEL: This is Terry Kungel. I voted
16 yes, and I thought that they did an excellent job
17 of making the case for what the safety profile is.

18 I would also make two additional points,
19 which is, having been on tricyclics and MAO
20 inhibitors, there are very serious significant side
21 effects with what's already out there. You have a
22 population, when you look at the data, that is

1 willing to accept some fairly enormous risks in the
2 Janssen material just to improve mood, so I
3 absolutely thought it was a yes.

4 DR. BESCO: Kelly Besco. I also voted yes.
5 One thing I do want to bring up that I don't think
6 we talked a lot about today was the role of
7 interacting medications. I'm somewhat questioning
8 in my mind, especially with thinking about practice
9 and actual application of this medication and
10 thinking about patients that might already be on
11 drugs that have sedative effects, and I'm wondering
12 if there needs to be a precaution to hold maybe
13 something that is used as needed on the day that
14 their esketamine would be administered so they
15 would not potentially experience increased sedation
16 when their dose is due.

17 DR. MEISEL: Steve Meisel. I voted no,
18 though it was a close call. This drug's been
19 around for 50 years, so I think we know what
20 ketamine does, but not when it's used once a week
21 or thereabouts for life. I think that's a
22 different scenario that we don't know a whole lot

1 about.

2 The long-term trial had, by my count here,
3 a total of 297 patients in it. That's not a lot,
4 and a lot of them didn't last for a whole year or
5 whatever. There is drop off and that sort of
6 thing. Yes, we know that this can raise blood
7 pressure transiently. What we don't know is what
8 is the impact of that constantly raising and
9 lowering blood pressure with every dose, and pulse
10 rate for that matter, week after week after week
11 after week. That hasn't been characterized I don't
12 think at all, nor well studied.

13 I think the 5 or 6 suicides that we saw
14 were all ascribed to, well, we don't think it had
15 anything to do with this, but it's interesting that
16 we didn't see that in the placebo arm. So is there
17 something there that we haven't fully understood?

18 I'm not sure I believe -- and maybe it's
19 true -- the whole issue of the nightmares, and the
20 night terrors, and that sort of thing that we see
21 commonly when it's used IV. Maybe it's a
22 dose-related thing. Maybe it's a situational

1 thing. But the fact that we didn't see any of that
2 reported by either the FDA or the sponsor raised a
3 question in my mind as to how hard we looked for
4 that sort of thing, particularly since that might
5 have occurred long after the patient left the
6 clinic the next day or that sort of thing. They
7 may or may not have been asked about that; may or
8 may not have been reported that. Then the long-
9 term cognitive impact as well, I think is something
10 we have to be thinking about.

11 So I think, yes, we have a list of these
12 things that this drug can do. I think we
13 understand that. The drug's been around for 50
14 years. But I don't think that we really understand
15 what happens when you take this week after week for
16 weeks, and months, and years.

17 DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz.
18 I voted yes. I think there is enough
19 characterization for short-term effects in that
20 there are plans to collect further information to
21 answer the questions that remain and answer. There
22 is a plan to collect information, so I think there

1 is enough for now.

2 DR. RUHA: Michelle Ruha. I voted yes. I
3 thought the safety profile was very well
4 characterized.

5 DR. BILKER: Warren Bilker. I voted yes.
6 I thought the safety profile was well characterized
7 by the sponsor's presentation.

8 DR. COMPTON: Wilson Compton. I agreed
9 that it was well characterized during the
10 presentations and provided the analysis. I thought
11 they followed up all the expected leads from
12 preclinical and early clinical studies on related
13 compounds in a thorough way.

14 I particularly appreciated the discussion
15 we had before voting on the Olney's lesions.

16 DR. ZITO: Julie Zito. I voted yes because
17 I thought there was convincing evidence of dramatic
18 effects related to sedation, dissociation,
19 increased blood pressure, and heart rate, and
20 suicidal behavior.

21 I would hope that going forward, the REMS
22 is going to really lay out an agenda of what

1 interacting drugs are really going to affect the
2 sedation issue and other complications that are
3 going to be in the community population, like
4 cardiac effects in people with a history of serious
5 cardiac disease and hypertension. I'm not sure
6 what you have in mind, but those will be serious
7 concerns.

8 DR. HOFFER: Lee Hoffer. I voted yes, and
9 I thought the safety profile was well
10 characterized. I do have concerns, as many others
11 do, about the long-term effect of maintenance dose
12 of this drug.

13 DR. NARENDRAN: Just to summarize, it
14 sounds like people were pretty comfortable with the
15 full characterization of the short-term effects and
16 the risks, but there were some questions and most
17 of the committee shared concerns in terms of the
18 long-term safety on cognitive deficits, elevated
19 blood pressure, and suicides maybe needs to be
20 explored a little bit further. There is also some
21 concern that drug-to-drug interactions may need to
22 be kind of better characterized in terms of how it

1 impacts sedation.

2 Does that provide adequate summary?

3 DR. MEISEL: Steve Meisel. If I can just
4 supplement that, I think it was just stated here
5 that for people with underlying comorbidities,
6 whether it's hypertension, or cardiac disease, or
7 those kinds of things where a transient rise in
8 blood pressure might be more critical than for
9 somebody who doesn't have those conditions, I don't
10 think that's been well-characterized, in part,
11 because of the exclusion criteria in the studies.

12 DR. NARENDRAN: That makes sense, so we'll
13 add that in; subpopulations of who it could be more
14 dangerous or risky in terms needs to be
15 characterized better. Thank you.

16 So question number 3, which is a voting
17 question as well. Given the effectiveness and
18 safety of esketamine and the FDA's proposed risk
19 evaluation and mitigation strategy, do the benefits
20 outweigh the risks of esketamine for the treatment
21 of treatment-resistant depression?

22 Any questions or clarifications on the

1 question? Dr. Everett?

2 DR. EVERETT: Yes. I have a question for
3 FDA on the broadness of this question. Is this
4 narrowed to individuals or shall we also think of
5 this as whole population, or from a public health
6 perspective, impact on risks and benefits of this
7 in society versus on individuals?

8 DR. FARCHIONE: Basically, I not sure how
9 broad you want to go. I'm assuming that you're
10 thinking on the risk side. I think that would play
11 into the question if you're thinking about whether
12 the REMS goes far enough. So I guess you probably
13 could consider that.

14 DR. TEMPLE: But it refers to the
15 population that you're going to label the drug for
16 if you approve it. Do the benefits outweigh the
17 risks for that group?

18 DR. MEISEL: So if I can just further probe
19 on that question -- Steve Meisel -- this is, do we
20 approve the drug or not, basically; that's what the
21 question is. But there may be improvement in
22 X population and not Y; as an example perhaps not

1 in the age over 65. We're not being asked to
2 subcategorize this at all. We're just saying, yes
3 or no, approve the drug. Is that right?

4 DR. FARCHIONE: Basically, yes. Again,
5 this is the question that we always ask. When we
6 go through and we do our reviews, we have a whole
7 benefit-risk framework that we're asked to fill in,
8 so it's much more complicated than just one
9 question.

10 That's all the things that you're going to
11 take into account as you come up with your yes or
12 no dichotomous answer here. So when we get to the
13 discussion part of that, depending on what you do
14 decide, you can state your reasons, and that will
15 help inform our risk-benefit framework as well when
16 we do ultimately make our decisions.

17 DR. NARENDRAN: Any other questions?

18 (No response.)

19 DR. NARENDRAN: I'll read the question
20 again, question number 3. Given the effectiveness
21 and safety of esketamine and the FDA's proposed
22 REMS, do the benefits outweigh the risks of

1 esketamine for the treatment of treatment-resistant
2 depression? Please vote.

3 (Voting.)

4 MS. BHATT: The voting results, yes, 14;
5 no, 2; abstain, 1; no voting, zero.

6 DR. NARENDRAN: I just want to go around
7 the room. We'll start from this side of the table,
8 Dr. Hoffer?

9 DR. HOFFER: Yes. I think that,
10 ultimately, the benefits outweigh the risks. The
11 thing I'm most concerned about, really, is
12 diversion, and misuse, and things like that.
13 That's the research that I do, and I think the REMS
14 will have to be monitored. That's the point of a
15 REMS anyway, to keep an eye on it.

16 DR. ZITO: Since I voted no on question 1,
17 I felt I had to vote no on question 3 in terms of
18 not yet knowing fully what the possibilities are
19 for a really serious REMS that will stand up as a
20 phase 4 study that's so badly needed. So we'll
21 see.

22 DR. COMPTON: I voted yes. I thought it

1 had demonstrated adequate effectiveness in
2 comparison to the risks and the risks are well
3 described. Certainly, there are some limitations
4 and remaining questions. I thought the long-term
5 outcomes were particularly persuasive and unusual
6 in this space, so I appreciated that.

7 DR. BILKER: Warren Bilker. I voted yes.
8 There are certainly important risks that were well
9 characterized, but I believe, for the intended
10 patient population, the benefits outweigh the
11 risks.

12 DR. RUHA: Michelle Ruha. I voted yes. I
13 do think the benefits outweigh the risks, but I'm
14 very happy to see that there's going to be strict
15 REMS. I also hope that in any postmarketing
16 studies or with the REMS program, we really can
17 look at, as was mentioned, sedative hypnotics like
18 other benzos that are being taken, if that affects
19 sedation, and try and identify who are at high risk
20 for adverse effects. Drug interactions would be a
21 nice thing to look at more closely in the future.

22 DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz.

1 I voted yes because I think there is a modest
2 benefit and substantial meaningful risk. Given the
3 alternatives and the situation of the population,
4 and given the very careful plan with the REMS and
5 to collect further information, we will further
6 identify the patients that will benefit the most
7 and will keep the risk under control.

8 DR. MEISEL: Steve Meisel. I voted yes.
9 Let's make no bones about it. Ketamine is a nasty
10 drug. It's been around for 50 years. I think
11 those of us who have seen it used in anesthesia and
12 elsewhere, sometimes with pain, the adverse effect
13 profile is large. It's a nasty drug. But
14 obviously, we're using lower doses in this case.

15 I am persuaded. I thought the survey that
16 was done by the sponsor of a patient saying,
17 knowing the experiences you've had, the adverse
18 effects that you're seeing and experiencing,
19 dissociation and everything else, would you still
20 take this? And the answer was yes. I think
21 that's, to me, a very important data point. We
22 don't take that patient voice into account as often

1 as perhaps we should in this space.

2 I think should the drug get approved, I
3 think a strong effort has to be given as part of
4 the REMS or part of something, the informed
5 consent, that patients really know what they're
6 getting themselves into with this, what their risks
7 really are, needs to be highlighted first and
8 foremost.

9 They can't be surprised by the
10 dissociation, the sedation, the blood pressure, the
11 whatever that goes along with this, the bladder
12 problems, whatever else it may be. I think there's
13 got to be some heart-to-heart talks up front as to
14 what those risks are, and then sort of let them
15 make up their mind with that.

16 I think patients with this problem, a good
17 deal with them, if not the vast majority of them,
18 will say, yes, I'll take the risk because my
19 condition is just unbearable to myself and to my
20 family. So I think that's very important.

21 One thing I do want the agency to be
22 thinking about, though, and it's on a broader

1 context, two of the studies failed to meet the
2 primary endpoint. The primary outcome that was
3 set, 0.08 is maybe close to 0.05, but it failed.
4 What precedent is set, not for this drug, but for,
5 in general, the agency to be approving a drug where
6 2 out of the 3 short-term efficacy trials did not
7 meet the primary endpoint?

8 I think that's a philosophical question
9 beyond the scope of this committee, but I think
10 it's something that the agency has to wrestle with
11 because if we indeed approve this, and then some
12 other drug for some other condition -- epilepsy,
13 infection, cardiac disease, whatever -- has the
14 same pattern, do we set a precedent that may be
15 hard to step back from if it makes more sense to
16 step back from it in that kind of a situation?

17 I think it's important for the agency to be
18 considering that as a long-term strategy.

19 DR. TEMPLE: It's worth noting that,
20 historically -- and we've got publications that
21 show this -- 50 percent of trials of acute
22 depression fail, where the drugs are known to be

1 effective. So sometimes that's 4 out of 7 and
2 things like that, so it's not unprecedented.

3 DR. BESCO: Kelly Besco. I also voted yes,
4 mainly also because I voted yes for 1 and 2. But I
5 did want to make a comment about the REMS program.
6 I was pleased with the REMS program as outlined by
7 both the sponsor and FDA. I felt like it was less
8 passive than some of the other REMS strategies that
9 we've seen in the past, Dear Healthcare letters
10 that are really largely ineffective. So I think
11 the program, as outlined, will help set consistent
12 safety standards.

13 One request I would have is that the
14 program be very clear on what needs monitored, like
15 the frequency of blood pressure, what sedation
16 scale to use. These sort of details are often left
17 up to the people utilizing and interacting with the
18 medication. So I think, if that could be specified
19 as part of the REMS program, it will help more
20 consistent use in monitoring standards associated
21 with the therapy.

22 MR. KUNGEL: Terry Kungel. I voted yes. I

1 thought the effectiveness was high. I thought the
2 risk was low to moderate, so it was a fairly easy
3 call. The key point that I will make is that the
4 risks the patient community is willing to accept is
5 vastly higher than what the FDA is likely to
6 consider.

7 MS. WITCZAK: Kim Witczak. I voted no,
8 although I will say I appreciated the comments that
9 came in from the audience because I know there's a
10 lot of issues with people trying multiple drugs,
11 and to your point, people are more willing to take
12 a risk. But I think there are still some
13 things -- it seems like the new strategy of getting
14 drugs that are kind of controversial is always
15 going back and relying on the REMS program to save
16 us, and this has the potential with so many people
17 out there.

18 Also, I keep going back to the marketing
19 side of things, probably because that's my
20 background, but I can see this. There's a lot of
21 potential for people that just want that quick fix.
22 So I really would be cautious.

1 I don't know where that comes in with REMS,
2 and it might be more of a legislative thing to do
3 with advertising programs, but I think that's
4 something to consider because I think there are a
5 lot of people that are out there that are desperate
6 and have tried many different programs.

7 I also think, too -- I think it was Steve's
8 point -- the informed consent is a huge piece, that
9 I think we need to make sure that the patients
10 understand the full risks because I think there
11 will be a lot of marginal people that will do it
12 because, again, this was a controlled clinical
13 trial, but once it gets into the real world -- but
14 I appreciate all the work that you guys did to try
15 to come up with new treatments as well.

16 DR. W. DUNN: Walter Dunn. I voted yes
17 because I believe esketamine has the potential to
18 be a game changer in the treatment of depression.
19 I use the term "game changer" because they've
20 demonstrated that the rates of response in this
21 treatment-resistant population is better than what
22 we've seen for any of our current modalities.

1 Number two, the rapid timeline of response
2 isn't precedented. There's nothing currently
3 approved that gets patients better this fast. Then
4 third, the novel mechanism of action. Although
5 it's not a novel compound in terms of approved
6 antidepressants, if it does get approved, it will
7 be novel. I think we may talk about 2019 as we
8 talk about the 1980s as the beginning of SSRIs as
9 the first glutaminergic-based antidepressant.

10 I use the term "potential" because I think
11 issues of cost and patient accessibility, those
12 need to be addressed. If the cost is too high,
13 patients aren't going to get access to it or we're
14 not going to be treating the numbers of people that
15 need this medication.

16 I remind the sponsor that racemic ketamine
17 is out there in the wild. It's generic. It's
18 available in ketamine clinics in IV formulation.
19 There are psychiatrists prescribing it intranasally
20 through compounding pharmacies. So I think there's
21 already a competitor out there. And I think if
22 this medication gets approved, potentially, if the

1 cost is too high, psychiatrists, other
2 practitioners, may look to these compounding
3 pharmacies for the generic form.

4 The second point about patient access, I'll
5 save the bulk of my comments for the next question.
6 But really, I think, for the REMS, it's certainly
7 important to address potential for diversion,
8 abuse, and then also post-induction or post-use
9 side effects. However, I think there needs to be a
10 pathway to reduce the monitoring requirements,
11 perhaps after the patient is on the medication for a
12 year or so, something similar to what we see with
13 clozapine and blood draw monitoring.

14 I say this because the number one predictor
15 for symptom relapse is non-adherence. Even though
16 this medication is novel, I think once patients
17 achieved remission, if it's too much of a burden to
18 go in and sit for 2 hours to be monitored, they
19 might skip a dose here or there, and they're going
20 to be back to square one.

21 So I think something to be considered
22 long term is perhaps a pathway to make it easier

1 for patients to remain on this medication.

2 DR. NARENDRAN: Raj Narendran. I voted
3 yes. I feel the one thing that I'm really struck
4 by, always sitting here, is even when you know the
5 drug possibly works like ketamine has been shown in
6 the past 10 years, it's so hard to come up with two
7 positive trials and there's always a high rate of
8 failure in depression, I feel comfortable that this
9 is well-grounded in basic science. The field has
10 known for a while that this drug works rapidly.

11 I really commend the sponsor for having
12 taken the effort to really making an easier
13 formulation, which would make it a lot more widely
14 accessible and provide a great benefit to people
15 who suffer from treatment-resistant depression.

16 The risks are there. I agree it's a dirty
17 compound and it has a lot of side effects, but I
18 think they're very manageable in the context of a
19 good REMS, at least in the short-term.

20 Dr. Fiedorowicz on the phone?

21 DR. FIEDOROWICZ: Yes. This is Jess
22 Fiedorowicz, University of Iowa. I abstained. As

1 previously mentioned, I think the magnitude of the
2 benefit, if any, is not clear, so I could not
3 answer the question. I think it's almost certainly
4 exaggerated. And even then, it was positive in
5 only 1 of 3 short-term phase 3 trials.

6 I subsequently disagree with the
7 characterization of these effects this large. I
8 share some of Kim's concern about desperate
9 patients flocking to this as some sort of panacea,
10 particularly with people touting large effects
11 here. The REMS appears to be appropriate to the
12 safety profile.

13 DR. PINE: Danny Pine. I voted yes.
14 Again, at least to me, it seemed relatively clear.
15 I think the only other comment that I would make is
16 that I thought it was very helpful to see the data
17 randomizing subjects to two medications,
18 essentially, at the start of the trial. I think
19 that that's an important avenue to look at,
20 comparative efficacy.

21 I do think in the future, though, I would
22 power studies to find small to medium effects with

1 that design, where people are essentially starting
2 on two new treatments at the same time, one of
3 which is a placebo of some sort.

4 DR. HILLEFORS: Mi Hillefors, NIMH. I
5 voted yes as I looked at the risk-benefit, although
6 I did vote no when it came to the have they
7 demonstrated effectiveness. And I'm still doubtful
8 if there is sufficient data to really demonstrate
9 that there is an efficacy or effectiveness.

10 However, this is an area that's really a
11 great public health concern, and we really have no
12 new medications in this very severely ill patient
13 group. And as we've heard in some of the public
14 comments, that's really suffering where there are
15 not really a lot of options.

16 So I think with the risk, it's relatively
17 well known what the risks are, and even if the
18 benefit hasn't yet been demonstrated, there are
19 compelling data and compelling results from the
20 different studies.

21 I do think that it is important not just to
22 inform patients about the risks, but also that

1 there really is a processing place to both try to
2 minimize side effects as much as possible as well
3 as mitigate or treat any side effects that would
4 emerge during the treatment for these patients
5 because even if there were the risks, when they
6 happen, there needs to be plans in place for that.
7 So I think that would be really important to have
8 those processes in place.

9 But ultimately, I think when it came to
10 risk-benefit, I felt that was still on the
11 favorable side of that.

12 DR. RUDORFER: Matthew Rudorfer. I also
13 voted yes. I thought the benefits clearly outweigh
14 the risks, and I think we're all agreeing on the
15 very important and sometimes life or death risk of
16 inadequately-treated depression that factored into
17 my equation.

18 I think we are also mainly agreeing on the
19 need for long-term studies, and I'd just add that
20 in addition to the risk side, on the benefit side,
21 it certainly is reasonable to think that esketamine
22 is not going to be the answer for everybody, as no

1 treatment for depression is, and I think long-term
2 studies could help address that in terms of for
3 whom this treatment might be particularly helpful.
4 Thank you.

5 DR. EVERETT: Thank you. This is Anita
6 Everett from SAMHSA. I was somewhat of a reluctant
7 yes when it came to this question. The clinician
8 side of me that's seen people suffer with
9 depression and have limited options really is very
10 excited about this as an opportunity for those
11 folks.

12 The no side of me was to the concerns
13 mentioned earlier about how is this going to be
14 marketed and presented to people who are looking,
15 particularly in our society in the context that
16 we're in right now for quick fixes, to really
17 complex and deep-seated issues that have biologic
18 and other needs for treatment elements that are
19 part of it.

20 So I'm very excited on one hand, but on the
21 other hand concerned about the context in which
22 this is available to folks.

1 DR. NARENDRAN: So overwhelmingly, people
2 felt the benefits outweighed the risks. However,
3 it seems like there's some questions, the people
4 were concerned about the adverse event profile
5 would have to be well communicated to the patient
6 and informed consent. Not only the informed
7 consent, the risks also have to be sort of
8 minimized and mitigated through the REMS. What I
9 heard was the REMS is pretty strong and well
10 laid out by the agency and the sponsor.

11 Some people felt the benefits perhaps gave
12 them a little bit pause that the one trial, the
13 short-term trial was positive, and some people had
14 some questions about the efficacy who voted no.
15 But overall, most of the people felt the benefits
16 for this particular population clearly outweighs
17 the risks.

18 Anybody want to add anything else?

19 (No response.)

20 DR. NARENDRAN: Next question is a
21 discussion question. Discuss whether the FDA's
22 proposed REMS would assure safe use of esketamine

1 and what additional safeguards would be needed, if
2 any. I think for this one, whoever is ready to go
3 can probably weigh in. Dr. Hillefors?

4 DR. HILLEFORS: So this may be just my
5 ignorance about how these REMS programs work and
6 how they're funded. So my question is, how would
7 it be funded? How would it be ensured that there
8 are sufficient funds for a sufficient time to keep
9 the REMS in place, as well as the RADARS, the other
10 program, the RADARS; so it doesn't stop because
11 there's lack of funding suddenly, and the drug is
12 out being used at these sites?

13 That was my question.

14 DR. LaCIVITA: Hi. This is Cynthia
15 LaCivita, and I'm with the Division of Risk
16 Management. The REMS program would be part of the
17 approval, and that is a program that the sponsor
18 would have to support and implement. The
19 assessment of the program is something that they
20 would submit on a predesignated time frame, and
21 then we would review those assessments with them.
22 The funding doesn't seem to lapse.

1 DR. HILLEFORS: Does FDA put a specific
2 time limit for how long they should be ongoing, or
3 is it just for a certain time, and then it gets
4 renewed?

5 DR. LaCIVITA: So REMS with elements to
6 assure safe use, it depends on whether the REMS is
7 necessary. There are situations where we've made
8 determinations that the REMS is no longer necessary
9 to support the safe use. It could be that it's
10 been integrated into the healthcare system. It
11 would really depend on our results and the findings
12 of the assessments moving forward.

13 DR. STAFFA: This is Judy Staffa. Can I
14 address the other part of the question? With
15 regard to the resources like RADARS, RADARS is a
16 system in the private sector that exists that many
17 sponsors take advantage of. It's an umbrella with
18 a lot of different types of resources that can
19 study issues usually related to drug abuse.

20 So the sponsor can use that. Sponsors
21 generally support that financially, their studies
22 in those areas. FDA can also require those studies

1 as postmarketing requirements, in which case they
2 would not have a choice about having to continue to
3 do that; just to clarify.

4 DR. NARENDRAN: Dr. Everett?

5 DR. EVERETT: Yes. I would like to see
6 more clarity in what's defined as healthcare
7 settings for the REMS of this particular product.
8 I'd like to see language that reflects the
9 following: assurance that the healthcare settings
10 or clinics have experience in the diagnosis and
11 treatment of psychiatric and mood disorders, and
12 that they've demonstrated, by policy and practice,
13 that they are capable of coordinating care and/or
14 have viable referral processes to providers that
15 can provide a full range of treatment.

16 So they're not just single-intervention
17 ketamine RS-type clinics, but they have a whole
18 range.

19 DR. NARENDRAN: You want to see them being
20 able to coordinate care and refer. What would you
21 recommend?

22 DR. EVERETT: I mean, ideally, they'd be in

1 a setting where they provide everything, but if
2 they don't and they become more narrow, which we've
3 seen with other products, that they be able to
4 demonstrate that they can coordinate care
5 themselves and refer out to a viable referral
6 source, not make an appointment, and at 6 months
7 before someone has an appointment -- but they stay
8 with the person until they're actually in care that
9 can work with them.

10 DR. NARENDRAN: Dr. Pine?

11 DR. PINE: So both from a safety and from
12 an efficacy standpoint, I do think some thought on
13 the part of the FDA should go into how to handle
14 the 65 and above. I felt comfortable voting to
15 approve without any specifier on the one hand. On
16 the other hand, I do think the fact that the safety
17 concerns in general would be higher with the
18 elderly and the fact that one of the notable
19 negative studies specifically targeted individuals
20 who are 65 or above creates some problems and
21 requires an extra note of caution, I think, in that
22 age group.

1 DR. NARENDRAN: Ms. Witczak?

2 MS. WITCZAK: Kim Witczak. A couple ideas
3 or things, in the registry, finding out what other
4 drugs that they're -- even psych drugs, I'd love to
5 have that as part of the patient registry. Then
6 also, are there any guidelines around who actually
7 is going to do this?

8 I keep going back, and I know you heard me
9 earlier, and I probably sound like a broken record,
10 but with primary care, that's where a lot of people
11 get their -- that's where they're going to go. I
12 know we keep saying that they'll be trained, but
13 who is training them? Are there guidelines?
14 Because most of these people are going to still
15 probably going to go there, and it goes to your
16 thing about access. And even if it has to go, does
17 it have to go through a psychiatrist?

18 So I'd love to have some more information
19 around that because I think you're going to throw
20 this into GPs that, quite honestly, don't know a
21 whole lot about even antidepressants, and they just
22 keep throwing things on top of each other, and it's

1 just one big experiment. And we're the ones -- the
2 public's paying the price for experiments.

3 DR. NARENDRAN: Mr. Kungel?

4 MR. KUNGEL: Terry Kungel. I think Kim's
5 focus on what's actually going to happen in the
6 real world is an important question, and I think
7 going to what Dr. Meisel said earlier, we live in
8 Maine, and there's a real issue about access. And
9 if you've got to drive an hour or two hours each
10 way to get there, everything that we're doing with
11 REMS, I'm concerned is sort of setting up access
12 issues and barriers to a group of people that have
13 difficulty getting and doing normal stuff.

14 I would also say I think the FDA does a
15 terrific job of capturing the data on the adverse
16 events, but the concern here is what we won't be
17 measuring. We've got, according to the document, 2
18 million life-years every year of people living in
19 significant difficulty. That piece of the equation
20 isn't being captured when we're doing this
21 reporting.

22 DR. NARENDRAN: Dr. Besco?

1 DR. BESCO: Kelly Besco. This is going to
2 seem really trivial, but I did wince a little bit
3 just thinking about a paper patient medical form or
4 monitoring form. I think that was mentioned
5 earlier. I'm not sure if that's planned to be
6 paper, but these programs work a little more
7 seamlessly for us that have to comply with the
8 recommendations when we can integrate those
9 different forms and things into our electronic
10 health records.

11 So I would just advocate for working with
12 or partnering with our HR vendors to see if we
13 could get those forms integrated into our
14 platforms.

15 DR. NARENDRAN: Dr. Meisel?

16 DR. MEISEL: Steve Meisel. I made a few
17 other comments earlier, and I just want to
18 reemphasize a couple and add a new one or two. The
19 term "medically supervised healthcare setting" has
20 been used by both the agency and by the sponsor. I
21 think we need to define what does the term
22 "medically supervised" mean.

1 Does that mean that there has to be a
2 licensed nurse on site, a physician on site? Does
3 it mean that there's got to be access to EMS
4 personnel? Does it mean there has to be access to
5 an emergency department? What does that mean?

6 I remember some discussions here in this
7 committee some months ago about a different
8 medication, brexanolone, and there was talk about a
9 medically supervised healthcare setting could be a
10 sleep lab.

11 Well, would we allow this drug to be
12 administered in a sleep lab? I hope not. But we
13 need to define what we mean by medically supervised
14 healthcare setting and what does that really
15 involve. What are the credentials of the staff
16 that would be overseeing the administration of this
17 medication? I think that's critically important.

18 Dr. Dunn mentioned this before and I
19 alluded to this earlier. The issue of access
20 versus control and safety here is a very important
21 one. The patient that goes on vacation, responds
22 and then has to go on vacation, and wants to go on

1 vacation; they're feeling well and they want to
2 take a 3-week cruise, but they need this drug once
3 a week, what do you do?

4 The person who lives in Maine or the middle
5 of No Place, North Dakota, and they have their
6 appointment that's a 3-hour drive, and now there's
7 a snowstorm and they can't get there, and tomorrow
8 the clinic is full up, and they can't get back
9 until next week, and now they had a relapse. How
10 do we deal with that?

11 Those are real-life situations, and there's
12 going to be great pressure to loosen this up in
13 some manner. The patients responded well. You
14 mentioned this before, Dr. Dunn. It's been
15 6 months. They've not had any side effects, or at
16 least nothing that they can't manage themselves.

17 Do we open it up and let them have some
18 self-supply at home to get through those kinds of
19 situations, let them have some stuff on the cruise
20 ship or those kinds of things? But then, if we do
21 that, what protects us from the 16-year-old
22 teenager taking a bottle or two of those, and going

1 to a party, and it becomes the party drug? There's
2 got to be some offsets of that.

3 I don't have any answers, but those are the
4 real-world difficulties here when we try to
5 establish a REMS in a world that also expects and
6 demands access to needed therapy. I think it's
7 probably a day-long conference of its own to figure
8 out how to balance this stuff, but I think that's a
9 conversation we ought to have.

10 The last comment I'd want to make -- and I
11 think, Kelly, you made it earlier -- the REMS has
12 got to engage the conversation and some guidelines
13 about drug interactions. What do we do if a
14 person's on a benzodiazepine? What do we do if a
15 patient's on hypertensive agents?

16 What do we do if they're on all sorts of
17 other medications? Do they hold it? Do they not
18 hold it, whatever? What do we do if they're taking
19 over-the-counter CBD oil, which is technically
20 illegal but is available all over the place? Is
21 there an interaction there? What about the medical
22 cannabis patients? What do we do in that setting?

1 I think there's got to be some guidelines
2 within the REMS to give to providers so it isn't a
3 free-for-all, let's just guess sort of thing. And
4 you mentioned also let's provide some specific
5 recommendations about what sedation scores to use,
6 what cognitive scores to use, what are the specific
7 discharge criteria, how often do we measure blood
8 pressure and this sort of thing.

9 I think we have to have some level of
10 specificity there, more than just to say monitor
11 the patient and discharge when you think they're
12 ready.

13 DR. NARENDRAN: Dr. Michelle Ruha?

14 DR. RUHA: Thanks. I was just going to
15 give my perspective. I do think it's important not
16 to limit access too much. It's really hard to get
17 into a psychiatrist a lot of time, although I
18 totally agree with Dr. Everett on you don't want
19 ketamine RS places opening up, which would
20 encourage abuse and diversion.

21 Really, any healthcare provider office
22 should really be able to do this. I was at the

1 brexanolone meeting, too, and the thing about the
2 safety profile here, which is encouraging, is that
3 we didn't hear about any immediately
4 life-threatening effects where an emergency
5 department needs to be on site. There was no
6 hypotensions, arrhythmias. There was no
7 respiratory depression.

8 So the safety profile is pretty manageable
9 for any healthcare provider office that has a blood
10 pressure machine and can do some basic monitoring.
11 I think as long as the FDA certified the site as
12 being capable of doing it -- I just wouldn't want
13 to over-restrict. I think any primary care
14 physician hopefully should have access to this so
15 that more patients can get it if needed.

16 DR. NARENDRAN: Dr. Compton?

17 DR. COMPTON: Thank you. This applies a
18 little bit to this item as well as perhaps the next
19 one. Given that the populations studied excluded
20 persons of most particular interest to me, which
21 are those with substance-use disorders, at least
22 those with current significant substance-use

1 disorders, I think the real-world use of this
2 medication may differ from the clinical trials, so
3 paying attention to that, particularly in the first
4 roll-out phases, will be important.

5 One thing that seemed to be missing from
6 the REMS was data from the clinicians reporting
7 about potential misuse by their patients. Perhaps
8 it's in there and I just didn't see it. I saw
9 quite a bit about patient-reported outcomes, but I
10 didn't see the clinicians reporting on the
11 potential misuse by their patients.

12 I am struck by the discussion of access to
13 care, particularly in rural areas and those with
14 significant impediments to attend in clinical
15 settings at a distance. There might be an
16 opportunity to consider use of echo models or
17 telemedicine to support less well-equipped
18 healthcare settings that would like to do this, but
19 will only do it once in a blue moon, so they won't
20 really develop the expertise. But these kind of
21 models could allow it to be done safely at a
22 distance, at times, and I hope that would be

1 considered.

2 Maybe I'll bring this up at the next one,
3 but ill mention it now. I thought the data on
4 suicidality was very much a concern and deserves
5 special attention during follow-up. I'm not
6 exactly sure what I'd recommend, but the topic
7 needs to be addressed very carefully.

8 DR. NARENDRAN: Dr. Zito?

9 DR. ZITO: Yes. I was impressed with a lot
10 of efforts that you've expressed for running a
11 REMS, and I'm hopeful that some elements can be
12 built into the REMS that will be a whole new day
13 for REMS in the sense that it will provide a really
14 serious eventually published study from your
15 registry data with a fixed time point in the
16 future, that we're going to look at 18 months
17 outcomes, that we're going to go beyond symptom
18 improvement to functional improvement as metrics
19 for what we need because I really, from my
20 perspective, think that if we don't have restricted
21 prescribers who are really trained and the right
22 setting in which this can take place, I would like

1 to say that there would be no direct-to-consumer
2 advertising until the REMS is done and out there.

3 So we really would be saying we need
4 phase 4. We need real assurances that the people
5 who have been excluded from these studies, for whom
6 we say this is the reason for the study, we have
7 not really looked at ED visits, we have not really
8 looked at prior psychiatric hospitalizations. I
9 have the sense that we could goose up the
10 definition of treatment-resistant depression, and
11 as everybody over here has been saying, all those
12 comorbidities, oh, my god.

13 So we have work to do to find that subset
14 in these various analyses that you've done, who
15 speak as eloquently as people have here who have
16 had the benefit of being part of the group for whom
17 it works.

18 DR. FARCHIONE: Can I just for one second?

19 DR. NARENDRAN: Sure, go ahead.

20 DR. FARCHIONE: This is Tiffany Farchione.
21 I'm a little bit confused about what you're looking
22 for, for what would be in the REMS. It sounds a

1 little bit like you're asking for, actually, a
2 postmarketing study, which would be more in line
3 with probably the next question.

4 The problem I'm having here with
5 differentiating between what you're asking for and
6 what the question is, is that the REMS is just
7 there to make sure that the drug is being used
8 safely. We might include a registry and things
9 like that. You could probably ask for a
10 postmarketing commitment or requirement, depending,
11 that could enroll from patients in the registry.
12 But I think you might be asking beyond our
13 regulatory authority, I guess I could say.

14 DR. ZITO: The problem with REMS has been
15 their impact or their lack thereof, so we don't
16 usually know too much. It takes a couple years or
17 more, if ever, for a REMS to be published. So we
18 sort of have stopped thinking about phase 4 as an
19 essential drug development process. I don't know
20 why we couldn't get back onboard to thinking very
21 seriously about that as a possibility.

22 DR. FARCHIONE: Yes. I'm just not sure

1 that the REMS is the tool we can use to do that.

2 DR. ZITO: Call it as you wish.

3 DR. NARENDRAN: Dr. Hoffer?

4 DR. HOFFER: Yes. I would just like to
5 follow up on Dr. Compton's comments about people
6 who are using substances and how they might be
7 understood within the context of both the REMS,,
8 but also potentially postmarketing surveillance,
9 which I think is part of the REMS, although I don't
10 know the definitions of these things.

11 Then I did notice that the sponsor is doing
12 some behavioral surveys and things like this, at
13 least to look at sort of the performance of the
14 drug. I would also like to see some qualitative
15 more in-depth sort of interviews with folks about
16 how the drug might be influencing their lives if
17 they're taking it, especially if they're on a
18 maintenance medication dose, and considering the
19 diversion of the drug, the potential diversion of
20 the drug, I think that would be useful.

21 But as far as postmarketing, getting this
22 on a radar for -- not only RADARS, but like

1 Monitoring the Future, or NSDUH, and part of the
2 other drug categories that people are sometimes
3 asked about, you could maybe even have some
4 announcement going out to keep an eye on ketamine
5 as we move forward because the distribution of the
6 drug is going up, and it's only going to go up
7 more.

8 DR. NARENDRAN: Dr. Hillefors?

9 DR. HILLEFORS: Mi Hillefors. This is
10 maybe a different question, maybe back to the
11 process. I don't know who would do the
12 certification, who would set the certification
13 criteria for the pharmacist and the healthcare
14 centers.

15 The question, why I'm just bringing it up,
16 whether it's the FDA, or with an independent
17 organization, or the drug manufacturer, if it is a
18 drug manufacturer, how do you avoid the appearance
19 of a conflict of interest or that they are
20 certifying how to use the drug?

21 So it may be a question or just something
22 to think about. I'm not sure.

1 DR. NARENDRAN: Dr. Everett?

2 DR. EVERETT: I just wanted to make sure my
3 notion was clear. What I'm concerned about -- I'm
4 not as much concerned about the primary care
5 administering or being involved in this with the
6 REMS. What I am concerned about is people who
7 don't respond to this not setting up the
8 possibility that that feels like a cliff to the
9 patient.

10 So I want to see, if it's possible within
11 the authority of the REMS, that to be certified,
12 you have to have some policy, some list of referral
13 sources or things like that, so the patient doesn't
14 feel like they're high risk for suicide.

15 We know, from emerging literature on
16 suicide, that falling out of treatment is a
17 particularly high risk that results and culminates
18 in suicide, not infrequently. So that's what I'm
19 the most worried about, is having a system set up
20 that has a dead end rather than we'll refer you;
21 our relationship is with the university of this,
22 whatever, and that's where we send you if you don't

1 respond.

2 DR. NARENDRAN: Sorry. Dr. Hillefors'
3 comment, if FDA wants to respond to that.

4 DR. LaCIVITA: Hi. This is this Cynthia
5 LaCivita. With regard to the requirements in the
6 REMS, we will have ongoing discussions with the
7 sponsor to come up with requirements for the
8 certification. The program is implemented by the
9 sponsor, so it will be their program, and the
10 requirements will be spelled out in the REMS, which
11 is a legal document, so if that helps at all.

12 DR. NARENDRAN: I have a quick question. I
13 also share the comments like Dr. Compton raised in
14 terms of substance users and how this would impact
15 them with the sponsor, and know before they
16 dispense the medication that this person is on
17 buprenorphine, or Xanax. Is there a way to capture
18 that?

19 If someone is using heroin and the provider
20 wants to give them ketamine, and they just give it
21 to them, or if they're on buprenorphine and it adds
22 up to a very fatal reaction, is there a way to

1 deter it ahead of time?

2 DR. FARCHIONE: We haven't thought about
3 putting anything like that into the REMS yet.

4 DR. NARENDRAN: It would be nice to capture
5 that information because, typically, that doesn't
6 come through a postmarketing database, so I don't
7 know if you could.

8 DR. FARCHIONE: I imagine the practice of
9 medicine type stuff that, probably, if a patient
10 had a history or active ongoing substance use, a
11 physician might be less inclined to use this, but
12 that's the practice of medicine.

13 DR. NARENDRAN: They'll know who the
14 provider is of buprenorphine or if somebody else is
15 doing it.

16 DR. FARCHIONE: Right, right. You actually
17 have to ask your patient what they're using.

18 DR. NARENDRAN: Or check the database.

19 Dr. Dunn, do you have comments?

20 DR. W. DUNN: Walter Dunn. There is always
21 this tension between safety and access, and I'm
22 really encouraged to hear my colleagues on DSaRM

1 advocating for more accessibility. Last time we
2 had a joint meeting, we were on kind of opposing
3 ends.

4 A couple of points; for our IV ketamine
5 use, we're using at much higher doses, and most of
6 these clinics are monitoring for an hour
7 afterwards, and even academic centers and research
8 studies are only monitoring for an hour. I'm not
9 saying that's what we should start off with, but
10 just give context to the level of standard of
11 practice right now.

12 A general philosophical observation; I
13 think it's always easier to start off with less
14 restrictions, and if you see a signal for adverse
15 events, ratcheting it up. If you start off with a
16 highly restrictive kind of policy, no one's ever
17 going to say let's back down on it because, if you
18 don't see any events, they're going to say, well,
19 it's obviously working. So that's possibly one
20 thing to consider.

21 Then as I mentioned previously, potentially
22 a pathway to a less burdensome monitoring protocol,

1 again like what we do with clozapine. Potentially
2 if there's no sedation or elevated blood pressure
3 events within the first 6 months or first year,
4 these patients could graduate to a 1-hour
5 monitoring or potentially taking this medication
6 home.

7 Using the clozapine as another example, I
8 think there's actually good evidence that the level
9 of monitoring we have now actually prevents a good
10 number of patients from getting the medication, and
11 the potential harms from that actually outweigh the
12 benefits in that the incidence of agranulocytosis
13 is actually low enough such that if we didn't do
14 the monitoring, had patients, and had better access
15 to clozapine, the number of lives saved would
16 actually outweigh the potential harm of these
17 events, just as an example; where we start off with
18 a pretty high bar and we've never brought it down,
19 despite the evidence saying that perhaps we don't
20 need that level of monitoring.

21 So something to consider here, maybe
22 starting off with something low, and then with

1 postmarketing surveillance, if we do pick up these
2 untoward events in the RADARS and we say, okay, we
3 need to make this more restrictive, the things that
4 we'd be missing, if we start with the high bar of
5 regulation, are these relapses. That's not
6 something that we have a formal mechanism to pick
7 up, so we'd never see that signal.

8 So we have a mechanism in place to see
9 untoward events from too liberal of use, but we
10 don't have a mechanism really to account for bad
11 outcomes if this medication is not widely
12 available.

13 DR. NARENDRAN: I think that's all the
14 questions we have. I assume you have tons of
15 information about the REMS.

16 Do we want to power through and finish, or
17 do you want a 10-minute break? 3:20 is our break
18 time. Break? Okay. The panel wants to power
19 through; agency wants a break. We'll do a break,
20 10-minute break.

21 (Whereupon, at 3:30 p.m., a recess was
22 taken.)

1 DR. NARENDRAN: I think we are going to
2 start. We're missing a couple panel members.
3 We'll wait a second for them.

4 (Pause.)

5 DR. NARENDRAN: It's a discussion question.
6 I guess we could perhaps start. We'll go ahead and
7 start. They'll be here.

8 Question number 5 is a discussion question.
9 Are additional data needed pre- or post-approval to
10 address outstanding issues? Discuss whether such
11 data will be required prior to approval.

12 So we're just going to go with whoever's
13 ready. Dr. Meisel?

14 DR. MEISEL: Steve Meisel. I don't think
15 this data is required prior to approval, but I
16 think it's important. It was mentioned earlier
17 that the data we have is on the MADRS score,
18 period. We don't have functional data,
19 quality-of-life data, those kinds of things. I
20 think it's important for a medication like this to
21 understand whether improving that score actually
22 improves people's lives.

1 I think that's important postmarketing data
2 that can happen. I don't think that's a barrier to
3 approving the medication, but I think it's
4 necessary postmarketing.

5 DR. NARENDRAN: Dr. Hernandez-Diaz?

6 DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz.
7 I have a list of post-approval data. One thing
8 that we have heard that needs to be collected
9 somehow is the suicidality, whether it is related
10 to the medication or not. Unfortunately, we know
11 there is going to be cases of patients on this
12 medication, and based on past experiences, that can
13 trigger problems. So I think being proactive,
14 collecting information to be ready to respond to
15 questions, that will be useful.

16 Then some questions we have discussed
17 already. One is the effectiveness in patients over
18 65 or over 75 years old, also, when to stop. We
19 have data up to 38 weeks with sufficient numbers,
20 but if we are going to consider when to stop or
21 when to continue the medication, that would be
22 something to explore.

1 Interactions with polytherapy, including of
2 course psychotropics and also illegal drugs; the
3 potential dose effects for effectiveness, we have
4 considered two doses and they were consistent. In
5 some studies, the higher dose was apparently
6 better, but we didn't find that in phase 3, so keep
7 an eye on the dose for efficacy but also for
8 potentially adverse effects, and the long-term
9 adverse effects that have been mentioned.

10 Finally, the adherence that has been
11 discussed well, not only in terms of the patients
12 complying with treatment, but who can afford this
13 type of studies, of treatment, in that sense, like
14 who can get these choices, and try to, as much as
15 possible, keeping the safety, but trying to reach
16 out to the population that can benefit from it.

17 DR. NARENDRAN: Mr. Kungel?

18 MR. KUNGEL: Something that I think does
19 need to get done prior to approval is we've got a
20 distressed population, and I think it's going to be
21 really important to be able to do informed decision
22 making well. When you've got people as desperate

1 as some of these are, can we really get an informed
2 consent? I think we're going to have people so
3 desperate, they'll say yes to anything, and I'm
4 concerned about premature closure; I don't care,
5 yes, where do I sign? So I think that's an issue
6 that I would like to see get addressed and worked
7 before we go out.

8 Post-approval, I think there are two
9 additional questions. One is, I've been involved
10 in prostate cancer for 10 years. One of the things
11 we spend a lot of time on is the heterogeneity.
12 There may be something like 40 different forms.
13 I'd love to understand the level of heterogeneity,
14 particularly in the treatment-resistant depression,
15 to identify who's the market that we can address.

16 I would also like to be able to say are
17 there screening tests, genetic tests, that can
18 start to identify the best responders and the
19 non-responders so we can really focus on what's
20 most critical.

21 DR. NARENDRAN: Dr. Rudorfer?

22 DR. RUDORFER: Yes, thank you. Matthew

1 Rudorfer. This is not required, but as thoughts
2 for going forward. As with many treatments, I'm
3 not sure that the last word is in, in terms of
4 relapse prevention in terms of the long term. And
5 I just wanted to remind everybody there's a body of
6 literature that's often overlooked, and that's the
7 post-ECT data.

8 ECT is very effective in the short-term
9 treatment of severe depression, but it has a
10 horrendous relapse rate if nothing further is done
11 after a course of treatment.

12 NIMH has supported some follow-up studies,
13 and what's interesting is that when people have
14 tried various antidepressants, what has always come
15 out on top has been a combination of an
16 antidepressant, most recently venlafaxine and
17 lithium. The combination has tended to beat the
18 antidepressant alone, so I just thought that's
19 worth considering.

20 The other point I wanted to make is a
21 follow-up and paraphrase to Dr. Everett's comments
22 before about having referral sources available.

1 That is, as with any new and exciting treatment
2 development, and certainly that's what we're
3 talking about here, I think when we put our
4 clinician's hat on, it's probably particularly
5 important that people don't get the idea that this
6 is either magical or, what's worse, the treatment
7 of last resort, which is a very precarious position
8 to be in if we want to instill hope for people.

9 Thank you.

10 DR. NARENDRAN: Dr. Compton? No. You're
11 good. Dr. Everett?

12 DR. EVERETT: I have a question and then a
13 comment. The question is, we've used the word
14 "informed consent" quite a bit, but I didn't see
15 that in the REMS proposed as such. So there's
16 informed consent that's written like before you
17 have anesthesiology or anesthesia, but I don't
18 think that it would be the same as outpatient oral
19 pill or something.

20 Informed consent's not envisioned as part
21 of that or is it? That's my question.

22 DR. LaCIVITA: I think that we were

1 thinking about patient registration, and the
2 sponsor may want to comment on that, too, but that
3 would be an opportunity to inform the patient about
4 that.

5 DR. EVERETT: But it would be a discussion,
6 not a signed consent form, not a formal process
7 like you have pre-surgery for instance. That's not
8 the vision.

9 MR. KUNGEL: I wasn't being technical.

10 DR. EVERETT: Well, I'm wondering.

11 MR. KUNGEL: But it's a good point.

12 DR. EVERETT: It is a point with some
13 medicines that are in REMS, Clozaril in particular.

14 DR. LaCIVITA: We were considering
15 something signed, written, that the patient signs.

16 DR. EVERETT: Yes. I do have three
17 comments about future questions that we have.
18 Because of the association with dissociation,
19 individuals with psychosis were excluded. But I
20 think we have to look at that major depression
21 itself is not uncommonly associated with psychotic
22 features, and then there's a whole other grouping

1 of individuals who have psychosis, who frequently
2 have comorbid depression.

3 So I think moving forward, for me, that
4 wouldn't be a stopper for premarketing, but for me
5 moving forward, I sure would like to know what
6 happens with psychotic episodes and this agent in
7 particular, so to me, that seems important.

8 Of course, the use in children, but
9 particularly adolescents, I'd be really interested
10 in that and what we can learn about that moving
11 forward. We're probably aware that that will
12 happen somewhat off label, so we might have a
13 chance to sort of observe what happens,
14 particularly in adolescence there.

15 Then we've said this, but I'll just say it
16 for the record. The abuse potential and what
17 happens when this is used in real time is really
18 important to understand. It seems like a pretty
19 low diversion risk, but maybe there's creative ways
20 to divert it that we're not thinking of right now
21 and things like that. So I would recommend that we
22 think about some way to track that in some way.

1 DR. NARENDRAN: Next is Dr. Dunn.

2 DR. W. DUNN: Walter Dunn. This is my wish
3 list. This is not anything I recommend prior to
4 approval. I'd like to see further studies in
5 bipolar depression given our lack of approved
6 treatments -- or limited treatments for that
7 condition.

8 What the chairman mentioned before; there
9 have been some studies potentially implicating that
10 if you have naltrexone on board, you're not going
11 to get the antidepressant effect. Given the
12 current opioid crisis, I think that's something
13 that should be explored. It could be a significant
14 patient population that could benefit from
15 esketamine.

16 Then to echo my colleague, Dr. Everett,
17 about looking at this treatment for psychotic
18 depression, given that the standards of treatment
19 for that condition have a pretty high side effect
20 burden; ECT, use of antipsychotics.

21 So if this could be a treatment for
22 psychotic depression, I think that would be an

1 important population to look at.

2 DR. NARENDRAN: Dr. Zito?

3 DR. ZITO: There was a mention just a
4 minute ago about adolescent depression. I'd like
5 to say that coming from the pediatric depression
6 world, there's a whole different take on the story
7 of managing adolescent depression, which is clearly
8 modeled on a biopsychosocial model, and we haven't
9 had any discussion here today about that approach.
10 No arm of any study was involved in a
11 psychotherapeutic, well-researched, and recognized
12 psychotherapeutic model.

13 I understand people with many years of
14 negative experience are not going to necessarily be
15 jumping on that, but I do hope that we are only
16 talking about adult depression at this point in
17 time, because I think adolescent depression -- this
18 kind of wave that we can roll out the experience of
19 using this drug; you need to go after the serious
20 long-term adult depressives and demonstrate real
21 effectiveness there, then we can talk about
22 adolescence.

1 DR. FARCHIONE: So there is actually a plan
2 for a waiver of pediatric studies for this.

3 DR. ZITO: What does that mean?

4 DR. FARCHIONE: So part of the initial
5 pediatric study plan for this indication, they
6 asked for a waiver of adolescent studies. This is
7 only an adult communication.

8 DR. ZITO: Right. Good.

9 DR. NARENDRAN: Dr. Hillefors?

10 DR. HILLEFORS: Mi Hillefors. Coming from
11 more translational therapeutics arena, I think it
12 would be important to maybe -- and this has not to
13 do maybe with the approval process and approval of
14 esketamine, but in the future to further understand
15 how esketamine works and the mechanism of action,
16 because it could also inform us if there are
17 certain antidepressant medications or drugs that
18 would have more beneficial effect.

19 I know that the FDA looked at the four
20 different antidepressant treatments that were used
21 in these trials for the combination treatment, but
22 there were no differences detected. But the sample

1 size is still small, and we don't know exactly what
2 the mechanism of action is, so more information
3 about that could help identify if there are
4 specific antidepressants that will be more
5 beneficial as the combination treatments.

6 DR. NARENDRAN: Tiffany, do you have a
7 comment?

8 DR. FARCHIONE: You're talking about the
9 different individual antidepressants that are used
10 in combination. I forget who it was, but somebody
11 earlier in one of the clarifying questions, either
12 after ours or after the applicant, I can't
13 remember, had asked about why there wasn't a
14 monotherapy.

15 I'm wondering if anyone has thoughts on
16 that. Is that something you would want to see as a
17 postmarketing study?

18 DR. HILLEFORS: My understanding from what
19 your initial comments were, that it was really a
20 lot in the way from an ethical perspective to do
21 the -- because there's a breakthrough process, and
22 that taking the subjects -- I do think from a

1 scientific perspective, really to learn more about
2 esketamine as the compound, a monotherapy would
3 probably have told us maybe more directly what
4 exactly and tease it out, because you do have the
5 problem, especially like with ketamine studies,
6 where there is a very high placebo effect, whether
7 they understand is it placebo, is it esketamine, is
8 it a combination? Now, you may not really have
9 that ability to distinguish.

10 DR. FARCHIONE: Early on, in designing the
11 studies, if you look at anything, well, we've got
12 this unknown, and we've got patients who are
13 really, really sick, and we do have a standard of
14 care, and we should probably at least have a
15 standard of care at baseline and then see what
16 happens if we add stuff on top. But if we were to
17 approve this product, then we would be saying it
18 looks like this works.

19 So now it's less of an unknown and less of
20 a concern from that standpoint if you were to
21 compare this thing to something else. That's why
22 I'm asking if there's an appetite for that in

1 postmarketing.

2 DR. NARENDRAN: Dr. Michelle Ruha?

3 DR. RUHA: I assumed, and maybe I
4 understood wrong, that if it was approved, it
5 wasn't going to be required that another
6 antidepressant be used because my understanding
7 was, for the studies, you had to do something
8 because we don't know if it works before you study
9 it, so you have to get something that works. But
10 now we're saying we believe it works from the
11 studies, so once it's approved --

12 DR. FARCHIONE: Right. But the proposal in
13 the labeling is to give it with another
14 antidepressant because we don't have any
15 monotherapy.

16 DR. TEMPLE: That's what we studied, after
17 all.

18 DR. RUHA: Because we don't have a study,
19 right.

20 DR. FARCHIONE: Right.

21 DR. RUHA: So postmarketing, if people keep
22 failing other agents, presumably -- they might have

1 to be put on one just to be put on the ketamine
2 even though it's assumed that it doesn't work, so
3 likely, some people will be given ketamine without
4 another agent at some point. So yes, I would
5 collect the data on that, too, or do postmarketing
6 study on just ketamine alone

7 DR. TEMPLE: But collecting the data is not
8 going to be informative. People improve so much on
9 these things. You've got to do a study.

10 DR. RUHA: Yes. We need a study. That's
11 true.

12 DR. TEMPLE: If you want to know.

13 DR. RUHA: Yes, that's true.

14 DR. NARENDRAN: Dr. Compton?

15 DR. COMPTON: Just to follow up on that
16 last point, I think there's certainly the
17 possibility of several important comparative
18 effectiveness studies. It may not be appropriate
19 within this particular paradigm for you all
20 requiring it, but there may be a role for PCORI or
21 NIH in terms of some of that work.

22 But I think just to follow up on the last

1 question, I think you all might consider whether a
2 monotherapy postmarketing study is the converse of
3 the removal study, where you start on both and you
4 leave people on the esketamine, but take away the
5 ancillary antidepressant.

6 DR. TEMPLE: Can I just comment? We ought
7 to know what you mean by comparative effectiveness.
8 This is territory where a non-inferiority study,
9 comparative study, cannot possibly be informative.
10 Only superiority is going to be informative.
11 Failing to find a difference in this setting where
12 the spontaneous changes are so large, it just makes
13 that kind of study impossible. It's not going to
14 be. So it has to be a different showing trial.

15 DR. NARENDRAN: Next, Ms. Witczak?

16 MS. WITCZAK: I would be curious about
17 long-term cognitive and memory loss, if that would
18 be in the postmarketing. And I'm not sure how you
19 guys measure that, but it would be interesting to
20 see.

21 DR. NARENDRAN: Raj Narendran. I know they
22 looked at the suicide in an acute setting. I think

1 there's also an opportunity to push that rapid-
2 acting antidepressant effect and look in the study
3 to see any emergency rooms or crisis centers, where
4 you can just do one dose and make them feel better,
5 and then they can continue down the line.

6 So maybe it's more important to know
7 whether the drug esketamine can be used 24 hours,
8 48 hours in emergency rooms in a single-dose
9 setting just to make people better when you admit
10 them to inpatient or when you send them home. The
11 long-term cognitive deficits, I think, is something
12 that needs to be examined as well.

13 Dr. Hough?

14 DR. HOUGH: Sure. A couple of years ago,
15 we undertook a proof-of-concept study. It was a
16 small study, only 68 participants, but it was
17 positive in terms of rapid reduction of depressive
18 symptoms, and also the second was the clinical
19 global judgment of suicide severity.

20 That was published in the American Journal
21 of Psychiatry last summer, and it was encouraging
22 enough for us that we went ahead with the phase 3

1 program. Currently, we're completing one of the
2 studies and the other one is still enrolling, and
3 we hope to have some of the results later this
4 year, so we're very encouraged by that.

5 I'd also like to address the adolescent.
6 We have a program with this same indication,
7 patients with major depression and at imminent risk
8 for suicidality. Right now, we're doing a PK and
9 safety study, and that study is enrolling. And if
10 positive, then we would move forward with
11 confirmatory studies as well.

12 DR. NARENDRAN: Thank you. Dr. Dunn?

13 DR. W. DUNN: Walter Dunn. Back to the
14 question about whether we would like a study
15 looking at monotherapy; definitely as it pertains
16 to patient access. So I envision a couple of
17 scenarios where that is going to be needed or be
18 desired in the labeling.

19 Number one, for third-party insurance, I
20 can imagine this is going to require pre-approval,
21 and they're going to require the patients to be on
22 an existing antidepressant because that's what the

1 labeling says.

2 For those of us who treat patients in these
3 specialty mood disorders clinics, these patients
4 have failed 5 or 6 different treatments, and the
5 likelihood that a seventh one is going to provide
6 any additional benefit over the esketamine is
7 fairly low. So I think all we're doing is putting
8 patients on a medication and perhaps causing extra
9 side effect burden without any likely clinical
10 benefit. That's one scenario.

11 The second scenario, in a healthcare such
12 as the VA Administration or the Veterans
13 Administration, again, this is probably going to
14 require pre-approval and the pharmacists are going
15 to look at the labeling and say, "Why isn't your
16 patient on an existing antidepressant? And that's
17 the only condition where we're going to approve
18 esketamine."

19 Again, a lot of patients we treat in our
20 specialty clinics either can't tolerate it,
21 tolerate antidepressants, our current ones, or have
22 failed so many that the likelihood of a new one, if

1 they haven't exhausted all of them, is going to
2 provide really a minimal benefit.

3 So I think it's important, for patient
4 access issues, to give us the flexibility to
5 provide it as a monotherapy.

6 DR. NARENDRAN: Any other questions,
7 comments? If not, I'll hand it over to the agency
8 for any last comments, closing comments.

9 (NO response.)

10 DR. FARCHIONE: I think in closing, I would
11 want to, again, thank everybody who was here today.
12 I think we had a really useful discussion with a
13 lot of important points that we can take back with
14 us in terms of our final risk-benefit assessment
15 and our final decision-making process.

16 I want to also take a moment to thank the
17 folks who spoke during the public comment session.
18 I know that that can sometimes be difficult for
19 people. So it means a lot that you guys were able
20 to be here, again, on short notice, with all of the
21 snafus that happened leading up to the meeting. We
22 really appreciate the time and the effort people

1 took to be here, so thank you.

2 **Adjournment**

3 DR. NARENDRAN: Thank you. The meeting is
4 adjourned. Panel members, leave your name badge
5 here on the table so they may be recycled. Please
6 also take all your personal belongings with you, as
7 the room is cleaned at the end of the meeting day.
8 Meeting materials left on the table will be
9 disposed of. We will now adjourn the meeting.
10 Thank you.

11 (Whereupon, at 4:07 p.m., the meeting was
12 adjourned.

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